CONCEPT 1

FOR GI DISORDERS AND DISEASES

NANCY B. LIPKO, MD MBA

KNOWING :

Inflammatory bowel disease

Etiology involves **local inflammation, dysregulated immunity, the gut microbiome, the integrity of the intestinal epithelium**, genetics and environmental factors (primarily sun and diet).

Photobiomodulation

PBM has been shown to **modify** **blood flow, vascular endothelial growth factor (VEGF), local inflammation, dysregulated immunity, the gut microbiome, the integrity of the epithelium,** genetics (expression) and environmental factors (primarily sun and diet).

DISCOVERY OF PHOTOBIOMODULATION

Who	When	Where	What	Reference
Endre Mester	1967	Budapest, Hungary	Ruby laser and Helium Ion laser cause hair growth	*Kiserl Orvostud*
Endre Mester	1971	Budapest, Hungary	Lasers stimulate wound healing	*Am J Surg*
Endre Mester	1976	Budapest, Hungary	Immune system modulation by light	*Acta Chir Acad Sci Hung*
Endre Mester	1987	Budapest, Hungary	Increased blood supply	*New Scientist*
AP Sommer	2001	Ulm, Germany	Energy and Intensity refined	*J Clin Laser*
Pereira	2002	São Paulo, Brazil	3-4 J/cm2 optimal for proliferation	*Lasers Surg Med*
JC Sutherland	2002	Brookhaven, NY, USA	Dose-response functions of photoreactivation of visible light	*Protochem Photobiol*
Ying-Ying Huang	2009	Boston, MA, USA	Need to supply correct dose, biphasic response to light	*Dose Response*
Hoon Chung	2012	Boston, MA, USA	Biphasic dose response (Amdt-Schulz)	*Ann Biomed Eng*
LF Freitas and MR Hamblin	2016	Boston, MA, USA	Complete theory of Photobiomodulation	*BBA Clin, IEEE*

LIGHT ENERGY DRIVES PHOTOBIOMODULATION

Wavelenth	Spectrum	Photons absorbed by	Direct Effect	Indirect Eeffects Via	Indirect Effects
600-700 nm	Red	CCO + Other light sensitive ion channels	↑ Energy ↑ NO ↑ ATP	Signaling pathways, Transcription factors, Protein expression	↑ Anti-apoptosis, ↓ immune system, ↑Anti-oxidants, ↓Inflammation
760-940 nm	Near-infrared	CCO + Other light sensitive ion channels	↑ Energy ↑ NO ↑ ATP	Signaling pathways, Transcription factors, Protein expression	↑ Anti-apoptosis, ↓ immune system, ↑Anti-oxidants, ↓Inflammation
980 nm 1064 nm 1072 nm	infrared	Light sensitive ion channels	Some beneficial effects of Photobiomodulation are seen using these wavelengths of light.		
Broad band infrared (LED)	Infrared	Light sensitive ion channels			

WAVELENGTH, POWER DENSITY, ENERGY DENSITY & TOTAL ENERGY ARE DETERMINANTS OF EFFICIENCY

MECHANISMS OF PHOTOBIOMODULATION

Target	Phase	Light interaction	Direct Action	Reference
Mitochondria	Early, Short term	NO dissociates from cytochrome C oxidase in mitochondria	↑ oxygen consumption ↑ glucose metabolism ↑ ATP production	LF de Freitas, MR Hamblin 2016 *IEEE*
Cytochrome C Oxidase (CCO)	Early, Short term	Heme and copper absorb light	↑ electron transport ↑ mitochondrial membrane potential ↑ ATP production	Lane 2006 *Nature*
Reactive Oxygen Species (ROS)	Early, Brief	Causes brief increase in ROS	Trigger pathways for cytoprotective, antioxidant and anti-apoptotic effects	Waypa 2016 *Molecular Aspects of Med*
Nitrous Oxide (NO)	Early, Short term	NO dissociates from cytochrome C oxidase in mitochondria	Dilation of blood vessel and lymphatics	Zhao 2015 J *Pharmacol Sci*
Ca++	Long term	Opening of Ca ion channels	Signaling pathways activated	Palazzo 2013 *Current Topics in Med Chem*
Signaling Pathways	Days, weeks months	Exposure to light after acute injury, hypoxia, trauma	Activation of transcription factors	LF de Freitas, MR Hamblin 2016 *IEEE*
Transcription Factors	Days, weeks months	Change in protein expression	↑ anti-apoptotic proteins ↑ antioxidants ↓ excitotoxicity ↓ inflammation	LF de Freitas, MR Hamblin 2016 *IEEE*

QUESTIONS ASKED :

Why has nobody tried PBM for the GI tract?

Knowing:

- the signs and symptoms of IBD and Barrett's esophagus,
- and their long-term risks for cancer,
- wouldn't a scheduled, possibly weekly half hour, visit to a clinic be worth it?

Why not a GI/PBM clinic?

RESPONSES FROM MIKE HAMBLIN 18 JANUARY 2021

"I think what has put people off is the difficulty of delivering light into the intestines…I would expect whole-body led beds to help via the anti-inflammatory action."

"The Australian group delivers light to the abdomen to affect the gut microbiota."

"I did talk to some folks who wanted to make a swallowable LED capsule that would be switched on to emit red/NIR light by the pH change in the intestines" PhotoPill, Israel

GI DISEASES THAT ARE APPROACHABLE VIA CONCEPT 1

- Odontophagia during CRT treatment for cancer (mucositis involving oropharynx and esophagus)
  - *Compatible with other Photobiomodulation treatments for Oral Mucositis*
- **Barrett's Esophagitis**
- **Eosinophilic Esophagitis**
- Gastritis
- Gastric Ulcers
- Menetrier's disease
- GI mucositis of rectum and anal canal due to pelvic radiation therapy
- **Ulcerative Colitis, rectum and anal canal**
- Microscopic Colitis
- Proctitis

WHY WOULD CONCEPT 1 TECHNOLOGY WORK FOR INFLAMMATORY BOWEL DISEASES?

- Inflammatory bowel diseases (IBD) prevalence
  - 500,000 Crohn's Disease USA
  - 6-900,000 Ulcerative Colitis USA
  - Estimates of 2 million in USA, 0.2 million in Japan
  - 100 per 100,000 in US and Europe
- IBD cause-unknown
  - genetics,
  - gut microbiome,
  - Vitamin D/sunlight/UB light exposure,
  - western diet,
  - widespread antibiotic use,
  - dysregulated immune response,
  - impaired colonic epithelial defense system
- IBD treatment – biologicals $50,000/year per patient

CAN WE USE CONCEPT 1 TO PREVENT ADENOCARCINOMA OF THE ESOPHAGUS BY PREVENTING AND/OR TREATING BARRETT'S ESOPHAGUS?

- Esophageal cancer risk factors (adenocarcinoma and squamous cell carcinoma)
  - Gastro-Esophageal Reflux Disease (GERD) and subsequent Barrett's esophagus-impaired epithelial integrity
  - Smoking
  - Heavy alcohol drinking
  - Diabetes
  - Obesity
  - Hypercholesterolemia
- Esophageal cancer incidence 570,000 globally
- Esophageal cancer incidence 22,000 USA
- 5-year survival 19.9%

PREVALENCE

Region	USA	Europe	Japan
Population	**328M**	**741M**	**126M**
POSSIBLE PHOTOBIOMODULATION TREATMENT VIA CONCEPT 1			
Reflux Esophagitis ~25% US	7% endoscopic GERD 18-28% 65 million	2% endoscopic GERD 9-26% 14 million	1.5-5% endoscopic GERD 7-10% 3 million
Barrett's Esophagus (metaplasia, dysplasia) ~10% US	2% (asymptomatic) 7% (GERD symptoms)	Not comparable because EU definition (does not require goblet cells)	
Esophageal Cancer (squamous cell and adeno-carcinoma) 18,000 annually	48,000 USA preval. 18,000 diagnosed annually 7/100,000	5/100,000 diagnosed annually	SCC Diagnosed annually 23,900 7th most common cause of death
Eosinophilic Esophagitis (immune/antigen mediated)	60/100,000 children and adults 150,000 in USA	22-60/100,000	20/100,000
Gastrointestinal mucositis (oral cavity to anus)	500,000 annually 1-15% of chemo regimens (diarrhea) RT field includes GI		
Ulcerative Colitis	6-900,000 chronic		
Gastric Ulcers, gastritis	4.6M annually		
Proctitis (incidence and prevalence unknown)	30-50% of UC patients 2-20% RT patients Lymphogranuloma venereum		

WHAT WE DO KNOW

- GI tract should have ample mitochondria and cytochrome C oxidase (COX,CCO) for photon reception
- PBM causes increase in local ATP
- PBM causes increased migration in wound healing
- PBM causes increased blood flow and increased vascularity (via VEGF)
- PBM interacts with immune system
- PBM increases cell replication
- PBM is considered harmless
- 1-10 J/cm^2
- Several minutes of exposure best efficiency
- Light works with medical grade silicone
- Lights available commercially for bench top studies
- Esophagus is easiest to reach via Concept 1

WHAT WE DON'T KNOW

- 660nm vs. 780/800 nm or both
- Most efficient way to propagate even distribution of light to flexible elongated cylinder (360^{o})
- Can we test on epithelial cell lines (benign, metaplastic, dysplastic, malignant)?
- Can we test on organoids/3D cultures?
- Can we test on a mouse model (humanized)?
- Can we do computer modeling (Monte Carlo)?
- Do we need to study phantoms?
- Can we do a clinical study for esophagitis?

CONTRAINDICATIONS AT CURRENT STAGE OF DEVELOPMENT

- GERD with known dysplasia of lower esophagus (Barrett's esophagus)
- Untreated colon cancer
- Untreated gastric or esophageal cancer
- Untreated head and neck cancers

PHS 2020 omnibus solicitation of the NIH, CDC and FDA for small business innovation research grant applications (PA 20-260)

SBIR/STTR programs enable US-owned and operated small businesses to conduct research and development that has a strong potential for commercialization.

- R43/R44 Small Business Innovation Research (SBIR) Grant
- Phase I, Phase II, and Fast-Track
- Cycle 1 Due Date is Sept 5, 2021
- Earliest start date April 2022

Objectives of SBIR/STTR

phase I

- is to establish the technical merit and feasibility of the proposed research and development efforts

phase II

- to continue the R&D efforts to advance the technology toward ultimate commercialization
- NIH Fast-Track: Both Phase I and Phase II applications are submitted and reviewed together as one application to reduce or eliminate the funding gap between phases.

PA 20-260 NIH SBIR PROPOSED AIMS

AIM 1	Optimize safety and efficacy for illuminating the esophagus under various pathologic conditions, in vitro studies.
AIM 2	Research, develop and produce a prototype of an optimized light delivery medical device for a cylindrical living body organ
AIM 3	Testing of optimized Photobiomodulation dose (J/cm2) and wavelength(s) using in vivo animal models and/or in vitro 3D esophagus cultures and/or esophageal organoids

Mission:

HARNESS THE POWER OF LIGHT TO IMPROVE THE CONDITION OF MORTAL BEINGS…

Vision:

To restore productive lives

NANCY B. LIPKO MD MBA

- Biology Physiology BS 1982
- Medicine MD 1987
- Urology & General Surgery 1987-1988
- Pathology/Neuropathology 1989-1996
- NIH, NINDS, Special Expert 1996-1999
- Business Administration MBA 2003
- Biotech Medical Devices 2005-present
  - Optical Coherence Tomography 2005-2013
  - Photobiomodulation 2019-


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