Photoprotection Beyond UV Spectrum

Henry W. Lim, MD
Department of Dermatology
Senior Vice President for Academic Affairs
Henry Ford Hospital, Detroit, Michigan
Disclosure

• **Investigator:**
  – Estée Lauder
  – Ferndale
  – Unigen
  – Incyte

• **Speaker, educational session:**
  – Pierre Fabre
Learning Objectives

Be able to:

• Understand principles of photoprotection beyond the UV spectrum
• Describe agents that have this property
Photoprotection

- Shade
- Clothing
- Hat
- Sunscreens
- Sunglasses
- Non-topical agents

Sunscreens: Photoaging and Skin Cancer

(Hughes, MCB.... Green, AC. Ann Intern Med 6/13; 158:781; Green, A., Lancet 1999; 354:723.

- A 4.5 yr + 8 yr f/u study of 1621 residents of Nambour, Queensland, randomly assigned to daily SPF16 broad spectrum sunscreen group, vs. control
- Sunscreen group had decreased
  - SCC
  - BCC
  - Photoaging
  - Melanoma
Spectrum of Sunlight Reaching the Earth’s Surface at Sea Level

Approximately 5% UV (280-400 nm), and 50% VL (400-700 nm)
Beyond UV: Visible Light and Infrared
Photoprotection Beyond UV

• UV filters in sunscreens: designed to absorb UVB and/or UVA, not visible light or infrared

• External agents that protect against visible light: has to be opaque
  – Clothing
  – Tinted make-up or sunscreens (iron oxide)
  – Zn oxide paste

• Need to consider agents that are not filters
James Tissot (1836-1902)
The Ball. 1880
Musée d’Orsay
Paris
UVA1 vs Visible Light

(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

UVA1: 340-400 nm

Immediate 1 week
UVA1 vs Visible Light

(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

Immediate

Visible light
320 J/cm²

1 week
Visible light (VL)-induced Pigmentation

- In SPT III and IV: induced by 415 nm (blue/violet light), but not by 630 nm (red light)
  - Duteil, L, ... Passeron, T. Pigment Cell Melanoma Res 2014; 822. Nice, France

- Opsin-3 is the key sensor in melanocytes of dark skinned individuals responsible for the VL-pigmentary response
  - Regazzetti, C, .. Passeron, T. J Invest Dermatol 2018; 138:171. Nice, France
Synergistic Effect of Visible Light and UVA1

(Kohli, I, ..., Lim, HW, Hamzavi, I. Br J Dermatol 2018 May;178(5):1173)

- 10 subjects; SPT IV-VI
- VL 480 J/cm², in the presence or absent of UVA1 (340-400 nm; 0.05%)
Synergistic Effect of Visible Light and UVA1

(Kohli, I, ..., Lim, HW, Hamzavi, I. Br J Dermatol 2018 May;178(5):1173)

IPD Day 0
PPD Day 1
DT Day 7
DT Day 14

VL+UVA1     Pure VL

Average IGA score for Pigmentation

* * *
Clinical Implications

- Visible light may have a role on conditions aggravated by sun exposure such as PIH and melasma, esp. in dark-skinned individuals.
- Currently available organic (chemical) UV filters are not sufficient to protect the skin from the effect of visible light.
- Tinted sunscreens, or antioxidants may be beneficial
Sunscreen and Melasma

(Boukari, F, ... Passeron, T. JAAD 2015 (Jan); 72: 189)

• 39 pts (SPT III-V) with melasma:
  – 19: sunscreen A
  – 20: sunscreen B (= sunscreen A, tinted with iron oxide)

• 6 mo study; assessed with MASI (melasma area and severity index)

• Sunscreen B (tinted): better than sunscreen A
Antioxidants in Sunscreens
Sunlight & Reactive Oxygen Species

ROS is generated following exposure to:

- UV, especially UVA
- Visible light

(Liebel, F. JID 7/12; 132:1901)
Antioxidants & Sunscreens

Sunscreen + antioxidants >> sunscreen alone in:

• Suppressing UV-induced pigmentation, depletion of Langerhans cells, induction of MMP9

• Suppressing infrared A induction of MMP1
Antioxidants in Sunscreens

• Beneficial, provided they are stabilized and biologically active
Non-topical forms of photoprotection
Polypodium leucotomos
Extract
Polypodium leucotomos Extract


- Fern plant extract from Central America
- Antioxidative and anti-inflammatory properties
- Suppresses:
  - Clinical changes induced by UVB, PUVA
  - Development of PMLE
- Role in visible light photoprotection
PLE: Safety


• Pubmed search: 19 human and 6 basic science studies; over 40 years.
• Oral PLE: 120 mg to 1080 mg per day.
• No adverse effects were reported in laboratory studies.
• In humans, side effects (gastrointestinal complaints and pruritus) were mild to moderate. 16/1016 (2%)
• PLE: well tolerated with a negligible risk of side effects.
Acute Effects of *Polypodium leucotomos* Extract

(Kohli, I, ...Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July); 77:33)

- 22 subjects
- PLE, 240 mg 2 hr and 1 hr before UVB irradiation resulted in:
  - Decrease of UV erythema
Acute Effects of PLE (n=22 subjects)
(Kohli, I, …Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July); 77:33)

Assessement by Colorimeter ↓ 18% (p<0.05)

“Shift” of skin phototype
Acute Effects of *Polypodium leucotomos* Extract

(Kohli, I, ...Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July; 77:33)

- 22 subjects
- PLE, 240 mg 2 hr and 1 hr before UVB irradiation resulted in:
  - Decrease of UV erythema
  - Inhibition of markers of DNA damage and apoptosis (sunburn cells, cyclobutane pyrimidine dimers), inflammation (COX-2), and proliferation (cyclin D1, Ki67, PCNA)
Polypodium leucotomos Extract (PLE) and Visible Light
(Kohli, I, ...Lim, HW, Hamzavi, I. In progress. 2019)

• Preliminary in vivo data indicate that PLE:
  – ↓ persistent pigment darkening (PPD)
  – ↓ delayed tanning (DT)

• PLE may be beneficial for the protection of VL-induced pigmentary changes on the skin
Oral *Polypodium leucotomos* Extract (PLE)

- Safe and effective adjunctive tx (with hydroquinone and sunscreen) for melasma

- Study of 6 PLE preparations:
  - Fernblock® (Heliocare): Most efficient photoprotector (the preparation used in all published clinical studies)
Nicotinamide
Oral Nicotinamide

Chen, AC,… Halliday, GM. Photodermatol Photoimmunol Photomed 4-6/14; 30:102. Sydney)

• UV inhibits ATP production → energy crisis → prevents optimal skin immune response and DNA repair
• Oral nicotinamide (500 mg bid):
  – Blocks the inhibitory effect of UV on ATP production
  – Minimizes UV-immunosuppression
  – Enhances DNA repair
  – Unlike niacin, does not produce flushing reaction (niacin: lower lipid levels)
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

Oral Nicotinamide


- Phase 3 trial (= confirms effectiveness, monitor safety)
- Double-blind, randomized, controlled trial
- 386 participants with hx of NMSCs, randomly assigned (1:1):
  - Nicotinamide 500 mg bid
  - Placebo
- No differences in side effects
Oral Nicotinamide


![Graph showing change from baseline to month 12 in number of actinic keratoses.](image)

**Actinic keratoses**
### Oral Nicotinamide


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Nicotinamide</th>
<th>Rate Ratio (95% CI)</th>
<th>Relative Difference, % (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>12-mo intervention period</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>NMSCs</td>
<td>2.4</td>
<td>1.8</td>
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<td>23 (4 to 38)</td>
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<tr>
<td>BCCs</td>
<td>1.7</td>
<td>1.3</td>
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<td>20 (−6 to 39)</td>
<td>0.12</td>
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<tr>
<td>SCCs</td>
<td>0.7</td>
<td>0.5</td>
<td></td>
<td>30 (0 to 51)</td>
<td>0.05</td>
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<tr>
<td><strong>6-mo postintervention period</strong></td>
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<tr>
<td>NMSCs</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
<td>−17 (−59 to 14)</td>
<td>0.33</td>
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<tr>
<td>BCCs</td>
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<td>0.5</td>
<td></td>
<td>−6 (−53 to 26)</td>
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<tr>
<td>SCCs</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
<td>−59 (−163 to 4)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

The graph shows the relative difference in lesions between placebo and nicotinamide for different subgroups over two intervention periods.
Afamelanotide
Erythropoietic Protoporphyria
Solar Urticaria

Immediate

24 hrs
Afamelanotide


• Potent analogue of human alpha-melanocyte stimulating hormone
• Bind to melanocortin 1 receptor (MC1R) → induces production of eumelanin, which is photoprotective
• Melanogenesis may provide a major antioxidant defense in melanocytes
α-Melanocyte Stimulating Hormone Analogues


**EPP:**
- Afamelanotide, 20 mg s.c., twice, 60 days apart

**Solar urticaria:**
- Afamelanotide, 16 mg s.c., once

**Both:**
- Increased tolerance to artificial light
- Increased melanin content
Afamelanotide for Erythropoietic Protoporphyria

Afamelanotide for EPP: EU & US


- Randomized, double-blind, placebo-controlled study
- EU (74 pts): 5 subcutaneous implants, every 60 days
- US (94 pts): 3 implants
- Duration of pain-free time following sun exposure was longer in the treatment gr.
- Improved quality of life
- Adverse effects: headache, nausea, nasopharyngitis, and back pain
Non-topical Photoprotection

• Promising as an adjunctive photoprotective measure
• Not to replace current regimen of photoprotection
Learning Objectives

Be able to:

• Understand principles of photoprotection beyond the UV spectrum

• Describe agents that have this property
A Sunday on La Grande Jatte – 1884-86

Georges Seurat (French, 1859-1891). The Art Institute of Chicago