2018 Biennial Meeting
American Society for Photobiology

Tampa Bay, Florida · May 12–15, 2018
Tampa Marriott Waterside Hotel & Marina

PROGRAM AND ABSTRACTS


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Social Media Channels

Please share your pictures and impressions taken during the meeting. Use **#photobio2018** when posting about the event!

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WELCOME

TO THE 2018 AMERICAN SOCIETY FOR PHOTOBIOLOGY BIENNIAL MEETING

Dear conference attendee, dear ASP members and friends,

Welcome to the 39th scientific meeting of the American Society for Photobiology!

You will be taking part in an absolutely vibrant conference covering many aspects of contemporary photochemistry and photobiology with attendees from all corners of the globe. The meeting is being held at the Tampa Marriott Waterside Hotel & Marina, a breathtaking venue with all state of the art accommodations ensuring an enjoyable and productive meeting.

The scientific program includes informative and diverse scientific sessions and special symposia, as well as two poster sessions. We have an outstanding lineup of plenary speakers including Wolfgang Gaertner, Tayyaba Hasan, and Rutao Cui. The program is also featuring the 'ASP Special Session - Photobiological Research Frontiers: An African Perspective', the ASP PanAmerican symposium 'Organic and inorganic photochemistry of functional materials', the ASP Special Session 'Direct and Sensitized Photochemistry in Biological Molecules', and the 'Distinguished Lecture Symposium: Photoprotection in the 21st Century'.

We are excited to announce the 'Kendric C Smith Interdisciplinary Symposium: 55 Years Photochemistry and Photobiology' chaired by Jean Cadet and Irene Kochevar. There will also be signature presentations from the recipients of the ASP Research and New Investigator Awards. We are particularly pleased to welcome Santi Nonell, the current president of our sister society, the European Society for Photobiology, for a special presentation.

The Associate members have a number of exciting events planned that are distributed throughout the meeting schedule. These include the ASP Associate Member Scientific Symposium, the ASP Associate Member 'Presidential Get Together Party', the Mentoring Lunch, and other events.

Finally, be sure to explore beautiful Tampa located on the Western Gulf Coast of Florida surrounded by fun and entertaining activities!

We look forward to seeing you in Tampa!

Georg T. Wondrak, University of Arizona, ASP President
Keith A. Cengel, University of Pennsylvania, ASP Past President
Yu-Ying He, The University of Chicago, ASP President Elect

ASSOCIATE MEMBER ACTIVITIES

Dear Associate members,

The associate council of the American Society for Photobiology (ASP) is very excited to host the following networking and mentoring events for students and postdoctoral fellows (Associate Members) at the upcoming ASP meeting from May 12th to May 17th at Tampa, FL. The goal of our events is to provide associate members with resources to further their knowledge on career paths in academia and industry, to foster a sense of community, and to support advancements in communicating Photobiology and Photochemistry. We encourage all associate members to participate and take advantage of these FREE events at the ASP meeting:

1. **3-Minute Thesis Competition (Saturday, May 12th, 4:00 PM – 5:30 PM):** Competitors from the Associate Members will give 3-minute presentations of their doctoral work as an "elevator pitch." Guest judges will award cash prizes for first and second place. Audience members are invited to vote for their favorite presentation – which will also win a cash prize!

2. **K99/R00 Grant Writing Workshop (Sunday, May 13th, 8:00 AM – 9:00 AM):** Dr. Haung-Chaio (Joe) Huang (University of Maryland) will present strategies for writing the Career Development and Mentoring portions of the NIH K99/R00 application. These often-neglected but critical pieces of the K99/R00 application are among the hardest portions to write. Whether you are a postdoctoral candidate preparing to write a K99 of your own, or a graduate student who plans to write one later in life, it is never too soon to start planning ahead for this challenge!

3. **Associate Member Presidential Get Together Party (Sunday, May 13th, 9:00 PM – 11:00 PM):** At this popular, informal event you will have the opportunity to socialize with other fellow students and enjoy FREE appetizers and adult beverages (2 complimentary drink tickets for Associate Members).

4. **Mentoring Luncheon (Monday, May 14th, 11:30 AM – 1:00 PM):** During this mentoring session, the students will have the opportunity to interact with early career scientists as well as experienced principle investigators from both academia and industry and gain insights on career development, research interests, and much more. Associate Member elections will also occur at this event.

   Invited Mentors: Dr. Caradee Wright; Dr. Ariane Dimitrov; Dr. Kolbe Ludger; Eduardo Ruvolo, M.S.; Dr. Florian Gruber; Dr. Shosuke Ito; Dr. Imran Rizvi

Please be advised that all of the above events are FREE and open to all ASSOCIATE MEMBER attendees REGISTERED for the 2018 ASP meeting. Also remember to share your pictures and impressions taken during the meeting. Use **#photobio2018** when posting about the event. Looking forward to meeting you in Tampa!

Best Regards,
Richard W. Davis IV and Damilola Fajuyigbe
Associate Councilors, ASP 2018

THE 2018 MEETING ORGANIZATION

ASP EXPRESSES ITS WARM APPRECIATION TO THE FOLLOWING INDIVIDUALS FOR THEIR OUTSTANDING CONTRIBUTIONS TO THE ORGANIZATION OF THE SCIENTIFIC PROGRAM

Chairs

Georg Wondrak, Keith A. Cengel, Yu-Ying He

Session Organization

Luis Arnaut
Theresa Busch
Jean Cadet
Keith Cengel
Marcus Cooke
Carlos Crespo
John D'Orazio
Mike Davies
Richard Davis
Ariane Dimitrov
Regina DiScipio
Thierry Douki
Damilola Fajuyigbe
Wolfgang Gaertner
Beth Galliard
Frank Gasparro
Edith Glazer
Alec Greer
Arjan Griffioen
Florian Gruber
Iltefat Hamzavi
Yu-Ying He
Bernd Herzog
Joe Huang
Lisa Kelly
Irene Kochevar
Ludger Kolbe
Doug Learn
Jon Lovell
Bice Martincigh
Sherri McFarland
Giorgia Miolo
Michael Pigula
Patrick Rochette
Lesley Rhodes
Imran Rizvi
Eduardo Ruvolo
Tadeusz Sarna
Christian Schoeneich
Bryan Spring
John-Stephen Taylor
Andrés Thomas
Joanna Turner
Caradee Wright
Shiyong Wu
Jin Xie
Xiaojing Yang

ASP OFFICERS AND COUNCILORS

Officers

Georg Wondrak, President
Yu-Ying He, President-Elect
Keith Cengel Past-President
Theresa M. Busch, Treasurer
Doug Learn, Secretary
Brett Burk, Executive Secretary

Councilors

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Scott Davis
Thierry Douki
Imran Rizvi
Sherry McFarland
Bernhard Ortel
Charles Simone
Brian Spring
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John-Stephen Taylor
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Associate Councilors

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EXHIBITOR LISTING

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2018 AWARDS

ASP Research Award

2018 – Thierry Douki

ASP New Investigator Award

2018 – Shobhan Gaddameedhi

ASP Lifetime Achievement Award

2018 – TBD

Editor's Student Research Award

2018 – Marvin Pollum

Photocite-A Award

2018 – So Yeong Lee and Sang-Woo Joo

Photocite-B Award

2018 – Douglas Brash

Frederick Urbach Memorial Student Travel Award

2018 –

Sepalika Bandara

Gwendolyn Cramer

Richard Davis IV

Marie Dorr

David du Preez

Anne-Sophie Gary

Ryan Lang

Richard Lincoln

Arvind Mohan

Kaitlin Moore

Kylie Morgan

Yi Hong Ong

Luis Ortiz-Rodriguez

Michael Pigula

Palak Shah

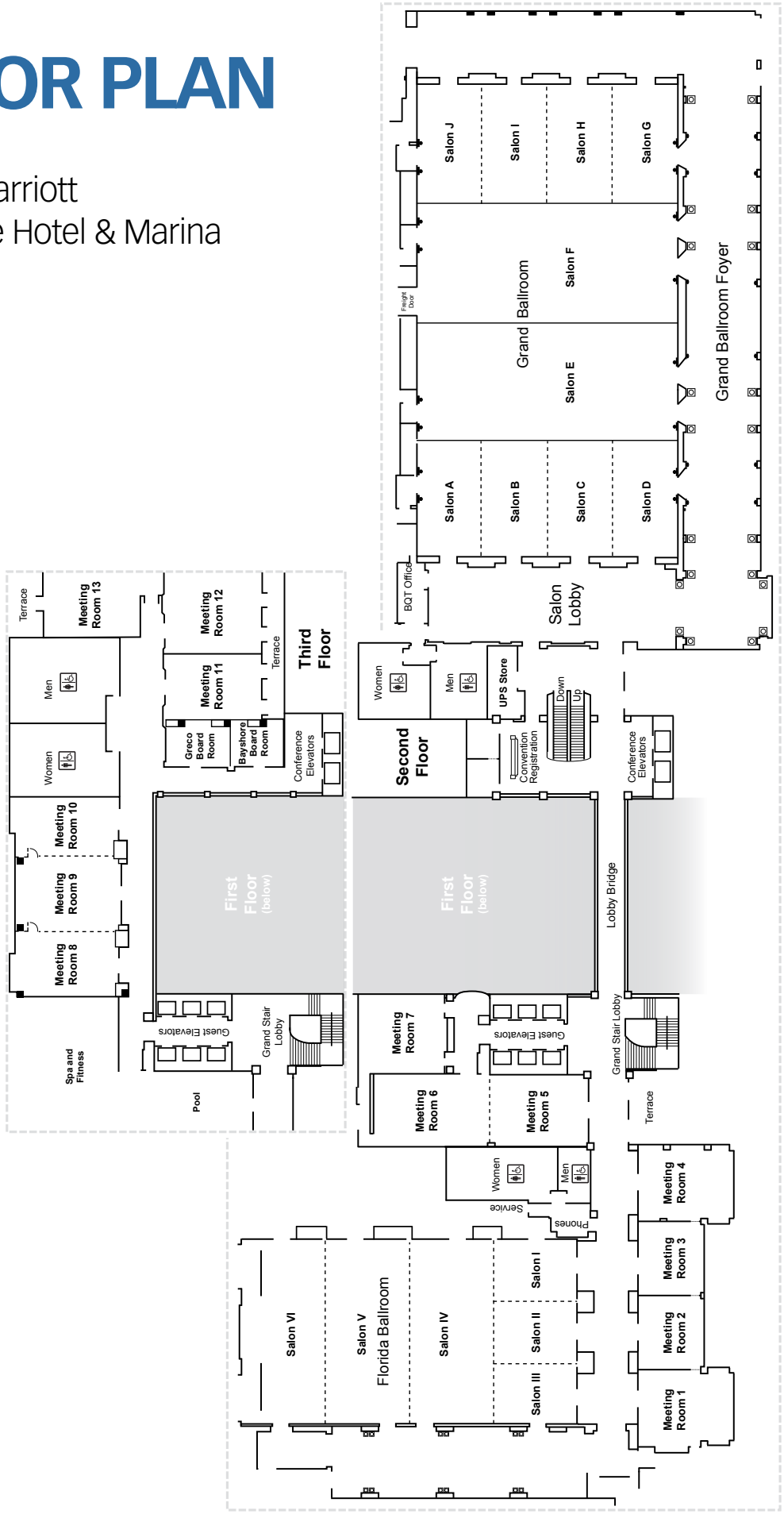
Ajeet Srivastav

Giselle Tian

Kai Zhang

FLOOR PLAN

Tampa Marriott
Waterside Hotel & Marina



ABBREVIATED SCHEDULE

DAY 1 – Saturday, May 12

TIME	EVENT	CHAIR(s)	ROOM
10:00 AM – 12:00 PM	ASP Executive Committee		Meeting Rooms 5-6
10:00 AM – 3:00 PM	Exhibitor Set-up		Ballroom Foyer
1:00 PM – 4:00 PM	ASP Council Meeting	Georg Wondrak	Meeting Rooms 5-6
3:00 PM – 5:00 PM	Poster Set-up		Florida 6
4:00 PM – 5:30 PM	ASP Associate Members' Elevator Talk Competition and Grant Writing Workshop	Richard Davis, Damilola Fajuyigbe	Florida 4
4:00 PM – 7:00 PM	REGISTRATION OPEN		Ballroom Foyer
5:00 PM – 6:00 PM	POSTER SESSION I		Florida 6
6:00 PM – 8:00 PM	WELCOME RECEPTION		Il Terrazo
8:00 PM – 9:00 PM	Presidential Lecture: From Skin Photooxidative Stress to Novel Molecular Strategies for Photoprotection and Cancer Photochemoprevention New Investigator Award: Emerging Roles of the Circadian Clock in Photocarcinogenesis and Skin Cancer Prevention	Georg Wondrak, Shobhan Gaddameedhi	Florida 4

DAY 2 – Sunday, May 13 (Happy Mother's Day)

TIME	EVENT	CHAIR(s)	ROOM
8:00 AM – 4:00 PM	REGISTRATION OPEN		Ballroom Foyer
9:00 AM – 12:00 PM	Biomolecular Skin Photoprotection	Ludger Kolbe, Florian Gruber	Meeting Room 3
8:00 AM – 12:45 PM	Organic and Inorganic Photochemistry of Functional Materials: A Panamerican Perspective	Alec Greer, Lisa Kelly	Florida 3
9:00 AM – 12:00 PM	Frontiers in Ocular Photobiology and Photodamage	Beth Galliard, Patrick Rochette	Florida 4
8:00 AM – 12:00 PM	Frontiers in Nucleic Acid Photochemistry and Photobiology	Thierry Douki, John-Stephen Taylor	Florida 5
1:00 PM – 2:00 PM	Keynote Lecture: A Chemist Seeing Colors	Wolfgang Gaertner	Florida 5
2:00 PM – 4:00 PM	ASP Special Session - Photobiological Research Frontiers: An African Perspective	Caradee Wright, Bice Martincigh	Meeting Room 3
4:00 PM – 6:00 PM	Applied Photobiology: Opportunities and Options	Doug Learn	Meeting Room 3
2:00 PM – 6:00 PM	Protein Photo-oxidation: Mechanisms and Biological Consequences	Mike Davies, Christian Schoeneich	Florida 3
2:00 PM – 5:00 PM	New Nanotechnology Approaches to PDT	Jon Lovell, Jin Xie	Florida 4
2:00 PM – 5:00 PM	Direct and Sensitized Photochemistry in Biological Molecules, Part 1	Carlos Crespo, Andrés Thomas	Florida 5
5:00 PM – 7:00 PM	ASP Associate Member Scientific Symposium: From First Principles to Applications of Photomedicine	Regina DiScipio, Michael Pigula	Florida 4
7:00 PM – 9:00 PM	Photodynamic mechanisms in cancer: resistance and combinatorial approaches	Imran Rizvi, Joe Huang	Florida 4

ABBREVIATED SCHEDULE

DAY 2 – Sunday, May 13 (continued)

TIME	EVENT	CHAIR(s)	ROOM
7:00 PM – 9:00 PM	Direct and Sensitized Photochemistry in Biological Molecules, Part 2	Carlos Crespo, Andrés Thomas	Florida 5
7:00 PM – 9:00 PM	Distinguished Lecture Symposium: Photoprotection in the 21st Century	Bernd Herzog, Ludger Kolbe	Florida 3
9:00 PM – 10:30 PM	Photochemistry and Photobiology Editorial Board Meeting	Jean Cadet	Meeting Room 2
9:00 PM – 11:00 PM	ASP Associate Member Presidential Get Together		The Pit, Champions Sports Bar

DAY 3 – Monday, May 14

TIME	EVENT	CHAIR(s)	ROOM
8:00 AM – 3:00 PM	REGISTRATION OPEN		Ballroom Foyer
8:00 AM – 10:00 AM	Structures and Spectral Tuning of Bilin-based Systems	Xiaojing Yang, Wolfgang Gaertner	Meeting Room 3
10:00 AM – 12:00 PM	Dynamics, Mechanisms and Applications of Light-sensitive Systems	Xiaojing Yang, Wolfgang Gaertner	Meeting Room 3
8:00 AM – 12:00 PM	ASP-ESP Joint Symposium: Cutaneous DNA Damage: New Insights and Approaches from Translational Human Studies	Lesley Rhodes, Marcus Cooke	Florida 3
8:00 AM – 11:30 AM	Broadening Horizons in Photochemistry and Photobiology	Joanna Turner	Meeting Room 2
8:00 AM – 9:30 AM	PDT: Personalization and Optimization	Bryan Spring	Florida 5
10:00 AM – 12:00 PM	21st Century Frontiers in Psoralen Photochemistry and Photomedicine	Frank Gasparro, Giorgia Miolo	Florida 4
10:00 AM – 12:00 PM	Theranostics and Beyond: Targeting and Tailoring PDT	Luis Arnaut	Florida 5
11:30 AM – 1:00 PM	ASP Associate Member Mentoring Luncheon Assoc Member Councilor Election		Florida 4-5
12:00 PM – 1:00 PM	ASP Past Presidents' Luncheon Board Room		Meeting Room 1
1:00 PM – 2:00 PM	Keynote Lecture: Photochemistry and Photobiology: A Bridge to Science, Technology and Medicine	Tayyaba Hasan	Florida 5
2:00 PM – 5:00 PM	K.C. Smith Symposium: 55 Years Photochemistry and Photobiology Celebratory Symposium	Jean Cadet, Irene Kochevar	Florida 4
5:00 PM – 6:00 PM	ASP Business Meeting		Florida 4
6:00 PM – 8:00 PM	POSTER VIEWING		Florida 6
8:00 PM – 11:00 PM	ASP BIENNUAL MEETING 2018 BANQUET & DANCE		Il Terazzo

ABBREVIATED SCHEDULE

DAY 4 – Tuesday, May 15

TIME	EVENT	CHAIR(s)	ROOM
8:00 AM – 8:30 AM	ASP Research Award Lecture	Georg Wondrak	Florida 5
8:30 AM – 9:00 AM	ESP Presidential Keynote		Florida 5
8:00 AM – 12:00 PM	REGISTRATION OPEN		Ballroom Foyer
9:00 AM – 12:00 PM	Emerging Photodynamic Compounds for Targeting Cancer and Infection	Sherri McFarland, Edith Glazer	Meeting Room 3
9:00 AM – 12:00 PM	Frontiers in Melanin Research: From Photoexcitation to Physiology and Pathology	Tadeusz Sarna	Florida 3
9:00 AM – 12:00 PM	UVA and Beyond: Frontiers in Photodamage and Photoprotection	Eduardo Ruvolo, Iltefat Hamzavi	Florida 4
9:00 AM – 12:00 PM	DNA Repair and Inflammation in UV Damage and Tumorigenesis	Yu-Ying He, Shiyong Wu	Florida 5
11:30 AM – 12:30 PM	Exit Council Meeting	Yu-Ying He	Meeting Room 2
1:00 PM – 2:00 PM	Keynote Speaker: Why Red Haired Individuals are so Prone to Developing Melanoma	Rutao Cui	Florida 5
2:00 PM – 5:00 PM	New Insights in Vascular and Immune Response to PDT	Arjan Griffioen	Florida 3
2:00 PM – 5:00 PM	The Skin Exposome: From Environmental Exposure to Biological Response	Ariane Dimitrov, Georg Wondrak	Florida 4
2:00 PM – 6:00 PM	Epigenetics and Molecular Machinery in UV-induced SCC and Melanoma	Yu-Ying He, John D'Orazio	Florida 5

GENERAL INFO

Registration Desk Hours

Location: Il Terrazo Foyer

Day	Time	Location
Saturday, May 12	4:00 PM – 7:00 PM	Il Terrazo Foyer
Sunday, May 13	8:00 AM – 4:00 PM	Florida Ballroom Foyer
Monday, May 14	8:00 AM – 3:00 PM	Florida Ballroom Foyer
Tuesday, May 15	8:00 AM – 12:00 PM	Florida Ballroom Foyer

Morning Refreshments

Coffee, hot tea, and breakfast items will be available near the registration desk each morning 30 minutes before presentations begin.

Sunday, Monday, and Tuesday
7:30 AM – 8:30 AM

Social Media Channels

Please share your pictures and impressions taken during the meeting. Use #photobio2018 when posting about the event!

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Explore Tampa!

The Visit Tampa Bay will be available during Saturday evening's Welcome Reception to answer all of your questions about our host city. Whether you're looking for the best pizza in town or fresh seafood, this is where you'll find the answers. They can also recommend museums, local tours, outdoor adventures, and local shopping areas.

If you aren't able to connect with the Visit Tampa Bay on Saturday night, no worries! City maps and visitor's guides will be available at the registration check-in desk.

TECHNICAL PROGRAM

PRESENTER'S NAME IS ASTERISKED (*) IF OTHER THAN FIRST AUTHOR.

Saturday, May 12, 2018

ASP Associate Members' Elevator Talk Competition & Grant Writing Workshop

4:00 PM – 5:30 PM Florida 4 Co-chairs: Richard Davis, Damilola Fajuyigbe

Registration Open

4:00 PM – 7:00 PM Il Terrazo Foyer

Poster Session

5:00 PM – 6:00 PM Florida 6

P-1 Oxidative stress induced by UV-B and sunlight mediated photoactivation of carbazole inhibits normal human skin cells physiology
Srivastav A, Singh J, Dubey Divya, Chopra D, Mohd A, Agnihotry S, Mujtaba SF, Singh Ray R
CSIR-Indian Institute of Toxicology Research, Sanjay Gandhi Post Graduate Institute, Shia P.G. College

P-2 Oxidative stress mediated apoptosis and DNA damage by triclosan in human keratinocyte under environmental UV radiation
Dubey D, Amar S, Goyal S, Chopra D, Singh J, Srivastava AK, Ray RS
CSIR-Indian Institute of Toxicology Research

P-3 Site-Specific Chemo-enzymatic Photocaging of Peptides and Proteins
Zhou ZS, Moulton K, Sadidi A
Northeastern University

P-4 Sustained Release Drug Delivery Of Bevacizumab To Treat Ocular Angiogenesis
Skrypai Y, Thomas A, Uwensuyi A, Karumanchi DK, Gaillard ER
Northern Illinois University

P-5 Kinetic Control in the Alkylation of Pterin Photosensitizers: Synthetic, Photochemical, and Theoretical Studies
*Walalawela N, Vignoni M, Urrutia MN, Belh SJ, Greer EM, Thomas AH, Greer A**
CUNY Brooklyn College, INIFTA and Universidad Nacional de La Plata, CUNY Baruch College

P-6 In vitro viral photostimulated inactivation by a synthetic halogenated anthraquinone
*Mugas ML, Konigheim BS, Roumana A, Aguilar JJ, Contigiani MS, Fousteris M, Nunez Montoya SC**
Universidad Nacional Cordoba and CONICET, University of Patras

P-7 Melanocyte-specific and Melanin-specific Antibodies Useful in Photobiology, Pigment Cell and Melanoma Research
Coelho SG, Wakamatsu K, Ito S, Valencia JC, Hearing VJ
National Cancer Institute, National Institutes of Health and Center for Drug Evaluation and Research, Food and Drug Administration, Fujita Health University School of Health Sciences

P-8 3D Bioprinting with UVA1 Radiation and Photoinitiator Irgacure 2959: Can the ASTM Standard L929 Cells Predict Human Stem Cell Cytotoxicity?
Godar DE, Gurunathan C, Ilev I
Food and Drug Administration, BeneVir Biopharm, Inc.

P-9 The Effect of Endothelia Cells on UVB-induced DNA Damage and Transformation of Keratinocytes In 3D polycaprolactone scaffold Co-culture System
Zhao H, Wu S
Ohio University

P-10 The mechanism of CIRP in regulation of Stat3 phosphorylation and Bag-1/S expression after UVB radiation
Sun W, Liao Y, Yi Q, Tang L, Tong L
Ohio University, Third Military Medical University, South West Medical University, Chongqing University

P-11 Mechanisms and products of the photosensitization of amino acids and nucleotides by pterins
*Serrano MP, Reid LO, Estébanez S, Castaño C, Oliveros E, Thomas AH, Lorente C, Dantola ML**

P-12 Fabrication Of A Fast Fiber Scanner For Fluorescence Microendoscopy
Mohan A, Ducourthial G, Kercher EM, Spring BQ
Northeastern University

P-13 Effect of the Antioxidant Resveratrol on Photosensitized Processes
*Gaspar Tosato M, Neyra Recky J, Serrano M, Miñan A, Schilardi P, Fernández Lorenzo de Mele M, Thomas A, Dántola ML, Lorente C**
Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Universidad Nacional de La Plata (UNLP), CCT La Plata-CONICET

P-14 Proteomic and Transcriptional Profiling of Molecular Stress Response Pathways Underlying the Pronounced UV-resilience of Human Dermal Fibroblasts
Perer J, Wondrak GT
College of Pharmacy and UA Cancer Center, University of Arizona

P-15 Phospholipid Membrane Damage Produced by Photosensitization with Decylpterins
*Vignoni M, Urrutia MN, Junqueira HC, Greer A, Reis A, Baptista MS, Itri R, Thomas AH**
INIFTA (CONICET-UNLP), Universidade de Sío Paulo, Brooklyn College, City University of New York, ICETA/REQUIMTE/LAQV, University of Porto

P-16 Nanoliposome-Based Modulation of Photosensitizer Localization to Enhance Photodynamic Therapy Efficacy
Moore KM, Rizvi I, Obaid G, Ruhi MK, Nath S, Kessel D, Hasan T
Massachusetts General Hospital, Northeastern University, Bogazici University, Wayne State University School of Medicine

P-17 Interfacial Strategies to Study Reactive Oxygen Intermediates
*Walalawela N, Belh SJ, Malek B, Greer A**
CUNY Brooklyn College

P-18 Computational algorithms for in-vivo fluorescence microendoscopy image mosaicking
Lang R, Tatz J, Kercher E, Spring B
Northeastern University

P-19 Laser-assisted vascular anastomosis: comparison of photothermal vs. photochemical tissue bonding
Pabittei DR, Karismananda K, de Mol BA, Heger M
Academic Medical Center Amsterdam, Hasanuddin University Indonesia

P-20 Superhydrophobic Photosensitizers: Airborne 1O2 Killing of a In-vitro Oral Biofilm at the Plastron Interface
Pushalkar S, Ghosh G, Xu QF, Liu Y, Ghogare AA, Atem C, Greer A, Saxena D, Lyons AM*
New York University College of Dentistry, CUNY Brooklyn College, SingletO2 Therapeutics LLC, CUNY College of Staten Island

P-21 Enhancing Rose Bengal-Photosensitized Protein Crosslinking in Cornea
*Wertheimer CM, Elhardt C, Kaminsky SM, Afshar S, Kochevar IE**
Massachusetts General Hospital, Harvard Medical School

P-22 Comparison of Affordable and Portable Real-Time UV-B Sensors in Relation to Fixed Sensors for Personal Sun Exposure Scoping Studies in Developing Countries
*du Preez DJ, Wright CY**
University of Pretoria, South African Weather Service, South African Medical Research Council

Opening Reception and Welcome to Tampa Bay
6:00 PM – 8:00 PM Il Terrazo

Presidential Lecture and New Investigator Award
8:00 PM – 9:00 PM Florida 4

From Skin Photooxidative Stress to Novel Molecular Strategies for Photoprotection and Cancer Photochemoprevention
Wondrak GT
University of Arizona

Emerging Roles of the Circadian Clock in Photocarcinogenesis and Skin Cancer Prevention
Gaddameedhi S
Washington State University

Sunday, May 13, 2018 - Happy Mother's Day

Registration
8:00 AM – 4:00 PM Florida Ballroom Foyer

Biomolecular Skin Photoprotection

Sponsored by: Beiersdorf

9:00 AM – 12:00 PM Meeting Room 3 Co-chairs: Ludger Kolbe, Florian Gruber

1-1 9:00 AM – 9:25 AM
Effective Endogenous Skin Photoprotection by Active Ingredients Requires Nrf2-induction
*Eggers K, Mann T, Kolbe L**
Beiersdorf

1-2 9:25 AM – 9:50 AM
The aryl hydrocarbon receptor induces the proteolysis of the tumor suppressor p27KIP1 in UVB-exposed keratinocytes
Pollet M, Mescher M, Shaik S, Krutmann J, Haarmann-Stemmann T

1-3 9:50 AM – 10:15 AM
Necroptosis: A Novel UVB-Induced Cell Death Pathway
Gary AS, Rochette PJ
Centre de recherche du CHU de Quebec – Universite Laval, Hopital du Saint Sacrement

1-4 10:15 AM – 10:40 AM
A quest for biomarkers and strategies in skin stress and -aging - 5 years Christian Doppler Laboratory for the Biotechnology of Skin Aging
Gruber F
Medical University of Vienna

1-5 10:40 AM – 11:05 AM
Mycosporine-like amino acids (MAA) - biocompatible, photoprotective compounds from nature
Lawrence KP, Gacesa R, Long PF, Young AR
King's College London

1-6 11:05 AM – 11:30 AM
Pharmacological Modulation of TLR4 as a Novel Molecular Strategy for Skin Photoprotection
Wondrak GT, Dickinson S
University of Arizona, College of Pharmacy and UA Cancer Center

Organic and Inorganic Photochemistry of Functional Materials: A Panamerican Perspective

Sponsored by: JASCO, Shimadzu Scientific Instruments

8:00 AM – 12:45 PM Florida 3 Co-chairs: Alec Greer, Lisa Kelly

2-1 8:00 AM – 8:30 AM
Pterin photosensitizers free in solution and bound to DNA and biomembranes
Thomas AH
INIFTA (CONICET-UNLP)

2-2 8:30 AM – 9:00 AM
Photoswitchable cell toxicity of (5-oxo-2-dibenzothienylmethyl)triphenylphosphonium
*Isor A, O'Dea A, Arnatt CK, McCulla RD**
Saint Louis University

2-3 9:00 AM – 9:30 AM
Singlet Oxygen in Nano-Matrices: from Entombing to Enhancing
*Kabanov V, Macia N, Press DJ, Heyne B**
University of Calgary

2-4 9:30 AM – 10:00 AM
Photochemistry of Supramolecular Complexes between Cucurbit[n]urils and Photosensitizers
*Robinson-Duggon J, Pérez-Mora F, Divona-Villanueva L, Valverde-Vásquez L, Fuentealba D**
Pontificia Universidad Catolica de Chile

2-5 10:15 AM – 10:45 AM
Conjugated polymers with photocleavable solubilizing chains
Thomas SW
Tufts University

2-6 10:45 AM – 11:15 AM
Photosensitized oxidations aiming specific cellular targets
Baptista MS
Universidade de São Paulo

2-7 11:15 AM – 11:45 AM
Photocatalytic NADH-analog systems for fuel-forming reactions
Glusac KD
UIC/Argonne

2-8 11:45 AM – 12:15 PM
Interaction Between Metal Complexes and Materials in Multiple Dimensions
Marti A
Rice University

2-9 12:15 PM – 12:45 PM
Perfluorocarbon nanoemulsions for imaging and phototherapy
Sletten E, Day R, Estabrook D, Cosco E, McLaughlin R, Logan J
UCLA

Frontiers in Ocular Photobiology and Photodamage

9:00 AM – 12:00 PM Florida 4 Co-chairs: Beth Galliard, Patrick Rochette

3-1 9:10 AM – 9:35 AM
Rose Bengal Depth in Human Donor Cornea after Rose Bengal Photodynamic Antimicrobial Therapy
Peterson JC, Naranjo A, Martinez JD, Gaidosh G, Arrieta-Quintero E, Amescua G, Parel JM*
University of Miami, Bascom Palmer Eye Institute

3-2 9:35 AM – 10:00 AM
Re-Examining Corneal Photokeratitis Thresholds at UV-C Wavelengths
Sliney D
Johns Hopkins Bloomberg School of Public Health

3-3 10:00 AM – 10:25 AM
Ultraviolet A-induced oxidation in cornea: characterization of the early oxidation-related events
*Zinflou C, Rochette PJ**
CHU de Québec research center – Université Laval, Hôpital du Saint-Sacrement

3-4 10:35 AM – 11:00 AM
Age related modification to ocular melanin modulates its photoprotective ability
Gaillard ER, Yacout SM, McIlwain KL, Mirza SP
Northern Illinois University, Univ Wisconsin Milwaukee

3-5 11:00 AM – 11:25 AM
Age-related Macular Degeneration: Defining Toxic Wavelengths In The Solar Spectrum Using Cell Models
Picaud S, Marie M, Arnault E, Barrau C, Fradot V, Erishmann C, Gondouin P, Villette T, Sahel JA
Institut de la vision, ESSILOR internation R&D

3-6 11:25 AM – 11:40 AM
Enhancing Rose Bengal-Photosensitized Protein Crosslinking in Cornea
*Wertheimer CM, Elhardt C, Kaminsky SM, Afshar S, Kochevar IE**
Massachusetts General Hospital, Harvard Medical School

3-7 11:40 AM – 11:55 AM
The Effect of All-trans-Retinal on Susceptibility of the Retina to Photodamage Induced by Visible Light
Rozanowska M, Golczak M, Maeda A, Palczewski K
Cardiff University, Case Western Reserve University

Frontiers in Nucleic Acid Photochemistry and Photobiology

8:00 AM – 12:00 PM Florida 5 Co-chairs: Thierry Douki, John-Stephen Taylor

4-1 8:00 AM – 8:30 AM
Effect of sequence context, nucleosomes, and tertiary structure on DNA photochemistry
*Lu C, Cannistraro VC, Wang K, Harelimana I, Taylor JS**
Washington University

4-2 8:30 AM – 9:00 AM
A varying kinetic isotope effect observed during spore photoproduct formation
*Ames D, Lin GJ, Jian YJ, Cadet J, Li L**
IUPUI, University of Sherbrooke

4-3 9:00 AM – 9:30 AM
Nucleosomes And ETS Transcription Factors Induce Unique UV Damage Signatures That Promote Mutagenesis In Melanoma
*Mao P, Brown AJ, Esaki S, Lockwood S, Poon GMK, Smerdon MJ, Roberts SA, Wyrick JJ**
Washington State University, Georgia State University

4-4 10:00 AM – 10:30 AM
The molecular mechanism of photodimerization in DNA
Improta R
LIDYL-CNRS/Université Paris Saclay

4-5 10:30 AM – 11:00 AM
Photosensitized Formation Of DNA Lesions
Ravanat JL, Gomez Mendoza M, Douki T, Markovitsi D, Silerme S, Dumont
CEA Grenoble, CNRS, ENS Lyon

4-6 11:00 AM – 11:30 AM
Theoretical studies of photochemistry in nucleic acids
Matsika S, Lee W
Temple University

Keynote Lecture: A Chemist Seeing Colors

1:00 PM – 2:00 PM Florida 5

KL 1-1 1:00 PM – 2:00 PM
A Chemist Seeing Colors
Gaertner W
University of Leipzig

ASP Special Session - Photobiological Research Frontiers: An African Perspective

2:00 PM – 4:00 PM Meeting Room 3 Co-chairs: Caradee Wright, Bice Martincigh

5-1 2:00 PM – 2:25 PM
It's Not Always Black and White: Key Findings from the South African Skin Photobiology Study 2014-2018
Wright CY
Environment and Health Research Unit, South African Medical Research Council

5-2 2:25 PM – 2:50 PM
Melanin distribution in human epidermis affords localized protection against DNA photodamage and concurs with skin cancer incidence difference in extreme phototypes
Fajuyigbe D, Lwin SM, Diffey BL, Baker R, Tobin DJ, Sarkany RPE, Young AR
King's College London, Newcastle University, University of Bradford

5-3 2:50 PM – 3:15 PM
A Photobiology Course At University Of Education, Winneba, Ghana
Annan JN
University of Education, Winneba

5-4 3:15 PM – 3:40 PM
How Effective Are Plant Extracts At Photostabilising Sunscreen Absorbers?
Martincigh BS
University of KwaZulu-Natal

Applied Photobiology: Opportunities and Options

4:00 PM – 6:00 PM Meeting Room 3 Chair: Doug Learn

6-1 4:00 PM – 4:30 PM
Toxicology: Moving a Compound Across the Bench to First in Man
Learn DB
Charles River Laboratories

6-2 4:30 PM – 5:00 PM
The Scottish Photobiology Service
Eadie E, McGuire V, Fullerton L, Dawe RS, Ibbotson SH
Ninewells Hospital and Medical School

6-3 5:00 PM – 5:30 PM
Lighting Technology and the Illuminating Engineering Society
Sliney DH
The Johns Hopkins School of Public Health

6-4 5:30 PM – 6:00 PM
American Society for Photobiology Presentation on Intellectual Property
Maxey-Fisher BJ
Maxey-Fisher, PLLC

Protein Photo-oxidation: Mechanisms and Biological Consequences

Sponsored by: Bruker BioSpin, Taylor & Francis

2:00 PM – 6:00 PM Florida 3 Co-chairs: Mike Davies, Christian Schoeneich

7-1 2:00 PM – 2:25 PM
Characterization Of Singlet-Oxygen Induced Damage On Proteins
*Leinisch F, Mariotti M, Rykaer M, Lopez-Alarcon C, Hagglund P, Davies MJ**
University of Copenhagen, Technical University of Denmark, Pontificia Universidad Catolica de Chile

7-2 2:25 PM – 2:50 PM
Photochemical and Peroxyl Radical-Mediated Oxidation of Î±- and Î²- Caseins: Role of Tyrosine and Tryptophan in Protein Crosslinking
López-Alarcón C, Fuentes-Lemus E, Silva E, Lorentzen LG, Leinisch F, Davies MJ
Pontificia Universidad Católica de Chile, University of Copenhagen

7-3 2:50 PM – 3:15 PM
Novel Photodegradation Mechanisms of Proteins Via Side Chain Cleavage of Aromatic Amino Acids
Schoneich C
University of Kansas

7-4 3:15 PM – 3:40 PM
Photochemistry of proteins - an industry perspective
Alavattam S

7-5 3:40 PM – 4:05 PM
Analytical Method Development and Discovery of Photo-Crosslinking of Proteins
Zhou ZS, Moulton K
Northeastern University

7-6 4:05 PM – 4:30 PM
Photo-oxidation of extracellular matrix proteins
*Hibbert SA, Ozols M, Mellody KT, Bell M, Griffiths CEM, Watson REB, Sherratt MJS**
University of Manchester, Walgreens Boots Alliance

7-7 4:30 PM – 4:55 PM
Cholecystokinin 1 Receptor As A Unique G Protein-Coupled Receptor Activated By Singlet Oxygen (GPCR-ABSO) - A Photodynamic Toolkit For Physiology
Cui ZJ, Jiang HN, Li Y, Jiang WY, Liang HY, An YP
Beijing Normal University

7-8 4:55 PM – 5:20 PM
UV-A damage to proteins in the eye lens and model systems
Sherin PS, Sormacheva ED, Zelentsova EA, Duzhak TG, Tsentalovich YP
International Tomography Center

7-9 5:20 PM – 5:45 PM
Potential Clinical Applications of Protein Photocrosslinking
Redmond RW
Wellman Center for Photomedicine

New Nanotechnology Approaches to PDT

2:00 PM – 5:00 PM Florida 4 Co-chairs: Jon Lovell, Jin Xie

8-1 2:00 PM – 2:30 PM
From Molecules to Mammal: Inventing Luminescent Nanoparticles for Photomedicine
Han G
University of Massachusetts-Medical School

8-2 2:30 PM – 3:00 PM
Nanotechnology for photoimmunotherapy
Huang H, Pigula M, Fang Y, Hasan T
University of Maryland College Park, Harvard Medical School

8-3 3:00 PM – 3:30 PM
Chemophototherapy Using Porphyrin-phospholipid Liposomes Loaded with Doxorubicin
Lovell JF
SUNY Buffalo

8-4 3:30 PM – 4:00 PM
Nanoparticle ensembles for Photo-based Imaging and Therapy
Nie ZH, Liu YJ, Yang KK, Chen XY
University of Maryland College Park, National Institutes of Health

8-5 4:00 PM – 4:30 PM
Nanoparticles to Mediate Photodynamic Therapy and X-ray Induced Photodynamic Therapy
*Zhou S, Zhang W, Jiang W, Xie J**
University of Georgia

Direct and Sensitized Photochemistry in Biological Molecules, Part 1

2:00 PM – 5:00 PM Florida 5 Co-chairs: Carlos Crespo, Andrés Thomas

9-1 2:00 PM – 2:25 PM
Photooxidation Reactions of Cellular DNA
Cadet J
Université de Sherbrooke

9-2 2:25 PM – 2:50 PM
Radical Generation in DNA by Direct Absorption of Low-Energy UV Radiation
Markovitsi D
CNRS LIDYL

9-3 2:50 PM – 3:15 PM
UV-Induced Charge Transfer in DNA Strands
Kohler B, Zhang Y, Kohl FR, de La Harpe K
The Ohio State University, US Air Force Academy

9-4 3:35 PM – 4:00 PM
DNA Damage: When the Danger Comes from "Insiders"
Lhiaubet-Vallet V
Instituto de Tecnologia Quimica, Universitat Politècnica de Valencia-CSIC

9-5 4:00 PM – 4:25 PM
Dynamics and mechanism of DNA repair by photolyases
Zhong D
Ohio State University

9-6 4:25 PM – 4:50 PM
To probe pyrimidine dimerization mechanisms using photochemically inert aromatic residues
*Jian Y, Maximowitsch E, Domratcheva T, Li L**
Indiana University-Purdue University Indianapolis (IUPUI), Max-Planck Institute for Medical Research

ASP Associate Member Scientific Symposium: From First Principles to Applications of Photomedicine

5:00 PM – 7:00 PM Florida 4 Co-chairs: Regina DiScipio, Michael Pigula

10-1 5:00 PM – 5:17 PM
Bacteriochlorins as efficient PDT Photosensitizers: Molecular Design, Mechanisms and Applications
Dabrowski JM, Pucelik B, Korzeniowska P, Ptaszek M, Yu Z, Meares A, Rocha LB, Pereira MM, Arnaut LG
Jagiellonian University, University of Maryland, University of Coimbra

10-2 5:17 PM – 5:34 PM

Observations by Ultrafast Transient Absorption Spectroscopy: Insight into Photoreactivity of Pterin Biomolecules

DiScipio R, Crespo C
Case Western Reserve Unversity

10-3 5:34 PM – 5:51 PM

Photochemical Relaxation Pathways in O6-Methylguanosine and S6-Methylthioinosine Upon Absorption of Ultraviolet-B Radiation

Ortiz-Rodriguez LA, Ashwood B, Crespo-Hernandez C

10-4 5:51 PM – 6:08 PM

Modular Antibody-directed NIR Photoactivatable Nanoconstructs Penetrate and Selectively Destroy Pancreatic Cancer Cells in a Heterocellular 3D Tumor Model

Obaid G, Bano S, Mallidi S, Kuriakose J, Broekgaarden M, Silber Z, Bulin AL, Simeone D, Hasan T
Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, New York University Langone Health, Harvard University, Massachusetts Institute of Technology

10-5 6:08 PM – 6:25 PM

Conjugation Of Photoimmunoconjugates To Nanoparticles Enhances Theranostic Efficacy In Tumor Cells

Pigula ML, Huang HC, Fang Y, Yim J, Hasan T
Harvard Medical School, Massachusetts General Hospital, University of Maryland, Massachusetts Institute of Technology

10-6 6:25 PM – 6:42 PM

Uniform light distribution as a design criterion in artificial daylight photodynamic therapy

O'Mahoney P, Haigh N, Wood K, Brown CTA, Ibbotson S, Eadie E
University of Dundee, NHS Tayside and The Scottish Photodynamic Therapy Centre, Blueside Photonics, University of St. Andrews

Photodynamic Mechanisms in Cancer: Resistance and Combinatorial Approaches

7:00 PM – 9:00 PM Florida 4 Co-chairs: Imran Rizvi, Joe Huang

11-1 7:00 PM – 7:20 PM

Photodynamic Therapy-based Combinations to Target Resistance in Ovarian Cancer

Rizvi I, Nath S, Huang-Chiao H, Obaid G, Ruhi MK, Moore K, Pouli D, Georgakoudi I, Kessel D, Hasan T
Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, University of Maryland, Bogazici University, Northeastern University, Tufts University, Wayne State University

11-2 7:20 PM – 7:40 PM

Sub-cytotoxic photodynamic priming to re-shape cancer care

Huang H, Rizvi I, Liu J, Hasan T
University of Maryland College Park, Harvard Medical School

11-3 7:40 PM – 8:00 PM

Targeting stromal determinants of therapeutic resistance with PDT

Celli JP
University of Massachusetts Boston

11-4 8:00 PM – 8:20 PM
PDT: Improved Efficacy By Directed Sub-Cellular Targeting
Kessel DH
WSU School of Medicine

11-5 8:20 PM – 8:40 PM
Photodynamic Therapy as an Intraoperative Adjuvant to Surgical Debulking.
Cengel KA
University of Pennsylvania

Direct and Sensitized Photochemistry in Biological Molecules, Part 2

7:00 PM – 9:00 PM Florida 5 Co-chairs: Carlos Crespo, Andrés Thomas

12-1 7:00 PM – 7:25 PM
Natural anthraquinones as new photodynamic sensitizers with antimicrobial potentiality
Nunez Montoya SC, Marioni J, Dimmer JA, Mugas ML, Cabrera JL
Universidad Nacional Córdoba and CONICET

12-2 7:25 PM – 7:50 PM
Dithionated Nucleobases as Effective Photodynamic Agents Against Human Epidermoid Carcinoma Cells
Pollum MM, Lam M, Jockusch S, Crespo-Hernández CE
Case Western Reserve University, Columbia University

12-3 7:50 PM – 8:15 PM
Lipid Oxidation Impact on Lipid Bilayers Representing Biological Membranes: Optical Microscopy and Small Angle X-Ray Scattering (SAXS) Combined Data
Itri R
University of Sao Paulo

12-4 8:15 PM – 8:40 PM
Lipofuscin accumulates in skin cells turning keratinocytes photosensitive to visible light
Tonolli PN, Chiarelli-Neto O, Santacruz-Perez C, Junqueira HC, Watanabe I, Severino D, Martins WK, Baptista MS
IQ-USP, UNESC, ICB-USP, UNIAN

12-5 8:40 PM – 9:00 PM
Photosensitized oxidation of tyrosine: protein damage and a novel synthetic approach to tyrosine dimers
Dántola ML
Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Universidad Nacional de La Plata (UNLP) - CONICET

Distinguished Lecture Symposium: Photoprotection in the 21st Century

Sponsored by: Beiersdorf and BASF

7:00 PM – 8:30 PM Florida 3 Co-chairs: Bernd Herzog, Ludger Kolbe

DLS-1 7:00 PM – 7:30 PM
Anti-inflammatory activity of ingredients of sun care products? Implication for sun protection
Kolbe L
Beiersdorf

DLS-2 7:30 PM – 8:00 PM
Wavelengths longer than 380nm cause photodamage to skin cells that is not adequately protected by application of conventional sunscreens.
Lawrence KP, Douki T, Sarkany RPE, Acker S, Herzog B, Young AR
King's College London, Université Grenoble Alpes, SyMMES, & CEA, INAC, King's College London, BASF Grenzach GmbH

DLS-3 8:00 PM – 8:30 PM
The Formula for Best Sunscreen Performance – Beer-Lambert's Law Under the Microscope
Herzog B
BASF Grenzach GmbH

Monday, May 14, 2018

Registration
8:00 AM – 3:00 PM Florida Ballroom Foyer

Structures and Spectral Tuning of Bilin-based Systems
8:00 AM – 10:00 AM Meeting Room 3 Co-chairs: Xiaojing Yang, Wolfgang Gaertner

13-1 8:00 AM – 8:40 AM
Structural Analysis of Phycobilisomes from Red Alga and Cyanobacteria
*Li XY, Zhao JD**
Peking University, IHB-CAS

13-2 8:40 AM – 9:10 AM
Step Forward, Step Back: Evolution of Spectral Tuning in Cyanobacteriochromes
Rockwell NC, Martin SS, Lagarias JC
UC Davis

13-3 9:10 AM – 9:40 AM
Computational Insight Into the Red-Green Spectral Tuning Mechanism in the Cyanobacteriochrome Slr1393g3
*Wiebeler C, Rao AG, Schapiro I**
The Hebrew University of Jerusalem

13-4 9:40 AM – 10:00 AM
Crystal structure of a Far-red-absorbing Photoreceptor
Bandara S, Zeng X, Rockwell N, Ren Z, Shin H, Lagarias JC, Yang X
University of Illinois at Chicago, University of California Davis

Dynamics, Mechanisms and Applications of Light-sensitive Systems

10:00 AM – 12:00 PM Meeting Room 3 Co-chairs: Xiaojing Yang, Wolfgang Gaertner

14-1 10:20 AM – 10:50 AM
Dynamics and mechanism of UV-B perception by UVR8
Zhong D
Ohio State University

14-2 10:50 AM – 11:20 AM
Photolyases of Agrobacterium fabrum: PhrA is a CPD class III photolyase related to plant cryptochromes, and PhrB is the first prokaryotic 6-4 photolyase
Lamparter T, Elstner M, Gillet N, Holub D, Krauß N, Ma H, Scheerer P, Zhang F
KIT, Charite

14-3 11:20 AM – 11:40 AM
Opsins in action-light directed subcellular signaling and cell behaviors
*Ratnayake K, Senarath K, Siripurapu P, Kankanamge D, Karunarathne A**
University of Toledo

14-4 11:40 AM – 12:00 PM
Elucidating the Signaling Mechanism of a Dual-sensor Photoreceptor
Heewhan Shin , Zhong Ren , Xiaoli Zeng , Sepalika Bandara , Xiaojing Yang
University of Illinois at Chicago

ASP-ESP Joint Symposium: Cutaneous DNA Damage: New Insights and Approaches from Translational Human Studies

8:00 AM – 12:00 PM Florida 3 Co-chairs: Lesley Rhodes, Marcus Cooke

15-1 8:00 AM – 8:30 AM
DNA damage in skin cells: methods and mechanisms
Cooke MS
Florida International University

15-2 8:30 AM – 9:00 AM
Co-exposure to benzo[a]pyrene and simulated sunlight affects both formation of DNA adducts and repair of pyrimidine dimers
Douki T, von Koschembahr A, Youssef A, Béal D, Leccia MT, Maitre A
Univ Grenobles Alpes, CEA, CNRS, CHU Grenoble

15-3 9:00 AM – 9:30 AM
Enhancement of UV-induced DNA damage repair in human dermal fibroblasts by a chronic low-dose UVB pre-stimulation
*Drigeard Desgarnier MC, Bérubé R, Douki T, Rochette PJ**
CHU de Québec research center – Université Laval, Hôpital du Saint-Sacrement, INAC/LCIB UMR-E3 CEA-UJF/ Commissariat à l'Énergie Atomique (CEA)

15-4 9:30 AM – 10:00 AM
Regulation of the DNA damage response in aged versus young human skin
Kemp MG, Choi JH, Spandau DF, Travers JB
Wright State University, Korea Research Institute of Standards and Science, Indiana University

15-5 10:00 AM – 11:00 AM
SSR-induced epidermal DNA damage in humans across skin types I-VI
Rhodes LE
University of Manchester

15-6 11:00 AM – 11:20 AM
Influence of the dermis on epidermal UV-induced DNA damage repair efficiency
Dorr MM, Rochette PJ
Centre de recherche du CHU de Québec - Universite Laval, Hopital du Saint Sacrement

15-7 11:20 AM – 11:40 AM
UV-induced 6-4 photoproducts block DNA replication and activate the ATR-Chk1 DNA damage response pathway
Kawasumi M, Hung K, Sidorova JM, Nghiem P
University of Washington

15-8 11:40 AM – 12:00 PM
Roundtable Disucssion

Broadening Horizons in Photochemistry and Photobiology

8:00 AM – 11:30 AM Meeting Room 2 Chair: Joanna Turner

16-1 8:00 AM – 8:25 AM
Longitudinal study of the skin responses to UVB challenges using non-invasive multimodality microscopy
Tian GY, Lui H, Zhao J, Wu Z, Kalia S, Richer V, Seo IS, Ou-Yang H, Zeng H
University of British Columbia, BC Cancer Research Center, Johnson and Johnson Consumer Inc

16-2 8:25 AM – 8:50 AM
Low-cost fabrication of LED arrays for photomedicine
Zhang K, Spring BQ, Kercher E, Mohan A, Selingo J
Northeastern University

16-1 8:50 AM – 9:15 AM
Coloring in the Boxes: Spectroscopic Characterization of Cation-pi Interactions in Aromatic, Ligand-binding Pockets
Juszczak LJ, Eisenberg AS, Stein H
Brooklyn College

16-2 9:15 AM – 9:40 AM
The end-Permian Extinction as a Warning for the Anthropocene*
Moore TA, Vaughn MD
Arizona State University, BioLogic

16-3 9:40 AM – 10:05 AM
Knowledge of personal SPF use varies significantly by multiple demographic and social factors among American sunscreen users: Data from the 2015 National Health Interview Survey
Bater KL, Fischer AF, Chien AL
Johns Hopkins

16-4 10:05 AM – 10:30 AM
Pilot Study Provides New Insights on Skin Types V & VI Ability to Make Vitamin D
*Skinner Jr. RB, Dowdy JC, Garriott MJ, Stentz FB, Williams-Cleaves BJ, Skinner III RB, Sayre RM**
Veterans Administration Medical Center, Rapid Precision Testing Laboratories, University of Tennessee Health Science Center, Rapid Precision Testing Laboratories

16-5 10:30 AM – 10:55 AM
Measurement Of Solar UVB Radiation By Smartphone And Its Applications: Total Ozone Column
*Igoe DP, Parisi AV, Amar A, Downs NJ, Turner J**
University of Southern Queensland

PDT: Personalization and Optimization

8:00 AM – 9:30 AM Florida 5 Chair: Bryan Spring

17-1 8:00 AM – 8:20 AM
Targeting drug-resistant cancer stem cells using photodynamic therapy
Spring BQ
Northeastern University

17-2 8:20 AM – 8:40 AM
Combination strategies to optimize PDT responses of skin cancer and precancer
Maytin EV
Cleveland Clinic

17-3 8:40 AM – 9:00 AM
ROS explicit dosimetry of type I and II photodynamic therapy
Zhu TC, Ong YH
University of Pennsylvania

17-4 9:00 AM – 9:20 AM
Integrating mathematical modeling to personalize radiation therapy
Enderling H
Moffitt Cancer Center

17-5 9:20 AM – 9:30 AM
IR Navigation System for Light Dosimetry During Pleural Photodynamic Therapy
Kim MM, Ong YH, Finlay JC, Dimofte A, Singhal S, Glatstein E, Cengel KA, Zhu TC
University of Pennsylvania

21st Century Frontiers in Psoralen Photochemistry and Photomedicine

10:00 AM – 12:00 PM Florida 4 Co-chairs: Frank Gasparro, Giorgia Miolo

18-1 10:10 AM – 10:40 AM

PBL (Psoralens + Blue light): How Blue Light Activates Furocoumarin Derivatives Triggering Tumor Cell Apoptosis

Miolo G, Sturaro G, Menilli L, Tasso A, Conconi MT

University of Padova

18-2 10:40 AM – 11:10 AM

Psoralen Activation With No UV lamp - Teaching An Old Drug New Tricks

Walder HM, Fathi Z, Beyer WB, Oldham M, Adamson J, Yoon P, Alcorta DA, Nolan MW, Spector N

Immunolight, Duke University, North Carolina State University

18-3 11:10 AM – 11:40 AM

A Panel of Psoralen Derivatives Reveals New Molecules with Enhanced Functionalities

Buhimschi AD, Gasparro FP

Yale University, Hamden Hall Country Day School

Theranostics and Beyond: Targeting and Tailoring PDT

10:00 AM – 11:30 AM Florida 5 Chair: Luis Arnaut

19-1 10:00 AM – 10:20 AM

Can the Same (Atom Connectivity in a Photosensitizer) Be Different (Phototoxicity)?

Arnaut LG, Pereira MM, Gonçalves NPFG, Santos TPCM, Costa GPN, Monteiro CJP, Schaberle FA, Alfar SC, Abreu ACR

University of Coimbra, Luzitin SA, Luzitin SA

19-2 10:20 AM – 10:40 AM

Fine tuning metal complexes as reporters, drug delivery agents, and cytotoxins

Glazer EC

19-3 10:40 AM – 11:00 AM

Tailoring Photodynamic Therapy to its Environment: Considering the Intraoperative Setting

Busch TM

University of Pennsylvania

19-4 11:00 AM – 11:10 AM

An Update on Nanobody-Targeted Photodynamic Therapy: the First Long Term Study Shows Significant Tumor Regression

*Kijanka MM, Deken MM, Beltan Hernandez I, Slooter M, de Bruijn HS, Robinson DJ, van Bergen en Henegouwen PMP, Lowik CWGM, Vahrmeijer AL, Oliveira S**

Utrecht University, Leiden University Medical Center, Erasmus Medical Center

19-5 11:10 AM – 11:20 AM

EGFR Inhibition Improves PDT Efficacy in a 3D Model of Malignant Pleural Mesothelioma

Cramer GC, Hagan S, Busch TM, Cengel KA

University of Pennsylvania

Keynote Lecture: Photochemistry and Photobiology: A Bridge to Science, Technology and Medicine

1:00 PM – 2:00 PM Florida 5

KL 2-1 1:00 PM – 2:00 PM
Photochemistry and photobiology: a bridge to science, technology and medicine
Hasan T
Harvard Medical School, Massachusetts General Hospital

Kendric C. Smith Symposium: 55 Years Photochemistry and Photobiology Celebratory Symposium

2:00 PM – 5:00 PM Florida 4 Co-chairs: Jean Cadet, Irene Kochevar

20-0 2:00 PM – 2:10 PM
Introductory Remarks

20-1 2:10 PM – 2:40 PM
From Fluorogenic Probes to Dormant Singlet Oxygen Photosensitizers: Opportunities in Cellular Sensing and Cellular Probing
Cosa G
McGill University

20-2 2:40 PM – 3:10 PM
One-Electron Oxidation Coupled to Proton Transfer Processes in Artificial Photosynthetic Constructs
*Mora SJ, Odella E, Wadsworth BL, Kodis G, Liddell PA, Moore GF, Gust D, Moore TA, Moore AL**
Arizona State University

20-3 3:10 PM – 3:40 PM
Microbial Rhodopsins: Diversity and Optogenetic Applications
Spudich JL
University of Texas Medical School at Houston

20-4 4:00 PM – 4:30 PM
Death pathways associated with PDT
Kessel DH
Wayne State Univ Sch of Medicine

20-5 4:30 PM – 5:00 PM
DNA Repair In Photosensitive Disease(s); Reflections On 50 Years
Cleaver JE

ASP Business Meeting

5:00 PM – 6:00 PM Florida 4 Chair: Georg Wondrak

Registration
8:00 AM – 12:00 PM Florida Ballroom Foyer

ASP Research Award Lecture
8:00 AM – 8:30 AM Florida 5

ASP-1 8:00 AM – 8:30 AM
Sunlight Genotoxicity: A Challenge to Action Spectra
Douki T
University of Grenoble Alpes, CEA, INAC, SCIB, LAN

ESP Presidential Keynote
8:30 AM – 9:00 AM Florida 5

ESP-0 8:30 AM – 9:00 AM
Optogenetic Photosensitisers: From Understanding To Engineering
Nonell S
IQS-University Ramon Llull

Emerging Photodynamic Compounds for Targeting Cancer and Infection
Sponsored by: Continuum, an Amplitude Laser brand, Edinburgh Instruments Ltd, HORIBA Scientific, Modulight, Photodynamic, Thorlabs, Inc., Ultrafast Systems, UNCG

9:00 AM – 12:00 PM Meeting Room 3 Co-chairs: Sherri McFarland, Edith Glazer

21-1 9:00 AM – 9:25 AM
Intra-Vital Fluorescence Distribution and Photodynamic Therapy Responses of EGFR Targeted Nanobody-Photosensitizer Conjugates
De Bruijn HS, Mashayekhi V, Lowik CWGM, ten Hagen TLM, van Bergen en Henegouwen P, Robinson DJ, Oliveira S
ErasmusMC, Utrecht University

21-2 9:25 AM – 9:50 AM
Light-Activated Anticancer Activity of Ruthenium(II) Polypyridyl Complexes Incorporating the 1,4,5,8-Tetraazaphenanthrene (TAP) Ligand
Poynton FE, Keane PM, Hall JP, Bright SA, Sazanovich IV, Williams DC, Cardin CJ, Quinn SJ, Kelly JM, Gunnlaugsson T
Trinity College Dublin, University of Reading, Central Laser Facility, STFC Rutherford Appleton Laboratory, University College Dublin

21-3 9:50 AM – 10:15 AM
Photosensitizer-Modified Polymers as Anti-infective Materials: From Nanofibers to Textiles
Ghiladi RA, Wang Q, Wei Q
North Carolina State University, Jiangnan University

21-4 10:15 AM – 10:40 AM
Cationic Iridium(III) Complexes as in vitro Theranostic Photodynamic Therapy Agents
Sun W, Liu B, Wang L, Wang C, Yin H, Monro S, Hetu M, Cameron CG, Colon K, McFarland SA
North Dakota State University, Acadia University, University of North Carolina at Greensboro

21-5 10:40 AM – 11:05 AM
Photopharmacology: Towards Light-Swtichable Therapy
Szymanski W, Hansen MJ, Velema WA, Wegener M, Lerch MM, Hoorens MWH, Ferigna BL
University Medical Center Groningen, University of Groningen

21-6 11:05 AM – 11:30 AM
Rational Design of BODIPY Singlet Oxygen Photosensitizers for Photodynamic Therapy
Lincoln R, Cosa G
McGill University

21-7 11:30 AM – 11:55 AM
Recent Highlights from the Development of Metal Complex Photosensitizers for Photodynamic Therapy
McFarland SA, Monro SMA, Yin H, Cameron CG
University of North Carolina at Greensboro, Acadia University

Frontiers in Melanin Research: From Photoexcitation to Physiology and Pathology

9:00 AM – 12:00 PM Florida 3 Chair: Tadeusz Sarna

22-1 9:00 AM – 9:45 AM
Chemical Characterization of Eumelanin and Pheomelanin and Its Application to Evaluate Melanin Photodegradation
Ito S
Fujita Health University

22-2 9:45 AM – 10:30 AM
Quantitative study of ultraviolet radiation-induced DNA damage and its repair in extreme skin phototypes with evidence for delayed cyclobutane pyrimidine dimer formation in vivo.
Fajuyigbe D, Douki T, Sarkany RPE, Young AR
King's College London, Laboratoire 'Lésions des Acides Nucléiques', Université Joseph Fourier – Grenoble 1/ CEA/Institut Nanoscience et Cryogénie/SCIB

22-3 10:30 AM – 11:15 AM
Photoreactivity of Synthetic Pheoemalnin Models
*Zadlo A, Szewczyk G, Sarna M, Ito S, Wakamatsu K, Mitoraj M, Sagan F, Sarna TJ**
Jagiellonian University, Fujita Health University

22-4 11:15 AM – 11:45 AM
Photoreactivity of natural melanin pigments
Sarna M, Mokrzynski K, Zadlo A, Szewczyk G, Sarna T
Jagiellonian University

UVA and Beyond: Frontiers in Photodamage and Photoprotection

Sponsored by: BAYER

9:00 AM – 12:00 PM Florida 4 Co-chairs: Eduardo Ruvolo, Iltefat Hamzavi

23-0 9:00 AM – 9:30 AM
Introductory Remarks

23-1 9:30 AM – 10:00 AM
UVA: Effects on the Skin and Protective Mechanisms
Chien A
Johns Hopkins School of Medicine

23-2 10:00 AM – 10:30 AM
Visible and UVA light: Stronger together
Hamzavi I
Hamzavi/Dermatology Specialists, Henry Ford Hospital

23-3 10:30 AM – 11:00 AM
The interaction of UVB, UVA, visible light and IRA: Scientific evidence and clinical implications
Krutmann J
IUF Leibniz Research for Environmental Medicine

23-4 11:00 AM – 11:30 AM
Revisiting the Correlation of Indoor Solar Simulator and Natural Sunlight Testing of Sunscreens: 40 years later
Hughes S
Sun Protection Foundation

23-5 11:30 AM – 12:00 PM
The Impact of Trace Amounts of long wavelength UVA1 on Visible Light Induced effects
Kohli I, Braunberger TL, Nahhas AF, Kollias N, Ruvolo E, Lim HW, Hamzavi IH
Henry Ford Hospital, Bayer HealthCare Pharmaceuticals Inc.

DNA Repair and Inflammation in UV Damage and Tumorigenesis

Sponsored by: University of Chicago Dermatology

9:00 AM – 12:00 PM Florida 5 Co-chairs: Yu-Ying He, Shiyong Wu

24-1 9:00 AM – 9:25 AM
Emerging Role of TC-PTP in the Suppression of UVB-induced Keratinocyte Survival and Proliferation.
Kim DJ
University of Texas Rio Grande Valley

24-2 9:25 AM – 9:50 AM
Circadian Clock Regulates Melanin Pigmentation in Mouse and Human
*Sarkar S, Dakup P, Porter K, Gaddameedhi S**
Washington State University

24-3 9:50 AM – 10:15 AM

The Effect Of cNOS Inhibitor On UVB-Induced DNA Lesions Formation and Skin Cancer Development in Cell Culture and Animal Models

*Tong L, Bahamondes Lorca VA, Richardson LG, Heusey HL, Wu S**

Ohio University

24-4 10:15 AM – 10:40 AM

Absence of cutaneous tumor development in C/EBPÎ² knockout mice after UVB exposure: Identification of apoptosis and carcinogenesis signaling pathways by global gene expression profiling

Anand S, Maytin EV

Cleveland Clinic

24-5 11:30 AM – 12:00 PM

UV-induced extracellular ATP and the ecto-ATPase CD39 oppositely regulate DNA damage responses and the skin cancer microenvironment

Suwanpradid J, Lai C, Cook J, Zelac D, Degan S, Spasojevic I, Erdmann D, Healy E, MacLeod AS

Duke University, University of Southampton, Scripps Clinic

24-6 11:05 AM – 11:30 AM

Toll-Like Receptor-4 mediated inflammation enhances ultraviolet radiation induced carcinogenesis

*Ahmad , Rihan M, Nasti H, Elmets A, Yusuf**

Israr, Heba, Tahseen, Craig, Nabiha

24-7 11:30 AM – 11:55 AM

Autophagy pathways regulate UV-induced skin tumorigenesis through promoting protumorigenic inflammatory microenvironment

*Qiang L, Sample A, Shea CR, Soltani K, Macleod KF, He YY**

University of Chicago

Keynote Speaker

1:00 PM – 2:00 PM Florida 5

KL 4-1 1:00 PM – 2:00 PM

Why Red Haired Individuals are so Prone to Developing Melanoma

Cui R

Boston University

New Insights in Vascular and Immune Response to PDT

2:00 PM – 5:00 PM Florida 3 Chair: Arjan Griffioen

25-1 2:00 PM – 2:20 PM

Proinflammatory Activity of Vascular Targeted Therapy Against Cancer

*Grima Sopesens N, Schultz R, Griffioen CJ, Nowak-Sliwinska P, Griffioen AW**

VU University Medical Center, University of Geneva

25-2 2:20 PM - 2:40 PM
Phenotypic-based cancer treatment on the era of combination therapies
Nowak-Sliwinska P
University of Geneva, University of Lausanne

25-3 2:40 PM – 3:00 PM
PDT: A Novel Immunotherapeutic Modality
Gollnick SO, Falk-Mahapatra R, Ramsey K
Roswell Park

25-4 3:00 PM – 3:10 PM
Surgical Resections Alter Anti-Tumor Immunity Generated by Photodynamic Therapy
Davis RW, Snyder E, Houser C, Miller J, Yuan M, Carter S, Klampatsa A, Albelda SM, Busch TM
University of Pennsylvania

25-5 3:10 PM – 3:20 PM
Metronomic versus conventional photodynamic therapy: Comparison of mechanisms underlying the therapeutic response in a murine model of actinic keratosis
Anand S, Denisyuk A, Maytin EV
Cleveland Clinic

25-6 3:40 PM – 4:00 PM
Study Design: A Randomized Multi-Center Phase I/II Study Comparing Porfimer Sodium Mediated Interstitial Photodynamic Therapy Followed by Standard of Care (SoC) versus SoC alone in Patients with Locally Advanced or Recurrent Head and Neck Cancer.
Shafirstein G, Arshad H, Bellnier DA, Oakley E, Habitzruther M, Tworek L, Hutson A, Henderson BW, Gollnick S
Roswell Park Comprehensive Cancer Center

25-7 4:00 PM – 4:20 PM
Negative Effects of Nitric Oxide on Anti-Tumor Photodynamic Therapy
Girotti AW
Medical College of Wisconsin

25-8 4:20 PM – 4:30 PM
Blood-flow-informed Photodynamic Therapy Improves Therapeutic Efficacy
Ong YH, Miller J, Chandra M, Zhu TC, Yodh AG, Busch TM
University of Pennsylvania

25-9 4:30 PM – 4:40 PM
Enhanced Aggressiveness of Bystander Cells in an Anti-tumor Photodynamic Therapy Model: Role of Nitric Oxide Produced by Targeted Cells
Korytowski W, Bazak J, Fahey J, Wawak K, Girotti AW
Jagiellonian University, Medical College of Wisconsin

25-10 4:40 PM – 4:50 PM
Light Dose Guided Interstitial Photodynamic Therapy of Locally Advance Head and Neck Cancer - A Translational Study
Oakley E, Bellnier DA, Habitzruther M, Tworek L, Sexton S, Curtin L, Hutson A, Henderson B, Shafirstein G
Roswell Park Comprehensive Cancer Center

The Skin Exposome: From Environmental Exposure to Biological Response

Sponsored by: L'Oreal

2:00 PM – 5:00 PM Florida 4 Co-chairs: Ariane Dimitrov, Georg Wondrak

26-1 2:00 PM – 2:30 PM

The aryl hydrocarbon receptor protects keratinocytes against the UVA phototoxicity of 6-formylindolo[3,2-b]carbazole, an AHR ligand formed after UVB irradiation

Rolfes KM, Nakamura M, Krutmann J, Haarmann-Stammann T

IUF-Leibniz Research Institute for Environmental Medicine, Nagoya City University

26-2 2:30 PM – 3:00 PM

A novel role for NUPR1 in the keratinocyte stress response to UV oxidized phospholipids.

*Narzt MS, Nagelreiter IM, Oskolkova OV, Bochkov VN, Latreille J, Fedorova M, Ni Z, Sialana FJ, Lubec G, Filzwieser M, Laggner M, Bilban M, Mildner M, Tschachler E, Grillari J, Gruber F**

Medical University of Vienna, University of Graz, CHANEL R&D, University of Leipzig, University of Vienna, Paracelsus University Salzburg, Medical University of Vienna, BOKU University

26-3 3:00 PM – 3:30 PM

Combined exposure to UVA1 and polycyclic aromatic hydrocarbons impairs histological quality in reconstructed epidermis

Dimitrov A, Zanini M, Beauchêne C, Belaïdi JP, Denat L, Jones C, Perez P, Zobiri O, Soeur J, Marrot, Mezzache S, Erdmann D, Eilstein J L

L'Oréal Advanced Research

26-4 3:30 PM – 4:00 PM

Solar exposure-induced modulation of skin endocrine function

Slominski AT

University of Alabama at Birmingham

26-5 4:00 PM – 4:30 PM

The Aryl Hydrocarbon Receptor Represses Nucleotide Excision Repair And Contributes To UVB-induced Photocarcinogenesis.

Haarmann-Stemmann T

IUF - Leibniz-Research Institute for Environmental Medicine

26-6 4:30 PM – 5:00 PM

Topical NRF2 Activation for Epidermal Photoprotection and Prevention of Environmental Stress-induced Hair Graying

*Rojo de la Vega M, Perer J, Zhang DD, Wondrak GT**

College of Pharmacy and UA Cancer Center, University of Arizona

Epigenetics and Molecular Machinery in UV-induced SCC and Melanoma

Sponsored by: University of Chicago Dermatology

2:00 PM – 6:00 PM Florida 5 Co-chairs: Yu-Ying He, John D'Orazio

27-1 2:00 PM – 2:30 PM

Medicine of Skin Cancer: Targeted Prevention and Therapy

Dong Z

The Hormel Institute, UMN

27-2 3:00 PM – 3:30 PM

Regulation of nucleotide excision DNA repair by cAMP signaling in melanocytes

D'Orazio JA

University of Kentucky

27-3 4:00 PM – 4:30 PM

All the Roads Lead to Rome: Paracrine factors Activate Different Signaling Pathways Yet Converge on Common Targets in the DNA Damage Response of Human Melanocytes to Ultraviolet Radiation

Abdel-Malek ZA, Swope V, Starner R, Rauck C

Univeristy of Cincinnati

27-4 4:30 PM – 5:00 PM

CDC25 and 14-3-3 in UV-induced skin cancer progression

Hansen LA

Creighton University

27-5 5:00 PM – 5:30 PM

Long Noncoding RNA LincRNA-p21 is the Major Mediator of UVB-Induced and p53-Dependent Apoptosis in Keratinocytes

Hall JR, Messenger ZJ, Jima DD, Smart RC

North Carolina State University

27-6 5:30 PM – 6:00 PM

Phosphorylation Of Xeroderma Pigmentosum Group C Regulates Ultraviolet-Induced DNA Damage Repair

Shah P, Zhao B, Qiang L, He YY

The University of Chicago

ABSTRACTS

All the Roads Lead to Rome: Paracrine factors Activate Different Signaling Pathways Yet Converge on Common Targets in the DNA Damage Response of Human Melanocytes to Ultraviolet Radiation

Abdel-Malek ZA, Swope V, Starner R, Rauck C
Univeristy of Cincinnati

Endothelin-1 (End-1) and Î±-melanocyte stimulating hormone (Î±-MSH) are two keratinocyte derived paracrine factors that are essential regulators of human melanocyte (HM) proliferation, survival and pigmentation. End-1 binds to the Endothelin B receptor (EndBR) on HM, and activates PLCÎ² to increase intracellular Ca2+ mobilization and PKC activity, while Î±-MSH binds the melanocortin 1 receptor (MC1R), and mainly activates the cAMP pathway. We reported that both factors reduce oxidative stress and enhance repair of DNA photoproducts induced in HM by exposure to ultraviolet radiation (UV). We hereby report that End-1 and Î±-MSH target common effectors of DNA damage response (DDR) and nucleotide excision repair (NER) pathway in HM. The common effects include activation of the DNA damage sensors ATR and ATM, regulation of chromatin localization of the two DNA damage recognition enzymes DDB2 and XPC, and increased chromatin-bound p97 secretase the damage verification enzyme XPA, and Î³-H2AX that facilitates the recruitment of DNA repair proteins to DNA lesions. Additionally, End-1 and Î±-MSH increase the phosphorylation of the stress-induced MAP kinases JNK and p38, and the levels and transactivation of p53. Our results reveal that although End-1 and Î±-MSH activate distinct signaling pathways, both factors enhance common targets that participate in global genome repair and the DDR. We conclude that the MC1R and EndBR signaling pathways represent redundant mechanisms that reduce the genotoxic effects of UV on HM, and prevent their malignant transformation to melanoma. We have found that other paracrine factors, namely 1,25(OH)2 vitamin D3 and neuregulin-1, also enhance repair of DNA photoproducts in UV-irradiated HM, suggesting that a network of paracrine factors activate their cognate receptors leading to preservation of the genomic stability of HM and prevention of UV-induced melanomagenesis.

Toll-Like Receptor-4 mediated inflammation enhances ultraviolet radiation induced carcinogenesis

Ahmad , Rihan M, Nasti H, Elmets A, Yusuf*
Israr, Heba, Tahseen, Craig, Nabiha

Ultraviolet (UV) irradiation of the skin induces inflammation, and is linked to the progression of skin cancer. Our previous studies indicate the role of Toll-like receptor 4 (TLR4), a component of innate immunity, in regulation of UVB induced DNA damage and immunosuppression. There is no information on the role of TLR4 in photocarcinogenesis, and the mechanism involved in this process. To determine the role of TLR4 in this process, TLR4 proficient and deficient mice were exposed to multiple doses of UVB radiation (200 mJ/cm2) for 40 weeks. Carcinogenesis was retarded in terms of tumor incidence, and tumor latency, in TLR4 deficient mice compared to TLR4 proficient mice, whereas significantly greater ($p<0.001$) numbers of tumors occurred in TLR4 proficient mice. There was significant ($p<0.001$) up-regulation of inflammatory markers like cyclooxygenase (COX)-2, prostaglandin (PG)E2, inducible nitric oxide synthase (iNOS), and S100A8/9 in the skin of TLR4 proficient mice compared to skin of TLR4 deficient mice. Furthermore, we found that TLR4 proficient mice had significantly ($p<0.001$) higher number of Gr1+CD11b+ myeloid cells than TLR4 deficient mice (18.86ï,±1.64% versus 6.24ï,±0.87%). Nod-like receptor family, pyrin domain-containing 3 (NLRP3) is known to assemble with active caspase-1 to cleave pro IL-1Î² to active IL-1Î². There is a cross talk between TLR and NLR signaling to trigger inflammatory responses, including production of IL-1Î². IL-Î² was found to be significantly up-regulated ($p<0.05$) in TLR4 proficient mice compared to TLR4 deficient mice. Our results clearly show that the level of NLRP3 and caspase-1 was significantly ($p<0.001$) higher in UVB exposed TLR4 proficient mice compared to UVB exposed TLR4 deficient mice. Together, our data indicate that crosstalk between TLR4 and NLRP3 enhances the development of UVB induced skin tumors. These findings may allow us to develop preventive and therapeutic approaches for management of UVB induced skin cancer.

Photochemistry of proteins - an industry perspective

Alavattam S

Proteins contain a variety of chromophores that absorb in the 200-400nm range. Amino acids such as Trp, His, Tyr and disulfide bonds from Cys-Cys are particularly photosensitive. We have previously reported that surface exposed Trp in monoclonal antibodies can act as generators of reactive oxygen species when exposed to light, especially generating copious amounts of hydrogen peroxide. In addition to Trp residues, various other amino acids including His, Met and disulfide bonds undergo photochemical reactions. The reaction products may lead to novel products that could impact safety and efficacy of therapeutic proteins. This talk will cover recent literature on novel products formed during photo-stability studies and provide an industrial perspective on the importance of understanding the photochemistry of proteins.

A varying kinetic isotope effect observed during spore photoproduct formation

Ames D, Lin GJ, Jian YJ, Cadet J, Li L*
IUPUI, University of Sherbrooke

The dominant DNA photolesion detected in UV irradiated bacterial endospores is 5-thyminyl-5,6-dihydrothymine, i.e. the spore photoproduct (SP). Different from cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts that are formed via [2+2] cycloaddition mechanisms, SP is initiated via a radical mediated hydrogen abstraction step. SP formation is slower when thymine residues with a deuterated methyl group are used, leading to an observable deuterium kinetic isotope effect (KIE). Interestingly, this KIE varies with the thymine context examined. In the dinucleotide TpT where UV irradiation leads to the formation of a dinucleotide SP containing a 5R chiral center at the 5'-residue, a clean deuterium transfer from the deuterated 3'-methyl group to the C6 position at the 5'-residue of SP is observed, which is accompanied by a moderate deuterium KIE of 3.5 ± 0.3. UV irradiation of the monomer thymidine residues in solid states also leads to SP. Due to the lack of restriction from the phosphodiester linkage, this reaction generates a pair of dinucleoside SP enantiomers containing a 5R and a 5S chiral center respectively. Strikingly, when the reaction is conducted in ice, the formation of 5R-SP and the 5S-SP exhibits KIE of 16.8 ± 1.5 and 10.0 ± 0.7 respectively. Such large KIEs indicate that the small amount of unlabeled thymine impurity undergoes a drastic enrichment in the formed SP. Moreover, when SP formation is examined in dry film, these KIEs are reduced to 5.9 ± 0.9 and 6.5 ± 0.8 for the dinucleoside 5R-SP and 5S-SP respectively. How the local thymine stacking conformation results in such large KIE variations for an essentially same chemical reaction is unclear. Given that SP formation represents a unique DNA photoreaction where H-atom abstraction is involved as a key step, a better understanding of the associated KIE changes as a consequence of the local environment may be of great significance.

Metronomic versus conventional photodynamic therapy: Comparison of mechanisms underlying the therapeutic response in a murine model of actinic keratosis

Anand S, Denisyuk A, Maytin EV
Cleveland Clinic

Aminolevulinic acid based photodynamic therapy (ALA-PDT), involving protoporphyrin IX (PpIX) as a photosensitizer to induce target-specific cell death in the presence of light and oxygen, is a popular and efficacious treatment for actinic keratosis (AK). However, standard PDT can elicit stinging pain during illumination, and hence is not always favored by patients. In a new regimen called metronomic PDT (mPDT), similar to daylight PDT but using blue light, the illumination is delivered concurrently with ALA application rather than after a 1-hour pre-incubation (conventional regimen, PDT). In the clinic, mPDT is not only painless but also nearly as effective as PDT for AK lesion clearance. In this investigation, a murine AK model (generated by UVB exposure of SKH-1 mice; thrice weekly for 15 weeks) along with normal skin controls were treated with either mPDT or PDT. Lesion clearance was followed by area measurement, and samples were harvested at 24 and 48 h post PDT. Compared to pretreatment (100%), the average lesion area was reduced to 47% and 32% in PDT, and to 57% and 40% in mPDT at 1 and 2 weeks post PDT, respectively. Some lesions remained unchanged or increased in size during the observation period, indicating the need for additional treatments. Relative to untreated controls, enhanced cell death (histomorphology by H&E staining and apoptosis by TUNEL assay), generation of Reactive Oxygen Species (ROS; CM-H2DCFDA staining) and autophagy (Atg 5 and Atg 7 expression) were observed in both PDT and mPDT samples. Activation of cleaved Caspase-3 was specifically observed only in PDT samples. Studies to evaluate additional mechanisms that may underlie the therapeutic response to mPDT, such as immunomodulation by inflammatory cells and/or cytokines, are underway. Our results suggest that metronomic PDT can be just as effective as conventional PDT for treatment of AK, but the mechanisms may be quite different.

Absence of cutaneous tumor development in C/EBPÎ² knockout mice after UVB exposure: Identification of apoptosis and carcinogenesis signaling pathways by global gene expression profiling

Anand S, Maytin EV
Cleveland Clinic

The CCAAT/enhancer binding proteins (C/EBP), a family of six leucine zipper transcription factors (C/EBP Î±, Î², Î³, Î´, Îµ and Î¶), is involved in the regulation of cell growth, metabolism and differentiation. Recently, several roles for C/EBPs in hematologic and solid organ malignancies, including breast, colon and skin carcinoma, have been reported. Although C/EBPÎ² is clearly involved in the regulation of skin development and differentiation, its role in skin carcinogenesis is not so clear. To investigate the role of C/EBPÎ² in the onset of non-melanoma skin cancer (NMSC), C/EBPÎ² knockout mice (C/EBPÎ² KO), along with wild type (WT) littermates, were exposed to UVB for 20 weeks. At week 25, WT mice had developed many tumors, whereas C/EBPÎ² KO mice completely lacked any tumors. To characterize possible alterations in underlying signaling pathways that might contribute to the tumor-resistant phenotype, mice were exposed to UVB and RNA extracted from skin was for gene-level whole-transcriptome expression profiling by Affymetrix Clariom S assay. Signaling pathways were analyzed using Ingenuity Pathway Analysis (IPA). In response to UVB exposure, a total of 1115 genes were differentially regulated. Of these, 632 were upregulated indicating transcriptional activation by UVB in C/EBPÎ² KO skin. Some of these genes belonged to crucial pathways regulating (i) Apoptosis (TNFR/Fas, Ras, Casp8/10, Bim and NFÎºB), (ii) Kinase signaling (PI3K, PKC, JNK, Rsk2, Integrin and Src), and (iii) Inflammasome pathway (Casp8 and IL1Î²). Some of these genes were validated by western blots. Transcriptional activation of each pathway, either alone or in parallel with others, could potentially contribute to the observed phenotype in C/EBPÎ² KO mice skin. Our results suggest that C/EBPÎ², in addition to its well-established functions in skin physiology, may also play an important role in skin cancer development through the regulation of apoptosis-, inflammation-, and carcinogenesis-signaling pathways.

A Photobiology Course At University Of Education, Winneba, Ghana

Annan JN
University of Education, Winneba

The Department of Biology Education in the University of Education, Winneba, Ghana started a Photobiology course in August 2015. This course is part of the first year courses taken by registered graduate students who are admitted to the Master of Philosophy in Science Education degree programme with specialization in Biology. One of the objectives for introducing this course is to promote photobiology education. The genesis of this course dates back to the interests developed by the author during his MPhil and PhD studies completed in 1999 and 2008 respectively, conferences attended particularly the 36th Scientific Meeting of the American Society for Photobiology in Montreal, Canada in June 2012, the 15th Congress of the European Society for Photobiology, which was held in Liège, Belgium, in September 2013 and the 3rd ESP Photobiology School organized in Italy in June 2014 which was made possible by the Full Fellowship provided by the Education and Training Committee of ESP. The ultimate goal is to have Photobiology as a Specialization option in addition to being a core course in the new MPhil in Biology Education programme the Department of Biology Education is developing. In order for the department to receive accreditation to run this option, there is the need to have a photobiology lab where students may carry out research.

Can the Same (Atom Connectivity in a Photosensitizer) Be Different (Phototoxicity)?

Arnaut LG, Pereira MM, Gonçalves NPFG, Santos TPCM, Costa GPN, Monteiro CJP, Schaberle FA, Alfar SC, Abreu ACR
University of Coimbra, Luzitin SA, Luzitin SA

Atropisomers are molecules with the same atom connectivity that have a hindered rotation about a single bond. It is known that the presence of voluminous substituents in the ortho positions of aryl groups in tetraphenylporphyrin derivatives can lead to separable atropisomers [1]. Such atropisomers interact with light and oxygen very much in the same way, and all atropisomers of the same photosensitizer (PS) should be equally potent. Published work confirms this expectation [2]. Redaporfin is a tetraphenylbacteriochlorin with fluorine atoms in the ortho positions [3] that yields separable atropisomers although fluorine atoms are not voluminous substituents. The photophysical properties and singlet oxygen quantum yield of all redaporfin atropisomers are very similar. However, their phototoxicities, measured as the PS concentration required to kill 50% of the cells for a light dose 1 J/cm2, are dramatically different: they range from 0.343 μM to 0.084 μM for HT-29 cells and from 67 μM to 0.2 μM for CT26 cells. These differences reveal a dramatic effect of the orientation of the groups in the meta aryl positions on phototoxicity: the atropisomer with all the voluminous groups on the same side of the macrocycle is much more phototoxic. The phototoxicity differences between atropisomers are tentatively related to an unsuspected dependence of phototoxicity on subtle cell localization.[1] M. J. Crossley et al. J. Am. Chem. Soc. 109 (1987) 341.[2] W. J. Hagan et al. Cancer Res. 48 (1988) 1148.[3] L. G. Arnaut et al. Chem. Eur. J. We thank FCT for financial support (PTDC/QEQ-MED/3521/2014) and Luzitin (Portugal) for redaporfin atropisomers.

Crystal structure of a Far-red-absorbing Photoreceptor

Bandara S, Zeng X, Rockwell N, Ren Z, Shin H, Lagarias JC, Yang X
University of Illinois at Chicago, University of California Davis

Cyanobacteriochromes (CBCRs) are a group of newly characterized bilin-based photoreceptors that belong to the phytochrome superfamily[2]. In contrast to the classical phytochromes, a single GAF (cGMP phosphodiesterase, Adenylyl cyclase and FhlA) domain is sufficient for chromophore incorporation and photoconversion in CBCRs[1]. CBCRs display photo-activities in a wide range of wavelengths from near UV to far-red/near infrared[3]. The recently discovered far-red absorbing (FR) CBCRs are of particular interest because of their potentials in live-cell and deep tissue imaging[1]. In this work, we carry out X-ray crystallography studies of CBCRs that absorb in the far-red region. We have cloned, purified and crystallized the GAF_3 domain of Anacy2551 (denoted 2551g3) from Anabaena cylindrica PCC 7122. 2551g3 reversibly photo-converts between the far-red absorbing Pfr state (max: 728 nm) and orange absorbing Po state (max: 588 nm). We have determined the crystal structure of 2551g3 in the far-red-absorbing Pfr state at 2.97Å resolution by the molecular replacement method. We will present the structural results along with spectral and mutational analyses, which reveal the structural basis for red-shifted absorption properties in far-red CBCRs. Findings of this work will offer a structural framework for development of optogenetics tools and florescent reporter proteins that are photoactive in the optical therapeutic window of human tissue.

References
1. Rockwell, N. C., Martin, S. S. & Lagarias, J. C. Identification of Cyanobacteriochromes Detecting Far-Red Light. Biochemistry 55, 3907'3919 (2016).
2. Rockwell, N. C. & Lagarias, J. C. A brief history of phytochromes. ChemPhysChem 11, 1172'1180 (2010).
3. Narikawa, R. et al. Structures of cyanobacteriochromes from phototaxis regulators AnPixJ and TePixJ reveal general and specific photoconversion mechanism. Proc. Natl. Acad. Sci. 110, 918'923 (2013).

Photosensitized oxidations aiming specific cellular targets

Baptista MS
Universidade de São Paulo

In Photodynamic Therapy (PDT) synthetic photosensitizers (PS) and light are used to efficiently induce photosensitized reactions in specific tissues. We aim to increase the efficiency of PS by tailoring them to execute damage in well-defined cellular targets and consequently to induce specific mechanisms of regulated cell death. Several molecular-based and nanostructured PS will be used to alter cell localization and intracellular release of the PS including functionalized nanosilica, metal-based PS and PS adsorbed in biopolymers. Examples will be shown in which small damages in cytoplasmic membrane cause necrotic cell death, damages in mitochondria usually drive cells mainly to apoptotic cell death, while parallel damages in mitochondria and in lysosomes cause autophagy-related cell death. I will also compare the final efficiency of photosensitizers considering the presence of either/both type I and type II photosensitization mechanisms. We propose to discuss the development of nanostructured and target-specific PS aiming to improve the efficiency of PDT protocols against cancer and infection diseases.

Knowledge of personal SPF use varies significantly by multiple demographic and social factors among American sunscreen users: Data from the 2015 National Health Interview Survey

Bater KL, Fischer AF, Chien AL
Johns Hopkins

Despite the widespread use of sunscreen, there is evidence that consumer knowledge about these products remains limited. To date, population-based studies examining the prevalence of sunscreen use and personal knowledge about sun protection factor (SPF) are lacking. We aimed to characterize factors associated with the lack of knowledge of one's personal SPF use, a surrogate for sunscreen literacy. We computed adjusted odds ratios (aOR) using logistic regression, using data from the 2015 National Health Interview Survey, a cross-sectional population-based study offering nationally representative estimates of US adults. An estimated 61.7% (95%CI 60.9-62.5%) of Americans reported sunscreen use, of whom 7.7% (95%CI 7.2-8.4%) reported not knowing the SPF of sunscreen they personally used. Factors independently associated with unknown SPF included Black (aOR 2.2; 95%CI 1.7-2.9) and Asian (aOR 2.3; 1.7-3.1) race (relative to White), Hispanic ethnicity (aOR 1.7; 1.3-2.1), older age (p-trend<0.001), male sex (aOR 1.8; 1.5-2.1), residence outside of the western US (aOR 1.5; 1.2-1.8), no family history of skin cancer (aOR 1.7; 1.1-2.5), lower education level (p-trend<0.001), less frequent tanning bed use (p-trend=0.004), being unmarried (aOR 1.6; 1.4-1.9), less frequent exercise (p-trend<0.001), less frequent sunscreen use (p-trend<0.001), increasing time since last skin check (p-trend<0.001), and fewer recent sunburns (p-trend=0.001). Of Americans who used sunscreen, 44.5% (95%CI 43.4-45.5%) frequently used sunscreen with SPF 30+. The study was limited by self-reported and cross-sectional data. Knowledge of personal SPF varies widely by demographic and social factors. The factors associated with unknown personal SPF may point to specific groups among US sunscreen users with poor sunscreen literacy. These groups may benefit from targeted education to maximize knowledge about sun protection. This may ultimately lead to increased compliance and overall improved health outcomes.

Tailoring Photodynamic Therapy to its Environment: Considering the Intraoperative Setting

Busch TM
University of Pennsylvania

In the treatment of malignant pleural mesothelioma (MPM), extended pleurectomy/decorication can be used to surgically achieve macroscopic complete resection, and the subsequent intraoperative delivery of photodynamic therapy (PDT) is under investigation as a means to eradicate residual tumor burden. Median overall survival of patients treated with intraoperative PDT for MPM is nearly three years, and animal models corroborate a benefit to combinations of PDT with resection for MPM. However, it is well known that surgery promotes immunosuppression, and intraoperative PDT is delivered in the acute setting of surgically-induced inflammation. We have developed a murine model of surgical injury, the "tumor incision" (TI) model, that enables investigation of the effects of surgically-induced inflammation on PDT response without introducing tumor resection itself. Thus, this model enables mechanistic studies of how PDT outcomes are impacted by its delivery in the setting of surgical inflammation. It notably avoids the beneficial contribution of disease reduction by resection. In both patients on the clinical trial and in the murine TI model we document the inflammatory environment at the conclusion of MCR and report on tumor oxygenation as a key determinant of response to Photofrin-mediated PDT. Using the murine model, we demonstrate immunological implications of PDT delivery in the setting of surgical injury. We consider means of mitigating acute surgical inflammation toward the goal of better "tailoring" PDT to delivery in the intraoperative environment.

Photooxidation Reactions of Cellular DNA

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Solar radiation is able to trigger the formation of oxidatively generated damage to cellular DNA through essentially the contribution of the less energetic UVA photons. Evidence has been provided for the occurrence of type I and type II photosensitization reactions that are predominantly mediated by singlet oxygen and to a lesser extent by hydroxyl radical. However

the oxidation reactions provided by these two reactive oxygen species that mostly give rise to 8-oxo-7,8-dihydroguanine (8-oxoGua) represent a minor degradation process with respect to the overwhelming generation of bipyrimidine photoproducts. This is not the case when cellular DNA is exposed to high intensity 266 nm laser pulses. Under these conditions bi-photonic excitation of the purine and pyrimidine bases was found to induce related radical cations through an efficient ionization process that is followed by charge transfer reactions along the DNA chain with guanine being the preferential site of the hole migration. The main DNA oxidation product identified in human cells is 8-oxoGua whose formation is explained by hydration of the guanine radical cation and subsequent one-electron oxidation of the resulting 8-hydroxy-7,8-dihydroguanyl radical. In addition 5,6-dihydroxy-5,6-dihydrothymine, 5-hydroxymethyluracil, 5-formyluracil and 5-hydroxycytosine were also detected by HPLC-MS/MS in cellular DNA. The formation of these one-electron oxidation products of pyrimidine bases is rationalized in terms of competitive hydration/deprotonation reactions of initially generated radical cations as inferred from extensive model studies. Intra-strand crosslinks between guanine and thymine when the two bases are separated by one cytosine residue were also found to be generated in cellular DNA. Two other nucleophilic reactions involving the guanine radical cation give rise to intra-strand cross-links and DNA-protein cross-links as shown in model systems but not yet in cells.

Targeting stromal determinants of therapeutic resistance with PDT

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It is increasingly widely appreciated that the tumor microenvironment influences disease progression not only through paracrine crosstalk but also via mechanical interactions between tumor cells and stromal components. This may be particularly relevant to tumors of the pancreas, which are associated with having prominent involvement of stiff fibrotic stroma that limits drug delivery and plays multiple tumor-promoting roles. Here we examine the consequences of biophysical signals associated with stromal composition and rigidity on the response to photodynamic therapy (PDT), and conversely, the impact of PDT on stromal composition and mechanics. Using imaging and 3D tumor models with customizable extracellular composition we are able to evaluate the impact of extracellular matrix (ECM) rheology on tumor growth, while in situ particle tracking microrheology (PTM) provides concomitant longitudinal measurements of local mechanical changes associated with phenotypic alteration and therapeutic intervention. PTM allows us to resolve changes in matrix stiffness associated with fibrosis (increasing mechanical strength) as well invasive behavior (local breakdown of ECM). We use this approach to show altered matrix remodeling in chemotherapy-resistant tumor sub-populations that exhibit elevated sensitivity to verteporfin PDT relative to the parent cell line. At the same time photochemisry initiated by PDT can alter ECM rheology bi-directionally, catalyzing cross-linking which increases ECM rigidity but also leading to overall mechanical degradation at higher doses. More broadly, the methods integrated here comprise a research platform for screening PDT and chemotherapy strategies targeting biophysical tumor-stroma interactions in pancreatic cancer and other solid tumors.

Photodynamic Therapy as an Intraoperative Adjuvant to Surgical Debulking

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Intraoperative delivery of photodynamic therapy (PDT) provides a potentially unique opportunity for biologically directed, spatially conformal adjuvant therapy. In patients with serosal (peritoneal or pleural) spread of malignancies such as ovarian cancer, malignant mesothelioma, non-small cell lung cancer and breast cancer, we have performed multiple phase I and II clinical trials using a variety of photosensitizing agents. Overall, these studies demonstrate that PDT can improve local control and may enhance systemic anti-tumor immunity. Moreover, by optimizing PDT conditions and selecting patient specific/personalized PDT or immunologic response modifiers, this approach can offset or even reverse the potentially negative effects of surgical resection on both the tumor as well as host:anti-tumor immunity.

DNA Repair In Photosensitive Disease(s); Reflections On 50 Years

Cleaver JE

The human DNA repair deficient disease xeroderma pigmentosum (XP) was first reported to a Radiation Research Society meeting in 1967 and published the following year. Despite the passage of time, and great progress, many unsolved issues in DNA repair remain. The discovery of XP as mutation(s) in nucleotide excision repair (NER) of DNA damage caused by solar ultraviolet light (UV) was remarked as the first demonstration that cancer could be a genetic disease. This concept is rarely questioned today but was not generally understood at that time. XP patients who lack the main damage recognition proteins for global genome repair (GGR), XPC/HHR23B and XPE(DDB1/2), have greatly increased skin cancer rates and elevated mutation frequencies. In squamous cell carcinomas (SCC), mutations originate from unrepaired UV photoproducts in the nontranscribed regions of the genome and in nontranscribed strands of expressed genes. But the SCCs show no increased mutations in transcribed strands. In contrast, cancer is absent from Cockayne syndrome (CS) patients despite severe photosensitivity and defective repair of transcribed strands. CS cells, remarkably, show no elevation of UV induced mutagenesis implying that defective transcription coupled repair (TCR) is protective against mutagenesis and carcinogenesis. Mutation avoidance in CS may occur through arrested transcription that generates R loops, consisting of a parental DNA strand and a nascent mRNA strand. R loops result in S phase apoptosis or activation of ATM kinase that causes a delay in DNA replication until TCR, or transcript cleavage relieves the transcription block. Resumption of replication then occurs on repaired DNA without concomitant mutagenesis.

Melanocyte-specific and Melanin-specific Antibodies Useful in Photobiology, Pigment Cell and Melanoma Research

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In humans, the gradient from light to dark skin color can be seen throughout the world's population. These differences in pigmentation can be attributed to the quantity, quality (size and types) of melanins (eumelanin and/or pheomelanin) produced by epidermal melanocytes in response to a variety of melanogenic factors, environmental stresses, etc. Environmental cues such as ultraviolet radiation (UV) dramatically affect the processing and distribution of melanins by keratinocytes as they mature towards the surface of the skin. For example, we previously demonstrated that UV-induced skin pigmentation (tanning) elicited by UVA or by UVB can reach similar levels, but while UVB-induced tans involved the de novo synthesis of melanins, UVA-induced tans occurred in the absence of increased melanin synthesis. In order to characterize the regulation of human skin pigmentation, melanocytes and their diseases, melanosome structure and function, intracellular melanosomal protein trafficking, human skin responses to UV and the type of melanins produced in human skin, a legacy of antibodies has been generated to melanocyte-specific proteins. Augmenting this updated list is the characterization of melanin-specific antibodies via dot-blot assay and immunoblots that were generated based on synthetic melanin preparations of PHEO-melanin (DOPA+CYS-melanin), 5,6-dihydroxyindole (DHI)-melanin, 5,6-dihydroxyindole-2-carboxylic acid

(DHICA)-melanin and DHI/DHICA-melanin. All these antibodies may be valuable for supporting continued research through investigators involved in various areas of photobiology, pigment cell and melanoma research.

DNA damage in skin cells: methods and mechanisms

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A major form of DNA damage, which contributes to the risk of skin cancer, is the cyclobutane pyrimidine dimer (CPD), although a role for oxidatively damaged DNA cannot be ruled out. We were the first to describe a mass spectrometric assay for CPD in DNA, and report their presence in urine – a matrix in which we more frequently measure biomarkers of oxidative stress, such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG). More recently, we added single cell gel electrophoresis (the comet assay) to our repertoire, developing a simplified method for the analysis of DNA damage in just 5 µL of whole blood, along with a method for the high-throughput (HTP) processing of samples. The usefulness of such methods is best defined by their application. Urinary CPD from individuals exposed to sub-erythemal doses of solar simulated UVR, were below the limit of detection of our UHPLC-MS/MS assay. However, we noted intriguing differences in urinary 8-oxodG between phototype II and V individuals. We are using "blood comet" in a clinical trial, and our HTP comet assay has become automated. Using the repair enzyme-modified comet assay, we noted that the repair of UVA-induced CPD is much faster than for UVB, linked to a decreased propensity for apoptosis, following UVA. The induction of so-called "dark CPD" has been reported recently, due to UVA exposure of melanin. We corroborated, and added to, this by showing that they can also be generated in keratinocytes, in the absence of melanin, and that their formation can be effectively inhibited by vitamin E. Furthermore we, and others, have shown that they appear to be more rapidly repaired, compared to "light CPD", although (at the time of writing) the explanation for this still eludes us all. Most recently, we complemented our assessment of global DNA levels of damage, with mapping their location across the genome. The breadth of these tools and application give us the ability to perform translational studies of UVR exposure and risk.

From Fluorogenic Probes to Dormant Singlet Oxygen Photosensitizers: Opportunities in Cellular Sensing and Cellular Probing

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Chemoselective fluorogenic probes rely on the induction/enhancement of fluorescence upon activation of an otherwise dimly emissive fluorophore in the presence of a chemical cue. A number of photophysical/photochemical mechanisms may be exploited in designing this type of probes, where judicious choice of the mechanism may enable monitoring the spatiotemporal evolution of specific chemical species of interest. Our ongoing interest on the role of lipid peroxidation and associated byproducts - including lipid derived electrophiles (LDEs) - in cellular physiology and pathology have led to developing a number of fluorogenic probes over the years intended to monitor lipid peroxyl radicals, electron transport in membranes, and how LDE react and evolve within cells. In this presentation we will discuss the mechanism of action behind the probes we have developed, providing a rationale for the choices of trap and reporter (BODIPY dyes) segments utilized. We will provide recent examples for the use of the probes in bio-analytical assays and in state-of-the-art fluorescence imaging studies including super resolution imaging based on single molecule localization microscopy, of reactions in biological milieu. Imaging studies conducted on E. coli and HeLa cells will provide new insights on the role of reactive oxygen species (ROS) in the lipid membrane and cellular activity. We will close the presentation by extending the paradigm of activatable probes beyond fluorescence, showing that other photophysical or photochemical properties may be activated following a reaction of interest. In particular, we will show how singlet oxygen photosensitization may be activated following a redox reaction at the trap segment of a sensitizer in what constitutes an autocatalytic activation of 1O2 sensitization. The implications to cellular probing will be discussed.

EGFR Inhibition Improves PDT Efficacy in a 3D Model of Malignant Pleural Mesothelioma

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We have found that lung sparing surgery with intraoperative photodynamic therapy (PDT) produces remarkably extended survival for patients with malignant pleural mesothelioma (MPM). Nevertheless, most patients treated using this approach go on to experience local recurrence as a component of treatment failure, so it is essential to determine mechanisms of tumor resistance to these treatment options and identify ways in which tumor response can be enhanced. We have previously shown that BPD-mediated PDT transiently activates EGFR/STAT3 and induces EGFR nuclear translocation in ovarian and lung cancer, and inhibiting EGFR via erlotinib can increase sensitivity of these cells to benzoporphyrin-mediated PDT. Additionally, we have seen that higher EGFR expression is associated with worse outcomes in patients receiving Photofrin-mediated PDT for MPM, and the extensive desmoplastic reaction associated with MPM influences tumor phenotype and response to therapeutic interventions. Since extracellular matrix (ECM) proteins accrued during stroma development can alter EGF signaling within tumors, we have characterized 3D models of MPM to determine their response to Photofrin-mediated PDT after EGFR inhibition using erlotinib. Our MPM cell lines formed a range of acinar phenotypes when grown on ECM gels that recapitulate the locally invasive phenotype of MPM in pleura and endothoracic fascia. Using these models, we found that EGFR inhibition dramatically increases the direct cytotoxicity of Photofrin-mediated PDT through a mechanism that involves increased apoptotic cell death. Taken together with emerging evidence that EGFR inhibition may improve survival of lung cancer patients through both immunologic as well as direct cell killing mechanisms, these results suggest that erlotinib enhanced PDT may significantly improve outcomes in patients with MPM.

Cholecystokinin 1 Receptor As A Unique G Protein-Coupled Receptor Activated By Singlet Oxygen (GPCR-ABSO) - A Photodynamic Toolkit For Physiology

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Type II photodynamic action with sulphonated aluminium phthalocyanine (SALPC) activates cholecystokinin 1 receptor (CCK1R) in isolated rat pancreatic acini due to plasma membrane-delimited generation of singlet oxygen. Parallel experiments with other ROS showed no such activation. Whether the singlet oxygen-specific photooxidative activation property is a general property of CCK1R is not known. In the present work, CCK1R or genetically encoded protein photosensitisers were transduced into cell lines and photodynamic activation of CCK1R was assessed by Fura-2-based fluorescent calcium imaging. When CCK1R was transduced into HEK293 cells, photodynamic action with SALPC was found to activate CCK1R in CCK1R-HEK293 cells. When genetically-encoded protein photosensitizer KillerRed or miniSOG were transduced into rat pancreatic acinar tumor cell AR4-2J which express endogenous CCK1R, KillerRed or miniSOG photodynamic action at the plasma membrane was found to induce persistent calcium

oscillations, which were inhibited by CCK1 antagonist devazepide. When fused KillerRed-CCK1R or miniSOG-CCK1R were transduced into CHO cells, KillerRed or miniSOG photodynamic action also activated CCK1R leading to persisitent calcium oscillations. Therefore KillerRed and miniSOG either expressed independently, or fused with CCK1R can both activate CCK1R photodynamically. It is concluded that photodynamic / singlet oxygen activation is an intrinsic property of CCK1R, independent of photosensitiser used, or CCK1R-expressing cell types. All other GPCR examined did not show such clear-cut photooxidative activation. Photodynamic-driven singlet oxygen activation of CCK1R after transduction of genetically-encoded photosensitiser in situ will provide a convenient way to verify intrinsic CCK1R function in CCK1R-expressing cells and tissues, or to execute CCK1R function with fused KillerRed-CCK1R or miniSOG-CCK1R in vivo.

Regulation of nucleotide excision DNA repair by cAMP signaling in melanocytes

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Melanoma risk is determined by a combination of environmental and inherited factors. The melanocortin 1 receptor (MC1R) signaling pathway, which signals through cAMP second messenger generation, regulates a variety of important melanocyte physiologic responses to UV radiation including pigment (melanin) induction, antioxidant levels and repair of DNA damage. Loss-of-signaling MC1R polymorphisms are common and raise melanoma risk because of suboptimal nucleotide excision repair and higher rates of mutagenesis to UV and other environmental carcinogens. We have determined that the MC1R-cAMP signaling axis enhances nucleotide excision repair through activation of cAMP-dependent protein kinase (PKA) and phosphorylation of ataxia telangiectasia and Rad3-related protein (ATR) on the S435 residue. PKA-mediated ATR phosphorylation appears to "activate" ATR in a non-canonical, DNA repair-specific manner, accelerating and enhancing its association with XPA, a key nucleotide excision repair factor. PKA-mediated ATR phosphorylation is scaffolded by A kinase anchoring protein 12 (AKAP12), itself a phosphotarget of ATR that is critical for PKA-ATR interactions and that regulates translocation of the ATR-AKAP12-XPA complex to sites of UV photodamage in chromatin. cAMP induction promotes repair of photodamage by enhancing the 5' strand incision step of nucleotide excision repair, and this pathway augments clearance of a variety of nucleotide excision repair substrates including [6,4]-photoproducts, cyclopyrimidine dimers and intrastrand platinum adducts. Our studies implicate cAMP signaling as a critical regulator of genomic stability in melanocytes and offer potential opportunities for designing novel melanoma-preventive therapeutics.

Bacteriochlorins as efficient PDT Photosensitizers: Molecular Design, Mechanisms and Applications

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Photodynamic therapy (PDT) requires photosensitizer (PS), oxygen and light to produce cytotoxic reactive oxygen species (ROS). The crucial factor for the effective generation of ROS in PDT is a suitably selected PS. PS should have appropriate photochemical and photophysical properties including strong absorption in the NIR and high yield of ROS. The main purpose of this work is to determine the mechanisms of ROS generation by the set of chemical compounds belonging to the group of bacteriochlorins. The use of different functionalization paths of these photosensitizers made it possible to determine the relationship between the structure, physicochemical properties and biological activity conditioning their use in photomedicine.In undertaking the chemical aspect of the study, the spectroscopic, photophysical and photochemical characteristics of the modified bacteriochlorins and their analogues were carried out. An important aspect of the analysis of the obtained results was to determine whether and how the substituents introduced into the macrocyclic ring affect the ability to control the mechanisms of photoinduced electron transfer and energy transfer, as well as whether such modifications affect the place of ROS generation by the tested photosensitizers in cancer cells and improve their selectivity towards tumors. We have shown that the use of properly selected therapeutic protocols not only leads to the cure of laboratory animals, but also to induce long-term immune memory. This is manifested by no appearance of tumors in PDT-cured animals after repeated inoculation of cancer cells as well as a significant reduction in the number of metastases compared to untreated animals. Photodynamic therapy with redaporfin as PS performed in mice bearing B16/F10 tumors led to the 100% cure of the animals.The work was supported by Sonata Bis grant no 2016/22/E/NZ7/00420, (National Science Center, NCN).

Photosensitized oxidation of tyrosine: protein damage and a novel synthetic approach to tyrosine dimers

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Pterins belong to a family of heterocyclic compounds which are widespread in living systems and participate in relevant biological functions. In pathological conditions, such as vitiligo, oxidized pterins accumulate in the white skin patches of patients suffering this depigmentation disorder. It is known that pterins are able to photosensitize damage in nucleotides, DNA and amino acids by Type I (electron –transfer) and Type II (singlet oxygen) mechanisms. Proteins, due to their relatively high abundance and their ability to bind chromophores are one of the preferential targets of the photosensitized damaging effects of UV radiation on biological systems. One of the most important modifications is the dityrosine (Tyr2) cross-link, an oxidative covalent bond between two tyrosine (Tyr) residues, which is known to occur in many diseases. Therefore, given the biomedical ramifications of the photosensitizing properties of pterins, we set out to investigate the capability of pterin (Ptr), the parent and unsubstituted compound of oxidized pterins, to photoinduce chemical changes in free Tyr, and Tyr residues of Melanocyte Stimulating Hormone (ï ¡-MSH) and albumin, under UV-A radiation. In particular, we observed that the process is initiated by an electron transfer reaction from the Tyr to the triplet exited state of Ptr. The photosensitization reaction leads to the oxidation and dimerization of Tyr residues. The last process is responsible for the photo-oligomerization of albumin, yielding big protein structures. Despite the biomedical importance of Tyr2, the information of its physicochemical properties and reactivity is limited due to the drawbacks of its synthesis. Based on pterin photosensitization we developed a method to produce Tyr2 in a more economic, efficient and simple manner.

Surgical Resections Alter Anti-Tumor Immunity Generated by Photodynamic Therapy

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Treatment of malignant pleural mesothelioma is often palliative in nature, and consists of surgical resection in order to reduce local tumor burden. More recently, surgical procedures which spare the lung (radical pleurectomy) have been coupled with photodynamic therapy (PDT) of residual disease to achieve better overall survival. Due to the known effects of surgery on host immunity, we investigated the contribution of injuries

sustained during surgery to the efficacy of PDT. We previously observed in murine models that surgical injury prior to PDT impedes long-term tumor control. A role for surgical-induced inflammation in altering PDT-generated anti-tumor immunity was assessed in AE17O murine mesothelioma tumors, grown in C57BL/6 mice. CD8+ T cells were isolated from the spleens of animals treated with PDT or with an inflammation-promoting surgical injury followed by PDT (donors). These T cells were mixed with fresh cultures of AE17O cells and injected into naïve mice (recipients) that were then monitored for tumor growth. Anti-tumor immunity generated by PDT in the hosts was transferable to recipients as evidenced by slower tumor growth in the recipients. Moreover, the generation of anti-tumor immunity was thwarted when PDT was preceded by an inflammation-promoting injury. Consequently, as found in other treatment settings, the immunosuppressive effects of surgery could alter outcome to PDT. In continuing work we seek to further delineate the mechanism of this effect so as to reveal approaches for mitigating surgical-induced immunosuppression in the context of PDT.

Intra-Vital Fluorescence Distribution and Photodynamic Therapy Responses of EGFR Targeted Nanobody-Photosensitizer Conjugates

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Targeted photosensitizer delivery by nanobodies (NB-PS) has shown potential in pre-clinical studies. In-vitro, a clear relationship is found between level of epidermal growth factor receptor (EGFR) expression, fluorescence intensity and photodynamic therapy (PDT) efficacy for NB-PS's targeting EGFR and using the photosensitizer IRDye700DX (7D12-PS and 7D12-9G8-PS). In-vivo, quantitative fluorescence spectroscopy shows a tumor-to-normal tissue (T/N) peak 1-h post administration and histological examination 24-h post PDT showed extensive tumor necrosis with almost no toxicity in healthy tissues in a mouse tongue tumor model. In the current study, intravital optical imaging was used to investigate photosensitiser distribution and cellular/vascular responses to PDT in the skin-fold chamber model. Microscopy at low magnification confirmed previous results showing significantly more fluorescence at early time points for both NB-PS's. Similar T/N ratios were found for both NB-PS's at 1-h. Using higher magnification, colocalisation analysis between PS fluorescence and the GFP signal of tumor cells showed significant differences in the distribution within the tumor between the two NB-PS's. 7D12-9G8-PS showed a membrane bound fluorescence pattern for tumor cells whereas 7D12-PS showed more fluorescence in the space between tumor cells where tumor vasculature and stroma is localised. PDT using either a 1- or 24-h drug-light-interval (DLI) resulted in vascular constriction and leakage in tumor and normal tissue for both NB-PS's, 2-h after PDT, as detected by rhodamine-dextrane exclusion and diffuse fluorescence outside the vessels. Changes to the vasculature architecture were observed up to 48-h after PDT. More necrosis was observed in tumor after PDT using a 1-h DLI, as determined using the necrosis marker HQ4. This study provided more insights into the actual localisation of conjugates at time of illumination and the mechanism of toxicity generated by nanobody-targeted PDT.

Combined exposure to UVA1 and polycyclic aromatic hydrocarbons impairs histological quality in reconstructed epidermis

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Clinical studies showed a correlation between pollution and altered barrier function and skin aging signs such as wrinkles or pigmented spots. Nanomolar concentrations of pollutants such as Polycyclic Aromatic Hydrocarbons (PAH, pollutants present in air, water or food [Farmer et al 2014]), have been detected in the blood of smokers and individuals living in polluted areas [Song et al 2013]. This suggests that deep skin may be contaminated by systemic exposure. The well-known photo reactivity of some PAH upon UVA exposure could enhance their deleterious effects on skin [Wang et al 2005]. We have shown, on 2D cultures of keratinocytes, the biological effects of a combined exposure with particulate matter, PM extract or PAH with daily UV (d-UV 300-400 nm) or UVA1 (350-400nm). Surprisingly, UVA1 alone was associated with an equal or greater phototoxic effect than d-UV [Soeur et al 2017]. UVA1 represents around 80% of d-UV and penetrates deep into the skin, reaching the dermis. We therefore focused on the combined effect of UVA1 with PAH. PAHs are localized in the plasma membrane and in several intracellular compartments in keratinocytes. PAH combined with UVA1 were phototoxic at very low concentrations (nM), impaired keratinocyte clonogenic potential at subtoxic doses and generated oxidative stress.Here we developed a multiple exposure protocol to mimic a systemic chronic exposure on in vitro reconstructed epidermis with PAH and UVA1 at realistic doses. This treatment leads to a decrease of living epidermis thickness and to the appearance of morphological damages in the supra-basal layer in a 6-day protocol. Toxicity was only significant at the highest concentration of PAH and remained low (<20%). These results suggest that epidermis renewal and differentiation could be impaired.In such experimental conditions mimicking skin contamination in a polluted environment, our results suggest that chronic exposure to photo-polluting stress may impair cutaneous homeostasis.

Observations by Ultrafast Transient Absorption Spectroscopy: Insight into Photoreactivity of Pterin Biomolecules

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Pterins are a diverse class of photochemically-active biomolecules that are synthesized by every living cell. The context of their chemistry varies from bio-catalyzing neurotransmitter precursors and coenzymes for synthesis of nucleobases to photoaxis and photosensitizing damage of biomolecules with UVA light. To improve the understanding of their photoreactivity, the excited-state relaxation dynamics of the pterin free base and the derivatives biopterin, neopterin and formylpterin were examined using femtosecond-to-microsecond transient absorption spectroscopy supported by steady-state spectroscopies and quantum-chemical calculations. The ultrafast photodynamics were determined to be general for all studied pterins: ultrafast intersystem crossing competes with vibrational energy redistribution within the fluorescent singlet state to populate an 3nï€* state from which the population bifurcates. Part of the population internally converts to a 3ï€ï€* state that is thought to sensitize singlet oxygen. Alternatively, hydrogen abstraction by the population in the 3nï€* state generates a radical species from which a large portion of the reported photochemistry is thought to originate. The authors acknowledge the support from NSF (Grant # CHE- 1255084).

Medicine of Skin Cancer: Targeted Prevention and Therapy

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Based on early evidence of fossilized bone tumors that were found in ancient Egyptian mummies, cancer is an ancient disease. The term "carcinoma" to refer to cancer was first used around 400 BC by Hippocrates. The understanding of cancer mechanisms began when John Bennett and Rudolf Virchow observed the abnormal accumulation of white blood cells in patients in 1845, which was one of the first cancers detected by microscopy. In contrast to the long history of the disease, diagnosis and treatment of cancer at a cellular or molecular level is a relatively new strategy. Although the field of oncology has developed and expanded dramatically, a single drug has not yet been discovered that can cure all patients, even those with similar cancer types. We now know that cancer is an extremely heterogeneous

disease, which explains differences not only between cancer cells from different patients, but also between cancer cells within a single patient. Clearly, more effective strategies are critically needed to defeat the longstanding enemy known as cancer. The concept and practice of precision medicine is a methodical and systematic movement aimed at defeating diseases such as cancer. Cancer is a major focus of the precision medicine initiative and developments in precise and effective treatments could benefit many other chronic diseases. In the last few years our lab have discovered key pathways or targets for UV-induced cancer. By molecular modeling of the interactions of targeted proteins with the designed chemicals or nature compounds, we have provided knowledge for a better understanding of how these agents work and how to avoid or delay the development of drug resistance. Such knowledge will help the new clinical practice of precision medicine of skin cancer. (DOI:10.9777 / rr.2018.1078)

Influence of the dermis on epidermal UV-induced DNA damage repair efficiency

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Exposure of the skin epidermis to ultraviolet radiations (UVR) leads to the generation of cyclobutane pyrimidine dimers (CPD), a highly mutagenic DNA damage responsible for skin cancer driver mutations. CPD repair is one major way to avoid their conversion into mutations. The interaction between dermal fibroblasts and epidermal keratinocytes has been showed to play a role in promoting epidermal UV-induced CPD repair, but very little is known about the components responsible for this dermal-epidermal crosstalk. In this study, we have used reconstructed skin models to investigate the impact of dermal components on epidermal CPD repair. We have compared UVB-induced CPD repair in primary keratinocytes seeded on reconstructed dermis, on devitalized dermal matrix or directly on the petri dish plastic. Our results confirm that epidermal CPD repair is faster in the presence of dermis, and show that the extracellular matrix components alone are insufficient to influence the repair. This suggests that the positive impact of the dermis on epidermal DNA repair is driven by secreted molecules. Base on those evidences, we studied the secretion of 105 cytokines and identify one (cytokine X), that is secreted 45-times more by fibroblasts (5200pg/ml) than by keratinocytes. This cytokine is secreted to a very low level (2.5pg/ml) by reconstructed skin and even less (0.4pg/ml) when reconstructed skin is irradiated. We thus investigate the impact of cytokine X on CPD repair in keratinocytes. The addition of cytokine X to the culture media leads to a 18% repair decrease. When the cytokine is inhibited with neutralizing antibodies against the cytokine or its receptor, CPD removal is respectively 26% and 19% faster at 24h. This indicates that the cytokine X inhibits CPD repair in human keratinocytes. A better understanding of the impact of dermis on epidermal CPD repair could lead to the development of new tools to limit the initiation of the most widespread cancers, the skin cancers.

Co-exposure to benzo[a]pyrene and simulated sunlight affects both formation of DNA adducts and repair of pyrimidine dimers

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Skin is the outer organ of the body and is thus exposed to both physical and chemical agents. One main concern is solar UV radiation, which is known to induce mutagenic pyrimidine dimers in DNA. Exposure to genotoxic organic pollutants also occurs, mostly as the result of occupational activities. It is, therefore, important to determine whether co-exposure to both types of agents results in combined cutaneous deleterious effects.In the present work, we investigated the combined action of benzo[a]pyrene (B[a]P) and simulated sunlight (SSL) on skin explants and primary cultures of normal human keratinocytes (NHK). We first observed that metabolization of B[a]P was significantly reduced by SSL applied either before or after B[a]P treatment, both in explants and in NHK. Accordingly, exposure to SSL led to a lower level of DNA adducts to B[a]P-diol epoxide, the main genotoxic metabolite of B[a]P. These results were rather unexpected since some works reported a minor, but significant induction of the aryl hydrocarbon receptor (AhR) pathway after UV irradiation, which was associated with an increased metabolism of B[a]P. A more general cellular stress responses, such as NADH depletion and energy crisis, may be involved and thus contributes to our results.We also studied the converse effect, namely the impact of B[a]P on DNA photoproducts induced by SSL. Little effect was observed on the formation and repair in skin explants. In contrast, a strong decrease in the repair capacities was observed when NHK were treated with B[a]P before, but not after, exposure to SSL. At the largest B[a]P concentration studied (1 µM), a complete inhibition of repair was observed not only for cyclobutane pyrimidine dimers, but also for pyrimidine (6-4) pyrimidone photoproducts, which are usually removed within a few hours. A possible explanation is an interaction with AhR which has been proposed to play a role in DNA repair and is a major target of B[a]P.

Enhancement of UV-induced DNA damage repair in human dermal fibroblasts by a chronic low-dose UVB pre-stimulation

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Exposure to solar UVB leads to the formation of the highly mutagenic cyclobutane pyrimidine dimers (CPD), the DNA damage responsible for mutations found in skin cancers. The mutagenicity of CPD is caused, in part, by the fact that their recognition and repair by the nucleotide excision repair (NER) pathway is challenging and slow. It has been previously shown that a pre-stimulation with genotoxic agents improve NER efficiency of CPD, indicating a potential adaptive response of this repair pathway. We have pre-treated human dermal fibroblasts with repeated subletal doses of UVB (chronic low-dose of UVB; CLUV) to determine whether it could enhance NER capacity to repair CPD. We have shown that CLUV treatment greatly enhance CPD repair and increases the level of NER recognition proteins, DDB2 and XPC. However, the CLUV irradiation leads to the accumulation of residual CPD that seems unrepairable. Our results show that CLUV-induced residual CPD persist on DNA and are diluted via the semi-conservative replication. Hey are overrepresented in the heterochromatin and at the TT dipyrimidine sites, and they catalyze the incidence of sister chromatin exchange (SCE). Altogether, our results shed some light on the impact of chronic UVB exposure on repair and CPD accumulation.

Oxidative stress mediated apoptosis and DNA damage by triclosan in human keratinocyte under environmental UV radiation

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Triclosan (TCS) is a widely used preservative in PCPs such as toothpaste, soaps and cosmetics. We have investigated phototoxic effects of TCS in HaCaT cells under UVB (0.6mW/cm2) and sunlight. Photosensitized TCS induced significant O2.-, •OH generation and lipid peroxidation via type-I dependent. Thereafter, cell viability parameters were measured using MTT, NRU and LDH assays. Significant intracellular ROS generation was observed through DCFH2-DA/DHE assays. Apoptosis was confirmed by AO/EB and annexinV/PI staining with increase in sub G1 phase. Lysosomal integrity was measured by acridine orange and neutral red staining. Reduction of mitochondrial membrane potential was checked by JC-1 and mito/DAPI. Using comet assay and micronuclei, oxidative DNA damage was

detected. Our results were showed upregulation of proapoptotic proteins such as Bax, Caspase-3 and cyto C that confirmed apoptosis. Therefore, TCS exposure may be deleterious to human health at ambient environmental intensities. It should be replaced by safe preservatives.

Comparison of Affordable and Portable Real-Time UV-B Sensors in Relation to Fixed Sensors for Personal Sun Exposure Scoping Studies in Developing Countries

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Solar ultraviolet radiation (UVR) in Pretoria, South Africa is considerably high due to latitude and relatively clear skies year round. Factors such as stratospheric ozone, cloud cover and solar zenith angle (SZA) affect the amount of UVR reaching the surface of the earth. The accurate real-time measurement of UVR is important to access the excess personal exposure to solar UVR and the associated adverse erythema and skin cancer risks. Hand-held instruments are helpful to conduct epidemiological studies, to evaluate ambient solar UV-B levels in places without fixed instruments but the accuracy of these instruments is unknown. There have been three studies in South Africa which estimated the solar UV-B exposure of outdoor workers, a group exposed to potentially high daily solar UV-B levels, using hand-held UV meters which were compared to a meteorological grade UV-B biometer. These studies have taken place in Pretoria and data from the hand-held instruments have been compared to the same biometer data. A commercially available hand-held instrument overestimated UVR at large SZAs and compared better with the biometer at small SZAs. In another study, a Goldilux UV-B hand-held meter was compared to the same biometer. The UV-B meter measured values ~77% higher than the biometer. At smaller SZAs the UV-B meter had a moderately strong correlation with the biometer, although the UVR values were overestimated. In general, it was found that these hand-held devices could mimic the diurnal patterns but tended to overestimate solar UVR. Overestimation of UVR levels is less of a public health concern than underestimated UVR levels. These studies show that hand-held instruments can be used to conduct 'quick', relatively inexpensive personal solar UVR exposure risk assessments, but further studies are required to determine the conditions under which these instruments can be used to achieve synchronicity between their measurements and those of meteorological grade fixed instruments.

The Scottish Photobiology Service

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Ninewells Hospital and Medical School"The Scottish Photobiology Service (SPS) was established by the National Health Service (NHS) in Dundee in 1973 to meet the clinical needs of patients with suspected or confirmed photosensitivity. Since this time the department has been at the forefront of photodermatology and has expanded to offer:

- a National Photodiagnostic Service for Scotland,
- a National Cutaneous Porphyria Service,
- ultraviolet phototherapy,
- grenz ray therapy,
- photodynamic therapy (PDT),
- dermatological laser therapy. The SPS also hosts the Scottish PDT Centre, is a Euro-PDT Centre of Excellence and a member of the European Reference Network for rare or low prevalence complex Skin Disorders. A multi-disciplinary team comprising of clinicians, physicists, biochemists, nurses, technologists and researchers underpins the success of the Unit. Research is driven by patient need and supported by a robust quality system, with accreditation to ISO 9001 and an ultraviolet radiometer calibration service accredited to ISO 17025. Our staff present their research to global audiences and are responsible for hundreds of peer-reviewed publications.Multiple spin-out companies have occurred as a result of the work and research performed at the SPS, including: 1.

Ambicare Health – produce proprietary light emitting diode (LED) based devices for the treatment of a range of skin conditions and diseases.2.

Spectratox Ltd – provide a commercial service to test drugs, lasers, LEDs or other light sources for phototoxicity in health volunteers.Spectratox has a well-established reputation in the field of drug- and chemical-induced phototoxicity, using monochromator phototesting as the gold-standard photodiagnostic test.

Effective Endogenous Skin Photoprotection by Active Ingredients Requires Nrf2-induction

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For many years, photobiology research focused on the UV-portion of the solar spectrum since the high energy of UV-radiation induces skin damage after a short time of exposure. Consequently, current sunscreen products contain effective UV filters to provide high UVA and UVB protection. However, even with an SPF 50 product, still 2% of the UV radiation penetrates into the skin. In addition, there is accumulating evidence that also visible light (VIS) significantly affects skin physiology. Since UV filters do not protect against visible light other means of photoprotection are needed, e.g., to counteract VIS-induced reactive oxygen species (ROS) production. In our experiments, irradiation of cultured human skin cells with VIS (>400nm), in doses comparable to one hour of sunlight, induces considerable oxidative stress. In contrast, infrared radiation, even at very high doses and intensities, did not induce any oxidative stress in cell cultures.Nrf2 induction is now recognized as an effective mechanism to protect skin cells from environmental stress. Pretreatment of skin fibroblasts with the Nrf2-inducer Licochalcone A significantly reduced VIS-induced ROS at low concentrations (1 µM). Cell cultures protected with a sunscreen formulation revealed significant reductions of UV-induced ROS, but only cells incubated with Licochalcone A were also protected against VIS-induced ROS. Magnolia bark extract protected at 4 µM concentration. Surprisingly, Vitamin C and its derivatives acorbyl-palmitate and ascorbyl-phosphate did not significantly reduce VIS-induced ROS. Tocopherol only protected at irrelevant high concentrations (100µM) while tocopherol-acetate did not protect at all.Antioxidants are important ingredients in sun protection products, especially to protect human skin against VIS-induced oxidative stress. However, not all antioxidants are effective against VIS-induced ROS at relevant concentrations and Nrf2-induction seems to be an important mechanism for biomolecular skin photoprotection.

Integrating mathematical modeling to personalize radiation therapy

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Tumor growth and treatment response are remarkably complex, non-linear biological phenomena. Despite decades of research including clinical, population and basic science approaches, we continue to be challenged by the complexity, heterogeneity and adaptability of tumors in individual patients and across patient populations. Qualitative reductionism in artificial in vitro and in vivo modeling systems have lead to incremental increases in understanding tumor biology, often with limited success in translation to the human patient population in clinical studies. Prospective clinical trials predominantly focus on average outcome, with limited understanding why individual patients do or do not respond.The uniqueness of each patient at presentation due to tumor and normal tissue intrinsic properties creates a highly patient-specific set of circumstances, which can impact greatly on clinical response. The future of radiation oncology practice needs to focus on selecting the most applicable dose and dose fractionation to provide tumor control whilst sparing organs at risk for individual patients prior to clinical intervention, and on continuously evaluating response and

dynamically adapting to alternative protocols if necessary. Personalized medicine promises to deliver the right treatments in the right combination at the sequence at the right time to the right patient. We foresee a vital role for integrated mathematical modeling in achieving precision radiation oncology. Using retrospective data to forecast the behavior of complex dynamic systems using dynamic mathematical models has a long history. With ample radiation oncology experience, a wealth of historic patient response data, and quantitative methods already established, the personalization of radiation oncology may lead the way into the era of precision medicine.

Melanin distribution in human epidermis affords localized protection against DNA photodamage and concurs with skin cancer incidence difference in extreme phototypes

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Epidermal DNA damage, especially to the basal layer, is an established cause of keratinocyte cancers (KC). Large differences in KC incidence (20- to 60-fold) between white and black populations have been attributed to epidermal melanin photoprotection in the latter. The cyclobutane pyrimidine dimer (CPD) is the most mutagenic DNA photolesion; however, most studies suggest that melanin photoprotection against epidermal CPD is modest and cannot explain the considerable skin colour-based differences in KC incidence. Along with melanin quantity, solar-simulated radiation-induced CPD assessed immediately post-exposure in the overall epidermis and within 3 epidermal zones was compared in black West Africans and fair Europeans. Melanin in black skin protected against CPD by 8.0-fold in the overall epidermis and by 59.0-, 16.5-, and 5.0-fold in the basal, middle, and upper epidermis, respectively. Protection was related to the distribution of melanin, which was most concentrated in the basal layer of black skin. These results may explain, at least in part, the considerable skin colour differences in KC incidence. They also suggest that a DNA protection factor of at least 60 is necessary in sunscreens to reduce white skin KC incidence to a level that is comparable to that of black skin.

Quantitative study of ultraviolet radiation-induced DNA damage and its repair in extreme skin phototypes with evidence for delayed cyclobutane pyrimidine dimer formation in vivo.

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Solar ultraviolet radiation (UVR) exposure causes DNA damage. Its mutagenic potential is largely based on the rate and accuracy of repair. The aim of this study was to determine if skin colour modulates DNA repair kinetics using blood derived monocytes in vitro and epidermis in vivo in extreme skin types. DNA damage (cyclobutane pyrimidine dimers (CPD)) was quantified at comparable physical doses in vitro and at comparable erythemal doses in vivo at a range of time points up to 24h. Epidermal melanin afforded skin phototype (SPT) VI skin a DNA protection factor of ~10 fold (in the epidermis overall) against solar simulated radiation (SSR) but melanin in vivo or lack thereof in vitro did not affect the rate of CPD removal; which was similar in SPT I/II and VI under both in vitro and in vivo conditions. Our in vivo data also validate the mouse and in vitro evidence that some CPD are produced after (1-2h) UVR exposure, resulting in so-called 'delayed CPD'. Delayed CPD (dCPD) have been shown to be caused by intracellular oxidative stress. For dCPD, like 'light' CPD produced during UVR exposure, protection by melanin was related to its distribution in the epidermis, such that the upper epidermal layer of SPT VI had the most dCPD formation but the basal layer, with the highest melanin content layer, had none. This is unlike SPT I/II, which had similar dCPD formation across all epidermal layers. Our data reinforces the double-edged sword nature of melanin in its role as facilitator of UVR damage as well as photoprotection (at the high concentration location). The dCPD and melanin protection shown in these studies suggest that a combination of antioxidants and sunscreens may be beneficial in reducing immediate DNA damage and mitigating on-going damage at the most vulnerable basal layer in fair skin. This may help to reduce white skin cancer incidence to a level that is comparable to black skin.

A Chemist Seeing Colors

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Photoreceptors are systems composed of the light absorbing compound, the chromophore, and the protein moiety. Both components mutually modulate their properties in a very sophisticated manner. This is of particular importance for photosensory receptors that-in contrast to the proteins of the photosynthetic apparatus-adjust the lifestyle of organisms in relation to the illumination scenario. Only by this precise interplay it is possible to absorb light of a selected wavelength and intensity and to generate a biological signal and to transmit to the living organism in order to adapt to variations in illumination conditions. In the first part of this keynote lecture, an approach from the chemist's side will be presented for two photoreceptor systems, the 'red-light' absorbing phytochromes and the blue-light absorbing flavin-based receptors. It will be demonstrated how changes in both the protein's and the chromophore's structure act together to disclose the light-triggered mechanisms that bring these photoreceptors to action. As will be shown, in some cases probing a single atom in a protein of 60 kDa molecular mass yields conclusive information. In the second part of the talk examples will be presented, how the light-driven reactions of photoreceptors are exploited to allow ultimately fast, synchronous, and non-invasive steering of physiological processes in living organisms, even in proteins for which the combination of photosensory unit and enzyme activity does not exist in nature. Both above mentioned photoreceptor classes light-regulate activites of fused enzyme domains AND in addition exhibit a noticable fluorescence. Therefore, the phytochrome- and flavin-derived photoreceptors will complement the 'optogenetics' toolbox that is provided by channelrhodopsin and its derivatives AND the fluorescent proteins originating from the green fluorescent protein.

Age related modification to ocular melanin modulates its photoprotective ability

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With increasing age, there is an observable loss of melanin in retinal pigment epithelial (RPE) cells. It is possible that degradation of the pigment contributes to the pathogenesis of retinal disease, as the cellular antioxidant material is depleted. Functionally, intact melanin maintains protective qualities, while oxidative degradation of melanin promotes reactive oxygen species (ROS) generation and formation of metabolic byproducts, such as melanolipofuscin. Understanding the structural and functional changes to RPE melanin with increasing age may contribute to a better understanding of disease progression and risk factors for conditions such as Age-related macular degeneration (AMD). In this study, human donor RPE melanin is characterized using MALDI mass spectrometry to follow melanin degradation trends. In vitro models using ARPE-19 cells are used to assess photo-reactivity in re-pigmented cells. Significant protection against intracellular reactive oxygen species produced by blue light is observed in calf melanin pigmented cells versus

unpigmented and black latex bead controls ($p < 0.0001$). UV-B exposure to aged human melanin pigmented cells results in a significant increase in nitric oxide production versus control cells ($p < 0.001$). Peroxide treated synthetic melanin is characterized to elucidate degradation products that may contribute to RPE cell damage.

Necroptosis: A Novel UVB-Induced Cell Death Pathway

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Ultraviolet B (UVB) radiations can induce DNA damage, which are involved in non-melanoma skin cancer development. Programmed cell death, such as apoptosis, is considered a protective mechanism against cellular transformation. Necroptosis, a recently discovered programmed necrosis, involves RIPK3 and MLKL proteins. In this pathway, phosphorylation of RIPK3 proteins triggers their oligomerization. This complex then phosphorylates MLKL, ultimately leading to cytoplasmic membrane rupture. Unlike the apoptosis, nothing is known about a possible activation of necroptosis by UVB radiations. Some evidence led us to hypothesise that UVB radiation can induce necroptosis. Indeed, we observed both a necrotic population after lethal UVB irradiation and an increase in RIPK3 transcription level in fibroblasts treated with chronic low UVB (CLUV) irradiations. In this project, we aim to decipher the potential UV-induced necroptosis in dermal fibroblasts, by (1) demonstrating the induction of necroptosis by UVB and (2) investigating the impact of a CLUV pre-treatment on necroptosis activation. METHODS (1) Primary culture of human dermal fibroblasts was irradiated with a lethal UVB dose (20 kJ/m^2). Phosphorylation of the main necroptosis actors, i.e. RIPK3 and MLKL, was tested. The necrotic and necroptotic population was assessed by FACS after inactivation of MLKL by siRNA. (2) RIPK3 and MLKL protein levels were measured in CLUV-irradiated fibroblasts. RESULTS (1) UVB-induced MLKL and RIPK3 phosphorylation is observed in skin fibroblasts, showing necroptosis activation. The abolition of necrosis as measured by FACS following an siMLKL highlights the programmed nature of the UVB-induced necrosis. (2) CLUV treatment leads to an increase in RIPK3 and MLKL protein levels. Our results provide evidence of a UVB-induced necroptotic activation in skin cells. Experiments are ongoing to strengthen these evidences and to study the effect of a CLUV pre-treatment on this programmed cell death.

Effect of the Antioxidant Resveratrol on Photosensitized Processes

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Resveratrol (trans-3,5,4-trihydroxy-stilbene; RSV) is a natural compound,[1] which has been characterized as an efficient antioxidant.[2] Since reactive species are always involved in photosensitized processes, including Photodynamic Inactivation (PDI) of microorganisms, the presence of antioxidants may prevent the oxidative damage. In consequence, the capacity of RSV to avoid the oxidation of biomolecules or elimination of microorganisms during these processes by RSV was evaluated. Photosensitizing processes of biomolecules Pterin (Ptr) is a natural compound that under UV-A radiation is photoactive,[3] and photoinduces the degradation of biomolecules via both Type I and Type II photosensitized oxidations.[4,5,6] In this work, the antioxidant capacity of RSV during Ptr photosensitized oxidation of 2'deoxyguanosine-5'monophospate (dGMP), as a model photosensitized reaction.[7] Results obtained have demonstrated that RSV efficiently prevents the photodegradation of dGMP. Photodynamic inactivation of microorganisms The elimination of planktonic Staphyloccocus aureus during PDI therapy (visible radiation and methylene blue) was evaluated in the presence of RSV. Results show that the antimicrobial efficiency of the treatment is significantly diminished in the presence of RSV, improving bacteria survival.[8]

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Photosensitizer-Modified Polymers as Anti-infective Materials: From Nanofibers to Textiles

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The transmission of pathogens from improperly sterilized surfaces poses an escalating risk to human health. Towards our overall objective of developing potent antimicrobial materials to combat this threat, we have focused on photoactive materials in which porphyrin-based photosensitizers have been tethered or embedded to either cellulose nanocrystals (Photochem. Photobiol. 2012, 88, 527-536), cellulose fibers (Biomacromolecules 2015, 16, 2482-2492), polyacrylonitrile nanofibers (Nanomaterials 2016, 6, 77), or olefinic block copolymers. As an example, paper sheets comprised of cellulose-porphyrin fibers were found to be highly effective in mediating the photodynamic inactivation of pathogens: S. aureus, A. baumannii, P. aeruginosa and K. pneumonia all exhibited inactivation by 99.99+%, as well as inactivation of dengue-1 virus (>99.995%), influenza A (~99.5%), and human adenovirus-5 (~99%). As an alternative strategy, we have embedded a cationic porphyrin into polyacrylonitrile nanofibers using electrospinning, and demonstrated that this non-covalent approach is highly effective at mediating both antibacterial and antiviral activities. More recently, we have prepared photosensitizer-embedded olefinic block copolymers using melt-pressing, and demonstrated that this non-covalent strategy is able to produce highly antimicrobial materials against a range of microbes, including Gram-positive and Gram-negative drug-resistant bacterial strains, as well as antiviral activity against enveloped and non-enveloped viruses. Such materials may have widespread applicability for the elimination of a wide range of pathogens, and that further research into alternative materials, such as photosensitizer-cellulose conjugates, may lead to their application in hospitals and healthcare-related industries where novel materials capable of reducing pathogen transmission, particularly for antibiotic resistant strains, is desired.

Negative Effects of Nitric Oxide on Anti-Tumor Photodynamic Therapy

Girotti AW

Many malignant tumors employ endogenous nitric oxide (NO) as a pro-survival/expansion signaling molecule and also to resist eradication by various therapeutic agents. This NO is typically generated by inducible nitric oxide synthase (iNOS) and acts at relatively low steady state levels (e.g. <0.1 μM). Groundbreaking studies ca. 20 years ago revealed that NO generated by various mouse syngeneic tumors reduced Photofrin-PDT effectiveness, since tumor regression rate was significantly increased by administering nitric oxide synthase (NOS) inhibitors after irradiation. However, questions such as the following were not addressed in this early work: (i) whether resistance NO derives mainly from vascular cells, tumor cells per se, or both; (ii) which NOS isoform plays a dominant role in any given tumor; (iii) whether basal NOS/NO is sufficient or upregulation occurs after PDT; and (iv) underlying mechanisms of NO-mediated anti-PDT effects. Such questions have been

directly addressed in the author's laboratory over the past several years. Using 5-aminolevulinate (ALA)-induced protoporphyrin IX in mitochondria as a sensitizer, we found that several human cancer cell lines (prostate, breast, glioma) exhibited a rapid and prolonged upregulation of iNOS mRNA and protein after a moderate photodynamic challenge. In some cases, the basal iNOS level was barely detectable, and NO produced mainly by photostress-upregulated iNOS elicited a remarkable hyperresistance to photokilling on the one hand and stimulation of surviving cell proliferation and migration/invasion on the other. Recognition of iNOS/NO involvement was based on strong attenuation of these effects by inhibitors of iNOS activity, NO scavengers, or iNOS knock-down. More recent advancement to a breast tumor xenograft PDT model provided in vivo confirmation of our in vitro findings. These various negative effects of iNOS/NO on PDT and how they might be mitigated pharmacologically will be reviewed in this talk.

Fine tuning metal complexes as reporters, drug delivery agents, and cytotoxins

Glazer EC

Ruthenium complexes possess multiple excited states, each with different properties that can be exploited in the development of imaging agents and light activated cytotoxins. Both the properties of the inorganic metal center and the organic ligands can be individually optimized to achieve specific goals, though the interactions between the two components can lead to unexpected photochemical and photophysical behaviors. We are developing photoresponsive biological reporters and medicinal agents by balancing ground state steric and electronic features with reactive or ligand localized excited states. These systems include light switch sensors for specific nucleic acid structures, such as G-quadruplexes, and cellular and subcellular probes for imaging applications. Combining tunable photochemistry and drug conjugation, new complexes are being created that also release ligands that inhibit cytochrome P450 enzymes. This allows for spatial and temporal control over P450 activity. Specific P450 enzymes are involved in malignant transformation and drug resistance, motivating the development of activatable P450 inhibitors. Moreover, the combination of a DNA damaging metal center with a P450 inhibitor provides a single agent "cocktail" to target cancer. Lessons learned from redesigning both the photochemistry of the metal complex and the structure of the P450 enzyme inhibitor will be presented.

Photocatalytic NADH-analog systems for fuel-forming reactions

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In photosynthetic organisms, CO2 reduction is achieved via hydride transfer from NADH cofactors, while the catalytic cycle is closed using photochemical reduction of NAD+ by water. In our work, we attempt to mimic this chemistry using artificial NADH analogs adsorbed on photocathode surface for photochemical regeneration (see figure). In this biomimetic approach, the selectivity for methanol production will be achieved, while the undesired proton reduction will be suppressed by metal-free catalysts. We studied the photochemical recovery of a series of NADH-analogs using GaP photocathode and found that the NAD+ analogs with sufficiently long excited-state lifetimes can serve as photo-sensitizers, which leads to an increase in the light-harvesting efficiency of the GaP-NAD+ system. The second investigation involved the determination of thermodynamic hydricities of a series of NADH analogs. This study provided the structure-property relationships in model compounds and the results have pinpointed two molecular motifs that show promise as potential catalysts for CO2 reduction. This study provides important mechanistic insights into the CO2 reduction by metal-free catalysts.

3D Bioprinting with UVA1 Radiation and Photoinitiator Irgacure 2959: Can the ASTM Standard L929 Cells Predict Human Stem Cell Cytotoxicity?

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3D bioprinting often involves human mesenchymal stem cells (hMSC) that are differentiated into the desired cells to replace body parts like ears. Scaffolds of crosslinked hydrogels offer structural support during differentiation. Different photoinitiators are used to make free radicals that photocrosslink these hydrogels; the more penetrating UVA1 wavelengths (340-400 nm) can be used because Irgacure 2959 only absorbs in the UV region (100-400 nm). We questioned if the L929 mouse fibroblast cells used in the American Society for Testing Materials standard cytotoxicity assays (F895&F813) can predict the viability of hMSC after exposure to UVA1 radiation alone and in combination with Irgacure 2959 (0.05-0.5% w/v usual range). We exposed both cell types to a high dose of LED UVA1 (370±5 nm; 516 kJ/m^2) and side-by-side to increasing UVA1 doses from a glass-filtered black light source combined with either 0.05% (w/v) or 0.5% (w/v) of Irgacure 2959 and monitored their viabilities using flow cytometry. We found UVA1 radiation alone killed ~50% of the hMSC cells compared to ~8% of the L929 cells and significantly more hMSC than L929 died after UVA1 with Irgacure 2959. Thus, L929 cannot be used to accurately predict the viability of hMSC after these specific 3D bioprinting conditions.

PDT: A Novel Immunotherapeutic Modality

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PDT is a local anti-cancer modality that is primarily used to ablate or control tumors within the treatment field. However over the past decade multiple pre-clinical and clinical studies have demonstrated that PDT can result in enhanced anti-tumor immunity that has the capability of controlling tumors outside the local treatment field. Work in our laboratory has shown that PDT-enhancement of anti-tumor immunity is regimen dependent and that PDT regimens can be optimized to enhance anti-tumor immunity. These findings led us to hypothesize that PDT could be used, in combination with conventional ablative therapies such as radiation and surgery, as an immunotherapeutic modality that would not only contribute to elimination of a primary tumor, but could also provide control of distant disease. Furthermore we predict that PDT-activation of anti-tumor immunity would enhance efficacy of immune checkpoint blockade therapy, which relies on the presence of an activated anti-tumor immune response. We have used murine models of colon carcinoma and head and neck cancer to test our hypotheses and demonstrate both enhanced anti-tumor immunity following combination therapies of PDT and surgery as well as enhanced efficacy of immune checkpoint blockade when used in combination with PDT. We have also explored the mechanisms by which PDT enhances anti-tumor immunity and prevents tumor evasion/resistance to checkpoint inhibition.

Proinflammatory Activity of Vascular Targeted Therapy Against Cancer

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Vascular targeted therapies carried out by angiostatic compounds or strategies such as photodynamic therapy have previously been shown to induce an inflammatory response. In the treatment of cancer, a proinflammatory response is wanted and is correlated to prolonged survival. We have shown that tumor endothelial cells lack sufficient expression of adhesion molecules and that one of the mechanisms of enhanced immunity after exposure to angiostatic drugs is the induction of adhesion molecule expression in the tumor vasculature. We now demonstrate that sunitinib, a widely used drug for the treatment of

e.g. renal cell cancer (RCC), significantly augments endothelial intercellular adhesion molecule-1 (ICAM-1) expression, the most important adhesion molecule for leukocyte extravasation and infiltration of the tumor tissue. Other angiostatic targeted compounds, such as axitinib, erlotinib and crenolanib, showed similar results, further confirming the induction of endothelial adhesiveness by angiostasis. The induction of endothelial ICAM-1 has functional impact on the extravasation of leukocytes, as preliminary data show that sunitinib enhanced the number of transmigrated leukocytes, mainly CD3+ lymphocytes, in a trans-endothelial migration assay. To investigate whether the above mentioned results have impact on leukocyte infiltration in human cancer, tumor tissues of phase II trials of VEGF pathway targeted therapy, given prior to cytoreductive surgery, were used to quantify leukocyte infiltration. We observed a coincident pro-inflammatory effect of this treatment. Sunitinib as well as bevacizumab pretreatment resulted in a significant enhancement of leukocyte infiltration into the tumor. This was observed for all tested leukocyte subsets, such as (cytotoxic) T cells, neutrophils and macrophages. The results of the current study contribute to the important concept of anti-vascular therapy to boost immunity and the expected benefit of combining immunotherapy approaches with vascular targeted strategies.

A quest for biomarkers and strategies in skin stress and -aging - 5 years Christian Doppler Laboratory for the Biotechnology of Skin Aging

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The functional decline of cells, organs and tissues in aging is a major and growing challenge for pharmacologic and, in the case of the skin, basic skin science in cosmetic research. The Christian Doppler Laboratory for the Biotechnology of Skin Aging set out to identify novel markers and mediators of environmentally and intrinsically promoted skin aging. With a focus on cellular stress ranging from short term ultraviolet-A-light exposure stress to the state of cellular senescence, we have uncovered stress- and senescence associated secretory phenotypes (SASP) in various cutaneous cell types. We have identified reactive and signalling lipid mediators in fibroblasts, keratinocytes and melanocytes. We uncovered communication between dermal and epidermal cells which utilized microRNAs packaged in senescence associated vesicles. Translating our findings we have identified that an extract from solidago virgaurea ssp.alpestris that is able to delay the onset of cellular senescence in fibroblasts and to reduce expression and functionality of SASP mediators. Thus our approach uncovered not only novel types of markers for skin aging but also an lead extract for evidence based cosmetic strategies conteracting the negative effects of cellular senescence.

The Aryl Hydrocarbon Receptor Represses Nucleotide Excision Repair And Contributes To UVB-induced Photocarcinogenesis.

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Ultraviolet B (UVB) radiation induces mutagenic DNA photoproducts, in particular cyclobutane pyrimidine dimers (CPDs), in epidermal keratinocytes (KC). These DNA photoproducts must be removed by nucleotide excision repair (NER) or apoptosis in order to avoid skin photocarcinogenesis. One protein originally identified as an important regulator of the DNA damage-independent part of the cutaneous UVB response is the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor. In epidermal KC, AHR activation results from the absorbance of UVB rays by tryptophan and the subsequent generation of 6-formylindolo[3,2-b]carbazole. This tryptophan photoproduct is a high-affinity ligand for AHR and induces the expression of drug-metabolizing and pro-inflammatory enzymes. Here, we analyzed if AHR signaling also contributes to DNA damage-dependent responses in UVB-irradiated KC. In fact, we found that the AHR attenuates the clearance of UVB-induced CPDs in both human HaCaT KC and skin from SKH-1 hairless mice. Subsequent RNA interference studies in KC targeting XPC (damage sensor in global genome repair) and CSB (damage sensor in transcription-coupled repair) revealed that AHR specifically suppresses global genome but not transcription-coupled NER. Furthermore, our data revealed that the accelerated repair of CPDs in AHR-compromised KC depended on a modulation of the tumor suppressor protein p27. Accordingly, p27 protein levels were increased in AHR-silenced KC and skin biopsies from AHR-/- mice, and functionally critical for the beneficial effect on NER. Thus, the AHR is a negative regulator of NER and exhibits tumorigenic functions in UVB-exposed skin. Accordingly, AHR-/- mice developed 50% less cutaneous squamous cell carcinomas in a chronic photocarcinogenesis study than their AHR+/+ littermates. Taken together, our data demonstrate that AHR critically contributes to skin photocarcinogenesis and thus may present a suitable target for topical photoprotection.

Long Noncoding RNA LincRNA-p21 is the Major Mediator of UVB-Induced and p53-Dependent Apoptosis in Keratinocytes

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LincRNA-p21 is a long intergenic non-coding RNA (3,100nt). LincRNA-p21 expression can be regulated by p53, ING1b and HIF-1a. LincRNA-p21 can function in cis and trans to regulate; gene expression, translation and protein stability, apoptosis, proliferation, glycolysis and the Warburg effect. p53 plays a key role in the response of skin keratinocytes to UVB-induced DNA damage by inducing cell cycle arrest and apoptosis. In skin cancer development, UVB-induced mutation of p53 allows keratinocytes upon successive UVB exposures to evade apoptosis and cell cycle arrest. We hypothesized that lincRNA-p21 could have a key functional role in UVB-induced apoptosis and/or cell cycle arrest in keratinocytes and loss of lincRNA-p21 function in the evasion of apoptosis and/or cell cycle arrest. We observed lincRNA-p21 transcripts are highly inducible by UVB in mouse and human keratinocytes in culture and in mouse epidermis in vivo. LincRNA-p21 is regulated at the transcriptional level in response to UVB and the UVB-induction of lincRNA-p21 in keratinocytes and in vivo in mouse epidermis is primarily through a p53-dependent pathway. Knockdown of lincRNA-p21 blocked UVB-induced apoptosis in mouse and human keratinocytes in culture. Knockdown of lincRNA-p21 had no effect on cell proliferation in untreated or UVB-treated keratinocytes. Surprisingly, the ablation of lincRNA-p21 exon 1 from in vivo mouse epidermis did not diminish UVB-induced apoptosis. Moreover, deep RNA-sequence analysis of RNA isolated from UVB-exposed mouse keratinocytes in culture and RNA isolated from UVB-exposed mouse epidermis revealed differences in lincRNA-p21 transcript, with lincRNA-p21 transcript from cultured keratinocytes closely resembling the lincRNA-p21 reference sequence. These findings indicate further exploration of lincRNA-p21 in vivo is necessary to determine function of the highly inducible long noncoding RNA in the UVB-induced DNA damage response.

From Molecules to Mammal: Inventing Luminescent Nanoparticles for Photomedicine

Han G
University of Massachusetts-Medical School

Functional luminescent nanoparticles are promising materials for in vitro and in vivo optical imaging and therapy due to their unique optical and chemical properties. In this talk, I will present two new types of biocompatible luminescence nanoparticles. The first type of materials is upconversion nanoparticles (UCNPs). I will present new

developments regarding engineering UCNPs towards photodynamic therapy, optogenetic applications in immunotherapy. The second is a type of organic Biodpy nanoparticles that were tailored with outstanding NIR absorbing ability. Rather than the conventional laser light needed in PDT, I will present their ultralow power lamp operable PDT applications in deep tissue tumor treatment.

Photochemistry and photobiology: a bridge to science, technology and medicine

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Absorption of light by molecules within or associated with, cells and tissues creates photophysical and photochemical processes that are captured for diagnostics, surgical guidance, a treatment, and for gaining of simple mechanistic understanding of disease pathology. therapy (PDT) is a photochemistry-based process resulting from the light Photodynamic activation of chemicals localized at anatomical sites of disease and leading to photobiological outcomes that have significance in medicine, advance molecular understanding and stimulate the development of technology. An update on advances in our understanding of specific aspects photochemical and photobiologic science leading to translation in medicine will be presented.

Elucidating the Signaling Mechanism of a Dual-sensor Photoreceptor

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PPHK is a phosphorylation-responsive and photosensitive histidine kinase found in cyanobacterium Leptolyngbya sp. JSC-1. PPHK employs two distinct sensor domains to sense the phosphorylation and light signals. We have determined the crystal structure of the tandem sensor domains of PPHK, denoted RECGAF, at 1.95 Å resolution. In the parallel dimeric scaffold of RECGAF, the N-terminal REC (nREC) domain, which harbors an Asp phosphorylation site, is connected via a long linker helix to the light-sensing GAF domain, which covalently incorporates phycocyanobilin (PCB) as chromophore. PPHK is a cyanobacteriochrome (CBCR) and belongs to a newly characterized 3784 subfamily of red/green CBCRs1, which undergo reversible photoconversion between the green-light-absorbing Pg and red-light-absorbing Pr states. The RECGAF structure determined in the Pg state represents the first crystal structure in the 3784 subfamily. Our histidine kinase (HK) assays of PPHK demonstrate that the output HK activity is indeed regulated by a phosphorylation signal and a light signal, perceived by the nREC and GAF domains, respectively. To understand the structural basis of such allosteric regulation in PPHK, we apply dynamic crystallography to capture phosphorylation-induced and light-induced structural changes in the RECGAF crystals by ligand soaking and light illumination. We have collected >170 crystallography datasets in various signaling states of PPHK, from which we extract ligand-induced and light-induced structural changes using singular value decomposition2. We will present the crystallography evidence to establish a sequence of structural events along the reaction pathway, which originate in each sensory site and then propagate to the protein framework. We will also discuss the possible mechanistic roles of dimer asymmetry in allosteric actions of modular sensory proteins.

The Formula for Best Sunscreen Performance – Beer-Lambert's Law Under the Microscope

Herzog B
BASF Grenzach GmbH

Sunscreens are cosmetic or dermatological preparations for the protection of human skin against harmful effects of solar radiation. The key ingredients of sunscreens are UV absorbers. No protection would be possible without such substances. But the formulation of the sunscreen preparation is of equal importance as it comprises the vehicle by which the UV absorbers are brought onto the skin. When applying a sunscreen preparation on the skin, a film builds up, the structure of which depends on the type of the formulation. The more regular this film turns out to be, the better will be the protection. Sunscreen films on pig skin substrates were investigated with a profilometric technique based on confocal microscopy using the focal aberration principle. In that way distributions of the film heights of sunscreen films were obtained. Such distributions could be fitted with a Gamma distribution model. With that, using the spectral properties and amounts of the UV absorber composition, the overall film transmittance was calculated and the sun protection factor (SPF) simulated. The results showed good agreement with in vitro SPF data based on direct measurements of UV transmittance of the corresponding pig skin samples with the sunscreens applied. Different types of formulations were looked at. The best efficacy showed w/o-emulsions, the least clear alcoholic sprays. The calculation of SPF from film thickness distributions implies the validity of the Beer-Lambert law, at least for small increments of the film where a constant thickness is approximately given. As concentrations of UV absorbers in sunscreens can be quite high, dipole interactions may occur between them which could cause deviations from the Beer-Lambert law. However, it is shown that the law still applies for the high concentrations of UV absorbers present in sunscreens. This is in line with the good agreement of in vitro SPF results and SPF values simulated from film thickness distributions.

Photo-oxidation of extracellular matrix proteins

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The dermal compartment of human skin and its constituent extracellular matrix (ECM) proteins undergo profound remodelling with age. In contrast to the dynamic epidermis, many dermal ECM proteins are thought to be highly stable with half-lives measured in decades. As a consequence these proteins are prone to accumulating damage. We have previously shown experimentally that individual proteins are differentially susceptible to degradation by terrestrial UV radiation (UVR; 290-400nm). Protein susceptibility to UVR can be predicted bioinformatically from the relative proportion of UV chromophore amino acid residues (principally tryptophan, tyrosine and disulphide bonded cysteine). We now have experimental data which suggests that the UV-induced degradation of key ECM components (such as fibrillin microfibrils and fibronectin) is mediated primarily by the action of photo-dynamically produced reactive oxygen species (ROS). Crucially, in the in vivo environment proteins will be exposed to both photochemical degradation (via UVR and ROS) and photo-biological degradation as a consequence of upregulated protease expression and activity. Our data indicates that proteases (specifically matrix metalloproteinases 1, 3, 7 and 9) preferentially degrade UVR/ROS damaged proteins and that UV-exposed fibrillin microfibrils can profoundly influence the transcriptome of cultured dermal fibroblasts. As a consequence effective repair strategies for the damaged dermis may require the coordinated expression of key ECM degrading enzymes. In order to identify new biomarkers of ageing we are developing bioinformatic approaches to characterise the susceptibility of human skin proteins (http://www.manchesterproteome.manchester.ac.uk/) to post-translational modification by UV/ROS, glucose and proteases (https://prosper.erc.monash.edu.au/home.html). This work was supported by a programme grant from Walgreens Boots Alliance.

Sub-cytotoxic photodynamic priming to re-shape cancer care

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Cancer treatment based on maximum tolerated dose poses strong selection pressures that favor cells suited for relapse and dissemination of disease. Treatment strategies that preserve intratumoral competition between cancer sub-clones while controlling gross disease are needed to ensure durable long-term outcomes for cancer patients. Here, we discover that sub-cytotoxic photodynamic priming (PDP) modulates chemotherapy outcomes to produce balanced destruction of resistant populations that can, in turn, benefit on local control and survival. A single, low-dose photodynamic priming strategy not only improves the intratumoral pharmacokinetics and biodistribution of nanoliposomal irinotecan, but also suppresses chemotherapy-induced enrichment of CD44 and CXCR4 expressions to prevent rapid tumor regrowth and reduce metastatic escape for enhanced survival in orthotopic pancreatic tumor models. These findings offer new prospects to design PDP-based combination therapies that minimize selective pressures while enhancing long-term anti-tumor efficacy without increasing side effects.

Nanotechnology for photoimmunotherapy

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Light activatable immunoconjugates have shown promises for photoimmunotherapy and fluorescence-guided resection in patients suffering from incurable malignancies in early clinical trials. While possessing a number of unique advantages, photoimmunotherapy and fluorescence imaging for oncological diseases can be hampered by therapeutic inefficiency resulting from inadequate photosensitizer delivery. The study suggests that successful coupling of antibody-photosensitizer photoimmunoconjugates onto polymeric nanoparticles complements the promising attributes of simple photoimmunoconjugates in two significant ways: not only does it improve photosensitizer delivery to tumor, but also offers a forward-looking opportunity to deliver significant and diverse second agents, which can be an imaging agent or a different therapeutic agent, to further enhance the theranostic benefits of photoimmunoconjugates. This approach, based on nanoparticle engineering, achieves effective photoimmunoconjugate delivery and enhances the anti-tumor efficacy in vivo. In addition, we will demonstrate the use of our photoimmunoconjugated nanoplatform to mark the residual tumors at the surgical bed.

Measurement Of Solar UVB Radiation By Smartphone And Its Applications: Total Ozone Column

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Smartphones are increasingly being used for research measurement across a spectrum of applications. This includes such wide ranging applications from measurement of electromagnetic radiation (from cosmic radiation to UV radiation) to spectroscopic analysis of fluoroscopy, to wound and health care, to vitamin D analysis, amongst other applications. The last few years have shown an increase in the information surrounding detection of UV radiation by smartphone image sensors, gradually showing the UVA, then UVB radiation can be detected and used in robust measurements. This project will focus on the application of image capture of specific UV wavelengths, namely 305 nm, successfully characterised in earlier research, and 312nm, by a smartphone. These wavelengths are essential to the measurement of the ozone column, a key component that influences UV radiation reaching the earth's surface. The implications of this application, is that more widespread measurements of ozone column for unique locations can be carried out. Additionally, there is the opportunity to increase citizen science initiatives for the public and students due to the widespread availability of smartphones.

The molecular mechanism of photodimerization in DNA

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Based on accurate Quantum mechanical calculations on realistic oligonucleotide models in solution, and integrating the indication provided by ultra-fast time-resolved optical spectra, we shall discuss the most recent findings concerning photodimerization within DNA. The analysis of the main photodimerization paths (leading both to cyclobutane pyrimidine dimers and to 6-4 pyrimidine-pyrimidone adduct) of Thy/Thy (both in single and double strand),[R. Improta, J Phys. Chem. B, 2012, 116, 14261; A. Banyasz et al, J. Am. Chem. Soc. , 2012, 134, 14834-14845; I Conti et al, Chem. Eur. J., 2017, 23, 15177-15188] Thy/Cyt,[L. Esposito et al J. Am. Chem. Soc., 2014, 136, 10838-10841] Cyt/Thy, Thy/5methylCyt provides new insights on the main factors modulating the photoreactivity of dipyrimidine steps in DNA, e.g. nucleotide sequences, duplex conformation, presence of epigenetic bases. The mechanism of the photoactivated dimerization of Ade/Ade [A. Banyasz et al, J. Phys. Chem. Lett., 2016, 7, 2020] and Ade/Thy steps [L. Martinez Fernandez & Roberto Improta Photochem. Photobiol. Sci., 2017, 16, 1277] will be also described

Photoswitchable cell toxicity of (5-oxo-2-dibenzothienylmethyl) triphenylphosphonium

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Dibenzothiophene S- oxide (DBTO) and its derivatives undergo a photodeoxygenation upon irradiation with UV or Visible light. The addition of a triphenylphosphonium ligand has been proposed to promote the accumulation of small molecules into mitochondria. To examine the effects of the photodeoxygenation of a DBTO derivative on mitochondrial function, we prepared (5-oxo-2-dibenzothienylmethyl)triphenylphosphonium. During our investigation of the effects of photodeoxygenation on mitochondrial function, we observed photo switchable cell toxicity in breast cancer cells.

Chemical Characterization of Eumelanin and Pheomelanin and Its Application to Evaluate Melanin Photodegradation

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Mammalian melanocytes produce two types of melanin pigments, brown to black eumelanin and reddish-brown pheomelanin, in varying ratios (the concept of mixed-melanogenesis). They derive from the common precursor, dopaquinone, produced by tyrosinase oxidation of L-tyrosine, with the participation of L-cysteine leading to pheomelanogenesis. Eumelanin consists of 5,6-dihydroxyindole and its carboxylic acid units while pheomelanin contains benzothiazine and benzothiazole units. The ratio of eumelanin to pheomelanin and their subunits are important in controlling (photo)chemical properties of melanin pigments. Eumelanin is photoprotective for pigmented tissues while pheomelanin is phototoxic. To characterize mixed-melanogenesis, we developed methods to quantify those units using chemical degradations followed by HPLC analyses of specific degradation products. Alkaline hydrogen peroxide oxidation is employed to characterize eumelanin and benzothiazole-type pheomelanin, giving pyrrole-2,3,5-tricarboxylic acid (PTCA) and thiazole-2,4,5-tricarboxylic acid (TTCA), respectively. Reductive hydrolysis with hydroiodic acid gives 4-amino-3-hydroxyphenylalanine (4-AHP) from the benzothiazine units of pheomelanin. Using this methodology, we have shown that melanins produced in epidermis, hair follicles, and retinal pigment epithelium are composed of mainly eumelanin with incorporation of pheomelanin in varying degrees. A similar methodology can be applied to study photodegradation of eumelanin and pheomelanin. The results show that the photoaging of eumelanin gives rise to free PTCA (produced by peroxidation in situ) and pyrrole-2,3,4,5-tetracarboxylic acid (produced by cross-linking). The TTCA/4-AHP

ratio increases with photoaging, indicating the conversion of benzothiazine to the benzothiazole moiety. The (patho)physiological significance of those findings will be discussed.

Lipid Oxidation Impact on Lipid Bilayers Representing Biological Membranes: Optical Microscopy and Small Angle X-Ray Scattering (SAXS) Combined Data

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Lipid oxidation can promote changes in the physical properties of biological membranes which may lead to cell physiology malfunction. Some oxidized lipids have hydrophilic groups pendant on the hydrocarbon chains, as hydroperoxized groups for instance, some on the shortened acyl oxidized lipid chains. In this presentation, we will firstly show how lipid chemical transformations induced by oxidative stress alter plasma membrane structural features. SAXS results from liposomes, representing model lipid vesicles, composed of different amounts of unsaturated, oxidized and saturated lipids will be presented and discussed. Interestingly, the analysis of SAXS data points out to an increase in membrane surface area of hydroperoxized lipid bilayers, in good agreement with micropipette measurements on giant unilamellar vesicles (GUVs) under photo-oxidation and molecular dynamic simulation results. Further, SAXS also allows us localizing the oxidized species inside the vesicle lipid bilayer. In addition, we will also discuss lipid phase separation, as liquid order (Lo) – liquid disorder (Ld) phase coexistence, induced by the generation of oxidized lipids inside the membrane. However, the phase separation depends on the new chemical structure of the oxidized molecule formed. Finally, we extend our study to mimetic membranes of lysosomes with the aim to explore how lipid oxidation may affect cell death associated to autophagy.

To probe pyrimidine dimerization mechanisms using photochemically inert aromatic residues

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Pyrimidine dimers are the most common DNA photolesions generated under UV irradiation. In general B-form DNA, irradiation under 254 nm UVC light leads to the formation of two types of dimers: the cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts (6-4PPs). To reveal the molecular mechanisms behind the dimer formation, it is critical to examine the role of each involved pyrimidine residue. We thus replaced a thymine (T) residue within the dinucleotide TpT context with a photochemically inert toluenyl (To) or xylene moiety (X). To our surprise, when the 3'-residue is replaced by a To or X, the UVC irradiation excites the C5=C6 in the remaining 5'-T, which is sufficient enough to trigger [2 + 2] photo-cycloaddition reactions producing corresponding CPD analogs. The 6-4PP photochemistry however is completely quenched with these TpTo and TpX species. In contrast, when the 5'-residue is replaced by an X, the resulting XpT species completely abolishes the CPD formation under UV irradiation. Instead, a 6-4PP analog and an analog of the so-called spore photoproduct (SP) are generated as the major photoproducts and the structures of which indicate that they are formed via reaction at C4=O of the photo-excited 3'-T. Although X is photochemcially inert, it is electron-rich and can be readily oxidized but not reduced. Our quantum-chemical calculations demonstrated that photo-excited 3'-T accepts an electron from 5ï¸¢-X, leading to a clearly defined interbase electron transfer (ET) process. The resulting charge-separated radical pair lowers its energy upon formation of interbase covalent bonds eventually yielding 6-4PP. Given that no 6-4PP formation is observed in the TpX photoreaction, our data imply that it is the 5'3' but not the 3'5' ET that is responsible for the 6-4PP photochemistry. Moreover, because the dinucleotides used above only contain one excitable T, the occurrence of these photoreactions indicates that excitation of a single "driver" residue is sufficient to trigger pyrimidine dimerization reactions.

Coloring in the Boxes: Spectroscopic Characterization of Cation-pi Interactions in Aromatic, Ligand-binding Pockets

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The cation-pi interaction, a noncovalent interaction between a univalent cation and the pi electrons of an aromatic molecule, like the indole ring of tryptophan, has been shown to result in visible optical properties for tryptophan (Trp). The resultant charge-deficient, highest occupied molecular orbital (HOMO) of the indole, for example, provides for a visible transition from lower lying orbitals and visible fluorescence. Furthermore, the cation-pi charge transfer complex shares spectroscopic properties with the tryptophan neutral radical. These findings have broad implications for the study of several classes of physiologically significant proteins where cationic ligand-aromatic interactions are key to their function. In many cases, the cation-pi interaction occurs in a cavity lined with several aromatic residues, so-called aromatic boxes. Prior to the discovery of visible spectral characteristics for tryptophan, specific aromatic-ligand interactions could be deciphered only through sequential, single aromatic residue mutation. Results presented here elaborate and extend the earlier spectroscopic characterization of single Trp and Trp 'sandwich' cation-ï€ interactions.

Singlet Oxygen in Nano-Matrices: from Entombing to Enhancing

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As one of the most versatile reactive oxygen species and a well-known cytotoxic agent, singlet oxygen, the electronically excited form of molecular oxygen, is at the forefront of a vast window of applications. In a medical context, production of singlet oxygen via photosensitization has been widely used in photodynamic therapy to kill cancerous tumors and microbial pathogens. One of the remaining challenges of photodynamic therapy is the poor specificity of the photosensitizer towards tumour cells. A potential solution to this problem is to develop novel photosensitizer delivery systems based on nano-matrices which can be further modified to allow active tumour targeting. Although there are several reports of successfully packing a variety of photosensitizers into such nanocarriers and performing test photodynamic studies, one concern rarely addressed by researchers is the ability of produced singlet oxygen to escape the nanocarrier matrix. Herein, we will discuss how, by working with silica nanoparticle encapsulated photosensitizers, we have determined that singlet oxygen spends up to 85% of its lifetime inside the nanocarriers. On the other hand, nanoplasmonic materials offer one of the most promising strategies to improve singlet oxygen production by using light and metal nanoparticles, exploiting a phenomenon called "plasmon enhancement effect".

UV-induced 6-4 photoproducts block DNA replication and activate the ATR-Chk1 DNA damage response pathway

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Ultraviolet (UV) from one hour of sunlight generates 100,000 DNA lesions per skin cell that are potentially mutagenic, leading to the most prevalent cancers in humans. Understanding how cells respond to UV-induced DNA lesions could be helpful to selectively kill DNA-damaged cells and prevent UV-associated skin cancers. UV irradiation simultaneously generates two major structurally distinct types of DNA lesions: cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs). It has been difficult to determine the precise contribution of each lesion type to the DNA damage response pathways that regulate diverse biological processes including cell cycle checkpoints, DNA repair, mutation incorporation, and cell death. To generate human cells that carry only CPDs or 6-4PPs, we combined multiparameter flow cytometry with lesion-specific

photolyases that selectively eliminate either CPDs or 6-4PP using the energy of visible light. Although it has been thought that the 8-fold more abundant CPDs play a key role in DNA damage responses, we found that only 6-4PP lesions activated the ATR-Chk1 DNA damage response pathway. Importantly, these distinct effects of CPDs and 6-4PPs were observed in both established human cell lines as well as primary human cells. Mechanistically, 6-4PPs, but not CPDs, impeded DNA replication across the genome as revealed by microfluidic-assisted replication track analysis. Furthermore, single-stranded DNA accumulated preferentially at 6-4PPs during DNA replication, indicating selective and prolonged replication blockage at 6-4PPs. These findings suggest that 6-4PP, the less abundant type of UV-induced DNA lesion, is the relevant trigger for replication blockage and activation of the UV-induced ATR-Chk1 pathway.

Regulation of the DNA damage response in aged versus young human skin

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The majority of non-melanoma skin cancers (NMSCs) occur in individuals over the age of 60, though the mechanisms by which advanced age contributes to NMSC risk are not well understood. However, recent evidence has shown that increased dermal fibroblast senescence in geriatric skin is associated with a lower production of insulin-like growth factor (IGF-1) and with a reduced activation of IGF-1 receptors (IGF1Rs) on epidermal keratinocytes. Studies with human keratinocytes in vitro and human skin ex vivo and human subjects in vivo demonstrate that deficient IGF-1R signaling negatively impacts the cellular response to DNA damage caused by UVB radiation. Namely, IGF-1 deficiency results in slower rate of thymine dimer removal from genomic DNA and a failure to properly activate the DNA damage response kinase ATR to suppress DNA synthesis on damaged DNA templates. These abnormal responses to UVB DNA damage may therefore increase the likelihood of mutagenesis and NMSC initiation in IGF-1 deficient geriatric skin. Clinical interventions that involve dermal wounding, such as dermabrasion and fractionated laser resurfacing, have been shown to restore IGF-1 expression in geriatric skin and to correct some of the inappropriate UVB responses. Thus, dermal rejuvenation strategies may be useful to lower the risk of NMSC development in geriatric individuals. Lastly, to further improve our understanding of the DNA damage response in human skin, we have also been developing methods to more accurately quantify the activity of the nucleotide excision repair (NER) system in human skin exposed to UV radiation. We show that the small, excised, damage-containing DNA oligonucleotide (sedDNA) products of repair can be readily extracted and quantified from human skin epidermis, and thus we believe that the sedDNA detection assay will be useful for determining how aging as well as genetic, environmental, and other factors influence NER activity in human skin.

Death pathways associated with PDT

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Initial studies on tumor eradication by PDT suggested a strictly necrotic outcome with only vague hints concerning pertinent pathways to cell death. Later work revealed that reactive oxygen species evoked direct tumor killing, vascular shutdown and immunologic effects. We now know that multiple death and survival pathways are initiated by PDT depending on sub-cellular targets for photodamage which can vary with the photosensitizing agent. Among these pathways are apoptosis, paraptosis and autophagy. While studies relating to PDT have been useful with regard to cancer control, the ability of PDT to produce targeted effects has also been helpful in probing elements of cell biology related to both cytotoxicity and cytoprotection.

PDT: Improved Efficacy By Directed Sub-Cellular Targeting

Kessel DH
WSU School of Medicine

We have been exploring the ability of sub-cellular targeting to improve the efficacy of PDT in cell culture. Lysosomal photodamage can initiate a series of steps ultimately resulting in a significant enhancement of subsequent or simultaneous photodamage to mitochondria. PDT directed at mitochondria + ER can also promote the efficacy of ionizing radiation. While photokilling appears to be correlated with apoptosis, an additional and hitherto unexplored effect termed 'paraptosis' is associated with ER photodamage. Its role in the overall scheme remains uncertain but details are beginning to emerge.

An Update on Nanobody-Targeted Photodynamic Therapy: the First Long Term Study Shows Significant Tumor Regression

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In an attempt to improve selectivity of photosensitizers in oncologic photodynamic therapy (PDT), we have developed an approach using nanobodies as targeting moieties (Heukers et al., Nanomedicine 2014; van Driel et al., JCR 2016). Nanobodies are the variable domains of heavy chain antibodies that exist in animals of the Camelidae family (C. Hamers-Casterma, et al., Nature 1993). Nanobodies have been employed for distinct applications (Oliveira et al., JCR 2013), for which their small size is mostly associated with rapid tumor accumulation, homogenous distribution, and rapid clearance of unbound fractions. In this study, we have employed HER2-targeted nanobodies conjugated to the water soluble photosensitizer IRDye700DX. These nanobody-photosensitizer conjugates are very potent in vitro and their toxicity is selective to high HER2 expression. The effect of nanobody-targeted PDT was investigated in two orthotopic breast cancer models: HCC1954 which has high HER2 expression and is resistant to trastuzumab therapy and MCF7 which has low HER2 expression. Light was applied 2h p.i. of the nanobody-photosensitizer conjugates and tumor volumes were measured for 30 days post PDT. Results show a significant and prolonged tumor regression for the HCC1954 model, whereas no regression was observed in the MCF7 model. These results highlight the potential of this approach and encourage further studies.

Emerging Role of TC-PTP in the Suppression of UVB-induced Keratinocyte Survival and Proliferation.

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Phosphotyrosine-based signaling is one essential mechanism that mediates eukaryotic inter- and intracellular communication and thereby plays a critical role in cellular homeostasis. Chronic exposure to UV radiation can contribute to the development of skin cancer by promoting protein tyrosine kinase (PTK) signaling. PTKs are regulated by endogenous negative feedback mechanisms involving protein tyrosine phosphatases (PTPs), which negatively regulate the rate and duration of phosphotyrosine signaling. Studies have shown that exposure to UV radiation increases the ligand-independent activation of PTKs and induces PTP inactivation. However, our recent studies show that T-cell protein tyrosine phosphatase (TC-PTP) activity is stimulated during the initial response to UVB irradiation which leads to suppression of keratinocyte survival and proliferation via the down-regulation of signal transducer and activator of transcription 3 (STAT3) signaling. The nuclear form of TC-PTP (TC45) is a major form of TC-PTP and is known to primarily localize in the nucleus by bipartite nuclear localization signals in its C-terminus. Our studies showed that TC45 is mainly localized to the cytoplasm of keratinocytes and it is translocated to the nucleus in response to UVB irradiation. Inhibition of TC45 nuclear translocation resulted in a significant decrease in apoptosis and a significant increase

in cell proliferation of keratinocytes following UVB exposure which corresponded with an increase in nuclear phosphorylated STAT3. Combined, our recent results indicate that UVB-mediated activation and keratinocyte-specific nuclear localization of TC-PTP plays an important role in the STAT3-dependent regulation of keratinocyte proliferation and survival.

IR Navigation System for Light Dosimetry During Pleural Photodynamic Therapy

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University of Pennsylvania

Pleural photodynamic therapy (PDT) is performed intraoperatively for the treatment of microscopic disease in patients with malignant pleural mesothelioma. Accurate delivery of light dose is critical to PDT efficiency. As a standard of care, light fluence is delivered to the prescribed fluence using 8 isotropic detectors in pre-determined discrete locations inside the pleural cavity that is filled with a dilute Intralipid solution. An optical infrared (IR) navigation system was used during light delivery to monitor the position of the light source within the treatment cavity. The light source is tracked using a modified and improved treatment delivery wand with reflective passive markers that are seen by the infrared camera-based navigation system. This information was used to calculate the light dose, incorporating a constant scattered light dose and using a dual correction method. Calculation methods were extensively compared for 8 detector locations and 6 patient case studies. For the comparison of calculated and measured light dose, detector locations need to be known. Detector locations can be extrapolated using the measured light dose and the treatment wand data collected. The light fluence uniformity was also quantified by representing the unraveled three-dimensional geometry on a two-dimensional plane. For cases with known detector locations, extrapolated detector locations were compared and found to agree within 1.5 cm in x and y directions (relative to the wand) and within 43 cm in the z direction. Using a constant scattered dose for all detector locations along with a dual correction method, the agreement between calculated and measured light doses for each detector was less than 15%. This is useful in determining the light dose delivered to areas of the pleural cavity between detector locations, and can prove to improve treatment delivery with implementation in real-time in the surgical setting.

UV-Induced Charge Transfer in DNA Strands

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A large fraction of electronically excited states formed in single- and double-stranded DNA by UV radiation decay in tens to hundreds of picoseconds. These lifetimes are several orders of magnitude longer than ones observed in the nucleobase monomers, and they arise due to electronic coupling among nearby bases. Recent experimental and theoretical studies indicate that the long-lived singlet excited states are charge-transfer (CT) excited states. Femtosecond time-resolved IR (TRIR) measurements reveal vibrational marker bands associated with radical species produced by electron transfer (ET). In double-stranded DNA, neutral radicals produced by intrastrand ET coupled to interstrand proton transfer have been observed. Recently, we have investigated the excited-state dynamics of a variety of DNA strands in deep eutectic solvents made from 1 mole equivalent of choline chloride and 2 mole equivalents of glycerol or ethylene glycol. The latter solvents, which constitute an important class of ionic liquids, can stabilize DNA secondary structure in a non-aqueous environment. Transient absorption and TRIR measurements show that the reduced polarity of the deep eutectic solvent inhibits deactivation pathways that involve CT states and instead favor ones with neutral intermediates. This work provides new insights into the ultrafast events that maintain DNA's intrinsic photostability.

The Impact of Trace Amounts of long wavelength UVA1 on Visible Light Induced effects

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Our skin is exposed to visible light (VL) and long wavelength ultraviolet A1 (UVA1) radiation (370-400 nm) present in sunlight even after application of organic broad spectrum sunscreens. The effects of these wavelengths on pigmentation and erythema have been demonstrated. However, a dose response has not been investigated which can provide insight on how skin responses can vary based on the duration of sun exposure.Ten subjects with Fitzpatrick skin phototype IV-VI were enrolled. On day 0, subjects were irradiated with two light source; one comprising pure VL and the other VL with less than 0.5% UVA1 (VL+UVA1) at a dose of 80 J/cm2, 160 J/cm2, 320 J/cm2 and 480 J/cm2. The irradiance was set at 175 mW/cm2. Skin responses were evaluated immediately, at 24 hours, 7 days, and 14 days after irradiation. Assessment methods included investigator's global assessment (IGA), diffuse reflectance spectroscopy (DRS), and colorimetry. Clinical IGA scores suggest that 3/10 subjects for the 320 J/cm2 site, and 5/10 subjects for the 480 J/cm2 site had clinical erythema immediately after irradiation on the VL+UVA1 side only. No erythema was observed for the corresponding pure VL sites. Only the highest dose, 480 J/cm2, resulted in pigmentation response that was statistically significantly different at all time points between the two light sources (p-value less than 0.05). Pigmentation response from VL+UVA1 site was two times more intense than that of pure VL at the day 14 time point. Spectroscopy and histology data analysis are under progress.Wavelengths not covered by current broad spectrum sunscreens have implications on pigmentation and erythema. There appears to be a threshold dose of UVA1 which in combination with VL results in immediate erythema followed by darker and persistent pigmentation. The effects can be noticed at approximately two hours of outdoor sun exposure.

Anti-inflammatory activity of ingredients of sun care products? Implication for sun protection

Kolbe L
Beiersdorf

UV filters in sunscreen products are designed to absorb or reflect solar UV radiation and, hence, prevent the penetration of these damaging rays into the skin. The efficacy of sunscreen products is determined via their efficacy to prevent sunburn. More precisely, sunscreen products are designed to prevent erythema caused by an inflammatory skin reaction triggered by the damaging effects of sun exposure. Recently, some publications raised concerns that sunscreen products may have anti-inflammatory efficacy and actively suppress the sunburn reaction. This would result in labelling much higher SPF than justified by UV filter efficacy. Most sun care products contain antioxidants, which are described to have an impact on erythema development after long-term use at high concentrations. Even some UV filters are alleged to have anti-inflammatory effects themselves. But do current sun protection products indeed suppress erythema and, thus, give the consumer a false sense of security? Inflammation is known to be a driver of skin cancer progression.Therefore, anti-inflammatory mechanisms even might have some beneficial effects in photoprotection, provided that the anti-inflammatory action is not an anti-redness effect. Published and new data show that, if formulated properly, sun protection products do not suppress UV-induced erythema and the measured SPF reflects the true UV-protection capacity of the product.

Enhanced Aggressiveness of Bystander Cells in an Anti-tumor Photodynamic Therapy Model: Role of Nitric Oxide Produced by Targeted Cells

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A bystander effect can occur when cells exposed to a stress send pro-survival (or anti-survival) signals to non- or minimally-stressed neighboring cells (bystanders). Bystander effects of ionizing radiation have been widely studied, but much less is known in the context of non-ionizing photodynamic therapy (PDT). To study this, we developed a novel approach whereby two populations of human cancer cells (prostate PC3) on a large culture dish were separated by 2-4 impermeable silicone-tipped rings. The larger population (outside rings) was sensitized with 5-aminolevulinate (ALA)-induced protoporphyrin IX, while the smaller ones (inside rings) served as non-sensitized bystanders. At designated time(s) after broad-band visible irradiation, the rings were removed, leaving gaps with no physical contact between targeted and bystander cells. Examining bystanders at increasing post-irradiation times, we observed a striking increase in growth and migration rate compared with controls. These effects mimicked those seen for surviving ALA/light-targeted cells, and were strongly attenuated by inhibitors of inducible NO synthase (iNOS) or a NO scavenger. Moreover, iNOS and NO levels in bystander cells increased progressively from very low starting levels. Bystander iNOS/NO upregulation and accelerated growth/migration were markedly reduced by prior iNOS knockdown in targeted cells, which indicated that diffusible, stress-induced NO was a major driver of these effects. Other NO-mediated pro-survival/expansion responses included Akt and ERK1/2 activation, and cyclooxygenase-2 (COX-2) upregulation. These findings revealed that a previously unrecognized NO "feed-forward" or "field" effect could occur during PDT, whereby tumor cells outside the targeting range still respond, but in a negative way by becoming more proliferative and migratory. Such effects might be attenuated pharmacologically by using selected iNOS inhibitors as PDT adjuvants. (Supp. by NIH/NCI grant CA70823 and NCN grant 2017/26/M/NZ3/01232)P

Photolyases of Agrobacterium fabrum: PhrA is a CPD class III photolyase related to plant cryptochromes, and PhrB is the first prokaryotic 6-4 photolyase

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KIT, Charite

Photolyases repair UV induced damage on the DNA in a light dependent manner. CPD photoproducts and 6-4 photoproducts are repaired by CPD photolyases and 6-4 photolyases. We study the photolyases PhrA and PhrB of Agrobacterium fabrum. For both photolyases we have solved the crystal structure and obtained major insight into photoreduction and repair mechanisms. PhrA belongs to the class III CPD photolyases which is a phylogenetic sister group of plant cryptochromes. PhrB has an MTHF antenna chromophore as e.g. E. coli photolyase, which is bound to a different site. The PhrA binding site could be used by plant cryptochromes, for which the antenna chromophore is as yet unclear. PhrA contains the same photoreduction triade as photolyase from E. coli and most other species and a second Trp triade which has the central Trp in common with the classical triade. PhrB was the first bacterial 6-4 photolyase to be discovered. We could show that PhrB represents an ancient group of photolyases. Unlike members of the other groups, PhrB has an FeS cofactor and a DMRL antenna chromophore. The photoreduction of PhrB proceeds via a pathway different from the classical one, via two Trp and one central Tyr residue. Replacement of the Tyr by Phe had no effect on photoreduction, although Phe is generally used to interrupt electron transport. This effect is explained by tunneling. Another major difference between PhrB and other photolyases is the effect of Mg2+ on the repair of lesion DNA. In PhrB, Mg2+ and other divalent cations can stimulate the repair several thousand fold, whereas the repair of other photolyases is independent on Mg2+. Two highly conserved Asp residues next to the DNA binding site coordinate Mg2+ which probably stabilizes the lesion after electron transfer.

Computational algorithms for in-vivo fluorescence microendoscopy image mosaicking

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Fluorescence microendoscopy offers promise for the optical biopsy of cancer to inform precision medicine. However, microscopic resolution generally comes with the trade-off of a tiny field of view and tunnel vision. Micro-image mosaicking offers the capability of stitching together larger scenes of the tissue to aid visualization and interpretation. This approach is often challenged by the appearance of non-uniform scene deformations within individual images and the appearance of sample fragments that distort the otherwise uniform motion of tissue in the field of view. We present an algorithm that utilizes the motion of matched features to calculate and apply local transformations to compensate for these effects. A typical raster path to produce suitable data for mosaicking images the same location several times redundantly in different frames, ultimately providing the possibility for the construction of a high-fidelity mosaic even when artifacts are present.

Wavelengths longer than 380nm cause photodamage to skin cells that is not adequately protected by application of conventional sunscreens.

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King's College London, Université Grenoble Alpes, SyMMES, & CEA, INAC, King's College London, BASF Grenzach GmbH

The adverse effects of solar UVR (~295 – 400nm) on the skin are well documented, especially in the UVB region, and sunscreens have been shown to be beneficial in inhibiting photodamage. The effects of long-wave UVA1 (>380nm) and visible radiation on the skin are much less well known. Most sunscreen formulations provide little protection in the long wave UVA region (380-400nm) and almost none from high-energy visible wavelengths (400-420nm). We demonstrate photodamage in vitro and in vivo in this region with high irradiance, LED arrays at 385nm and 405nm.The endpoints investigated include cell viability, DNA damage, differential gene expression (including genes for inflammation (IL-1a, IL-6, IL-8, IL-10, IL-20, PTGS2), photoageing (MMP-1, MMP-3, MMP-9, MMP-10, MMP-12) and oxidative stress (PON-2, HMOX-1)), oxidative stress, and pigmentation, in vitro in HaCat keratinocytes and in vivo in human volunteers. For most endpoints we found a clear dose-response relationship. We demonstrate the production of 'dark' CPD in vivo in healthy volunteers. We also show that these sources induce changes in pigmentation in vivo across skin types.These endpoints were subsequently used to demonstrate that there is inadequate protection provided by a conventional sunscreen (SPF=15) labelled as UVA protective in the USA and Europe. The addition of a new filter, Bis-(Diethylaminohydroxybenzoyl Benzoyl) Piperazine (BDBP) to the formulation, which absorbs in this region (380-420nm), to a formulation of similar SPF (SPF=15.8) mostly provided significantly more protection when compared to the conventional formulation, returning damage to levels comparable with the unirradiated control.This work provides new insight into photodamage and may lead to new strategies to provide improved photoprotection in the currently poorly protected UV/visible radiation boundary region.This work was funded by BASF Grenzach GmbH. BASF produce the ingredients for the sunscreens used in this study.

Mycosporine-like amino acids (MAA) - biocompatible, photoprotective compounds from nature

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There is increasing evidence that UVR filters contained in sunscreens (both inorganic and synthetic organic filters) damage marine environments and may negatively affect human health. This has led to a search for natural, biocompatible UVR filters. Many marine microorganisms contain UVR absorbing molecules such as mycosporine-like amino acids (MAA), which are highly photostable and believed to be natural sunscreens, as well as providing protection at times of high stress. MAA accumulate in the food chain and are stored preferentially in UVR exposed tissues such as the skin and lenses of fish. We demonstrate evidence that MAA are highly effective in inhibiting a range of UVR induced damage in a human skin model. Endpoints measured include DNA damage, oxidative stress and gene expression changes associated with photoageing, inflammation and oxidative stress. We also show MAA to have several antioxidant properties, acting as chemical quenchers and biological antioxidants by activating the cytoprotective Nrf2 pathway. This work suggests that MAA may be developed as multifunctional photoprotective compounds, acting as photostable, biocompatible UV filters with potent anti-oxidant properties.

Toxicology: Moving a Compound Across the Bench to First in Man

Learn DB
Charles River Laboratories

Drug development is a continuum of discovery, safety and efficacy efforts, and all are interlinked to achieve the goal of the release of a safe and effective pharmaceutical to market that meets and unmet medical need and serves society. This presentation will briefly review the regulatory requirements that both drive and define the drug development process, and how a compound is evaluated using in vitro methods to determine both safety and efficacy, then the in vivo preclinical studies required by the current regulatory requirements to determine the safe dose that will be used in the first human clinical trials. Throughout the presentation, emphasis will also be placed on career opportunities in drug discovery and safety assessment that can integrate basic science knowledge and good management. This will be a dynamic presentation and questions on the process or topics related to the process will be encouraged.

Characterization Of Singlet-Oxygen Induced Damage On Proteins

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Protein oxidation is a well-established consequence of exposure to both UV, and visible light in the presence of a sensitizer. The reactions that occur are complex and poorly understood, but can generate major structural and functional changes, and multiple human pathologies are associated with the accumulation of damaged proteins. In this study, we have investigated the mechanisms and consequences of exposure of the key enzymes glucose-6-phosphate dehydrogenase (G6PDH) and RNase A to singlet oxygen ($^1O_2$) with an emphasis on identifying the role of specific amino acids. Cross-links and high mass aggregates were detected by SDS-PAGE and Western blotting using specific antibodies. Amino acid analysis has provided evidence for Met, Trp, Tyr and His consumption and formation of oxygenated products (e.g. diols, peroxides, N-formylkynurenine, kynurenine) from Trp, and di-tyrosine (from Tyr). Mass spectrometric data obtained after trypsin-digestion in the presence of O-16 and O-18 water, has allowed the mapping of specific cross-linked residues and their sites. These data indicate the formation of Tyr-Trp and di-Tyr cross-links in G6PDH, and for RNase A, Tyr-Tyr, Lys-Tyr, His-Arg and His-Lys cross-links. These inter- and intra-molecular cross-links are formed primarily from surface-accessible residues, with the extent of oxidation varying markedly between sites. Significant modification of Met, and limited damage at other residues is also detected, though these latter changes do not correlate with loss of function. Comparison with a peroxyl radical system shows marked changes and more limited damage at specific Tyr residues and less dramatic changes in enzymatic activity. These data indicate that Trp, Tyr and His residues are readily modified by $^1O_2$ with this resulting in species that impact significantly on protein structure and function. The formation of such cross-links may help rationalize the accumulation of damaged proteins in vivo on extensive light exposure.

DNA Damage: When the Danger Comes from "Insiders"

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In the last decades, the increase in the incidence of skin cancer has attracted a growing interest for the understanding of the mutagenic effects of solar radiation. In this context, the knowledge of the DNA photodamage and photorepair is a central topic as it has been shown that exposure to solar ultraviolet radiation is involved in the pathologies of carcinoma and melanoma. To protect themselves from these harmful effects, living organisms are equipped with enzymes that repair the damage to its original form, thus maintaining the genetic integrity. However, repair of some lesions such as multiply damaged sites represents a challenge for the organism. Formation of several lesions in close proximity within the DNA sequence is an interesting fact that has not been fully understood yet. In this context, our work is based on the hypothesis that some DNA damages can behave as intrinsic photosensitizers (insiders) capable of inducing chemical changes in their neighborood, leading this way to the formation of multiply damaged sites known as clustered lesions. Our recent outcomes obtained through the combination of analytical, photophysical and biochemical techniques will be reported here for the study of two thymine-derived lesions absorbing in the UVA, namely the (6-4) photoproduct and the 5-formyluracil.

Structural Analysis of Phycobilisomes from Red Alga and Cyanobacteria

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Light harvesting is the first step in photosynthetic conversion of solar energy to chemical energy, which is crucially important to life on earth. Photosynthetic organisms have developed a variety of light-harvesting systems to capture light energy. Phycobilisome (PBS) is the major light-harvesting antenna in cyanobacteria and red algae and it is the largest water soluble protein-pigment complex. Structurally PBS is composed of a central core with peripheral rods attached. Both the central core and the peripheral rods of PBS are composed of phycobiliproteins and linker proteins. While the dynamic process of PBS assembly remains to be revealed, recent determination of a red alga PBS structure at 3.5 Å resolution through single-particle cryo-electron microscopy shed some light on how PBS components are assembled together and how light energy transfers within PBS. It also provides some clues about energy transfer to photosystems and its regulation (state transitions). We found that the linker proteins are organized as linker skeleton within PBS and play a vital role in assembly of PBS. For the first time, the structures of §-linker are determined and their roles in light-absorbing as well as PBS assembly are revealed. The linker protein are also very useful in our understanding of protein-protein interactions in general. The energy paths within PBS and the routes to either photosystem I or photosystem II are deduced based on the distances among the bilins which are effectively spaced in PBS.

Mutagenesis was performed with ApcD and ApcF in the cyanobacterium Synechococcus 7002, the two key components in the central core, and the results demonstrated that ApcF is critical to energy transfer from PBS to PSII. We found an ApcD mutant that was performing a faster state II to state I transition, suggesting the cyanobacterial PBS is mobile in state transitions.

Rational Design of BODIPY Singlet Oxygen Photosensitizers for Photodynamic Therapy

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The rational design of chemical probes and photochemical/ photophysical schemes, when combined with state-of-the-art fluorescence imaging methods, in particular, single molecule imaging, provides powerful tools to study chemical and biological processes at the cellular level. During the course of my graduate work, and by combining in silico, spectroscopic, and electrochemical methods, we have mapped the excited state surface of boron-dipyrromethene (BODIPY) dyes in order to identify and tune non-fluorescent deactivation pathways such as photoinduced electron transfer, intersystem crossing, or internal conversion to develop new fluorogenic molecules for fluorescence imaging studies.[1-3] In this presentation, I will show how we have taken our understanding of the deactivation pathways present in fluorogenic probes to develop dormant singlet oxygen photosensitizers, whose phototoxicity is activated only after reaction with an endogenous cellular stimulus, i.e. chemicontrolled activation.[4] I will also discuss how we have developed BODIPY photosensitizers with improved stability toward photobleaching due to the generated singlet oxygen,[5] allowing for more efficient singlet oxygen production before the destruction of the photosensitizer. (1) Lincoln, R.; Greene, L. E.; Krumova, K.; Ding, Z.; Cosa, G.; J. Phys. Chem. A, 118, 2014, 10622-10630. (2) Lincoln, R.; Greene, L. E.; Bain, C.; Flores-Rizo, J. O.; Bohle, D. S.; Cosa, G.; J. Phys. Chem. B, 119, 2015, 4758-4765. (3) Lincoln, R.; Greene, L. E.; Zhang, K.; Louisia, S.; Cosa, G.; J. Am. Chem. Soc., 139. 2017, 16273-16281. (4) Durantini, A. M.; Greene, L. E.; Lincoln, R.; Martínez, S. R.; Cosa, G.; J Am. Chem. Soc., 2016, 138, 1215-1225. (5) Lincoln, R.; Durantini, A. M.; Greene, L. E.; Martínez, S. R.; Knox, R.; Becerra, M. C.; Cosa, G.; Photochem. Photobiol. Sci., 2017, 16, 178-184.

Photochemical and Peroxyl Radical-Mediated Oxidation of Î±- and Î²- Caseins: Role of Tyrosine and Tryptophan in Protein Crosslinking

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In whole milk, as consequence of riboflavin (RF)-sensitized photoreactions and lipid-peroxidation, Î±- and Î²-caseins can be oxidized leading to protein aggregation and/or fragmentation. The amount of oxygen modulates the photochemical mechanisms (type I or II) and the fate of the Trp- (Trp°) and Tyr-derived (Tyr°) radicals (formed in the type I process). Trp° and Tyr° dimerize producing cross-links, or alternatively react with O2 giving peroxyl radicals, hydroperoxides, other oxidized products, and protein fragments. In the present work, data showing the relevance of the O2 concentration in the oxidative damage of caseins induced by the triplet state of RF (3RF) will be presented. A comparison with the damage inflicted by peroxyl radicals (ROO°) derived from the thermolysis of AAPH (2,2'-azobis(2-methylpropionamidine) dihydrochloride) will be also reported. 3RF induced oxidative modifications on caseins and significant levels of cross-links. Under anaerobic conditions, the overall extent of damage was decreased, but the yield of cross-linked products was significantly elevated. These cross-links can be explained by inter- and intramolecular di-Tyr or di-Trp bridges. Alternative cross-links were evidenced in the presence of O2. Exposition of caseins to ROO° lead to fragmentation, cross-linking and protein aggregation. Amino acid analysis showed consumption of Trp and Tyr together with Met, His and Lys residues. Low levels of di-Tyr and di-Trp bonds were detected, indicating that casein aggregation was mostly associated with other mechanisms, probably involving Lys residues. Overall, these data demonstrate that radical-mediated, and O2-independent reactions can be important processes involved in milk protein modification reactions induced by visible light and sensitized by RF. Acknowledgements: This work was supported by FONDECYT (grant n°1141142). MJD gratefully acknowledges financial support from the Novo Nordisk Foundation (Laureate grant: NNF13OC0004294).

Chemophototherapy Using Porphyrin-phospholipid Liposomes Loaded with Doxorubicin

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Chemophototherapy (CPT), the combination of chemotherapy and phototherapy, is an emerging cancer treatment modality. CPT can simultaneously provide: 1) Systemic therapy consistent with existing standards of care for breast cancer patients with advanced disease and 2) Seamless ablation of problematic local tumors via clinically-relevant near infrared (NIR) light delivery. Porphyrin-phospholipid (PoP) stably incorporates in the bilayer of liposomes designed to have extended circulation times in vivo. PoP itself is non-toxic and is derived from a precursor of a porphyrin currently in clinical trials. Addition of just 2 mol. % PoP to long-circulating doxorubicin (Dox) liposomes imparts rapid near infrared (NIR) light-triggered release while maintaining long-circulation of Dox, yielding long-circulating Dox PoP liposomes (LC-Dox-PoP). LC-Dox-PoP composition and in vivo behavior is similar to FDA-approved PEGylated liposomal Dox (DOXIL), but LC-Dox-PoP administration followed by laser treatment induces drastic enhancement in local drug delivery and potent tumor ablation.

Effect of sequence context, nucleosomes, and tertiary structure on DNA photochemistry

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The lethal and mutagenic effects of UV light are the result of a complex interplay between factors that affect the formation of DNA photoproducts, their conversion to other photoproducts, their repair, and their bypass by polymerases. We will report on the development of DNA sequence libraries of the type NPyPyN for studying the effects of flanking sequence context on UVA/B/C and photosensitized cis,syn cyclobutane pyrimidine dimer (CPD) photoproduct formation. We will also report on the modulation of cis,syn CPD photoproduct formation and deamination in rotationally phased poly d(TC) containing nucleosomes, and on the formation of a new photoproduct of human telomeric G-quadruplex forming sequences containing tandem anti CPDs.

Nucleosomes And ETS Transcription Factors Induce Unique UV Damage Signatures That Promote Mutagenesis In Melanoma

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Ultraviolet (UV) light-induced mutations in skin cancers are enriched in regions of repressive chromatin and transcription factor binding sites. This has been attributed to less efficient repair of UV lesions at these sites, but it is not known whether variable lesion formation due to histone or transcription factor binding also contributes to elevated mutation rates. Here, we use a new sequencing method known as CPD-seq to map the distribution of UV-induced lesions throughout the human genome. Our results indicate that

DNA-binding proteins, including histones and transcription factors, modulate the frequency of UV lesions in cellular DNA. This was most apparent for oncogenic E26 transformation-specific (ETS) transcription factors, whose binding to DNA induces a unique signature of UV damage 'hotspots' that are highly correlated with recurrent noncoding mutations in melanomas. These findings establish variable lesion formation, due to nucleosomes and transcription factor binding, as a novel contributor to mutational heterogeneity in skin cancer and a mechanism for recurrent mutagenesis at ETS binding sites.

RADICAL GENERATION IN DNA BY DIRECT ABSORPTION OF LOW-ENERGY UV RADIATION

Markovitsi D
CNRS LIDYL

It is commonly accepted that the oxidative DNA damage by wavelengths longer than 230nm (5.4eV) requires mediation of other molecules because the ionization potential of nucleobases is higher than 7 eV. Yet, there is increasing evidence that absorption of low-energy UV photons directly by DNA is capable to induce oxidative damage.(1) Thus, 8-oxoguanine was detected following 295nm irradiation of naked genomic DNA and shown that its formation involves guanine radical cations. In parallel, the primary species related to oxidative damage (ejected electrons and base radicals) were characterized by time-resolved absorption spectroscopy.(2-5) The one-photon ionization quantum yield at 266nm is 0.001 for duplexes and 4 times higher for G-quadruplexes.(4) In the latter systems, deprotonation of radical cations is much slower compared to duplexes and, depending on their topology, delocalization of the electron hole may occur. The lifetimes of deprotonated radicals span from a few ms, in single and double strands, to tens of ms in G-quadruplexes. Furthermore, our time-resolved experiments provided the spectroscopic signature of oxidation products whose chemical structure remains to be determined. References: (1) Gomez-Mendoza, M., A. Banyasz, T. Douki, D. Markovitsi and J. L. Ravanat (J. Phys. Chem. Lett. 2016). (2) Marguet, S., D. Markovitsi and F. Talbot (J. Phys. Chem. 2006). (3) Banyasz, A., T. Ketola, A. Muñoz-Losa, S. Rishi, A. Adhikary, M. D. Sevilla, L. Martinez-Fernandez, R. Improrta and D. Markovitsi (J. Phys. Chem. Lett. 2016). (4) Banyasz, A., L. Martinez-Fernandez, C. Balty, M. Perron, T. Douki, R. Improta and D. Markovitsi (J. Am. Chem. Soc. 2017). (5) Banyasz, A., T. Ketola, L. Martínez-Fernández, I. Improta and M. D. (Faraday Discuss.2018).

Interaction Between Metal Complexes and Materials in Multiple Dimensions

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Nanomaterials have been the center of intense study for the last two decades. One, two, and three dimensional nanomaterials are being explored in a variety of settings and applications in areas that include electronics, optics and medicine. Our group have studied the synergistic interaction of nanomaterials and metal complexes in multiple dimensions. First, we will show how metal complexes have been used to disperse one dimensional structures such as carbon nanotubes and their photophysical properties studied by steady-state and time-resolved absorption and emission spectroscopies. We will present our studied of two dimensional structures such as graphene quantum dots and their interaction with lanthanide salts. Interestingly, the photosensitized photoluminescence quantum yield of terbium shows an order of magnitude dependence when changing the excitation wavelength, which is in contrast with the Kasha-Vavilov's rule. Three dimensional structures in which metal complexes have been immobilized in a supramolecular framework have been studied showing a remarkable effect on their photoluminescence properties including maxima, intensity and lifetime. The unconventional properties of these materials due to the synergy of nanomaterials of varied dimensions and metals complexes have opened applications in solar energy harvesting, anticounterfeiting, molecular detection.

How Effective Are Plant Extracts At Photostabilising Sunscreen Absorbers?

Martincigh BS
University of KwaZulu-Natal

The most common form of cancer, skin cancer, is attributed to exposure to ultraviolet (UV) radiation. The advocated first line of defence is protection from sunlight by use of clothing and application of sunscreens. However, a number of sunscreen preparations available in the market have been shown to degrade on exposure to UV radiation, thus affording the consumer less protection than expected. Efforts have been made to stabilise these products and minimise associated side-effects arising from photodegradation by-products. Plants extracts have been shown to provide a stabilising effect in addition to offering some degree of UV absorption. Also, plant polyphenols found in these extracts are known to be good antioxidants. In this work the photostabilising effect of a number of plant extracts on some commonly used sunscreens was investigated. All the extracts exhibited some degree of photostabilisation of both individual sunscreens and mixtures thereof. Photostability measurements indicated longer sun-protection ability with an initial improved UV absorption. We propose that inclusion of these extracts in sunscreen formulations will improve their photoabsorption efficacy and minimise photodegradation but they need to be chosen judiciously.

Theoretical studies of photochemistry in nucleic acids

Matsika S, Lee W
Temple University

DNA absorbs UV radiation which may lead to photochemical reactions and damage. A common photochemical product is the cyclobutane pyrimidine dimer (CPD). It has been shown that the formation of the photochemical product of thymine-thymine cyclobutane pyrimidine dimer is significantly affected by conformational flexibility as well as the nature of the bases adjacent to thymine. Theoretical techniques have advanced significantly in recent years and allow for accurate studies which can help us understand the underlying mechanisms involved in photochemical processes. Using a quantum mechanical / molecular mechanical (QM/MM) approach we have investigated CPD formation in oligomers and G-quadruplex structures and explored the conformational and electronic effects on the reactivity. In this talk we will discuss our findings on CPD formation, as well as repair by DNA photolyase.

American Society for Photobiology Presentation on Intellectual Property

Maxey-Fisher BJ
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Often lines around Intellectual Property are blurred in the field of science, academia and technology, as the swift impulse for publication and public disclosure of innovative ideas affixed in original manners are of paramount importance. A single hasty decision to publicly disclose your research, inventions or findings could be fatal in trying to obtain Intellectual Property protection at a later date. Developing optimal strategies to balance the financial and competing deadlines that Intellectual Property protection often requires with immediate goals, opportunities and potential issues on the horizon may prove to be difficult. But by establishing a solid foundation regarding what constitutes Intellectual Property, how to protect your Intellectual Property and the potential enforcement of your Intellectual Property you will be one step ahead of the others. This framework, understanding and appreciation of the significance of Intellectual Property is imperative as companies worldwide are turning to Intellectual Property in order to drive global economics and re-establish commitments to innovation and emerging technologies.

Combination strategies to optimize PDT responses of skin cancer and precancer

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Aminolevulinate (ALA)-based photodynamic therapy (PDT) has become very popular as a treatment for conditions featuring field cancerization of sun-damaged skin; these include actinic keratosis (squamous precancers) and Bowen's disease (squamous carcinoma in situ). While generally superior to cryotherapy or topical 5-fluorouracil, PDT still faces significant challenges due to the large inter-patient variability in therapeutic responsiveness to the therapy. Our studies are attempting to understand this variability and to develop new ways to tailor PDT regimens to the patient. In terms of known response predictors, vast differences in PDT sensitivity between different areas of the body (face > scalp > forearms/hands) must be taken into account when choosing ALA incubations times and light doses. Even when this is done, certain patients fail to respond. Therefore, to increase treatment efficacy we have explored several combination approaches in which lesions are pretreated for several days with a neoadjuvant prior to PDT, in order to increase ALA-to-protoporphyrin IX conversion. One of these neoadjuvantal agents is 5FU; the other is vitamin D. The scientific rationale and current status of these combination approaches will be reviewed. Another challenge for cutaneous PDT is the need to ameliorate pain during light exposure. For some patients, this stinging pain can be so severe that it prevents them from completing the PDT session, and/or makes them refuse any subsequent treatments. To address this problem, we developed a new exposure regimen called 'metronomic PDT' in which preincubation with ALA is eliminated. Instead, ALA is applied and illumination is begun immediately and for an extended time. This new approach is completely painless and works surprisingly well, but some compromises are required in terms of lower efficacy in thick lesions and PDT-resistant areas. The relative merits of metronomic PDT, and how it might be improved via combination with topical 5FU, will be discussed.

Recent Highlights from the Development of Metal Complex Photosensitizers for Photodynamic Therapy

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Photodynamic therapy (PDT) is a special branch of photomedicine that employs a sensitizer molecule, light, and oxygen to destroy target cells with spatiotemporal selectivity. Despite its enormous potential for treating certain diseases, including cancer and infection, PDT has yet to become mainstream. Over the past 10 years, my group has addressed key issues that have hampered bench-to-bedside progress in the field of PDT. Using a multidisciplinary approach, we have introduced both synthetic compounds and natural products (both currently being investigated in human clinical trials) as alternatives to existing porphyrin-based PDT agents for specific indications. This presentation will share some of our past experiences in developing metallodrug photosensitizers for treating bladder cancer with PDT, and will highlight new directions related to this work.

PBL (Psoralens + Blue light): How Blue Light Activates Furocoumarin Derivatives Triggering Tumor Cell Apoptosis

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BACKGROUND. Furocoumarins are natural and synthetic compounds with high chemotherapeutic potency under UVA irradiation. To improve their activity and avoid severe side effects likely related to the formation of interstrand crosslinks (XLs) with DNA pyrimidine bases, a variety of derivatives, hopefully monofunctionals, have been synthesized. Although angelicins, due to their angular geometry, do not generally form XLs, some of them, i.e. (TMA), can crosslink folded DNA upon UVA. The UVA photobiological effects of furocoumarins are mainly related to their capacity to covalently photoreact with DNA, but they can also produce ROS that impair cellular functions through lipid peroxidation, oxidation of guanine and DNA strand breaks , oxidation of proteins and inactivation of enzymes. To photoactivate 8- MOP and 4,6,4'-trimetylangelicin (TMA) towards human prostate (DU145 PCa) and bladder (T24) cancer cell lines, an alternative strategy based on less toxic and more penetrating visible radiation (BL, 420 nm) is here presented. RESULTS. TMA and 8-MOP show high antiproliferative activity towards cancer cells, through induction of apoptosis. Besides ROS generation (less efficient under BL than UVA), the proapoptotic effect seems related to the activation of p38 and inhibition of p44/42 phosphorylation. Interestingly, the decrease of Î² nuclear-catenin is coupled with dropping of CD44-positive cells. The strong photocytotoxicity of TMA and 8-MOP can be related to the kind and extent of DNA damage. Under BL, no mutagenic crosslinks, no photocleavage nor photooxidative lesions are detected on isolated DNA by TMA treatment, but only MAs form. However, formation of XLs still remains for 8-MOP under BL but in a lower amount than UVA. CONCLUSIONS. Overall, our results indicate that 8-MOP, and particularly TMA, can be efficiently activated by BL and may be considered good compounds for targeted phototherapy of prostate and bladder cancers and possibly for other solid tumors.

Fabrication Of A Fast Fiber Scanner For Fluorescence Microendoscopy

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Fiber optic scanning microendoscopy enables fluorescence microscopy deep within the body. These devices are essentially miniature laser scanning microscopes for linear (confocal or wide-field) and nonlinear (multiphoton) imaging applications. We present simple methods to fabricate a low-cost miniature fiber scanning microendoscope probe with specifications that promise video rate imaging applications.

Nanoliposome-Based Modulation of Photosensitizer Localization to Enhance Photodynamic Therapy Efficacy

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A major objective in developing new treatment approaches for lethal tumors is to reduce toxicity to normal tissues while maintaining therapeutic efficacy. Nanoparticles have a variety of applications, some of which can be exploited to address these translational barriers, and combined with mechanistically distinct modalities, such as photodynamic therapy (PDT), to improve outcomes. PDT involves light-based activation of a small molecule termed a photosensitizer (PS) to generate reactive molecular species (RMS) that are toxic to target tissue. Depending on the PS localization, various cellular and subcellular components can be targeted, causing selective photodamage to different tumor compartments. It has been shown that targeted lysosomal photodamage followed by (or simultaneous with) mitochondrial photodamage using two different PS results in a considerable enhancement of PDT efficacy (Kessel, J. Porphyrins and Phthalocyanines 2016). Here, two liposomal formulations of benzoporphyrin derivative (BPD): 1. Visudyne (clinically-approved) and 2.) an in-house formulation entrapping a lipid-conjugate of BPD, are used in combination to direct the simultaneous localization and targeting of the PS to mitochondria, endoplasmic reticulum and lysosomes, enabling photodamage of all three organelles using a single wavelength of light. Experiments were conducted in monolayer (Rizvi and Obaid et al, Lasers and Surgery in Medicine 2018) and 3D models of ovarian cancer (in progress) using NIH:OVCAR-5 cells. Simultaneous activation of BPD in lysosomes and mitochondria/ER significantly enhanced PDT efficacy at lower

light doses than treatment with each PS alone. The implications for this approach in designing PDT-based treatments as well as combinations with conventional chemo and biologic agents merits consideration.I have joined the Hasan lab to investigate how nanotechnology can be combined with PDT to overcome resistance to chemotherapy and targeted agents in cancer. I am applying my prior knowledge of nanoparticles to the principles I have learned here about PDT.

The end-Permian Extinction as a Warning for the Anthropocene*

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Over approximately 3 billion years photosynthesis has transformed Earth from a planet with limited available chemical potential in its crust to support life to one with abundant chemical potential in the form of living biomass and stored fossil fuels.1-3 Moreover, photosynthesis supports the chemistry/biology responsible for much of the lithosphere. Today, operating at ca. 300 TW gross primary production photosynthesis powers most of the biosphere and over multiple glacial/interglacial periods has been the major driver of the "fast" global carbon cycle in which the rate of CO2 uptake by photosynthesis is balanced by the rate of CO2 produced by respiration and decomposition. Prior to recent anthropogenic activity, photosynthetic energy flow was fully utilized for biosphere services and support. Today, human activity transfers carbon from the "slow" to the "fast" carbon cycle, which has overwhelmed the capacity of photosynthesis to control CO2 levels.4 As a consequence, CO2 levels are rising in the atmosphere and oceans and are higher than ever experienced by human societies.5,6 Worryingly, a new theory posits that 252 million years ago methanogens could have carried out a similar transfer of carbon resulting in the end-Permian extinction (3rd mass extinction event) in which 90+ % of species became extinct.7 We point out inconvenient parallels between the behavior of methanogens and humans when requisite factors are present and a seemingly limitless supply of chemical potential in the form of reduced carbon is available. *A similar abstract submitted to iCHAT 2017, Monteporzio Catone, Italy1. Schramski; et al., PNAS 2015, 112, 95112. Sherman; et al., Photosynth. Res 2013, 120, 593. Llansola-Portoles; et al., "From Molecules to Materials" 2015 4. Olah; et al., JACS 2011, 133, 128815. IPCC, Climate Change 2013: The Physical Science Basis, Cambridge University Press 6. Keeling, http://scrippsco2.ucsd.edu/home/index.php.7. Rothman; et al., PNAS 2014, 111, 5462

One-Electron Oxidation Coupled to Proton Transfer Processes in Artificial Photosynthetic Constructs

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In photosystem II, tyrosine Z (Yz) serves as a redox relay between the photo-oxidized primary donor (P680•+) and the oxygen-evolving complex (OEC), where water oxidation takes place. The oxidation of Yz by P680•+ likely occurs with the transfer of a proton to its hydrogen-bonded partner, histidine (His190). We designed and synthesized a series of benzimidazole-phenol (BIP) derivatives as mimics of the Yz-His190 pair (the phenol mimics Yz and the benzimidazole mimics His190). These models were studied theoretically, electrochemically and by IR spectroelectrochemical (IRSEC) techniques. We found that a concerted one-electron two-proton transfer (E2PT) process associated with the electrochemical oxidation of the phenol occurred in amino substituted BIPs, accompanied by a decrease in the redox potential of the phenoxyl radical/phenol couple by ~300 mV. The loss of 300 mV in BIP is a high price to pay for a proton translocation of ~ 7 angstroms, and it leaves the relay thermodynamically incapable of oxidizing water at pH near 7. BIP-imine constructs were synthesized as alternatives to the BIP-amino models of the Yz-His190 pair and preliminary results indicate that the phenol oxidation regains most of the 300 mV potential lost in the E2PT process of the amino-BIPs. IRSEC identified the formation of the protonated imine while the benzimidazolium ion was not detected, which confirms the assignment of an E2PT process in this case. These PCET processes could be light-driven. For that purpose, two isomeric tripentafluorophenylporphyrin-BIP dyads were prepared. The excited singlet state of the porphyrin (lifetime ~10 ns) is quenched to ~270 ps in one of the isomers, in acetonitrile. Because the quenching is solvent polarity dependent, it could be assigned to the electron transfer from the phenol to the excited state of the porphyrin. However, the resulting charge separated state has not been detected due to inverted kinetics, i.e., it recombines faster than it is formed.

In vitro viral photostimulated inactivation by a synthetic halogenated anthraquinone

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Anthraquinones (AQs) are an important class of natural compounds; some of them have showed antimicrobial activity that can be increased by light. Several synthetic pathways have been developed to obtain them. Since the introduction of a halogen atom has been widely adopted as a strategy for the development of highly effective photosensitizers, the aim of this work was to obtain a synthetic halogenated AQ and study its photostimulated ability to the viral inactivation on infected cells.Friedel-Crafts acylation of resorcinol with 4-bromophthalic anhydride afforded a synthetic brominated AQ that was identified by NMR spectroscopy and HPLC-DAD-ESI-QTOF analysis. Cytotoxicity on host cells (Vero cells) and viral inactivation (Herpes Simplex virus Type 1, HSV-1, KOS strain) were determined by means of the observation of the cytopathic effect (Optical microscopy) and evaluation of cellular viability (CV, uptake test of Neutral Red). Infected cells with HSV-1, were treated with AQ at Maximum Non-Cytotoxic Concentration (MNCC), and then were submitted under two experimental conditions: darkness and irradiation (actinic lamp) dose = 0.59 Jcm-2. Active viral particles were detected by extraction of cellular content and its subsequent inoculation in a new cell monolayer.6-bromo-xantopurpurin (6-BrX) was obtained as one of reaction products (yield = 1.27 %, purity = 91.9 %). In darkness, 6-BrX was not able to inactivate the extracellular virus, but a low inactivation of the intra cellular virus (28.3 %) was observed. Under irradiation, 72.6 % of extracellular virus and 83.3 % of intra cellular virus were inactivated by a 6-BrX photosensibilization process. Cytotoxicity test showed that the combination of 6-BrX (MNCC = 10 µM) with irradiation did not reduce the viability of the host cells (% CV = 97.1). In conclusion, 6-BrX has shown to be photoactive and able to inactivate HSV-1 in vitro by photostimulation without a deleterious effect on host cells.

A novel role for NUPR1 in the keratinocyte stress response to UV oxidized phospholipids.

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Ultraviolet light is the dominant environmental oxidative skin stressor and a major factor in skin aging. We studied which oxidized phospholipid (OxPL) species would be generated in primary human keratinocytes (KC) upon exposure to ultraviolet A light (UVA) and investigated the contribution of OxPL to UVA responses. Mass spectrometric analysis revealed dynamic UV-induced changes in abundance of 174 lipid species within 24 hours. We identified known

and novel bioactive and also chemically reactive lipids, and found indication for selective degradation of selected reactive lipid classes. Exposure to both UVA and to in vitro UVA - oxidized phospholipids activated, on transcriptome and proteome level, NRF2/antioxidant response signaling, lipid metabolizing enzyme expression and unfolded protein response signaling. We further identified NUPR1 as an upstream regulator of UVA/OxPL transcriptional responses and found this protein expressed in the epidermis and permissive to modification by oxidized lipids. Silencing of NUPR1 resulted in augmented expression of antioxidant and lipid detoxification genes and disturbed the cell cycle, making it a potential key factor in skin reactive oxygen species (ROS) responses intimately involved in aging and pathology.

Nanoparticle ensembles for Photo-based Imaging and Therapy

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Both inorganic and organic (or polymeric) nanoparticles have been widely explored for therapeutic and diagnostic applications. Among others, inorganic nanoparticles are attractive for the treatment, diagnosis, and detection of tumors, because of their unique features as compared with their organic and polymeric counterparts. For this purpose, single nanoparticles are often used and functionalized with organic or polymeric ligands to improve their stability, biocompatibility and functionality. While individual nanoparticles are no doubt exciting, ensemble of interacting nanoparticles can exhibit a rich variety of novel and extremely useful collective properties that can be radically different from their individuals. These new synergistic properties are originated from the coupling interactions between metallic, semiconductor or magnetic nanoparticles in the ensemble. For example, the organization of gold nanoparticles allows for tuning the absorption of nanoparticle ensembles in the near-infrared window which is highly desired for in vivo applications. The clustering of magnetic nanoparticles within micelles dramatically increases the magnetic resonance imaging contrast and responsiveness to external magnetic field. It is, therefore, expected that the ability to design assembled structures with tailored spatial arrangement of nanoparticles may facilitate the utilization of inorganic nanoparticles in biomedical applications. In this talk, I will present our efforts to develop new strategies for the self-assembly of polymer-functionalized inorganic nanoparticles into hybrid nanostructures and to evaluate these materials for enhanced cancer imaging and treatment. Specifically, I will focus on the design and application of vesicular structures containing gold nanoparticles, magnetic nanoparticles or both for effective multimodality cancer imaging (i.e., photothermal, photoacoustic, and magnetic resonance imaging) and combinational cancer therapy (i.e., photothermal ablation of tumor, photodynamic therapy, and targeted delivery-based chemotherapy).

Optogenetic Photosensitisers: From Understanding To Engineering

Nonell S
IQS-University Ramon Llull

Therapeutic proteins have recently attracted the attention of the biomedical community as novel biological drugs owing to their specific advantages over small-molecule based conventional drugs [1]. Photosensitizing proteins are generating increasing interest in the context of photodynamic therapy and photooxidation-based advanced imaging techniques due to their capacity of generating reactive oxygen species (ROS) with high spatial precision Two main families of photosensitizing proteins have been developed over the last few years, namely GFP-like [2] and flavin-binding proteins (FbFPs) [3-5]. In the GFP-like family, the chromophore is part of the protein sequence; in contrast, FbFPs incorporate it from their cellular environment. The protein's ability to generate and release ROS is determined by the nature of the chromophore and the interactions of the chromophore, oxygen and the ROS with the protein. In this presentation, we shall review our contributions to the field and our current understanding of the factors underlying ROS production by optogenetic photosensitizers. Acknowledgments. Part of the research described in this review has been supported by the Spanish Ministerio de Economía y Competitividad (CTQ2016-78454-C2-1-R). Financial support by the ASP to attend this meeting is gratefully acknowledged. References[1] R. J. Y. Ho and M. Gibaldi, Biotechnology and Biopharmaceuticals: Transforming Proteins and Genes into Drugs, John Wiley & Sons, New Jersey, Second Ed., 2013.[2] R. Ruiz-González, J. H. White, M. Agut, S. Nonell, and C. Flors, Photochem. Photobiol. Sci., 2012, 11, 1411.[3] X. Shu, V. Lev-Ram, T. J. Deerinck, Y. Qi, E. B. Ramko, M. W. Davidson, Y. Jin, M. H. Ellisman, and R. Y. Tsien, PLoS Biol., 2011, 9, e1001041.[4] R. Ruiz-González, A. L. Cortajarena, S. H. Mejias, M. Agut, S. Nonell, and C. Flors, J. Am. Chem. Soc., 2013, 135, 9564.[5] M. Westberg; M. Bregnhøj, M. Etzerodt, P. R. Ogilby, J. Phys. Chem. B 2017, 121 (40), 9366–9371.

Phenotypic-based cancer treatment on the era of combination therapies

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In recent years great efforts have been made towards the amelioration of all the parameters involved in PDT, such as new photosensitizers, their dosing or delivery systems and the light sources. Despite the progress in development of photodynamic therapy (PDT), its clinical application is still hampered by many factors. One important issue is the management of secondary post-PDT effects present at the vascular level, such as inflammation and the angiogenic switch. Therefore, various attempts have been made to further enhance the PDT effect via combining PDT with vascular therapeutic strategies that would inhibit neovessel formation. One of the major challenges in defining optimal drug combinations is the immense number of combinatorial possibilities. Not only must the selection of candidate drugs be taken into consideration, but also their relative dose ratios, affecting their potential for synergism or antagonism, and toxicity profiles. Already combining 10 drugs at 5 doses represents 510 possible drug-dose ratio combinations. Moreover, the 'one size fits all' approach of cancer therapy, where patients are given a treatment based on their cancer type or, in the best case, based on a common genetic marker (or mutant oncogene), remains unsatisfactory.

We used a phenotypic approach called the feedback system control (FSC) technique, with a population-based stochastic search algorithm to navigate through the large parametric space of nine angiostatic drugs at four concentrations to identify optimal low-dose drug combinations. This was done via an iterative approach of in vitro testing of drug combinations in endothelial cell viability assays and combined with data analysis. The synergistic optimized drug combination (ODC) contained three small molecule-based compounds acting on distinct signaling pathways. This drug combination had a strong effect on the inhibition of tip cells proliferation as assessed both in vitro and in vivo. FACS analysis showed a reduction in the number of CD34+ tip cells. Moreover, CD34+ tip cells treated with the ODC present with a clearly different cellular organization of the actin fibers stained with phalloidin, as compared to control cells. A significant reduction in the number of sprouting tip was observed in the group treated with the ODC following Visudyne®-PDT in vivo.

Natural anthraquinones as new photodynamic sensitizers with antimicrobial potentiality

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The world health organization strongly promotes the research in plants to obtain new therapeutic agents. In this framework, we initiated a research line to obtain photosensitizing compounds from nature, since the photosensitizers have shown to be highly active against microorganisms, especially when the photosensitization process is involved. Thus, they are projected as possible

drugs to be used in antimicrobial photodynamic therapy (APDT).We began with the chemical study of a plant popularly known for its phototoxicity, Heterophyllaea pustulata Hook f. (Rubiaceae), which grows in Argentina (Northwest) and Bolivia. It was established that its photosensitizing components were anthraquinone derivatives, isolating ten aglycon anthraquinones (AQs), three of which were found for the first time in nature (heterophylline, pustuline and bisoranjidiol). We continued with the chemical study of the other vegetal specie that belongs to this genus, H. lyciodes, obtaining seven AQs of which three were identified as new structures (5-chlorosoranjidiol, 7-chlorobisoranjidiol and lycionine). From lichens of the genus Teloschistes, parietin was isolated, a 1,8-dihydroxy AQ.After studying the photophysical and photochemical properties of each AQ, we evaluated its photodynamic effect over microorganisms and viruses. First, cytotoxicity was determined on a mammalian eukaryotic cell line (Vero cells), establishing a range of concentrations with low or no toxicity, which were subsequently used to evaluate the antimicrobial effects. We have shown that some of these AQs exhibit a significant photoinduced effect in vitro against Herpes Simplex Virus type 1, Candida spp., Leishmania amazonensis and different bacterial strains. Also, the photosensitizing mechanism was investigated for AQs in Candida tropicalis biofilm. Results project these AQs as new photodynamic sensitizers with potential use in APDT.

Uniform light distribution as a design criterion in artificial daylight photodynamic therapy

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Daylight photodynamic therapy (dPDT) is an effective and well tolerated treatment for field-change actinic keratoses. One drawback in advocacy of dPDT is relatively unpredictable weather conditions, and hence less reliable treatment outcomes. Light sources with low irradiances have been used in artificial dPDT in order to provide comparable and more reliable treatment indoors. For large treatment areas, such as the scalp or lower leg, uniform light distribution is imperative in ensuring effective treatment across the whole field. In order to address this challenge, we have developed a novel light source with tuneable direction of light emission.Control over the output of seven individual wavebands allows the matching of the protoporphyrin-IX (PpIX)-weighted spectra of the light source to that of daylight. Light distribution across three test surfaces - a flat surface, model head and model leg - is characterised alongside that of a typical PDT lamp. A comparison of both PpIX-weighted spectra from the light source and of daylight shows a good match, with the lamp capable of delivering 5.6 J cm-2 PpIX-weighted daylight dose at a distance of 240 mm for a 2-hour treatment, sufficient for effective dPDT. Significant improvements can be made in the uniformity of the light distribution - by optimising the direction of light emission, by improving the uniformity on curved surfaces four-fold for a 50 x 100 mm treatment area and two-fold for larger treatment areas.This light source innovates in approaches to uniform multiwavelength light distribution, meeting the challenges often associated with artificial dPDT.

Light Dose Guided Interstitial Photodynamic Therapy of Locally Advance Head and Neck Cancer - A Translational Study

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Interstitial Photodynamic Therapy (I-PDT) is a promising treatment option for patients with locally advanced head and neck cancer (LAHNC). This study focused on implementing our previously developed and verified finite element modeling (FEM) to optimize the delivery of the light dose during I-PDT of large VX2 carcinoma tumors. The VX2 carcinoma was surgically implanted into the sternomastoid muscle in the neck of New Zealand White (NZW) rabbits. The animals underwent periodic computerized tomography (CT) to assess tumor growth. Once the tumors reached approximately 2 x 2 cm (tumor volumes of 5-15 cm^3), CT scans were used to create computerized three-dimensional geometries representative of the tumor and surrounding critical structures. Using these geometries and our FEM, we determined the number and location of treatment fibers needed to deliver a prescribed light dose. I-PDT was performed on 5 rabbits based on the individualized treatment plans. The rabbits were injected with 5 mg/kg porfimer sodium 24 hours prior to light delivery. CT compatible surface fiducial markers were used to guide the insertion of the treatment fibers. Dosimetry measurements were taken during treatment to measure the delivered light dose. Two rabbits were declared cured. A cure was defined as surviving more than 12 weeks after treatment with no evidence of tumor recurrence or metastasis. In the other 3 rabbits, we observed local control however there was regional metastasis to the salivary gland (n = 1) and lung metastases (n = 2). The results suggest that FEM and dosimetry measurements can be used to guide the delivery of a safe and potentially effective light dose for I-PDT of LAHNC.
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Modular Antibody-directed NIR Photoactivatable Nanoconstructs Penetrate and Selectively Destroy Pancreatic Cancer Cells in a Heterocellular 3D Tumor Model

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The penetration and targeted destruction of antibody directed nanotherapeutics faces multiple obstacles that are not present in 2D in vitro screening platforms. In the case of pancreatic ductal adeonocarcinoma (PDAC), these obstacles include the tumor antigen binding site barrier in addition to desmoplasia that is conferred by the presence of stromal partners cells, such as pancreatic cancer-associated fibroblasts (PCAFs). Penetration and targeting become increasingly important in the case of NIR photoactivatable nanoconstructs, where the proximity of the photosensitizing entity to the target tumor cells during the photo-illumination time-window is critical for cancer-selective phototoxicity. Using a detailed modular copper-free click chemistry approach, we chemically tune Cetuximab (anti-EGFR mAb)-directed NIR photoactivatable nanoconstructs carrying a benzoporphyrin derivative (BPD) photosensitizer that exhibits up to 100-fold cellular binding specificities in 2D cell-based assays. In a complex heterocellular 3D tumor model of PDAC that contains patient-derived PCAFs, we demonstrate that our tuned antibody-directed NIR photoactivatable nanoconstructs efficiently permeate tumor nodules in under 60 minutes. We demonstrate that they retain up to 8-fold preferential tumor tissue binding specificity in 3D, with respect to non-targeted nanoconstructs, and deliver up to 16-fold improvements in targeted phototoxicity of cancer cells. The findings presented here demonstrate that the engineering of emerging antibody-directed NIR photoactivatable nanoconstructs can be facilitated and expedited using clinically relevant and high-throughput in vitro 3D models of PDAC and other cancers. The models validate both their penetration and targeted phototoxicity in a more architecturally and biochemically complex in vitro environment providing valuable predictions into their in vivo behavior and efficacy.

Blood-flow-informed Photodynamic Therapy Improves Therapeutic Efficacy

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The efficacy of photodynamic therapy (PDT) depends on photosensitizer accumulation and light delivery to a tumor, including to the tumor-supporting vasculature. Vascular response to PDT can be an important component of the treatment effect. Rapid decreases in blood flow during light delivery were found to correlate with poor PDT outcome. This relationship has been suggested to be a consequence of ischemia-introduced hypoxia during light delivery that limits the development of damage-creating reactive oxygen species. We hypothesized that blood flow response during PDT can be used in real time to inform the choice of light delivery parameters to conserve tissue perfusion for improved treatment efficacy. A real-time, blood-flow-informed light delivery system was built and tested. Diffuse correlation spectroscopy (DCS) was used to monitor blood flow continuously in radiation-induced fibrosarcoma murine tumors during Photofrin-mediated PDT. This interactive system measures PDT-induced changes in blood flow, and then automatically attenuates illumination fluence rate from 150 mW/cm^2 to 25 mW/cm^2 when flow reductions exceed a pre-determined threshold (-10%rBF/min) or adjusts illumination fluence rate back to 150 mW/cm^2 when blood flow recovers to pre-PDT value. Our results show that blood-flow-informed light delivery conserves tumor perfusion and improves PDT efficacy as compared to PDT treatment schemes that employed a constant light illumination fluence rate of either 150 or 25 mW/cm^2. Long-term therapeutic efficacy was achieved in 40% of mice treated with blood-flow informed PDT as documented by the absence of tumor recurrence within 90 days of PDT. This study demonstrated a noninvasive system for real-time monitoring of tumor blood flow during PDT that adjusts light delivery in an automated fashion. The results suggest that the ability to measure and modulate tumor physiologic properties can provide a mean for personalized delivery of PDT treatment.

Photochemical Relaxation Pathways in O6-Methylguanosine and S6-Methylthioinosine Upon Absorption of Ultraviolet-B Radiation

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O6-methylguanosine and S6-methylthioinosine are byproducts resulting from the interaction of exogenous and endogenous alkylating agents with DNA and from enzymatic reactions of sulfur-substituted prodrugs in cells, respectively. Their photochemistry has not been investigated and it is unknown whether absorption of ultraviolet-B radiation by these byproducts may pose any threat to the integrity of DNA. In order to start filling this gap, steady-state absorption and emission spectroscopies and transient absorption spectroscopy were performed for both O6-methylguanosine and S6-methylthioinosine in aqueous solution and in acetonitrile. The experimental results were complemented with ground- and excited-state calculations. Possible photochemical relaxation pathways are proposed and the results are compared with those reported in the literature for the guanine and 6-thiopurine monomers. It is shown that O6-methylation red-shifts the absorption spectrum of guanosine and decrease the internal conversion rate to the ground state in aqueous solution and in acetonitrile by ~40-fold and ~10-fold, respectively. The decrease in the internal conversion rate to the ground state may increase the probability of DNA damage. S6-methylation blue-shifts the absorption spectrum of 6-thiopurine and decreases the intersystem crossing rate to populate the lowest-energy triplet state. The population of the triplet state in S6-methylthioinosine suggests that ultraviolet-B radiation may lead to oxidatively-generated cellular damage, as has been shown for the thiopurine prodrugs.

Laser-assisted vascular anastomosis: comparison of photothermal vs. photochemical tissue bonding

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Introduction: The potential advantage of photothermal-based laser-assisted vascular anastomosis (LAVA), over mechanical and non-mechanical anastomosis, has been hampered by low welding strength and extensive thermal damage. In light of the latter concern, a photochemical-based bonding might be a better solution. However, the anastomosis strength remains a concern. This study investigated: (1) the feasibility of ex vivo sutureless end-to-end LAVA in medium-sized arteries and (2) feasibility of photochemical aortic bonding (PAB) using a combination of chitosan and Rose Bengal (RB) dye. Materials and methods: In the 1st substudy a 1-cm transverse incision was made in porcine carotid artery segments. PLGA or PCL scaffolds were drenched in semi-solid (48% bovine serum albumin /0.5% methylene blue /3% hydroxypropylmethylcellulos) solder or semi-solid solder containing 0.38% genipin, and wrapped around the entire circumference of the coaptation. The anastomoses were ssLAVAed with a diode laser (1.3W/cm2 for 25s/spot). The integrity of PCL and PLGA ssLAVAed arteries were compared under 24-h pulsatile pressure conditions (120/80mmHg, 100mL/min, 80bpm, 38ºC). The 2nd substudy compared breaking strength of ssLAVA (PCL-BSA-MB) and PAB (Chitosan-RB). Results: 8/10 PLGA ssLAVA remained intact under the 24-h pulsatile pressure test, compared to 3/10 of PCL group. In an acute experiment, PLGA ssLAVA obtained the highest bursting pressure of 923±56mmHg. However, histological analysis showed extensive thermal damage. PAB (Chi-RB) obtained comparable breaking strength to the PCL ssLAVA group. Conclusions: Although anastomoses made by PLGA ssLAVA could withstand the experimental stress conditions, the extensive thermal damage inflicted renders clinical application challenging. The comparable repair strength and absence of thermal damage of PAB suggest the possibility to replace photothermal-based LAVA.

Proteomic and Transcriptional Profiling of Molecular Stress Response Pathways Underlying the Pronounced UV-resilience of Human Dermal Fibroblasts

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Solar ultraviolet (UV) radiation is an established causative factor in skin photodamage and carcinogenesis. Previously, our laboratory has observed that cultured human dermal fibroblasts display a pronounced resilience to doses of full spectrum solar UV that cause apoptosis in primary epidermal keratinocytes. In this pilot study, we have pursued the proteomic and transcriptional identification of stress response pathways that determine the extraordinary UV-resilience displayed by dermal fibroblasts. First, the differential cytotoxicity of full spectrum solar simulated light was substantiated by comparing the dose response relationship of UV-induced cell death employing flow cytometric analysis of annexinV/PI-stained human Hs27 dermal fibroblasts and epidermal keratinocytes (24 h after solar simulated UV; up to 6.9 J/cm2 UVA + 360 mJ/cm2 UVB). Next, changes at the proteome level were analyzed 6 h after UV exposure employing Cy3/Cy5-fluorescent two-dimensional 'Difference Gel Electrophoresis' (DIGE), followed by mass spectrometric identification of differentially expressed proteins. UV-modulation of stress response gene expression was profiled using the Human Stress and Toxicity PathwayFinderTM RT2 PCR array technology confirming upregulated heat shock response gene expression (HSPA1A, HSPA6, HMOX1) that occurred together with early p38 MAPK-dependent dual Hsp27 phosphorylation (Ser15/Ser78) and UPR signaling (DDIT3; p-eIF2Î±). Consistent with the established role of p38-induced Hsp27 phosphorylation in survival and maintenance of redox homeostasis, we observed that pharmacological p38 inhibition enhanced UV-induced oxidative stress and cytotoxicity in Hs27 fibroblasts. Taken together, these data indicate that early activation of the heat shock stress

response determines the UV-resilience of human dermal fibroblasts.

Rose Bengal Depth in Human Donor Cornea after Rose Bengal Photodynamic Antimicrobial Therapy

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Infectious Keratitis (corneal infection) is a common ocular emergency; there are many cases in which antimicrobial drugs have limited success. Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT) has proven to be an effective therapy for treating resistant microbial keratitis both in vitro and clinically. Because of the lack of regeneration of the corneal endothelial cell layer, it is vital to evaluate if Rose Bengal (the photosensitizing agent) reaches the corneal endothelium during RB-PDAT. Similarly, to evaluate effectiveness of the therapy, it is important to demonstrate singlet oxygen (1O2) production in the cornea during RB-PDAT (1O2 is the primary antimicrobial agent of PDAT). Four human corneal grafts were used in the study: one positive control (fully immersed in Rose Bengal), two treated corneas (RB-PDAT), one negative control (sham PDAT). DAPI (a DNA stain) was used as counter stain and CellRox was used as a reactive oxygen species (ROS) stain. Frozen sections (10µm) were cut and examined under confocal fluorescence microscopy. Rose Bengal penetration into the cornea was variable. Uncorrected Rose Bengal depth ranged from 180 - 640µm, with a mean penetration depth of 300µm (±144µm). Correcting to an average cornea thickness of 550µm, Rose Bengal depth ranged from 57.6 - 238µm, with a mean penetration depth of 142.1µm (±75.7µm). Cornea thickness as measured by the confocal microscope ranged from 810µm - 1960µm, with average thickness of 1370µm (±362µm). The ROS stain distribution colocalized with the distribution of Rose Bengal in both treated corneas, and to a lesser degree, in the positive control. No ROS stain signal was detected in the negative control, confirming that Rose Bengal is necessary for ROS generation. Given these results, it appears that ROS are generated where Rose Bengal is present and that the Rose Bengal does not reach the corneal endothelium.

Age-related Macular Degeneration: Defining Toxic Wavelengths In The Solar Spectrum Using Cell Models

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Blue light is a risk factor in in age-related macular degeneration (AMD). Disease prevention requires to precisely define the toxic wavelengths. In AMD, although cone photoreceptor degeneration is causing the loss of vision, the dysfunction of the retinal pigment epithelium (RPE) is often considered as the etiology of the disease. With aging, the RPE accumulates lipofuscin containing derivatives of the visual pigment such as A2E, a known photosensitizer. AMD has thus often be modeled by A2E-loaded RPE cells, which are damaged by blue light. To further define the toxic wavelengths in AMD, we have generated a light box system to expose cells to 10nm wavelength bands with light intensities normalized to the light spectrum reaching the retina. We first screened for toxic wavelengths on A2E-loaded RPE cells and are now investigating the light toxicity on isolated cone photoreceptors. In A2E-loaded RPE cells, we found that the 415-455 nm blue range is the most toxic band for A2E-loaded RPE cells as indicated by the loss of cell viability and the increase in apoptosis. These wavelengths were associated with the production of both hydrogen peroxide (H2O2) and superoxide anion (O2ï‚Ÿ-). Filters removing only 20% blue-violet were sufficient to decrease cell apoptosis up to 40%. Finally, when cone photoreceptors were isolated from the porcine retina and exposed to light, we also observed a phototoxicity. In conclusion, using A2E-loaded RPE cells, we have defined the 415-455 nm blue-violet light, within the solar spectrum reaching the retina, to be the spectral band that generates the highest phototoxicity. These studies provide new evidence for light toxicity on retinal cells supporting the need for filter removing the blue-violet range (415-455nm) in AMD patients, a strategy without major concerns on color vision.

Conjugation Of Photoimmunoconjugates To Nanoparticles Enhances Theranostic Efficacy In Tumor Cells

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Photosensitizer-antibody conjugates have been studied for the past three decades as a therapeutic and diagnostic modality for various types of cancer. Their ability to selectively target cancer cells makes photoimmunoconjugates (PIC) a promising approach for fluorescence imaging and photodynamic therapy (PDT). However, the theranostic efficacy of these systems is limited by the low photosensitizer to antibody ratio required to maintain specificity, and the finite number of cognate receptors on tumor cells. In an effort to address these shortcomings, our team engineered a nanotechnology platform to enhance the delivery and efficacy of photoimmunoconjugates. We show that Benzophorphyrin Derivative (BPD)-Cetuximab PICs can be easily and efficiently conjugated to FKR-560 dye-containing polymeric nanoparticles using copper-free click chemistry, an approach we believe can be easily adapted to other PIC-nanoparticle (PIC-NP) systems. These nanoconstructs retain their tumor cell selectivity and enhance PDT efficacy by facilitating the uptake of photosensitizer in Epidermal Growth Factor Receptor (EGFR) overexpressing glioma and ovarian cancer cell lines. In a xenograft model of OvCar-5 tumors, we further demonstrate the improved delivery of photosensitizer in vivo using this nanoplatform, resulting in acute tumor reduction not seen with free PIC. We attribute this phenomenon to the "Carrier Effect", where a single PIC-EGFR binding event results in endocytosis of all nanoparticle conjugated PIC, greatly increasing intracellular photosensitizer accumulation and PDT efficacy.

The aryl hydrocarbon receptor induces the proteolysis of the tumor suppressor p27KIP1 in UVB-exposed keratinocytes

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Chronic exposure to UVB radiation is the most important risk factor for the development of cutaneous squamous cell carcinoma. Previously we found that an activation of the aryl hydrocarbon receptor (AhR) attenuates the removal of highly mutagenic DNA photoproducts (CPDs) in UVB-irradiated keratinocytes (KC) by inhibiting nucleotide excision repair (NER). Subsequent transient RNAi and overexpression studies revealed that a modulation of the tumor suppressor protein p27KIP1 (p27) is critically involved in the AhR-dependent repression of NER. In the current project, we therefore investigated the molecular mechanism by which the AhR controls the p27 level in KC.Specifically, we found that treatment of HaCaT KC with the AhR antagonist MNF results in an stabilization of p27 whereas AhR activation by benzo(a)pyrene reduces the protein level. These AhR dependent effects were not visible on mRNA level. Furthermore, treatment with the proteasome inhibitor MG 132 reversed the observed changes on p27 protein level upon AhR modulation. Subsequent Western-Blot analysis revealed an involvement of the EGFR and downstream PI3K/AKT signal transduction in phosphorylating and thereby reducing p27 protein level in response to AhR activation. Accordingly chemical inhibition of PI3K and EGFR in UVB exposed KC increased p27 protein level.Beside its beneficial effect on NER, both AhR inhibition and p27 overexpression also sensitized KC to UVB-induced apoptosis. Further mechanistic studies revealed that this was probably due to an inadequate response of the KC to DNA double strand breaks (DSB), which might occur when remaining CPD-positive cells start to divide. A reduced protein expression of checkpoint kinase-1 suggests an abrogation of homologous recombination repair in AhR-compromised KC. We conclude that AhR

inhibition stabilizes p27 protein level resulting in an enhanced elimination of damaged KC which may contribute to the prevention of UVB-induced skin carcinogenesis.

Dithionated Nucleobases as Effective Photodynamic Agents Against Human Epidermoid Carcinoma Cells

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Sulfur-substituted nucleobases (i.e. thiobases) are a prospective class of compounds for clinical and cosmetic topical phototherapies. Recent investigations of several thiobases have revealed the ultrafast and efficient population of reactive triplet states upon UVA irradiation and the subsequent generation of singlet oxygen in high yield. In this presentation, we examine the photosensitizing activities of three of the most promising thiobase derivatives discovered to date, 2,4-dithiothymine, 2,4-dithiouracil, and 2,6 dithiopurine. These derivatives are shown to decrease the proliferation of human epidermoid carcinoma cells by up to 63% in vitro, only upon activation with a low dose of UVA radiation (5 J/cm2). Interestingly, the generation of reactive oxygen species plays a minor role in the mode of action, suggesting these dithiobases may be effective within oxygen-deficient environments. The correlation we have found between in vitro photodynamic efficacy and solution-based excited-state measurements will be discussed.

Light-Activated Anticancer Activity of Ruthenium(II) Polypyridyl Complexes Incorporating the 1,4,5,8-Tetraazaphenanthrene (TAP) Ligand

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Ruthenium(II) polypyridyl complexes are a promising new class of drug molecule for light-activated anticancer therapies, as highlighted by the recent entry of the first such complex into clinical trials for the treatment bladder cancer by photodynamic therapy (PDT, NCT03053635).As PDT relies on the generation of reactive oxygen species to elicit photo-destruction of a target tissue, its dependence on the presence of oxygen at the disease site can be a considerable limitation to the efficacy of the therapy in hypoxic environments, which can be either naturally present in tumors or generated during the PDT treatment. By varying the nature of the ligands coordinating to the Ru(II) metal centre, the excited-state properties of Ru(II) polypyridyl complexes can be tuned, not only to allow optimal singlet oxygen generation for classical PDT, but also to impart additional, oxygen-independent, modes of action to these complexes, thereby avoiding such a limitation. Through the incorporation of two ancillary 1,4,5,8-tetraazaphenanthrene (TAP) ligands, we have synthesised complexes capable of eliciting photodamage to biomolecules through the generation of reactive oxygen species, as well as directly photo-oxidizing specific biomolecules, such as the guanine nucleobase, thereby providing an oxygen-independent mechanism to their photoactivity.This talk will highlight our investigations into the factors governing this photo-oxidation reaction with DNA and give an overview of the light-activated anticancer activity of these complexes from in vitro studies in cancer cell lines.

Superhydrophobic Photosensitizers: Airborne 1O2 Killing of a In-vitro Oral Biofilm at the Plastron Interface

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Singlet oxygen is a potent agent for the selective killing of a wide range of harmful cells. Limitations of current singlet oxygen delivery methods include: the need for direct contact of photosensitizer molecules with tissue; the short (3.5 µs) lifetime of the excited state in contact with water; the strong optical absorption of the photosensitizer, which limits penetration depth; and hypoxic environments, such as those found in deep periodontal pockets, that restrict the concentration of available oxygen. In this article, we describe a novel superhydrophobic singlet oxygen delivery device for the selective inactivation of bacterial biofilms. This treatment approach relies on transport of singlet oxygen from sensitizer particle surfaces, across the plastron, to the biofilm thereby preventing direct contact between sensitizer molecules and the organism. This approach precludes limitations due to oxygen diffusion, optical absorption, tissue sensitization and potential toxicity. The superhydrophobic surface was synthesized by partially embedding sensitizing particles on polydimethylsiloxane printed posts, capped with silica nanoparticles to prevent direct contact of sensitizer with the bacterial biofilm. Gaseous singlet oxygen is generated on sensitizer particle surfaces in the plastron of the superhydrophobic surface upon irradiation with visible light, and transported to inactivate Porphyromonas gingivalis biofilms on hydroxyapatite discs as monitored by colony counting and LIVE/DEAD staining. The biofilm killing efficiency correlated to the amount of singlet oxygen detected in a separate reaction with 9,10-anthracene dipropionate dianion. The work also compared two sensitizing particle types: a silicon phthalocyanine sol-gel (Si-Pc), and a chlorin e6 derivative covalently bound to fluorinated silica, the former resulted in higher biofilm killing and a 2.4 X higher concentration of trapped singlet oxygen. Thresholds for light fluence and singlet oxygen concentration were determined for complete biofilm inactivation (>5 log killing).

Autophagy pathways regulate UV-induced skin tumorigenesis through promoting protumorigenic inflammatory microenvironment

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Tumorigenesis requires not only the accumulation of genetic and epigenetic changes in epithelial cells, but also the evolution of a protumorigenic inflammatory microenvironment. However, the cellular mechanism connecting UV-induced inflammation and skin tumorigenesis is not well understood. One of the key regulators for inflammation is macroautophagy (hereafter autophagy), a catabolic process involving lysosomal turnover of proteins and organelles to maintain cellular homeostasis. Here we show that autophagy is induced in the epidermis by UV irradiation and epidermis-specific deletion of the essential autophagy gene ATG7 protected against UV-induced inflammation and skin tumorigenesis in mice through regulating COX-2 signaling. ATG7 regulated UV-induced cytokine expression and secretion, and promoted COX-2 expression through both an autonomous mechanism and a non-cell autonomous mechanism. Moreover, ATG7 loss altered energy metabolism and caused accumulation of endoplasmic reticulum (ER) and reduction of ER stress. Inducing ER stress and inhibiting calcium influx into the ER reverses the inflammation and tumorigenesis phenotype in mice with epidermal ATG7 deletion. In ATG7 knockdown keratinocytes, thapsigargin inhibited CRTC1 phosphorylation and increased COX-2 expression through calcium signaling. Overall, our findings demonstrate a crucial role of the autophagy pathways in UV-induced protumorigenic inflammatory microenvironment and skin tumorigenesis.

Opsins in action-light directed subcellular signaling and cell behaviors

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Asymmetric signaling-induced cell behaviors, including cell migration, play integral roles in biological processes such as immune-system function and cancer. Dearth of methods to control signaling in confined regions of single

cells hinders the ability to simulate in-vivo conditions experimentally. We developed optogenetic approaches to activate GPCR signaling in subcellular regions with precise spatiotemporal control. Using opsin-based optical triggers and fluorescence sensors, and employing distinct wavelengths, we control and image single-cell signaling and behaviors. We created a library of opsins to control all major GPCR pathways; Gi, Gs, and Gq. Using confined opsin activation-directed macrophage migration, we decoded the pathway that controls trailing-edge retraction of migratory cells. Using the temporal accuracy in opsin activation, we identified two G protein gamma subtypes that are crucial for regulating G protein betagamma signaling. In conclusion, our subcellular optogenetic approaches can have wide applicability in many disciplines experimentally as well as therapeutically.

Photosensitized Formation Of DNA Lesions

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During the last decade significant progress regarding the mechanisms of photosensitization reactions mediated formation of DNA lesions have been made. In this respect, the presentation will deal with for formation of DNA adducts with lysine and polyamines generated following one-electron oxidation in dsDNA exposed to type I photosensitizers. Formation of these lesions is explained by the nucleophilic addition of amino groups onto the C8 of guanine radical cation or rather its deprotonated form. Such a reaction is in competition with water addition that generates 8-oxodGuo. The proposed mechanism has been confirmed using theoretical approaches. In addition theoretical approaches have been used to revisit the mechanism of 8-oxodGuo formation upon reaction of DNA with singlet oxygen produced by type II photosensitizers. The newly proposed mechanism that implies the formation of a zwitterionic species (stabilized by the low ionization potential of guanine) explains why reaction of singlet oxygen is limited to guanine. Finally, the above obtained results have allowed us to delineate the mechanism of formation of 8-oxodGuo upon exposure of dsDNA to UVB or UVC light (in the absence of any photosensitizer). In contrast to previously publish works, our experiments unambiguously confirmed that UV-induced 8-oxodGuo formation (that remains low compared to pyrimidine dimers) is mediated by a one-electron oxidation mechanism and not singlet oxygen.

Potential Clinical Applications of Protein Photocrosslinking

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Light-activated protein crosslinking provides a number of interesting effects in tissue that lead to a myriad of potential clinical applications in surgery and medicine. Visible light and biocompatible photosensitizing dyes can be used under non-toxic conditions to modify the extracellular matrix of a variety of tissues leading to various chemical, physical and biological changes. For example, crosslinking imparts an increased strength and stiffness in tissues and can also be used for wound closure and in conjunction with biomaterials to augment and improve wound repair. Advantages over conventional methods include reduced inflammation and scarring and an improved wound healing response. Photochemical protein crosslinking has also been utilized in tissue engineering to modify matrices for optimal cartilage regeneration. This presentation will focus on the mechanisms involved using a variety of illustrative applications in eye, skin, blood vessel, nerve, bowel, cartilage and tendon.

SSR-induced epidermal DNA damage in humans across skin types I-VI

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Sun exposure recommendations are to limit personal exposure to beneath sunburn level, to minimise health risk whilst gaining benefit. However, it is unknown whether sub-sunburn exposures can gain vitamin D whilst avoiding epidermal DNA damage, or how this is influenced by skin type. Initially, the same low UVR dose (1.3 SED; 5%UVB, 95% UVA) was given to volunteers of skin type (ST)II and V in a repeated dose UVR study, mimicking a summer's sunlight exposures. They received UVR 3x weekly for 6 weeks in an irradiation cabinet, wearing casual clothing to expose ~35% skin surface. Considerably more epidermal CPD post-UVR occurred in STII than STV, but CPD did not accumulate over the course. STII volunteers became vitamin D sufficient, but STV did not. Next, a dose-response study was performed in humans through ST I-VI, i.e. with lightest to darkest skin, who were given a dose-series of UVR related to their individual sunburn threshold. Following single doses of 20-80% of their MED, significant UVR dose-responses were seen for whole epidermal CPD and 25(OH)D, with CPD and 25(OH)D produced after only 0.2 MED. Thus vitamin D could not be gained without epidermal DNA damage. Moreover, these fractional MED UVR doses generated equivalent levels of whole epidermal CPD and 25(OH)D independent of skin type. Pivotally, a DNA damage gradient was discovered, CPD formation increasing from deep to superficial epidermis, with the gradient strongly and significantly correlating with skin darkness. This ranged from darkest skin, where high CPD levels occurred superficially and none in the germinative basal layer, through to lightest skin, where CPD were induced evenly across the epidermal depth. Darker skin people gain vitamin D without damaging their basal cell layer, and can utilise sub-sunburn UVR exposure to enhance vitamin D with minimal skin cancer risk. Basal cell damage occurs at exquisitely low UVR levels in lighter skin people, explaining their high skin cancer incidence.

Photodynamic Therapy-based Combinations to Target Resistance in Ovarian Cancer

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It is increasingly evident that the most effective treatments will involve cooperative regimens that target multiple non-overlapping pathways, while minimizing systemic toxicities. Photodynamic therapy (PDT) can improve the therapeutic index of traditional and emerging treatments by exploiting photochemically-triggered cytotoxic mechanisms that damage sub-cellular organelles, prime tumor cells, disrupt stromal compartments, and enhance drug delivery. This presentation describes key principles that guide the development of PDT-based therapeutic regimens. A specific focus is on enhancing the efficacy of platinum-based chemotherapies and camptothecin analogues, which are commonly used to manage several cancers (including ovarian cancer), but suffer from significant toxicities, poor drug penetration, and resistance. PDT overcomes these barriers to efficacy, due to its distinct cytotoxic mechanisms and non-overlapping toxicities. Capturing these attributes in rationally-designed combinations leads to synergistic tumor reduction in 3D models, and durable tumor control in orthotopic xenograft mouse models. The mechanistic basis of these improved outcomes and recent results will be presented.

Photochemistry of Supramolecular Complexes between Cucurbit[n]urils and Photosensitizers

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Improving the overall performance of photoactive drugs used in Photodynamic therapy (PDT) continues to be an essential goal in this area of research. There are continued efforts from several groups around the world to develop new

PDT drugs.1 Our group has been interested in using a supramolecular strategy to take advantage of the encapsulation properties of a family of macrocycles called "Cucurbit[n]urils" and improve the photoactivity of well-known molecules.Cucurbit[n]urils (CB[n], n = 5-8, 10, 13, 15) are a family of molecular containers that show strong potential to improve drug delivery and protect the drugs from degradation. Moreover, drug delivery is easily achieved by competitive displacement with biomolecules or other drugs. Following pioneering work by J. C. Scaiano and Hermenegildo Garcia on the encapsulation of methylene blue (M. González-Bejar et al 2009, Langmuir, 25 10490), our group has investigated the photochemistry of supramolecular complexes between CB[n]s and well-known photoactive molecules. Such complexes show interesting properties for potential applications in PDT, e.g. enhanced singlet oxygen generation, enhanced fluorescence, protection from enzymatic degradation, decreased photobleaching, permeability through the cell membrane, and control on electron-transfer reactions and singlet oxygen generation depending on the type of macrocycle (J. Robinson-Duggon et al 2018, Isr. J. Chem., 10.1002/ijch.201700093). Some recent applications such as a singlet oxygen reversible switch (J. Robinson-Duggon et al 2017, J. Phys. Chem. C, 121, 21782) will be discussed.The authors thanks CONICYT for the financial support through their FONDECYT research program (Grant Nº1160443).

Step Forward, Step Back: Evolution of Spectral Tuning in Cyanobacteriochromes

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Cyanobacteriochromes (CBCRs) are diverse cyanobacterial photoreceptors. Like the distantly related phytochromes, CBCRs use 15,16-photoisomerization of a linear tetrapyrrole (bilin) to reversibly photoconvert between two photostates having distinct spectral and biochemical properties. However, CBCRs differ from phytochromes in several ways. CBCRs require only a single domain (<200 amino acids) for auto-assembly with bilin and for full, reversible photoconversion. Moreover, CBCRs are associated with spectral responses ranging from the near-ultraviolet to the near-infrared (320-750 nm), providing some cyanobacteria with complete coverage of the spectrum suitable for oxygenic photosynthesis using a single family of photoreceptors. Bilin chromophores do not themselves display such spectral diversity, and individual CBCR photocycles span much narrower bands. Therefore, CBCRs use spectral tuning mechanisms to achieve this diversity. Ongoing increases in available cyanobacterial genomes allow us to examine the evolution of these tuning mechanisms during the transition from phytochromes to CBCRs, identifying early-diverging sensors as detecting blue, green, or orange light. Subsequent evolution of additional tuning mechanisms allowed CBCRs to expand the active range of the spectrum. Remarkably, tuning mechanisms have been gained and lost repeatedly during CBCR evolution, including mechanisms for detecting light at both short (<480 nm) and long (>680 nm) wavelengths.

Topical NRF2 Activation for Epidermal Photoprotection and Prevention of Environmental Stress-induced Hair Graying

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Exposure to solar ultraviolet (UV) radiation is a causative factor in acute skin photodamage, chronic photoaging, and photocarcinogenesis. The redox-sensitive transcription factor NRF2 (nuclear factor-E2-related factor 2) has now been identified as a master regulator of skin barrier function, cellular defense mechanisms against environmental stress, and solar radiation response. NRF2 in epidermal keratinocytes and melanocytes can be activated using natural chemopreventive compounds such as the apocarotenoid bixin, an FDA-approved food additive and cosmetic ingredient from the seeds of the achiote tree (Bixa orellana). Here, we explored the topical use of bixin for NRF2-dependent skin photoprotection in two genetically modified mouse models. We observed that a bixin formulation optimized for topical NRF2 activation suppresses acute UV-induced photodamage in Nrf2+/+ but not Nrf2-/- SKH1 mice, a photoprotective effect indicated by reduced epidermal hyperproliferation and oxidative DNA damage. Moreover, topical bixin suppresses PUVA (psoralen+UVA)-induced hair graying observable in Nrf2+/+ but not Nrf2-/- C57BL/6J mice. These data suggest that topical NRF2 activation may represent a novel strategy for human skin photoprotection and prevention of environmental stress-induced hair graying.

The aryl hydrocarbon receptor protects keratinocytes against the UVA phototoxicity of 6-formylindolo[3,2-b] carbazole, an AHR ligand formed after UVB irradiation

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The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that is well known to mediate the toxicity of dioxins and related environmental chemicals. In epidermal keratinocytes (KC), AHR is activated by the tryptophan photoproduct 6-formylindolo[3,2-b]carbazole (FICZ), which is intracellularly generated in response to UVB-irradiation and induces the expression of pro-inflammatory enzymes, immunosuppression and anti-apoptosis. Thus, AHR inhibition is widely regarded as a suitable strategy to protect our skin against the detrimental effects of UVB radiation. Interestingly, FICZ has been recently identified as a potent UVA photosensitizer and is primarily metabolized by the AHR-dependent and UVB-inducible enzyme cytochrome P450 (CYP) 1A1.Therefore, we now asked if AHR antagonism still exerts beneficial effects in KC irradiated with UVA alone or UVB/UVA in combination. We found that the FICZ concentrations necessary to enhance UVA-induced apoptosis are ~10-fold higher than those required for AHR-dependent induction of CYP1A1 expression, which were in the range of 1- 10 nM. Hence, the FICZ level required to maintain basal CYP1A1 expression in KC is clearly below the UVA-sensitizing concentration. However, pre-treatment of KC with higher FICZ concentrations resulted in a dose-dependent sensitization to UVA-induced apoptosis and was associated with a more pronounced generation of oxidative stress. In AHR-silenced KC, the FICZ-mediated increase in UVA-induced apoptosis was significantly stronger. In contrast, in AHR-proficient KC, an induction of CYP1A1 expression by chemical agonists prior to UVA irradiation prevented the FICZ/UVA-induced apoptosis. Moreover, the induction of the NRF2-regulated gene hemoxgenase-1 was reduced in AHR-deficient KC pretreated with FICZ and irradiated with UVA. Our results indicate that AHR activation and thus CYP1A1 induction in KC in fact may prevent an accumulation of FICZ and associated UVA-induced photoxicity.

The Effect of All-trans-Retinal on Susceptibility of the Retina to Photodamage Induced by Visible Light

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Exposure of the retina to visible light leads to visual perception but also to a release of photoreactive all-trans-retinal (atRal). To determine the effects of atRal on modulating the susceptibility of the retina to light-induced injury we used C57B6 mice (WT) and knockout mice with delayed clearance of atRal: Abca4(-/-) (AKO), Rdh8(-/-) (RKO) and Abca4(-/-)Rhd8(-/-) (dKO). Dark-adapted mice were exposed for up to 30 min to 16 klx white fluorescent light (48 mW/cm2; WL) or light >460 nm providing similar fluxes of light absorbed by rhodopsin (33 klx; 79 mW/cm2; YL). Time courses of atRal clearance during light exposures were determined by HPLC analyses of retinoids extracted from eyes. Light-induced retinal injury was assessed by SLO-AF and OCT. 30 min exposure to WL caused no damage to WT

retina, partial loss of photoreceptors in the superior retina of AKO, and total loss of photoreceptors in the central retina in RKO and dKO. YW caused some photoreceptor loss in the superior retina of only in RKO and dKO. Retinal injury strongly correlated with the fluxes of absorbed light by atRal before its removal. To further test this hypothesis we exposed WT mice to blue LED enabling absorption of similar flux of light by atRal as that causing total damage to photoreceptors in RKO and dKO mice. This exposure to blue LED caused similar damage to WT photoreceptors as seen in RKO and dKO. Pre-exposure of WT to WL allowing for removal of >90% atRal totally protected from injury induced by blue LED. The susceptibility of RKO and dKO retinas to photodamage was also substantially reduced when WL was applied after 2 hour adaptation to ambient room light. Our results demonstrate that photoexcitation of atRal plays the major role in increasing the susceptibility of the retina to photodamage. Pre-exposure of the retina to non-harmful levels of light sufficient for clearance of atRal immediately before exposure to damaging light effectively prevents retinal injury.

Circadian Clock Regulates Melanin Pigmentation in Mouse and Human

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Solar light is the primary source of energy on Earth, which affects all photosensitive organisms including humans. The diurnal exposure of UV-B radiation from the Sun is responsible for various skin-related diseases including melanoma and non-melanoma skin cancers in humans. Evolutionarily, our skin has developed various protective biological mechanisms against the harmful effects of UV-B, the majority are influenced by the circadian clock. The skin clock is known to be involved in various important cellular pathways including cell cycle, metabolism, cell survival, and DNA repair by controlling the expression of specific target genes known as the clock-controlled genes (CCGs). In this study, we show that microphthalmia-associated transcription factor (MITF) a rate-limiting gene in melanin pigmentation is a novel regulatory target of the clock. We used human melanocytes and melanoma cells, as well as mouse skin tissues to establish the transcriptional regulation of MITF by the clock. We also show that BMAL1 is a positive regulator of MITF and upregulates melanin (UV-B protectant) levels both in human cells and mouse skin tissues. Further, we found BMAL1 protects human cells against solar UV-B exposure. Our experiments also show that the overexpression of BMAL1 improves cell survival by upregulating important DNA repair proteins through MITF regulation. Finally, we confirmed the above genetic findings pharmacologically using a RevErb-alpha agonist. Hence, understanding a mechanistic role of the circadian clock in melanogenesis and cell survival through MITF will help in the prevention of solar UV-B mediated genomic instability, photoaging, and skin carcinogenesis.

Photoreactivity of natural melanin pigments

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Melanin pigments are typically viewed as natural sunscreens and antioxidant agents protecting pigmented tissues against adverse reactions induced by solar radiation. However, photoprective efficiency of different natural melanins may differ. Indeed, while the brown-black eumelanin is known for its photoprotective properties, the yellow-reddish pheomelanin was found to be less protective and even phototoxic. Recently, it was shown that melanin can photogenerate singlet oxygen with pheomelanin being a much more efficient generator of this reactive oxygen species than eumelanin. Although photoreactivity of synthetic melanin models is well documented, relatively little is known of photochemical properties of natural melanin pigments. In this work we examined photoreactivity of melanin obtained from human hair of different color. Employing an array of advances biophysical techniques such as electron paramagnetic resonance (EPR) spectroscopy, EPR-oximetry, EPR-spin trapping and time-resolved singlet oxygen phosphorescence, we have determined action spectra and quantum yield of singlet oxygen photogeneration by the studied melanins. Our work demonstrate that natural melanins under certain conditions can be much more efficient generators of singlet oxygen than their synthetic models. Acknowledgements This work was supported by grant from the National Science Centre of Poland (grant no. SONATA-2015/19/D/ST4/01964). The Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University is a partner of the Leading National Research Center (KNOW).

Novel Photodegradation Mechanisms of Proteins Via Side Chain Cleavage of Aromatic Amino Acids

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Proteins are subject to photo-degradation in vivo and in vitro, where chemical modifications can lead to changes of sequence, conformation, activity, protein-protein interactions, and turnover. Especially, in vitro photo-degradation reactions may have significant consequences for the manufacturing and development of stable protein pharmaceuticals. Further, such in vitro photo-degradation reactions of protein pharmaceuticals can generate neo-epitopes, which may cause immunogenicity in patients. For a mechanistic understanding of photo-degradation-induced immunogenicity, a comprehensive characterization of protein photo-degradation products is mandatory. En route to such comprehensive characterization, we have characterized light-induced side-chain fragmentation mechanisms of Trp and Tyr in various proteins including monoclonal antibodies. These side-chain fragmentation reactions are likely initiated by the formation of aromatic radical cations through photoionization, followed by cleavage of the respective C(alpha)-C(beta) bonds. These side chain cleavages do not occur randomly but target specific Trp and Tyr residues. Mechanistic details of these reactions have been evaluated by measurements of product solvent isotope effects. Importantly, the products of side chain cleavage represent strong electrophiles, which can add to nucleophilic amino acid side chains, generating additional chemical modifications.

Mechanisms and products of the photosensitization of amino acids and nucleotides by pterins

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The biological and medical importance of photosensitized reactions is mostly related to their participation in processes involved in the development of skin cancer. Pterins are a family of heterocyclic compounds widespread in living systems. These biomolecules are photochemically active and, under UV-A excitation (320–400 nm), can fluoresce, produce organic radicals and reactive oxygen species, such as singlet oxygen, and undergo photooxidation reactions to generate various products. Our group has investigated for more than 10 years, the degradation of amino acids and nucleotides photosensitized by pterins under UV-A irradiation. Our studies included the interaction of singlet and triplet excited states of pterins with different substrates, radical species detection and identification of products under different experimental conditions. On the basis of these data, we present in this work a summary of the mechanisms involved in the pterin-photosensitized degradation of amino acids and nucleotides in aqueous solutions. We also discuss the products formed and the corresponding damage to DNA and proteins. Most of the processes are initiated by an electron transfer from the substrate to the triplet excited state of the photosensitizer (type I mechanism).The processes undergone by the radical cation (or the corresponding neutral radical formed after deprotonation) include hydration, reaction with oxygen, reaction with the superoxide anion, dimerization and reaction with the radical anion of the sensitizer. The singlet oxygen mediated oxidation may

also occur (type II mechanism). The relative contribution of the different pathways depends on the experimental conditions and on the nature of the substrate.

Study Design: A Randomized Multi-Center Phase I/II Study Comparing Porfimer Sodium Mediated Interstitial Photodynamic Therapy Followed by Standard of Care (SoC) versus SoC alone in Patients with Locally Advanced or Recurrent Head and Neck Cancer.

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Patients with locally advanced head and neck cancer (HNC) have dire prognosis, with 5% potential cure and 10-36% local control with clinically approve standard of care (SoC) therapy. Adjuvant photodynamic therapy (PDT) has shown promise in improving local control and overall survival in patients with other types of locally advanced tumors refractory to SoC therapy. Our ongoing preclinical study demonstrated that finite element method (FEM) based treatment planning could be used to guide interstitial PDT (I-PDT) with porfimer sodium (Photofrin®) to yield 70-90% cure in an animal model of locally advanced cancer. The FEM has been used to safely guide compassionate care of I-PDT for patients with HNC. We hypothesize that in comparison to SoC alone, Photofrin® mediated I-PDT, together with SoC therapy, will be safe and will improve tumor response in patients with locally advanced or recurrent HNC that failed radiation therapy. To test this hypothesis we propose to conduct a randomized multi-center phase I/II trial to test the safety and efficacy of I-PDT with Photofrin with SoC versus SoC alone. This study will include patients with locally advanced or recurrent HNC who will receive chemotherapy and/or targeted agents, and/or immunotherapy. The primary objective of the Phase I will be to determine the scheduling of I-PDT and SoC by evaluating safety, in up to 12 participants. In Phase II, efficacy will be determined by comparing the objective tumor response rates between the experimental treatment groups of I-PDT + SoC and SoC alone over 24 months, in up to 70 participants. In this talk we will present the study design and the FEM treatment planning and dosimetry to guide the I-PDT. Acknowledgements: This work was supported in part by NCI/NIH PO1 CA55791 (Gollnick) and R01CA193610 (Shafirstein). We thank Concordia Laboratories Inc. for providing the Photofrin®. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or Roswell Park.

Phosphorylation Of Xeroderma Pigmentosum Group C Regulates Ultraviolet-Induced DNA Damage Repair

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Nucleotide excision repair (NER) is the most versatile DNA repair system that removes bulky DNA damage induced by various endogenous and exogenous factors, including UV radiation. Defects in NER can lead to the xeroderma pigmentosum (XP) syndrome, mainly characterized by increased carcinogenesis in the skin. The function of NER factors, including xeroderma pigmentosum group C (XPC), can be regulated by post-translational modifications such as ubiquitination. However, the role of phosphorylation in XPC function remains unknown. Here, we show that phosphorylation of XPC acts as a novel post-translational regulatory mechanism of the NER pathway. We show that XPC is phosphorylated at serine 94. Moreover, after UVB irradiation, XPC phosphorylation regulates recruitment of ubiquitinated XPC and its downstream NER factors to the chromatin. In addition, upon evaluating the predicted kinases for XPC phosphorylation, we found that casein kinase II (CK2) promotes NER. Furthermore, CK2 kinase mediates XPC phosphorylation at serine 94, and also promotes recruitment of ubiquitinated XPC to the chromatin after UVB irradiation. Our findings have identified XPC phosphorylation as a new mechanism for regulating NER following UV-induced DNA damage.

UV-A damage to proteins in the eye lens and model systems

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UV-A radiation (315-400 nm) is capable to deeply penetrate inside the human eye lens. Under UV-A radiation, endogenous chromophores of the human lens, kynurenine and its derivatives, can generate the triplet states, which readily react with proteins yielding the radical species. The subsequent radical reactions can induce numerous irreversible modifications of proteins. Currently, the mechanisms and the products of these reactions are poorly known.In this work we studied mechanisms, dynamics and products of UV-A induced reactions of kynurenine derivatives with the eye lens proteins and with amino acids tryptophan and tyrosine as model systems. A key feature of the present work is the use of anaerobic conditions as the most relevant to the eye lens, which are characterized by extremely low level of molecular oxygen (less than 2 uM in the nuclear region).The major decay channel of UV-A generated radicals is the back electron transfer with the restoration of parent molecules. However, one of the radical reactions is the direct oxidation of substrate via the oxygen atom transfer from kynurenine derivatives to protein or amino acid. This reaction occurs without the participation of molecular oxygen; therefore, the protein oxidation can effectively occur within the tissue of the eye lens under anaerobic conditions. Another important consequence is an effective cross-linking of proteins and single amino acids via different sites in protein at various positions in aromatic systems of the tryptophan and tyrosine residues. The obtained results clearly show that UV-A induced radical reactions can damage proteins even in the absence of molecular oxygen, and give a contribution to the both normal aging of the eye lens and the progression of cataracts.Authors acknowledge Grant Council of President of RF (MK-1515.2017.3) and RFBR (17-03-00656) for financial support.

Pilot Study Provides New Insights on Skin Types V & VI Ability to Make Vitamin D

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Vitamin D deficiency and insufficiency (VDD/I) are increasingly prevalent in general, primarily due to inadequate solar ultraviolet exposure required for innate vitamin D production in skin. Natural dietary vitamin D sources alone are unable to maintain sufficient vitamin D. Supplemental vitamin D or UV effectively corrects VDD/I with variable efficacy. Darker skinned people suffer disproportionate VDD/I incidence because melanin pigmentation attenuates vitamin D producing UV. We conducted a randomized, prospective, intervention trial comparing efficacy of two treatment modalities for VDD (serum 25(OH)D <12 ng/ml) and VDI (12-20 ng/ml) in skin type V-VI patients. Interventions were oral OTC Vitamin D 2,000 IUs/day and twice weekly 2-SED UV tanning bed exposures. We found that mean serum vitamin D of both groups increased significantly and was restored to normal range at 3 and 6 weeks. There were no significant differences between the treatments at 3 and 6 weeks. At week-6 the OTC group achieved serum 25(OH)D of 35.8 ng/ml and the UV group was 30.1 ng/ml. No significant serum calcium and creatinine changes were observed. We conclude that both interventions proved effective for restoring vitamin D in this study. Tanning beds were more effective than anticipated, representing an unexpectedly practical alternative vitamin D intervention for darkly pigmented people.

Sustained Release Drug Delivery Of Bevacizumab To Treat Ocular Angiogenesis

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Diabetic Retinopathy (DR) and Age-related Macular Degeneration (AMD) are the most common ocular diseases and a leading cause of blindness in American adults. Laser treatments and drug intervention with Lucentis and Avastin are available for controlling angiogenesis by inhibiting the growth of new blood vessels. These antibody injections are given monthly into the eye which are inconvenient as well as very expensive. Our research focuses on encapsulating the protein drugs within the liposomes to obtain drug release over a longer period, thereby decreasing the frequency and cost of the injections. In vitro studies showed that liposomes can be used to deliver Avastin over a period of 6-8 months. Animal studies were conducted to corroborate the results, where a minimum effective dose was monitored over a period of 5 months. In order to extend the release, the liposomes were entrapped within biodegradable hydrogels as well as refillable drug depot implants, thereby extending the time of release. Overall, our research focuses on developing Avastin loaded liposomes for extended released drug delivery to treat ocular angiogenesis. In vitro biological activity, RPE cytotoxicity tests and animal experiments were conducted to determine the efficacy of the drug delivery system for potential human use.

Perfluorocarbon nanoemulsions for imaging and phototherapy

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UCLA

Perfluorocarbon (PFC) nanoemulsions are droplets of perfluorinated, also called fluorous, solvent kinetically stabilized in water by a surfactant. Previous biomedical applications of PFC nanoemulsions include leveraging the high oxygen content in fluorous solvent for artificial blood, low boiling point for ultrasound imaging, and the high local concentration of 19F for magnetic resonance imaging. We build from this existing literature and add complexity to the core PFC nanomaterial structure by 1) localizing fluorous-tagged therapeutics and diagnostics inside in the perfluorocarbon droplets and 2) designing custom, functionalizable surfactants. This talk will focus on our use of PFC nanoemulsions for photodynamic therapy through the introduction of a fluorous photosensitizer in the emulsions. Additionally, results toward the creation of bright fluorous nanomaterials for optical imaging will be presented.

Re-Examining Corneal Photokeratitis Thresholds at UV-C Wavelengths

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Johns Hopkins Bloomberg School of Public Health

Interest in germicidal applications of UV-C has recently increased because of the availability of new types of UV-C sources, such as UV LEDs. The argument for using very short-wavelength sources below 240 nm has been that such wavelengths are virtually only penetrating into the stratum corneum and certainly do not penetrate to the critical level of the basal layer of the epidermis. Some have argued for having separate safety limits for the skin and eye below 250 nm, but even if this becomes possible, the question arises over what levels are really safe for the cornea of the eye. There is very limited photokeratitis data at these short wavelengths. The shortest-wavelength examined was at the ArF 193-nm excimer laser line. However, the classical studies of human photokeratitis by Pitts et al. were carried out only down to 220 nm using a 5-kW mercury-xenon-arc monochromator. However, these threshold data were for a 10-nm bandwidth (FWHM), which can significantly distort the action spectrum where it steeply declines at short wavelengths. The 193-nm laser did not have this bandwidth uncertainty problem. Most recently, 207-nm KrBr and 222-nm KrCl far-UV excimer lamps have been used for germicidal studies; however these are not really monochromatic and emit UV-B as well to add uncertainty to the resulting data.

Lighting Technology and the Illuminating Engineering Society

Sliney DH
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Over the past decade a revolution in lighting has been taking place, fueled partly by new technologies of compact fluorescent lamps and solid-state (LED) lamps, and partly by efforts to reduce the consumption of electrical energy. Some of the new lamps have sufficiently different spectra that concerns have been raised about adverse photobiological effects on plants and trees and about potential health risks. Indeed as solid state (LED) lighting technology has been exploding around us, there are complaints about color rendering and harshness of some new lighting. But the discovery in 2001 of the presence of melanopsin in a small fraction of retinal ganglion cells has shown that short-wavelength (blue-indigo) light plays a key role in neurobiological and neurobehavioral effects that are sometimes referred to as "circadian" effects. Because particular attention has been played to blue light, concerns have arisen about potential circadian disruption and potential health effects. Therefore, there is intense interest in the areas of lamp technology, lighting design and public health in photobiological effects of lamps and lighting. Photobiologists seeking technical information such as spectral details of lamps, the standardized terminology for lamps and lighting systems as well as lighting science should be aware of the CIE and also the resources available from the Illuminating Engineering Society of North America (IESNA, or just IES), which has been active in promoting lamps, lighting science and engineering, and good practice since 1905. The lighting industry has been greatly affected by these changes and the "big three" in lamp technology (Philips, Osram-Sylvania, and GE) have been spinning off other companies dealing primarily with LEDs.

Solar exposure-induced modulation of skin endocrine function

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The skin operates as a fully functional peripheral neuroendocrine organ that, using the same mediators and signal transduction pathways as the ones operating in the central neuroendocrine, and together with cutaneous immune system, modifies/regulates local homeostasis in response to environmental and internal stressors. The skin also communicates in a bidirectional fashion with the central nervous (CNS), endocrine and immune systems and, therefore, after absorption of electromagnetic energy of solar radiation, it can control a systemic homeostasis and body adaptation to changing environment. Ultraviolet radiation (UVR) induces variety of pathological processes including cancerogenesis, skin aging and autoimmune and inflammatory responses. Skin stress response system, regulated by local neuro-endocrine-immune system, would counteract these pathologies with main regulatory elements buffering the damages or restoring homeostasis represented by cutaneous steroid/secosteroidogenic and serotonin/melatoninergic systems and elements of cutaneous equivalent of the hypothalamus-pituitary adrenal axis. Most recent data indicate that UVR can also regulate global homeostasis with beneficial for the body outcomes. These will be secondary to the induction by UV of chemical, hormonal and neural signals, triggered by interaction with specific chromophores. The involvement of UVB in this process is much greater than that of UVA as illustrated by its high potency to induce production of cytokines, neuropeptides, secosteroids and melatonin, which after entering circulation would modify body homeostasis. In addition, local activation of sensory nerves, secondary to UVR, would lead to rapid stimulatory effects on the CNS with downstream homeostatic effects. Thus, UVR (UVB in particular) triggers not only skin protective responses against stress, but also activates central neuroendocrine system to reset

global body homeostasis into the most desirable mode.

Targeting drug-resistant cancer stem cells using photodynamic therapy

Spring BQ
Northeastern University

Standard chemoradiation often enriches drug-resistant tumor cell populations that can lead to recurrent and treatment-refractory disease. For instance, preclinical models of several cancers suggest that the cancer stem cell subpopulation becomes enriched and re-populates the tumor milieu following conventional therapies. Here, we show evidence that photodynamic therapy (PDT) is effective against several patient-derived cancer stem cell cultures. Moreover, sub-lethal PDT results in re-sensitization of cancer cell phenotypes with induced drug-resistance to chemotherapy. This talk will also introduce some of our efforts to establish a new program aimed at developing personalized and targeted PDT to overcome drug-resistance.

Microbial Rhodopsins: Diversity and Optogenetic Applications

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Microbial rhodopsins are a large family of photoactive retinylidene proteins found in prokaryotes and lower eukaryotes throughout the oceans, lakes, rivers, in soil, and on the leaf surfaces of plants. They share a 7-transmembrane-helix architecture that forms an internal pocket for the chromophore retinal and undergo similar photochemical reactions that nevertheless carry out strikingly diverse functions. Their functions fall into two categories: light-driven ion pumps that use light to energize cells and photosensory receptors that use light to regulate cell processes. Known modes of sensory rhodopsin signaling are protein-protein interaction, enzymatic activity encoded in their cytoplasmic domain, and light-gated ion channel conduction (channelrhodopsins). Their study has contributed to our understanding of how evolution modifies protein scaffolds to create new protein chemistry. Also their use as tools to control membrane potential with light is fundamental to optogenetics, a transformative technology for neural circuitry research and potentially for clinical applications. Optogenetics entails genetically targeted expression of microbial rhodopsins whose photoreactions enable precise spatial and temporal control of transmembrane ion currents to regulate excitable cell action potentials. Optogenetic applications in research and optogenetic therapy in clinical trials use primarily membrane-depolarizing neuron-activating (cation-conducting) channelrhodopsins largely because efficient neural firing photoinhibitors have not been available. The talk will focus on our recently discovered anion channelrhodopsins (ACRs), whose potent hyperpolarizing light-gated chloride conductance enables orders-of-magnitude more efficient photoinhibition of action potentials than previous tools. The ACRs open the way for photosuppression gene therapy for conditions in which excessive neural firing is involved, including epilepsy, Parkinson's disease, and neuropathic pain.

Oxidative stress induced by UV-B and sunlight mediated photoactivation of carbazole inhibits normal human skin cells physiology

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Solar ultraviolet (UV) radiation causes skin cancer after prolongs exposure. Carbazole (CBZ) has tricyclic structure and produced from fossil fuels, cigarette smoke, eye kohl, black tattoo ink, coal and wood combustion. We have studied the photomodification of CBZ under UV-B (0.9mw/cm2) and sunlight. Phototoxicity of CBZ was done on human skin keratinocytes (HaCaT) through MTT, NRU and cell migration assays. CBZ generates reactive oxygen species (ROS) through type-I photodynamic reaction and measured through H2DCFDA and DHE fluorescence in cells. Photosensitized CBZ induced apoptosis which was confirmed through sub-G1 fraction, morphological changes, cytochrome c and caspase-12 release from mitochondria and ER, PS translocation, CPDs/6,4PPs/MN formation. Our RT-PCR and western blot results strongly supports our view point of apoptotic cell death through up-regulation of pro-apoptotic genes followed by antioxidant genes keap-1, nrf-2 and hmox-1. Therefore, much attention should be paid to concomitant exposure of carbazole and UV-R for its total environmental impact.

Cationic Iridium(III) Complexes as in vitro Theranostic Photodynamic Therapy Agents

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In recent years, Ir(III) complexes have emerged as a new type of photosensitizers for theranostic photodynamic therapy (PDT) applications because of their interesting photophysical properties, better cell membrane permeability, better photostability compared to organic PSs, and kinetic stability. Many of these complexes possess high triplet excited-state quantum yields and long-lived triplet excited states for efficient reactive oxygen species (ROS) generation even under hypoxia via electron or energy transfer. It has been reported that cationic Ir(III) complexes can target mitochondria, lysosome, endoplasmic reticulum, or nucleus in a variety of cancer cell lines; and a mitochondria-targeted Ir(III) complex PS was reported to show improved PDT effects under hypoxia. These complexes also exhibit bright intracellular luminescence. In this talk we present the synthesis, photophysics, and in vitro PDT effect and bioimaging of four series of cationic Ir(III) complexes that have strong absorption in the visible spectral region and are emissive in the red to the NIR region. The natures and energies of the lowest singlet and triplet excited states of these complexes are dramatically impacted by structural modification of the ligands. The complexes can generate singlet oxygen efficiently, and exhibit a photodynamic therapeutic effect upon visible or red light activation, with one of the Ir(III) complexes possessing the largest phototherapeutic index reported to date (> 1600) for Ir(III) complexes upon white light activation. Interactions with DNA suggest that other mechanism of action may be at play for the photosensitizing effect. These complexes also produce strong intracellular luminescence that highlights their potential as theranostic PDT agents.

The mechanism of CIRP in regulation of Stat3 phosphorylation and Bag-1/S expression after UVB radiation

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Cold-inducible RNA binding protein (CIRP) is a stress-inducible protein, which could be activated by various cellular stresses, such as hypothermia stress, hypoxia and UV irradiation. Our previous study indicated that UVB (3 mJ/cm2) induces CIRP expression, which promotes keratinocyte growth, survival and eventually transformation via activation of Stat3-Bag-1/S signaling cascade1. However, the mechanism(s) of CIRP in regulating p-Stat3 activation and Bag-1/S expression have not been fully elucidated. In this study, we demonstrate that repeating exposure of UVB (3 mJ/cm2) or overexpression of CIRP could lead to an elevation of the phosphorylation of Jak2 and Jak3 in HaCaT cells. The increased phosphorylation of the Jaks is correlated with an increased phosphorylation of Stat3 (p-Stat3) in the cells; and inhibition of the Jaks using JAK inhibitor I lead to a reduction of Stat3 phosphorylation and Bag-1/S expression in the HaCaT and CIRP stably transfected HaCaT cells with or without UVB exposure. Furthermore, our data indicates that inhibition of NF-ï «B, a downstream factor of CIRP, using BAY11-7085 could also decrease the p-Stat3; and CIRP could

directly bind to Bag-1/S mRNA. These results lead us to propose that CIRP mediates the activation of Stat3-Bag-1/S signaling cascade via activating the Jaks and NF-ï «B signaling pathways as well as directly binding to Bag-1/S mRNA.

UV-induced extracellular ATP and the ecto-ATPase CD39 oppositely regulate DNA damage responses and the skin cancer microenvironment

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Increase of extracellular ATP (eATP) acts as an early and sensitive signal of cellular stress and dying cells. Changes in eATP levels control biological responses through activation of purinergic receptors. Keratinocytes are sensitive to UVR and rapidly release ATP following UVR. However, the role of eATP and its metabolotes in cutaneous immune function and the DNA damage response is not well understood. Based on their sentinel role, we first hypothesized that skin-resident T cells sense UVR-induced ATP release and provide protective surveillance and repair functions in the context of keratinocyte UVR damage, early before carcinogenesis evolves. We show that UVR-induced ATP release indeed leads to skin-resident T cell activation in humans and mice. Surprisingly, UVR increased IL-17 production by skin-resident T cells in an eATP-dependent manner. IL-17, in turn, upregulated epidermal TNF-related weak inducer of apoptosis (TWEAK) and growth arrest and DNA damage–associated gene 45 (GADD45), two genes with known functions in DNA repair. We furthermore demonstrate that skin T cells play a critical role in limiting UVR-induced DNA damage–associated phosphorylated form of histone 2A (H2AX) and cyclobutane pyrimidine dimer (CPD) formation in keratinocytes. We concluded that this protective pathway becomes suppressed during UV-induced skin carcinogenesis and we hypothesized that ecto-ATPases, which facilitate degradation of the danger signaling molecule ATP and generation of immunosuppressive adenosine, may lead to suppression of skin immune cells. Indeed, we find that that the ecto-ATPase ENTPD1, also known as CD39, and the ecto-AMPase CD73 are highly abundant in human skin cancers and upon in vivo UV radiation and are associated with increased ATP metabolism, adenosine generation and disturbed DNA damage repair.

Photopharmacology: Towards Light-Swtichable Therapy

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Current pharmacological treatments relay on using bioactive compounds that evoke a response by interacting with molecular targets in the human body. The selectivity of this interaction is crucial and the lack of it leads to the emergence of severe side-effects in the body and toxicity in the environment. To solve this problem, drugs could be introduced whose activity could be reversibly switched on demand. The aim of this presentation is to describe the recent concept of photopharmacology which is currently being developed and applied i.a. in our labs to precisely control the activity of drugs using light. The key properties of drugs, such as their distribution and interaction with their molecular targets, are directly influenced by their molecular structure. Photopharmacological agents are designed by the modification of bioactive molecules with molecular photoswitches, i.e. moieties that change their structure upon irradiation with light. These changes are directly translated to the differences in drug activity. The presentation will describe: 1) chemotherapeutic inhibitors of histone deacetylases; 2) antibiotics that can be activated with light, designed to avoid the emergence of antibiotic resistance in the environmentand 3) light-regulated bacterial quorum sensing inhibitors used for photocontrol of gene expression. The aspects of molecular design, synthesis, optimization, photochemical characterization and biological activity will be discussed. An outlook on the prospects of bringing photopharmacology to clinical application, including the milestones and future landmarks, will be presented, together with the evaluation of organs in human body with regards to the feasibility of light-based therapy.

Pterin photosensitizers free in solution and bound to DNA and biomembranes

Thomas AH

Aromatic (oxidized) pterins are natural photosensitizers that accumulate in the skin of patients suffering from vitiligo, a chronic depigmentation disorder. These compounds absorb UV-A radiation, produce reactive oxygen species and photoinduce the oxidation of DNA, lipids and proteins. The photosensitizing properties of pterin (Ptr), the parent unsubstituted compound of oxidized pterins, and vitiligo-related pterin derivatives (biopterin, formylpterin and carboxypterin) have been studied using purine and pyrimidine nucleotides as substrates. The predominant mechanism involved in the pterin-photosensitized oxidation of these compounds is the type I, and is initiated by a one-electron transfer from the nucleotide to the triplet excited state of pterins. In the case of thymine (Thy) the nature of the photoproducts depends on the presence of oxygen in the media. In air-equilibrated solutions, the products can be explained taking into account the typical reactions of the Thy radical cation (Thy•+); but under anaerobic conditions, coupling of radicals takes place yielding a covalent adduct Ptr-Thy. This compound, which has the intact pterin moiety and retains some of its photochemical properties, can be also formed using DNA as a substrate. Pterins also photoinduce the oxidation of lipids of biomembranes. Ptr does not bind to phospholipids and is able to freely cross biomembranes, therefore the photooxidation is a dynamic encounter process. To increase the lipophilicity of pterins a new series of alkyl chain pterin conjugates have been synthesized, structurally characterized and their photochemical and photophysical properties have been investigated. Decyl-pterins efficiently intercalate in large unilamellar vesicles and are more efficient photosensitizers of phospholipids compared to Ptr.

Conjugated polymers with photocleavable solubilizing chains

Thomas SW
Tufts University

The semiconducting and optical properties of conjugated polymers present a wide range of prospective applications in biology and organic optoelectronics. The vast majority of these polymers use long, often branched alkyl side chains to render them soluble in organic solvents that enable solution-based processing and synthesis of high molecular weight polymers. These solubilizing chains, however, bring a range of disadvantages, such as reduced photostability and an inability to fabricate multilayer devices using all solution-based approaches. In response to the limitations inherent to this common design paradigm, our laboratory has developed a range of conjugated polymers with photocleavable solubilizing alkyl chains, which comprise polythiophene main chains with ortho-nitrobenzyl linkers. Upon photoinduced cleavage of the nitrobenzyl groups, these polymers become insoluble and therefore behave as negative photoresists upon irradiation with UV light. These polymers can therefore be photopatterned and stacked into multilayer films using solution-casting techniques. Structure-property relationships of different nitrobenzyl linkers revealed increased photolysis quantum yields with improved benzylic radical stabilizations. This talk will also present a polythiophene-based dual-tone photoresist, which behaves as either a negative or positive photoresist depending on whether the developer is organic solvent or aqueous base. This characteristic enables the fabrication of increasingly

complex film topographies. Overall, these new polymers open the door to combining the advantages of photochemistry with optoelectronically active polymers, with especially important functionality in aqueous environments.

Longitudinal study of the skin responses to UVB challenges using non-invasive multimodality microscopy

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Background/Purpose: Monitoring the dynamics of the epidermal cellular response following an acute UV exposure offers new insights into human skin responses to solar radiation. Previous studies have used histology to compare multiple time points at different skin sites. Only recently has non-invasive imaging such as reflectance confocal microscopy (RCM) been adopted. However, no studies have measured the same cells at different time points so far. We created a new method to revisit and image the same cells during a 2-week period using non-invasive, label-free multimodality microscopy. Methods: A solar simulator was used as the source of UV radiation from 280 to 400nm, in which the biological effect is dominated by UVB. Ten healthy volunteers were recruited for the study. The minimal erythema dose (MED) for each volunteer was determined. Two MED equivalents were applied to the upper inner arm using a 1mmX6mm beam which was aligned at the center of a customized ring shape tattoo. The time course of the skin responses was studied with a multimodality in vivo microscopy system capable of co-registered video rate RCM imaging, two photon fluorescence (TPF) imaging and second harmonic generation imaging. The RCM was used to localize the tattoo and select the imaging site (0.2mmX0.2mm). The fixed distances between the tattoo and the imaging field allowed precise revisiting of the same cells/superficial blood vessels at 6 time points (before, 1 hr, 24 hrs, 3 days, 1 week and 2 weeks after exposure). Results: Delayed pigmentation was quantified by TPF signal, showing up to 1.6 times increase in melanin content. The quantitative analysis also revealed that melanin distribution pattern changed with time, suggesting that melanin migrates towards the skin surface. Epidermis thickness calculated by vertical scanning image revealed hyperplasia and increased blood flow at 24 hrs time point was observed by RCM.

The Effect Of cNOS Inhibitor On UVB-Induced DNA Lesions Formation and Skin Cancer Development in Cell Culture and Animal Models

Tong L, Bahamondes Lorca VA, Richardson LG, Heusey HL, Wu S*
Ohio University

Our previous studies demonstrated that constitutive nitric oxide synthase (cNOS) plays an important role in regulation of UVB-induced nitric oxide (NO•)/peroxynitrite (ONOO-) imbalance and NF-kappa B activation, the two factors involved in DNA lesions formation and carcinogenesis. In this study, we further analyzed the role of cNOS in DNA lesions formation and skin cancer development post-UVB irradiation using HaCaT cells and SKH-1 mice models. Our data shows that treating HaCaT cells with L-NAME, a selective inhibitor of cNOSs, could reduce the amount of cyclobutane pyrimidine dimer (CPD), 6,4-photoproduct (6,4-PP) and DNA breakage in the UVB-irradiated cells; as well as the cell transformation after receiving multiple rounds of UVB exposure. Topically treating dorsal skin of SKH-1 mice with L-NAME prior to each UVB exposure increases the skin thickness and reduces the CPD formation and skin cancer development. Our results suggest that cNOS could potentially be a target for chemoprevention of UVB-induced skin cancer formation.

Lipofuscin accumulates in skin cells turning keratinocytes photosensitive to visible light

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The effects of UV radiation in human skin have been extensively studied and it is well accepted that it can cause photoaging and carcinogenesis. In contrast, little importance has been given to the effects of radiation in the visible range (400-800 nm). Recently, we reported that immortalized human skin keratinocytes (HaCaT) and primary normal human skin keratinocytes from neonatal foreskin (NHK) exposed to UVA became photosensitive to visible light. The photosensitivity to visible light was assigned to the accumulation of lipofuscin, a subproduct of incomplete lysosomal digestion of oxidized biomolecules, organelles, and membranes. In order to prove the mechanism of lipofuscin, accumulation we provoked a parallel damage in mitochondria and lysosome by photosensitizationwith 1,9-dimethyl methylene blue (DMMB) with red light (Î»= 633 nm, 11 J.cm-2), which cause an extensive accumulation of lipofuscin, allowing its characterization by fluorescence lifetime imaging (FLIM) and fluorescence spectroscopy. We demonstrated that both HaCaT and NHK cells show a typical perinuclear accumulation of lipofuscin after exposure to UVA radiation (Î»= 366 nm, 12 J.cm-2). If these cells are subsequently exposed to visible light there was: i) a significantly larger decrease in cell viability; ii) an increase level of peroxides and singlet oxygen. We also detected strand breaks in nuclear DNA and formation of premutagenic Fpg- and EndoIII-sensitive DNA lesions through comet assay. Thus, UVA and visible light amplify the effect of each other, since UVA generates an additional endogenous photosensitizer to visible light, which enhances the photoxidative processes and genotoxicity by solar radiation. Our results show the urgent need to develop sunscreens that also protect against the visible light.

A Collective Overview Of UV Albedo From Local Surface Types: Is There An Agreement?

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Understanding the reflectance from surrounding surfaces is important to the understanding of ambient UV exposure to people in the biosphere. The UV albedo from natural surfaces has been explored by different research groups, however there has not been a collective review of the data to confirm consistency between surface types. A number of possible discrepancies have been identified as influencers to differences in albedo measurement, including lack of clear explanation of method of measurement, or difference in measurement device, description of surface type and type of measurement such as broadband or spectral. A preliminary review of the existing published data will be presented, alongside a comparison for influence of reflectance on personal exposure from vertical built surface types.

Phospholipid Membrane Damage Produced by Photosensitization with Decylpterins

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Oxidative stress to biomembranes occurs in many physiological and pathological processes leading to peroxidation to biomolecules. Key targets include phospholipids bearing polyunsaturated fatty acids (PUFAs), which are abundant compounds of lipid membranes. In addition, PUFAs can undergo photooxidation reactions by the interaction of light, photosensitizer, and oxygen by two different mechanisms: reactions where the generation of radicals takes place (type I mechanism), and reactions where singlet oxygen is produced (type II mechanism). Both mechanisms lead to the generation of hydroperoxides and other oxidation products.Pterins are

heterocyclic compounds derived from 2-aminopteridin-4-(3H)-one in biological systems. They accumulate in human skin under pathological conditions. Also, they are photochemically reactive and can act as photosensitizers through both type I and type II mechanisms, inducing damage in proteins and DNA and inactivation of bacteria. Pterin (Ptr) can also photoinduce oxidation of lipids in membranes of large unilamellar vesicles (LUVs). Ptr is a small molecule with low lipophilicity, therefore does not bind to phospholipids and freely crosses biomembranes. We have previously synthesized and characterized a new series of alkyl chain pterin conjugates to increase the lipophilicity of pterins.In this work, we investigated the association of 4-(decyloxy)pteridin-2-amine to lipid membranes and its ability to photoinduce oxidation of phospholipids. The performance of the new decyl-pterin in large or giant unilamellar vesicles of different composition as biomimetic systems was evaluated by analyzing conjugated dienes and the formation of hydroperoxy derivatives using reverse-phase LC-MS detection. Conjugation of a decyl chain in the pterin moiety increases solubility in organic solvents and efficiently intercalate in LUVs. In addition, the decyl-pterins have high singlet oxygen quantum yields. Results were compared to those obtained with Ptr.

Interfacial Strategies to Study Reactive Oxygen Intermediates

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In this presentation we report on the production of reactive oxygen intermediates at air-water interfaces and air-solid interfaces. 'Ene' reactions of singlet oxygen at the air-water interface showed regioselectivity increases with longer chain prenylsurfactants. Here, unsymmetrical and synchronous attack by singlet oxygen occurred on the pi bond. Desolvated methyl groups were more prone to the 'ene' reaction and a long-chain surfactant wasted less airborne singlet oxygen by physical quenching being at a further distance from the water layer. Interfacial strategies were also used to study effects of sensitizers on the photolability of organic peroxides. Air-solid results show some spatial control for the photosensitized homolysis process. The sensitizer to peroxide distance (energy donor to O-O bond acceptor) on a silica surface shows a Gaussian-shaped trend centered around 6-9 Å implying a triplet mechanism. The results of these studies reveal insight into many interfacial mechanisms including photooxidative aging and the separation of reactive oxygen intermediates.

Kinetic Control in the Alkylation of Pterin Photosensitizers: Synthetic, Photochemical, and Theoretical Studies

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Alkylation patterns and excited state properties of pterins were examined both experimentally and theoretically. 2D NMR spectroscopy was used to characterize the pterin derivatives, revealing undoubtedly that the decyl chains were coupled to either the O4 or N3 sites on the pterin. At a temperature of 70 °C the pterin alkylation regioselectively favored the O4 over the N3. The O4 was also favored when using solvents in which the reactants had increased solubility, namely N,N-dimethylformamide and N,N-dimethylacetamide, rather than solvents in which the reactants had very low solubility (tetrahydrofuran and dichloromethane). Density functional theory (DFT) computed enthalpies correlate to regioselectivity being kinetically driven because the less stable O-isomer forms in higher yield than the more stable N-isomer. Once formed these compounds did not interconvert thermally or undergo a unimolecular "walk" rearrangement. Mechanistic rationale for the factors underlying the regioselective alkylation of pterins is suggested, where kinetic rather than thermodynamic factors are key in the higher yield of the O-isomer. Computations also predicted greater solubility and reduced triplet state energetics thereby improving the properties of the alkylated pterins as 1O2 sensitizers. Insight on thermal and photostability of the alkylated pterins is also provided.

Psoralen Activation With No UV lamp - Teaching An Old Drug New Tricks

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The use of psoralen originally dates back to the days of the ancient Egyptians, and in modern medicine was the primary therapeutic agent in both PUVA therapy and Extracorporeal Photopheresis (ECP). Psoralen based therapies have been limited to superficial or extracorporeal uses due to the need for UV activation of the drug, with the maximum effective depth of penetration of UV light into tissue less than 1mm. This work explored the development of novel ways to activate psoralen to treat deeply seated tumors with translation from the bench to companion animals to human patients. X-PACT (X-Ray Psoralen Activated Cancer Therapy) represents a novel solution to the classical limitation of requiring a UV lamp to activate psoralen. X-PACT converts deeply penetrating low dose X-ray energy into UV to activate psoralen directly at the site of the tumor, resulting in tumor cell kill, antigen processing and presentation, with the possibility of generating a systemic antitumor immune response. Multiple generations of energy converting particles were developed, each with differing emission profiles, morphologies and biocompatibility profiles. The efficacy of X-PACT was evaluated in both in-vitro and in-vivo settings. In-vitro, we show that X-PACT induces significant tumor cell apoptosis and cytotoxicity, compared to psoralen or energy converters alone ($p<0.0001$). In murine models of 4T1-HER2, a significant growth delay was demonstrated compared to saline controls ($p<0.0001$). Safety and efficacy were also demonstrated in spontaneous tumors in companion animals. In summary, X-PACT represents a new modality for activating psoralen in deeply seated tumors with enhanced cytotoxicity and the possibility of antitumor immune activation.

Enhancing Rose Bengal-Photosensitized Protein Crosslinking in Cornea

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Potential medical applications of Rose Bengal (RB)-photosensitized protein crosslinking have been demonstrated in preclinical and clinical studies. In solution, RB photosensitization via the RB excited triplet state generally involves energy transfer to oxygen to form singlet oxygen and electron transfer to the RB triplet producing radical ions. This study identifies mechanistic pathways in cornea tissue for RB-photosensitized crosslinking in order to enhance the treatment efficiency. METHODS: Rabbit corneas ex vivo were stained with 1 mM RB and irradiated at 532 nm (0.22 W/cm^2). The influences of oxygen, sodium azide, D2O, and arginine (an electron donor) on the rate of RB photodecomposition (by spectrophotometry, 18 corneas) and on cornea tensile strength (by linear tensiometry, 91 corneas) were evaluated. Controls were non-irradiated corneas without and with RB staining. RESULTS: In cornea, photobleaching in air of the RB 560 nm maximum was partially inhibited by azide and enhanced by D2O, suggesting a partial singlet oxygen pathway. In the absence of oxygen, the absorption maximum decreased and shifted to 530 nm. With arginine present during irradiation, the maximum shifted to 555 nm in air and 510 nm without oxygen, suggesting that electron transfer initiates RB photodecomposition. Tensiometry results showed that in air RB-sensitized a tensile strength increase that was inhibited by azide and unaffected by D2O. Removing oxygen blocked the photosensitized tensile strength increase but addition of arginine augmented the increase to the same level observed in air alone indicating a role for an electron transfer pathway.

CONCLUSIONS: These results suggest that in a solid tissue, cornea, both energy transfer/singlet oxygen and electron transfer mechanisms participate in RB-photosensitized tensile strength increase and that adding electron donors may increase the efficiency of this treatment.

Computational Insight Into the Red-Green Spectral Tuning Mechanism in the Cyanobacteriochrome Slr1393g3

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Cyanobacteriochromes (CBCR) have been recently discovered in cyanobacteria and constitute a new class of photoreceptor proteins with absorption from the near ultra-violet to the red. They bind bilin chromophores responsible for visible light absorption and are related to plant and cyanobacterial phytochromes. CBCRs are divided into at least four subfamilies based on their primary structure and underlying photochemistry. One of these subfamilies is the red/green one consisting of a red-light absorbing dark state (PR) and a green-light absorbing photoproduct (PG). In this subfamily, phycocyanobilin (PCB) is bound as a chromophore in one of several GAF domains and this single GAF domain is responsible for the entire photochemistry. One prototypical member of the red/green CBCR subfamily is Slr1393 from Synechocystis sp. PCC6803. Recently, the crystal structures of both forms (PR and PG) of Slr1393 were deposited in the protein database (PDB codes: 5DFY for in vitro and 5DFX for in vivo assembly of PR and 5M82 for PG). These structures exhibit a PCB chromophore that is located in a protein cleft covalently bound to CYS-528. We employ QM/MM modeling to understand the spectral tuning mechanism by simulating the absorption spectra of both forms of the Slr1393. This treatment combines the simulation of a full protein with the description of excited states via quantum chemical calculations. In order to simulate the spectra, we have run molecular dynamics simulations and then used 100 snapshots for each form to compute the vertical excitation energies. We find the outer rings of the chromophore to be more twisted in the PG form than in the PR, especially between the A and B rings. However, we find a correlation between the color tuning and the rotation between the rings C and D. Interestingly the protein binding pocket has a negligible contribution to the tuning mechanism in terms of direct electrostatic interaction with the chromophore.

Pharmacological Modulation of TLR4 as a Novel Molecular Strategy for Skin Photoprotection

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Environmental exposure to solar ultraviolet (UV) radiation causes acute photodamage, premature aging, and skin cancer, attributable to UV-induced genotoxic, oxidative, and inflammatory stress. The role of Toll-like receptor 4 (TLR4) as a key regulator of skin anti-microbial defense, wound healing, and cutaneous tumorigenic inflammation has now been recognized, and TLR4 may represent a novel molecular target for skin photoprotection. Accumulating evidence supports the mechanistic involvement of the alarmin and potent TLR4 ligand HMGB1 in skin UV responses. UV-induced inflammatory cutaneous signaling can be suppressed by pharmacological and genetic TLR4 antagonism with attenuation of NF-Î°B and AP-1 stress signaling observed in vitro and in vivo. Numerous TLR4-directed pharmacological antagonists [including eritoran, (+)-naloxone, ST2825, and resatorvid as well as natural compounds from dietary sources such as cinnamaldehyde and glycyrrhetinic acid] have now been identified. We explored TLR4 as a novel target for photochemoprevention of UV-induced nonmelanoma skin cancer (NMSC), selecting the clinical TLR4 antagonist resatorvid based upon target specificity, skin deliverability, and physicochemical properties. We observed that in a murine SKH-1 UV-induced skin tumorigenesis model, topical resatorvid displays photochemopreventive activity, significantly suppressing tumor area and multiplicity. Taken together, our data validate TLR4 as a novel target for topical skin photoprotection and photochemoprevention of NMSC amenable to modulation by drug-like synthetic and natural food factor-derived molecular entities.

From Skin Photooxidative Stress to Novel Molecular Strategies for Photoprotection and Cancer Photochemoprevention'

Wondrak GT
University of Arizona

The causative role of photooxidative stress in skin photodamage and carcinogenesis dictates the rational development of specific molecular strategies for photoprotection and photochemoprevention. Our long-term research efforts have focused on the ultraviolet A (UVA)-driven formation of excited states of endogenous skin photosensitizer chromophores, including advanced glycation end products (AGEs), with subsequent generation of reactive oxygen (ROS) and carbonyl species (RCS). For example, we have identified the lipid peroxidation-derived malondialdehyde-protein adduct and lipofuscin-chromophore dihydropyridine (DHP)-lysine [(S)-2-amino-6-(3,5-diformyl-4-methyl-4H-pyridin-1-yl)-hexanoicacid]asapotentUVA-photosensitizer detectable in human skin. DHP accumulates in response to acute UV exposure and also during tumorigenic progression to squamous cell carcinoma (SCC), suggesting a light-driven vicious cycle involving glycoxidative formation of sensitizer epitopes with subsequent generation of ROS and RCS upstream of additional sensitizer accumulation. Further potentiation of cutaneous photosensitizer activity might occur by UVA-driven oxidative inactivation of cysteine-dependent cathepsins (B&L), causing impairment of autophagic-lysosomal clearance of sensitizer epitopes and lipofuscin, a process with potential pathological relevance to human Parkinson's patients that display hypersensitivity to UVA-induced photooxidative stress in dermal fibroblasts. For pharmacological intervention targeting skin photooxidative stress we have explored feasibility of harnessing cellular antioxidant stress response pathways controlled by the transcription factor NRF2, employing diet-derived small molecule NRF2 activators. Since it is now appreciated that structurally diverse cutaneous sensitizer chromophores may also participate in photodamage acting as molecular ligands, we have recently explored the photoprotective and photochemopreventive efficacy of small molecule antagonists that target receptors involved in inflammatory signaling downstream of AGEs and DAMPs (damage-associated molecular patterns) including RAGE and TLR4.

It's Not Always Black and White: Key Findings from the South African Skin Photobiology Study 2014-2018

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Skin colour and melanin density (MD) are important factors to understand in skin-related diseases, especially for individuals with dark skin types among whom little research has been done. "The Skin Study" was initiated in South Africa comprising two sampling campaigns among adults in October 2014 (n=556) and May 2016 (n=50). Self-perceived natural skin colour and self-reported skin sensitivity (SRSS) (using Fitzpatrick Skin Type (FST) questions) were recorded. Quantitative measures of melanin, that is, either MD or melanin concentration (MC), were measured with a MX18 mexameter and a portable spectrophotometer with diffuse reflectance probe, respectively. Skin colour was assessed with a CL400 colorimeter and erythema was measured with the mexameter. A 2-mm skin biopsy was taken from May participants, prepared according to the Masson Fontana method and MC was assessed using Image Analysis. We made several inter-comparisons and found that FST terms, such as sunburn and tan, were poorly understood by

individuals with deeply-pigmented skin. When assessing an individual with 'black skin', one cannot assume that they will be classified as FST V or VI – population group name does not equate to FST. Melanin and erythema (measured by both DRS and mexameter) were highly correlated with each other in dark skin, however, this probably resulted from the complexity of separating brown and red pigment when using narrow-band reflectance techniques. We hypothesised that spectrophotometer-calculated MD would correlate well with biopsy MC – but the spectrophotometric MD previously shown to predict MC in fair skin was a weak, non-significant predictor of MC in people with deeply-pigmented skin. We shed light on skin colour and MD complexities. We need to better understand the relationships between skin colour, MD and SRSS in overlooked populations in whom health risks persist and require attention if we are to reduce photobiological health disparities across all population groups.

Photoreactivity of Synthetic Pheoemalnin Models

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Although synthetic pheomelanins are better photogenerators of singlet oxygen than eumelanins, under typical conditions the corresponding quantum yields are very low. Interestingly, the ability of synthetic melanins to photogenerate singlet oxygen dramatically increase after their partial photobleaching, which could be considered as experimental photoaging of the melanin pigments. Here, we studied how aerobic photolysis of pheomelanin derived from 5-S-cysteinyldopa (5SCD-M), modified its key physicochemical properties, such as UV-vis absorption, size of the melanin particles, content of representative monomers, paramagnetic properties, superoxide anion formation and quantum yield and action spectra of singlet oxygen photogeneration, employing chemical analysis, atomic force microscopy, X-band and W-band EPR spectroscopy, EPR-spin trapping, time-resolved 1270 nm phosphorescence and quantum chemical calculations of the spin density distribution for radical forms of the melanin representative monomer units. Our results show that experimental photobleaching of 5SCD-M induces significant changes in spectroscopic properties of the melanin and its molecular and supermolecular structure, which can be interpreted as a substantial decrease in the melanin content of benzothiazine units and increase in modified benzothiazole units, and reduction in the size of melanin naoaggregates. These changes are accompanied by a dramatic increase in the efficiency of photobleached pheomelanin to photogenerate singlet oxygen and a reduction in the melanin ability to quench this reactive oxygen species. Since human epidermis, regardless of the degree of pigmentation, almost always contains pheomelanin, the obtained results point to an alternative mechanism of skin phototoxicity based on in situ photoformation of photoreactive melanin products.The Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University is a partner of the Leading National Research Center (KNOW).

Low-cost fabrication of LED arrays for photomedicine

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Laser diodes have traditionally been used as the monochromatic light source for photodynamic therapy. Here, we present fabrication of a simple, customizable and low-cost light emitting diode (LED) array as a light source for photomedicine research. We discuss the maximum intensity that reaches the biological sample plane as well as the stability and spectral shift of the irradiation under conditions of practical use. Finally, a protocol for assembling a low-cost custom-built LED array electronic control circuit is described to automate the sample exposure time without the need for a mechanical shutter.

The Effect of Endothelia Cells on UVB-induced DNA Damage and Transformation of Keratinocytes In 3D polycaprolactone scaffold Co-culture System

Zhao H, Wu S
Ohio University

Our previous studies indicated that UVB-induced constitutive nitric oxide synthase (cNOS) activation and nitric oxide (NO•) production plays an important role in regulation of DNA damages and transformation of keratinocyte. The polycaprolactone scaffold 3D cell co-culture system was prepared using high voltage electro-spinning technique to achieve nano to micro scale polymer fibers as skeletons for cell attachment and support. The co-culture system was established by stacking two scaffolds together using agarose. HaCaT cells were co-cultured with HUVEC cells (co-cultured HaCaT) or with HaCaT (mono-cultured HaCaT) as the control. Our data shows that NO• level in co-cultured is increased approximately three folds more than in mono-cultured HaCaT cells within one-hour post-UVB irradiation (75 mJ/cm2) but then is reduced much quicker and remains lower in co-cultured HaCaT cells comparing to mono-cultured cells from 6-24 hours post-UVB irradiation. However, peroxynitrite (ONOOï€) level is higher in the co-cultured than in the mono-cultured HaCaT cells in the early and later periods post-UVB irradiation. Correlated to the elevation of ONOOï€, the levels of cyclobutane pyrimidine dimer (CPD) and 6,4-photoproduct (6,4-PP) as well as DNA breakage are also higher in the co-cultured post-UVB irradiation. Finally, our data shows that the co-cultured cells are more resistant to UVB-induced apoptosis and have a 72% increase of transformation efficiency after repeating UVB. Our results suggest that endothelial cells could enhance NO•/ONOOï€ imbalance and promote transformation of neighboring keratinocytes.

Dynamics and mechanism of DNA repair by photolyases

Zhong D
Ohio State University

UV radiation can damage DNA to mainly form cyclobutane pyrimidine dimer or (6-4) photoproduct. Such lesion may eventually lead to skin cancer. Photolyase, a flavin photoenzyme, can revert such damage with high repair efficiency. Here, we combined femtosecond spectroscopy and molecular biology and have completely mapped out the entire repair evolution at the most fundamental level by following the dynamics from the initial reactants, to the fleeting intermediates and to the final repaired products. By resolving ten elementary steps in the complex enzymatic reaction, we captured seven electron-transfer reactions and also bond breaking and forming processes. These dynamics are in synergy to achieve a maximum repair efficiency. We carefully examined the various photolyases and observed a unified electron transfer mechanism of electron bifurcation with determination of the critical role of the unique folded cofactor structure.

Dynamics and mechanism of UV-B perception by UVR8

Zhong D
Ohio State University

UVR8 (UV RESISTANCE LOCUS 8) proteins are a class of UV-B photoreceptors in high plants. UVR8 is a homodimer that dissociates into monomers upon UV-B irradiation (280 to 315 nm), which triggers various protective mechanisms against UV damages. Uniquely, UVR8 does not contain any external chromophores and utilizes the natural amino acid tryptophan (Trp) to perceive UV-B light. Each UVR8 monomer has 14 tryptophan residues. However, only the epicenter two Trp (W285 W233) residues are critical to the light-induced dimer-to-monomer transformation. Here, combining time-resolved spectroscopy and extensive site-directed mutations, we have revealed the entire dynamics of UV perception to lead to monomerization, including a series of critical dynamical processes of a striking energy-flow network, exciton charge separation and recombination, charge neutralization, salt-bridge zipping

and protein solvation, providing a complete molecular picture of the initial biological function.

Nanoparticles to Mediate Photodynamic Therapy and X-ray Induced Photodynamic Therapy

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Photodynamic therapy (PDT) is an emerging cancer treatment modality. Despite the focal treatment nature, it is desired that photosensitizers are delivered to tumors with high efficiency and selectivity in a PDT process. In the first half of this lecture, I will be presenting our recent work on using ferritin, a protein cage (~12 nm), as a photosensitizer carrier. Ferritin can encapsulate photosensitizers such as zinc hexadecafluorophthalocyanine (ZnF16Pc) at high efficiency (40 wt%) and they can be modified by both chemical and genetic methods. We have successfully introduced folic acid, RGD4C, and a FAP targeting scFv, onto the surface of ferritins. We then exploited the resulting ferritin cages to navigate PDT to different components in tumors, including cancer cells, cancer endothelial cells, and cancer associated fibroblasts (CAFs). In the second half of the lecture, I will be talking about X-ray induced PDT, or X-PDT, a new technology that is developed to address the shallow penetration issue of conventional PDT. The key component of the X-PDT technology is an integrated nanosystem called X-ray nanosensitizer, which consists of: 1) a nanoparticle scintillator that converts X-ray photos to visible photons and; 2) photosensitizer whose excitation matches the emission of the scintillator. Upon X-ray irradiation, the nanoscintillator works as a transducer, producing X-ray excited optical luminescence; the visible photons, in turn, activate the photosensitizers, producing reactive oxygen species, most importantly singlet oxygen. We have shown that X-PDT can be activated from beneath thick tissues to efficiently kill cancer cells. We also found that X-PDT is more than a simple derivative of PDT; rather, it is a unique combination of PDT and radiation therapy. The two modalities target different cellular components, and the damage overwhelms cellular repairs, leading to synergistic therapy outcomes.

Analytical Method Development and Discovery of Photo-Crosslinking of Proteins

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My laboratory, aka SunnyLand, has an abiding interest in the chemistry and analysis of protein modifications. Due to the intrinsic biochemical complexity of protein crosslinking, its analysis poses unique and tremendous challenges, particularly if the chemistry involved is unknown. To meet these challenges, my laboratory has recently developed a general workflow, XChem-Finder, that allows us to discover and elucidate crosslinks, notably without a priori knowledge of the chemical nature and site of crosslinking; for example, a novel crosslinking between two histidine residues induced by photo-oxidation (Analytical Chemistry, 2014, 86, 4940 and 2013, 85, 5900). Our ongoing (unpublished) work allows pan-specific affinity enrichment and spectrometric quantification of protein crosslinking.

Site-Specific Chemo-enzymatic Photocaging of Peptides and Proteins

Zhou ZS, Moulton K, Sadidi A
Northeastern University

We recently invented several site-specific chemo-enzymatic methods to install novel switches that can be removed reversibly. One example is to restore the native form by light – a process often referred to as photocaging. These methods are generally applicable to most proteins. Our method and newly developed switches have broad applications such as biological probes (e.g., for neurological studies), fusion proteins, light-controlled materials, antibody drug conjugates (ADCs) and controlled drug release.

ROS explicit dosimetry of type I and II photodynamic therapy

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University of Pennsylvania

Photodynamic therapy (PDT) is used for cancer treatment based on the interaction of a photosensitizer (PS), light, and oxygen. The photodynamic interaction is termed type I and II depending on whether the cytotoxic oxygen species is through an electron transfer, producing oxygen superoxide and its secondary reactive oxygen species (ROS) or an energy transfer, producing singlet oxygen ($^1O_2$). Most photosensitizer exhibit both type I and II interactions. Explicit dosimetry of light fluence rate ($\ddot{\imath}_\bullet$), PS concentration ([PS]), and oxygen concentration ([$^3O_2$]) has been developed for clinic use, however, it is important to integrate these explicit quantities to a reacted ROS concentration, [ROS]rx. A mathematical model has been developed to incorporate the macroscopic kinetic equations for [ROS] generation, photosensitizers in ground and triplet states, $^3O_2$, and tissue acceptors along with the diffusion equation for the light transport in tissue. In this study, the ROSED model has been applied to type I (e.g., WST09) and several type II (e.g., HPPH, BPD, Photofrin) photosensitizers. Cure index was computed from the rate of tumor regrowth after treatment and was compared against three calculated dose metrics: total light fluence, PDT dose (product of light fluence and PS concentration), and reacted [ROS] rx. The tumor growth study demonstrates that [ROS]rx serves as a better dosimetric quantity for predicting treatment outcome, as a clinically relevant tumor growth endpoint. Values of threshold dose of [ROS]rx for type I and II interactions are discussed.

Ultraviolet A-induced oxidation in cornea: characterization of the early oxidation-related events

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Exposure to sunlight ultraviolet-A (UVA), the main component of solar UV reaching the eyes, is suspected to play an important part in the onset of ocular pathologies. UVA primary biological deleterious effects arise from the photo-induction of oxidative stress in cells. However, the molecular bases linking UVA-induced oxidation to UVA toxicity in eyes remain poorly understood, especially with regards to the cornea. To shed some light on this issue, we have investigated the susceptibility and response potential of the different corneal cellular layers (epithelium, stroma and endothelium) to UVA-induced oxidation. We have monitored UVA-induced immediate effects on cellular redox balance, on mitochondrial membrane potential, on 8-Hydroxy-2'-deoxyguanosine (8-OHdG) accumulation in cellular DNA and on S-glutathionylated proteins (PSSG) levels along whole rabbit corneas. Higher redox imbalance was observed in the posterior part of the cornea following irradiation. Conversely, UVA-altered mitochondrial membrane potentials were observed only in anterior portions of the cornea. UVA-induced 8-OHdG were found in nuclear DNA of epithelia, while they were found in both nuclear and mitochondrial DNA in stromal and endothelial cells. Finally, significantly higher levels of cytosolic PSSG were measured in epithelia and endothelia immediately after UVA exposure, but not in stroma. Taken together, our findings indicate that while corneal epithelial cells are subjected to important modifications in response to UVA exposure, they efficiently limit the early manifestations of UVA-induced toxicity. On the other hand, the corneal endothelium is more susceptible to UVA-induced oxidation-related toxicity.

NOTES

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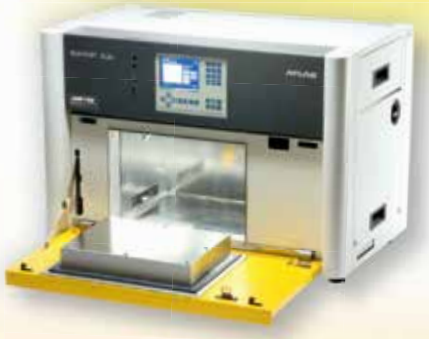

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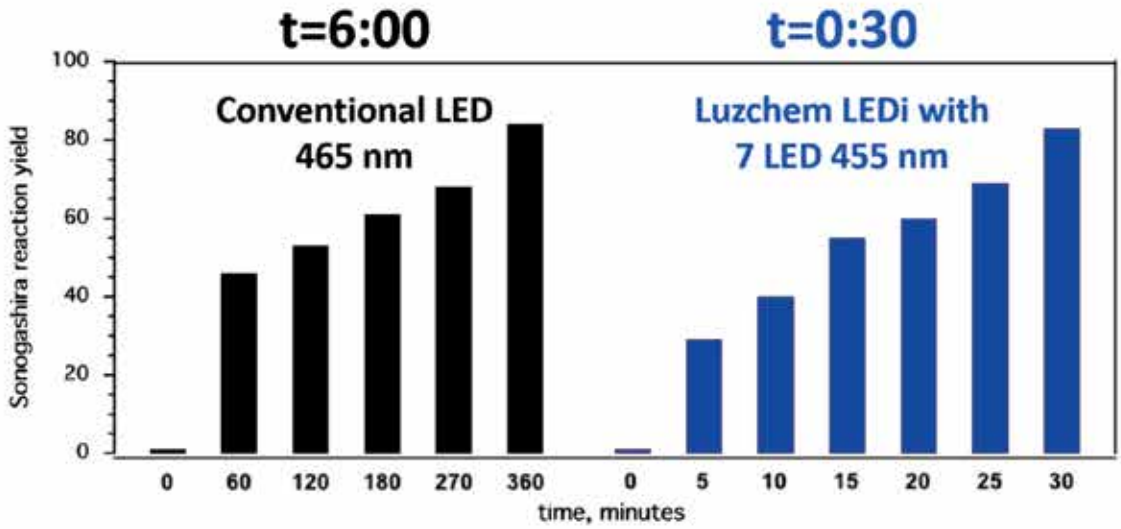

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