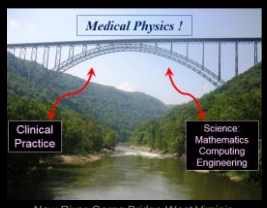
Opportunities for Medical Physicists: Radiation and Immunotherapy

Financial Disclosure:
Support from Immunolight LLC

Mark Oldham PhD, FAAPM
Professor, Radiation Oncology
Duke University Medical Center

Outline

- Radiation and Immunotherapy
  - Promise and potential
- Medical Physicists ?
  - Fluence and dose
  - Imaging (radiomics)
  - Modeling and Simulation
  - Radiation biology ..
  - *Scientific rigor, innovation and versatility*



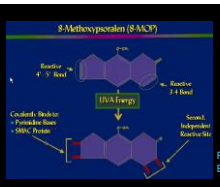
New River Gorge Bridge West Virginia

Opportunities for Medical Physics in Radiation and Immunotherapy ?

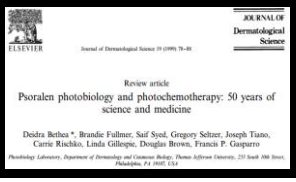
- Part I
  - Brief review of work at Duke
- Part II
  - Panel Discussion

X-ray Psoralen Activated Cancer Therapy (x-PACT)

- Planar, tricyclic structure..
- Photo-chemotherapeutic
- Long history of use
  - Skin cancer
  - Mycosis fungoides
  - Psoriasis, vitilgio
  - Proliferative and photodermatose disorders

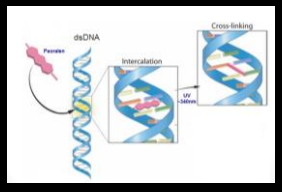


From Edelson R, et al.



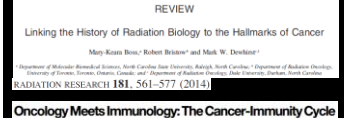
Psoralen

- Multiple Mechanisms:
  - DNA Cross-links
  - Protein Binding
  - Surface expression
  - Antagonize metabolizing enzymes
  - Cell signaling (e.g. ERBB2)
- Effects:
  - Apoptosis, necrosis
  - Abscopal (effect at a distant site)
  - Immunogenic effects



Learn Biology ! (see references in handouts!)

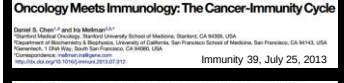
Reference Material


REVIEW

Linking the History of Radiation Biology to the Hallmarks of Cancer

Mary-Keara Boss,[a] Robert Bristow[a] and Mark W. Dewhirst[a]

RADIATION RESEARCH 181, 561–577 (2014)


Oncology Meets Immunology: The Cancer-Immunity Cycle

Immunity 39, July 25, 2013


Hallmarks of Cancer: The Next Generation

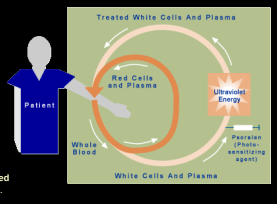
Cell 144, March 4, 2011 [a]

Psoralen in Extra-Corporeal Photopheresis (ECP)

R Edelson, MD
Yale Cancer Center

- First FDA selective immunotherapy
  - ECP: CTCL (Lymphoma)
  - Few adverse reactions
- Remarkable success ..

"To our astonishment, after only 6 treatments … , the first patient's debilitating and previously therapeutically resistant CTCL completely cleared. Seventeen years following cessation of the therapy, he remained disease free." (1987)



Kibbi et al., Induction of anti-tumor CD8 T cell responses by ECP-induced human dendritic antigen presenting cells. Translat Auther Sci 2016 Jun 6.

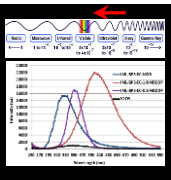
Psoralen is interesting !

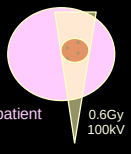
BUT ….

Limited to superficial applications (need UV light activation)

How to extend psoralen therapies to deep tumors?

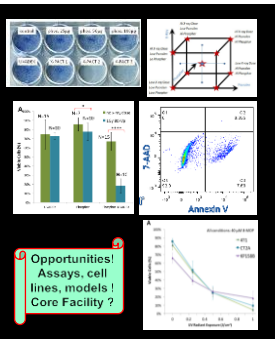
- Energy 'down-converting' particles
- Treatment Procedure
  - Administer psoralen+phosphor
  - Irradiate with x-rays
    - Photo-activation
  - Fractionate 6-9 fx
- X-PACT: X-ray Psoralen Activated Cancer Treatment





X-PACT development

- *In-vitro* experiments
  - Identify Tx parameters
  - Efficacy in different cell lines
- *In-vivo* Experiments (mice)
  - Tumor growth delay
  - Immune response
- Canine clinical trial



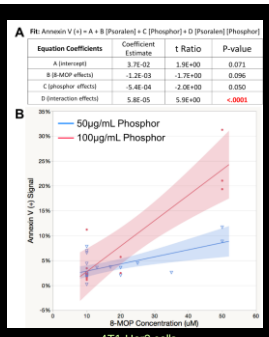
Opportunities! Assays, cell lines, models ! Core Facility ?

Cancer Treatment Utilizing X-PACT - WE-FG-BRA-1

X-PACT: In-vitro

Psoralen and Phosphor concentrations
- 36 independent experiments

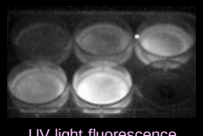
Rigorous data analysis (statisticians)



4T1-Her2 cells

Imaging UV fluorescence of phosphors under x-ray irradiation

Phosphor concentrations

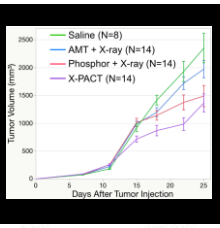


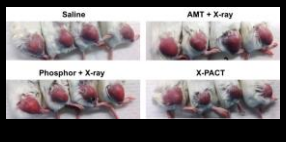
UV light fluorescence

X-PACT: in-vivo

BALB/c mice with syngeneic 4T1-HER2 tumors

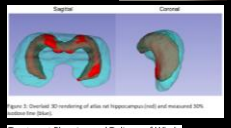
Strengthen pre-clinical Tx techniques.

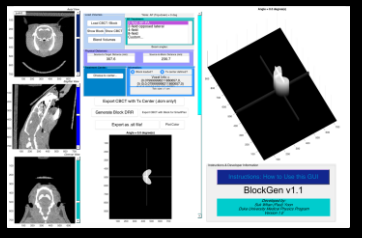




Conformal micro-SBRT for pre-clinical work

3D printed conformal blocks

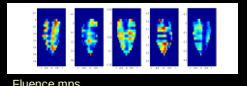




Treatment Planning and Delivery of Whole Brain Irradiation with Hippocampal Avoidance in Rats

PLOS ONE, 2015

IMRT rodent treatments



Fluence mps

Verification and QA !

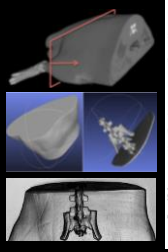
Investigating the accuracy of microstereotactic-body-radiotherapy utilizing anatomically accurate 3D printed rodent-morphic dosimeters

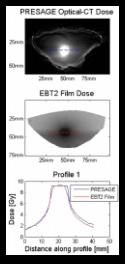
Steven T. Bache, Trivia Juang, and Matthew D. Belley
Duke University Medical Physics Graduate Program, Durham, North Carolina 27705
Bridget F. Koontz
Duke University Medical Center, Durham, North Carolina 27710
John Adamovics
Rider University, Lawrenceville, New Jersey 08648
Terry T. Yoshizumi, David G. Kirsch, and Mark Oldham[a)]
Duke University Medical Center, Durham, North Carolina 27710

(Received 19 May 2014; revised 1 December 2014; accepted for publication 22 December 2014; published 22 January 2015)

Purpose: Sophisticated small animal irradiators, incorporating cone-beam-CT image-guidance, have recently been developed which enable exploration of the efficacy of advanced radiation treatment

Med. Phys. 42(2), 2015





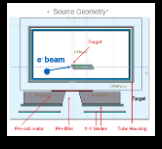
Initial work in mice was promising.

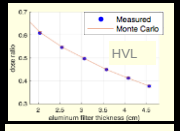
Move to a phase I clinical trial in dogs at NC State

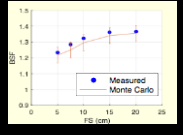
X-PACT commissioning at NC State Vet School

Implement new techniques


J Adamson, P Yoon







Commissioning 80kV
MC dose calculation **SU-C-204-6**

Clinical example X-PACT phase I dog patient

Small compassionate clinical trial (N=6).

X-PACT alone -> sustained clinical benefit (1 CR; 2 near CR) without significant toxicity.

Clinical responses ongoing at >12 months.

Consistent with the long-term responses reported in other psoralen studies (e.g. ECP)

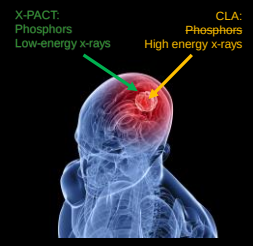
Cherenkov Light-Activation (CLA) ?

Advantages:
clinical MV radiation Tx
no need for additives

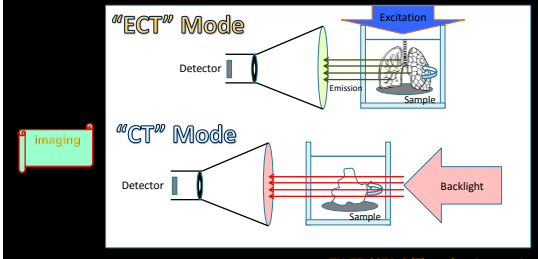
Cherenkov radiation fluence estimates in tissue for molecular imaging and therapy applications

Adam K Glaser[1], Rongxiao Zhang[1], Jacqueline M Andreozzi[1], David J Gladstone[1,2,3] and Brian W Pogue[1,2]

Phys. Med. Biol. 60, 2015

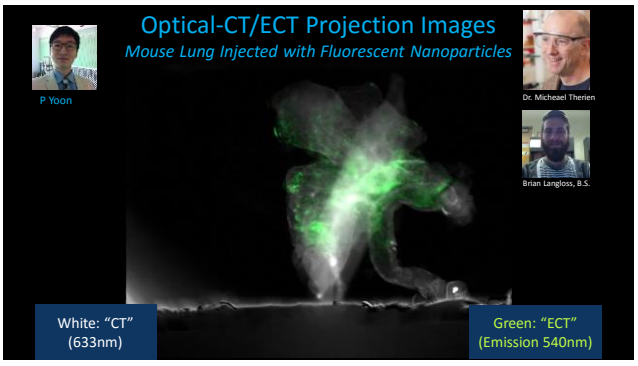


Optical-CT/ECT is… *CT/SPECT for Visible Light*



http://www.ncbi.nlm.nih.gov/pubmed/17343484

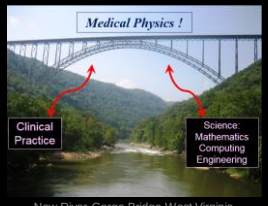
TH-EF-207A-6 (Thursday, August 4, 2016) 1:00 PM - 2:50 PM Room: 207A



Conclusions

Medical Physics bring real value :

- Scientific rigor
- Versatility and innovation
- Clinical interface



New River Gorge Bridge West Virginia

Acknowledgments

S Yoon[1] , B Meng[1] , Z Fathi[2] , W Beyer[2] , J Adamson[1] , D Alcorta[1] , T Osada[1] , K Lyerly[1] , M Dewhirst[1] , P Fecci[1], H Walder[2] , N Spector[1] ,
(1) Duke University Medical Center, Durham, NC
(2) Immunolight LLc, Detroit, MI

Mark Dewhirst, DVM, PhD

Michael Therien, PhD
Duke Chemistry

Neil Spector, MD
Duke Oncology

Harold Walder, PhD
Immunolight LLC

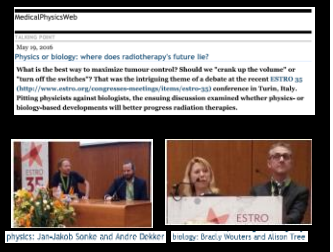
Michael Nolan, DVM, PhD, NC State

Peter Fecci, MD
Duke Neurosurgery

- Assays for immune response
  - http://www.nature.com/nri/journal/v4/n8/full/nri1416.html
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3360522/
- Other
  - http://www.ncbi.nlm.nih.gov/pubmed/24688774
  - http://www.ncbi.nlm.nih.gov/pubmed/27317354

AAPM Symposia 2016

- Radiomics (x3)
- Big Data In Radiation Oncology
- Connecting Radiation Physics with Computational Biology
- Biophysical modeling
- Knowledge guidance (x2)
- Modeling outcomes
- Radiation and Immunotherapy


MedicalPhysicsWeb

May 19, 2016

Physics or biology: where does radiotherapy's future lie?

What is the best way to maximize tumour control? Should we "crank up the volume" or "turn off the switches"? That was the intriguing theme of a debate at the recent ESTRO 35 (http://www.estro.org/congresses-meetings/items/estro-35) conference in Turin, Italy. Pitting physicists against biologists, the ensuing discussion examined whether physics- or biology-based developments will better progress radiation therapies.

Physics: Jan-Jakob Sonke and Andre Dekker

Biology: Bradly Wouters and Alissa Tree