Thunder and Light(ning):

Therapeutic applications of light and photo-activation

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Disclosures

- Intellectual property patents ..
  - X-PACT treatment
  - RECA treatment
- Consulting and funding from ..
  - Immunolight Llc

Outline

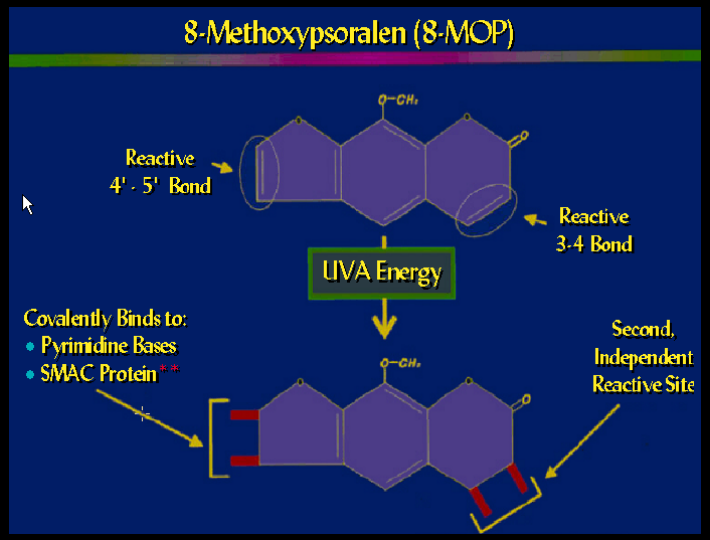
- Radiation and photo-therapy
  - X-PACT
    - X-ray Psoralen Activated Cancer Therapy
  - RECA
    - Radiation therapy Enhanced by Cherenkov photo-Activation

- X-PACT vs RECA
  - Both use psoralen
  - Differ in how light generated

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

Oldham et al. PlosOne, 2016

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



From
Edelson R, et al.

ELSEVIER

Journal of Dermatological Science 19 (1999) 78–88

JOURNAL OF Dermatological Science

Review article

Psoralen photobiology and photochemotherapy: 50 years of science and medicine

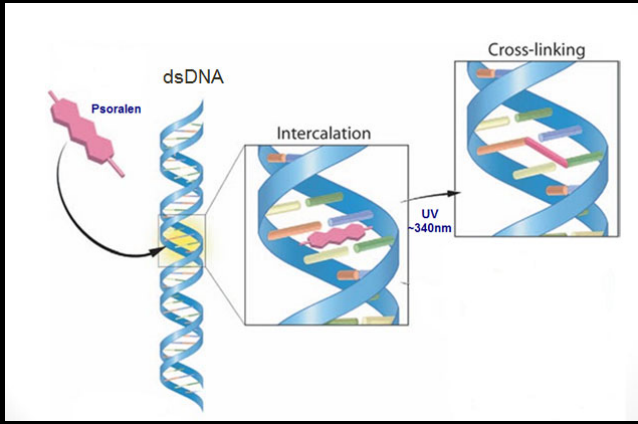
Deidra Bethea *, Brandie Fullmer, Saif Syed, Gregory Seltzer, Joseph Tiano, Carrie Rischko, Linda Gillespie, Douglas Brown, Francis P. Gasparro

Photobiology Laboratory, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107, USA

Psoralen

- Multiple Mechanisms:
  - DNA damage (17%)
  - Protein binding (54%)
  - Lipid binding (26%)

- Effects:
  - Apoptosis, necrosis
  - Immunogenic effects
  - Surface expression
  - Antagonize metabolizing enzymes
  - Cell signaling (e.g. ERBB2)



Psoralen Photobiology: The Relationship Between DNA Damage, Chromatin Structure, Transcription, and Immunogenic Effects

F.P. Gasparro[1], A. Felli[2], and I.M. Schmitt[2]

[1]Photobiology Laboratory, Department of Surgery, Yale University, New Haven, CT 06510, USA
[2]Department of Dermatology, University of L'Aquila, L'Aquila, Italy

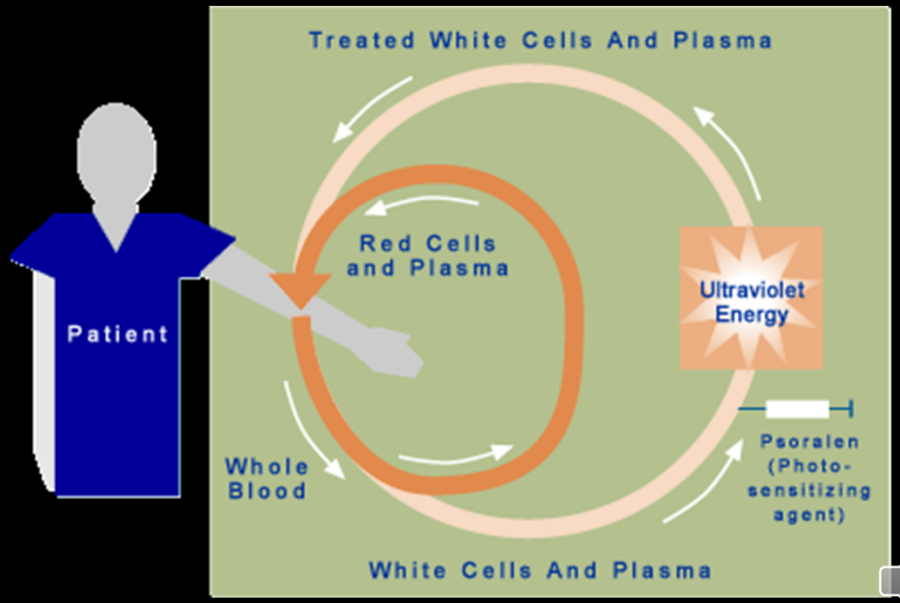
Recent results in Cancer Research, 1997

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

Psoralen in Extra-Corporeal Photopheresis (ECP)

R Edelson, MD
Yale Cancer Center

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



N Engl J Med 316:297-303, 1987

9 of 37 CTCL patients: >75 response

2000

"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."

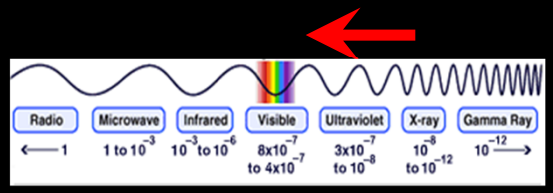
R Edelson, MD
Director, Yale Cancer Ctr

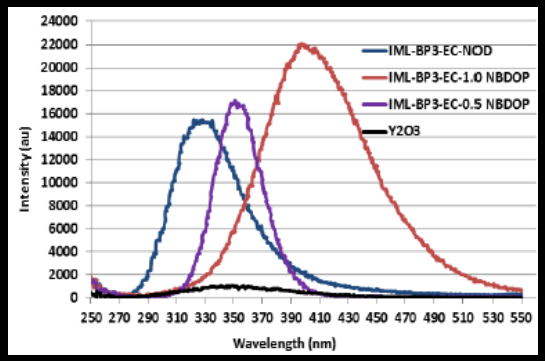
Psoralen is interesting !

BUT ….

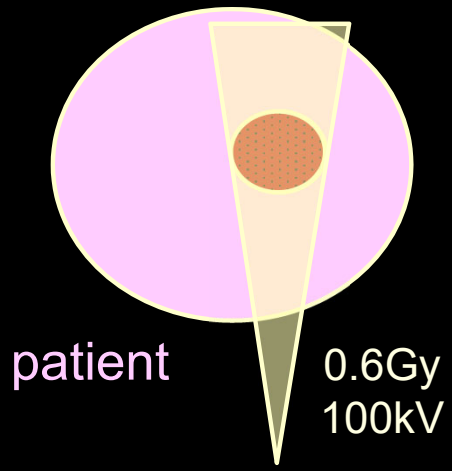
Limited to superficial applications
(need UV light activation)

Psoralen for deep tumors?

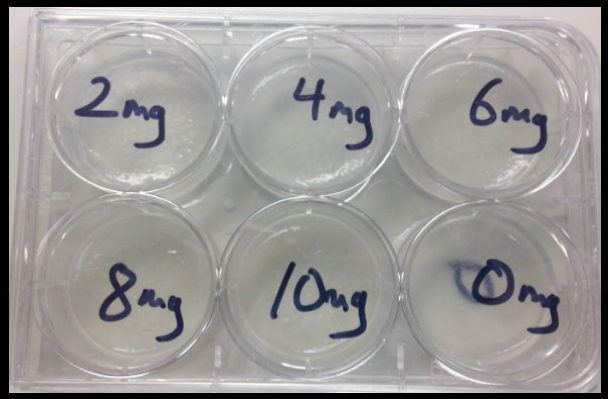




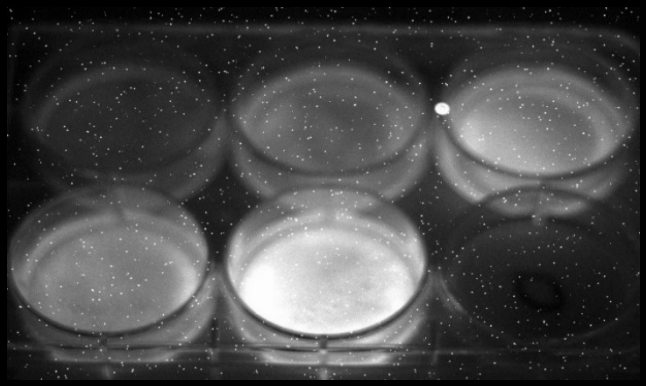
- Energy ‘down-converting’ particles
- Treatment Procedure
  - Administer psoralen+phosphor
  - Irradiate with x-rays
    - Photo-activation
  - Fractionate 6-9 fx
- X-PACT: X-ray Psoralen Activated Cancer Treatment



Imaging UV fluorescence of phosphors under x-ray irradiation



Phosphor concentrations

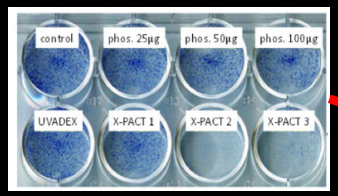


UV light fluorescence

X-PACT development

- *In-vitro* experiments
  - Identify Tx parameters
  - Efficacy in different cell lines
- *In-vivo* Experiments (mice)
  - Tumor growth delay
  - Immune response
- Compassionate use pilot Trial in companion dogs

kV x-ray dose from Varian OBI unit



Oldham et al. PLOS ONE, 2016

Initial work in mice was promising.

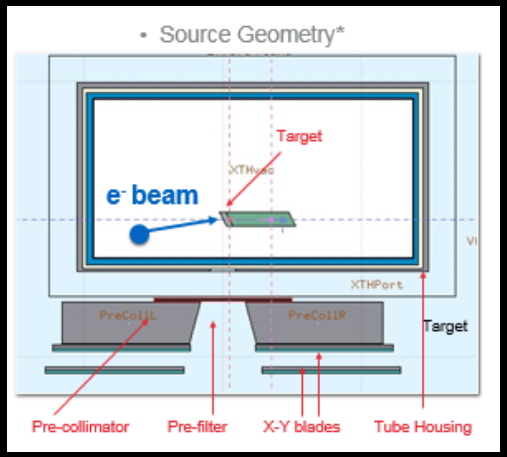
Move to a phase I clinical trial in dogs at NC State

Michael Nolan, DVM, PhD, NC State

X-PACT commissioning at NC State Vet School



J Adamson, P Yoon, B Meng



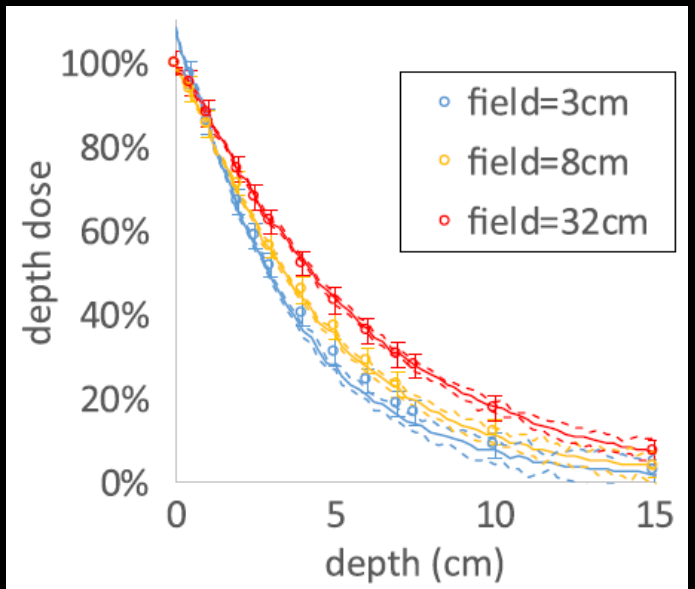


Figure 6. Depth dose curve for 80 kVp source at 80 cm source to surface distance for 3, 8, and 32 cm field sizes (defined at surface) and normalized at a depth of 1 cm. Open points represent measured values, while solid lines representing Monte Carlo (upper and lower uncertainty included as dashed lines).

Commissioning 80kV

MC dose calculation **SU-C-204-6**

Adamson et al., "Utilizing a diagnostic kV imaging system for x-ray psoralen activated cancer therapy (X-PACT), Biomed. Phys. Eng. Express 3 (2017)

X-PACT canine pilot study at NC State Vet School

Michael Nolan, DVM, PhD, NC State

6 dogs, compassionate care study:

- 9 fx over 3weeks
- 0.33-0.67mg phosphor/cc
- 3.35-6.67µg 8-MOP/cc
- 1.0Gy of 80kVp x-rays

- Follow-up
  - Lab work
  - Local tissue toxicity
  - PK of psoralen (8-MOP)
  - Elemental serum analysis

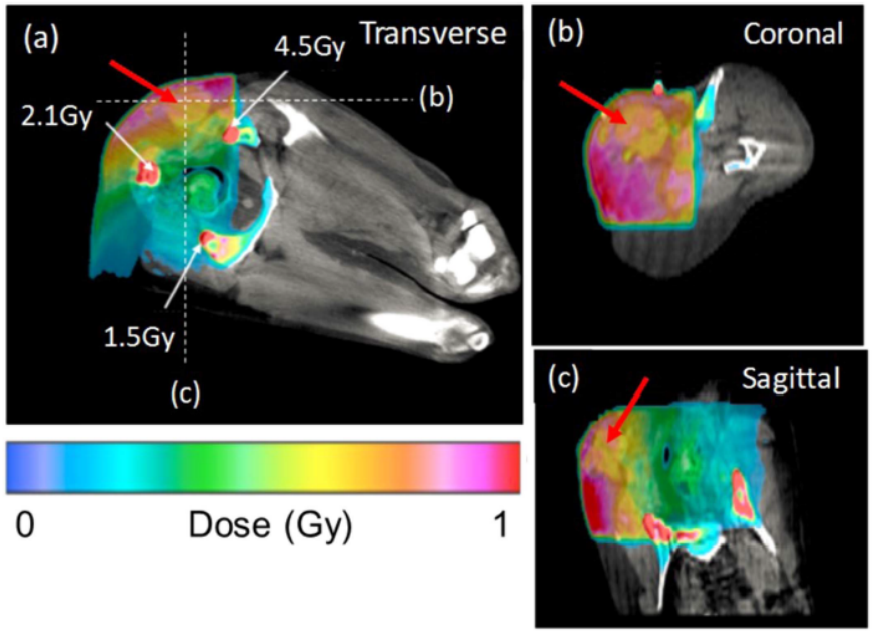


Figure 9. Final dose calculation using Monte Carlo modeling and canine CBCT for example case in figure 8; the location of the target treatment area is indicated by the red arrow(s). The dose colorwash scale was set to 0–1 Gy so as to easily visualize the dose throughout the volume; maximum dose to the bone is indicated as these values are outside the colorwash scale.

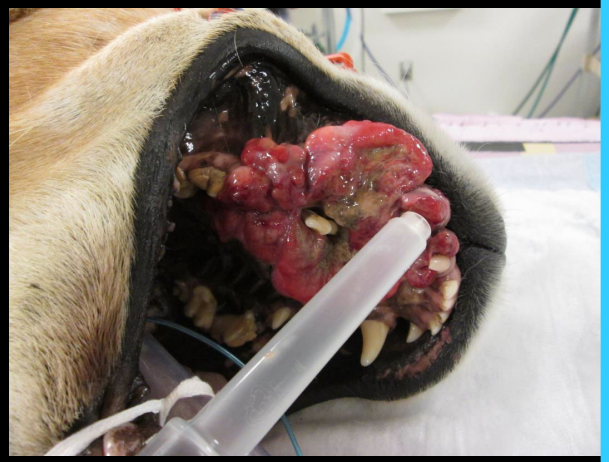
Clinical case study X-PACT phase I dog patient

Results:

CR 1/6 (> 1 year)
PR/SD 2/6 (> 1 year)
PD 3/6

Rostral maxillary tumor, round cell. (CD18,MelanA, PNL2, MUM1 –ve)

Pre Tx



Post Tx

X-PACT Conclusions ?

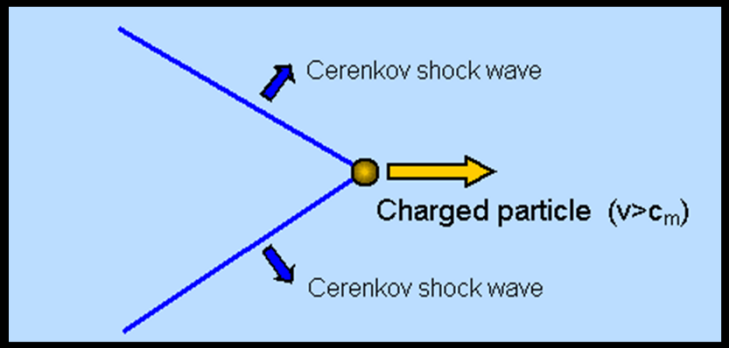
- X-PACT appeared to be
  - Safe and well tolerated
  - Treatment delivery was feasible
  - Limitations: phosphors and low energy

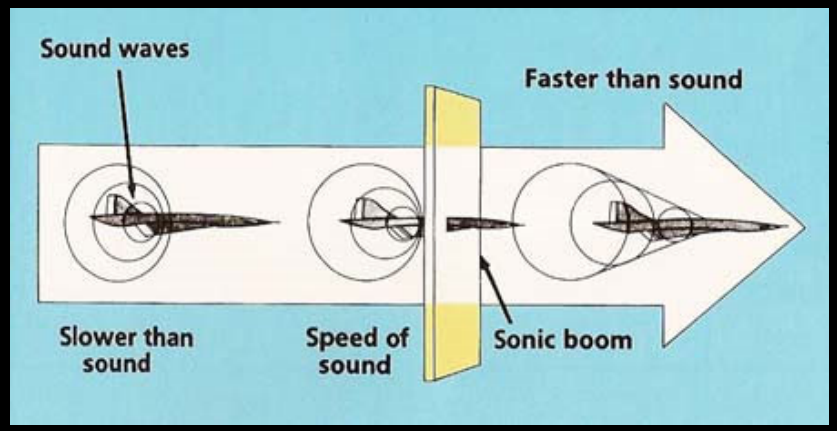
Cherenkov radiation fluence estimates in tissue for molecular imaging and therapy applications

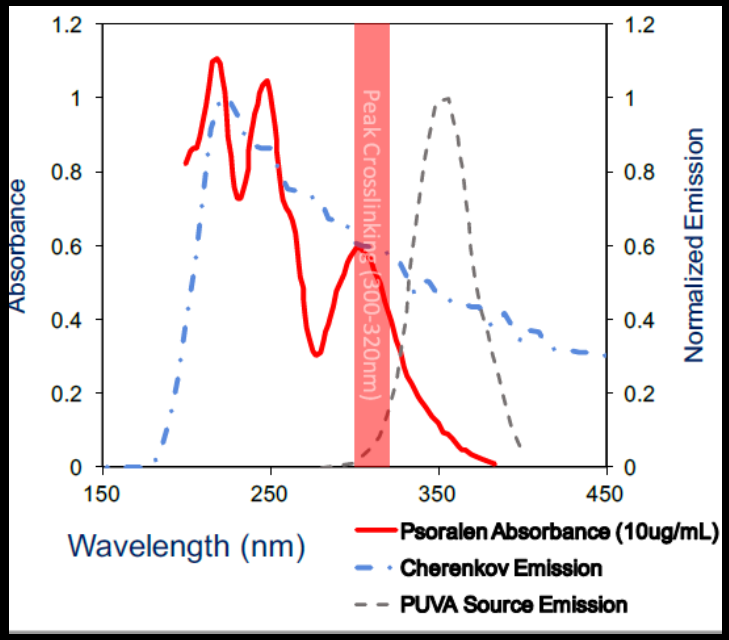
Adam K Glaser[1], Rongxiao Zhang[2], Jacqueline M Andreozzi[1], David J Gladstone[1,3,4] and Brian W Pogue[1,2]

Phys. Med. Biol. 60, 2015

Radiotherapy Enhanced by Cherenkov photo-Activation (RECA)

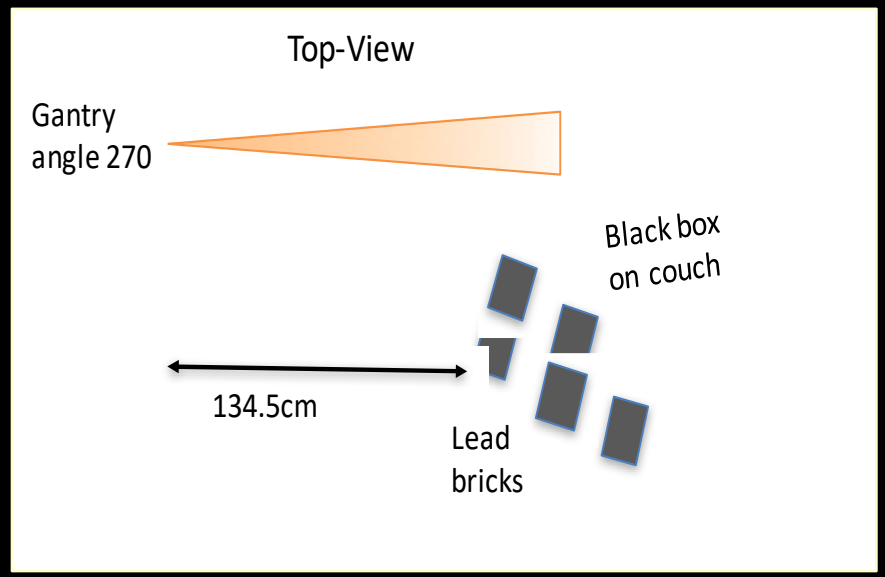


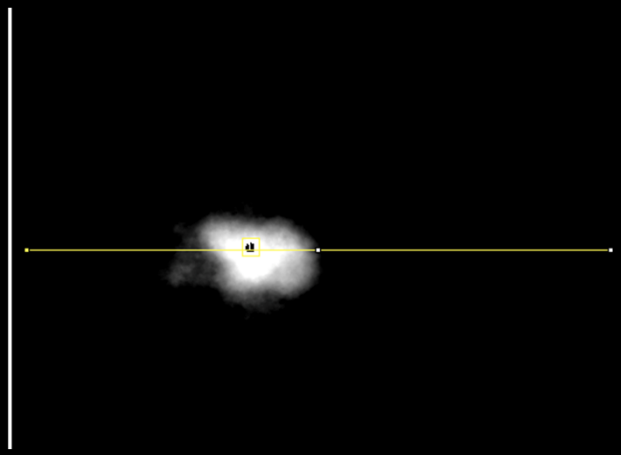


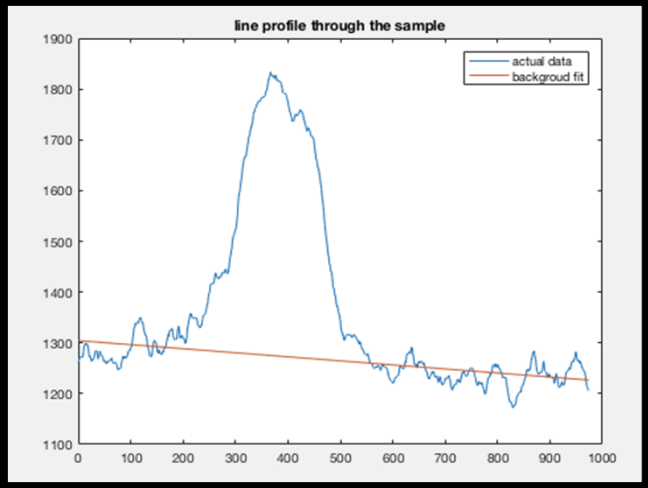


Cherenkov spectrum well-matched to psoralen

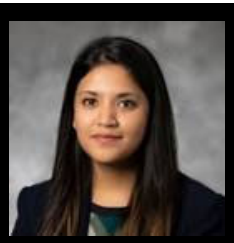
Linac MV generated Cherekov imaging experiments:



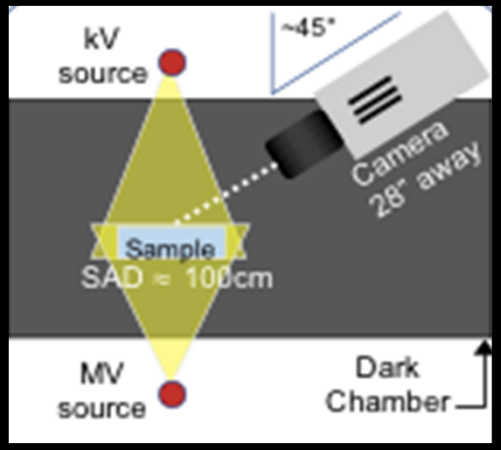


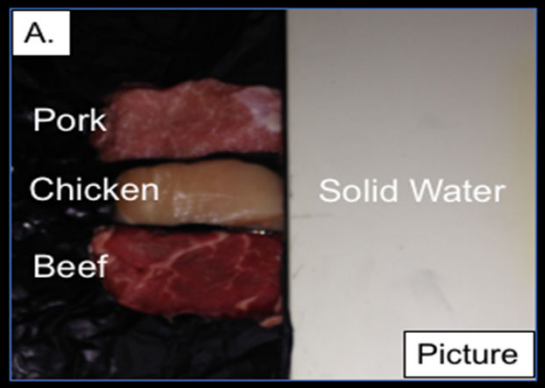


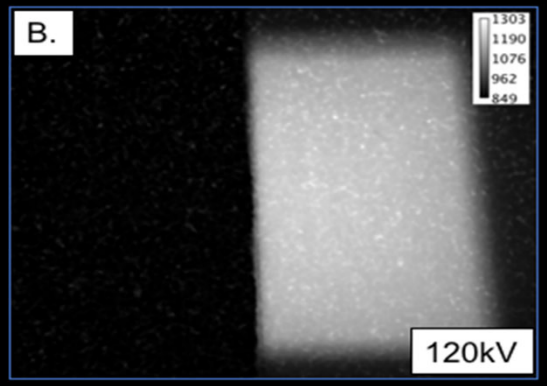
MV generated Cherenkov from tissue samples

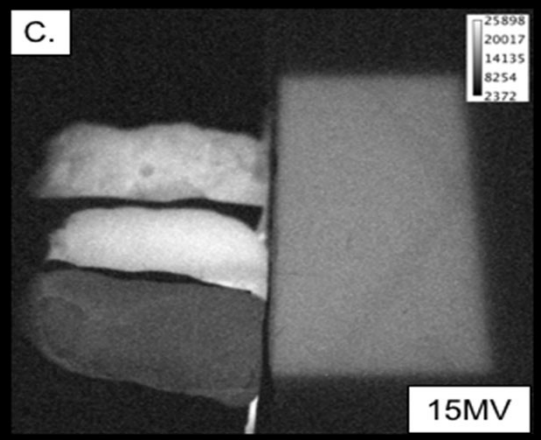


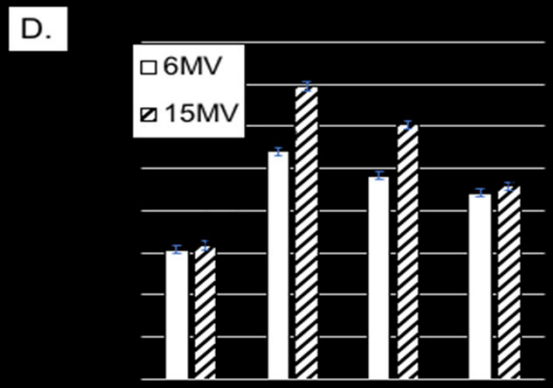
S Jain, MS











RECA in-vitro investigations

- 4T1 breast and B16 melanoma
  - Multiple independent assays
    - Cell Titer Glo Luminescence
    - Flow cytometry
    - Clonogenic survival
- MV beam optimization for Cherenkov output

Physics Contribution

Enhancing Radiation Therapy Through Cherenkov Light-Activated Phototherapy

Suk W. Yoon,* Vadim Tsvankin, MD,† Zachary Shrock,* Boyu Meng,* Xiaofeng Zhang, PhD,‡ Mark Dewhirst, PhD,§ Peter Fecci, MD, PhD,† Justus Adamson, PhD,§ and Mark Oldham, PhD§

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Received Jun 22, 2017, and in revised form Oct 20, 2017. Accepted for publication Nov 8, 2017.

IJROBP, 2017

Technical Note: On maximizing Cherenkov emissions from medical linear accelerators

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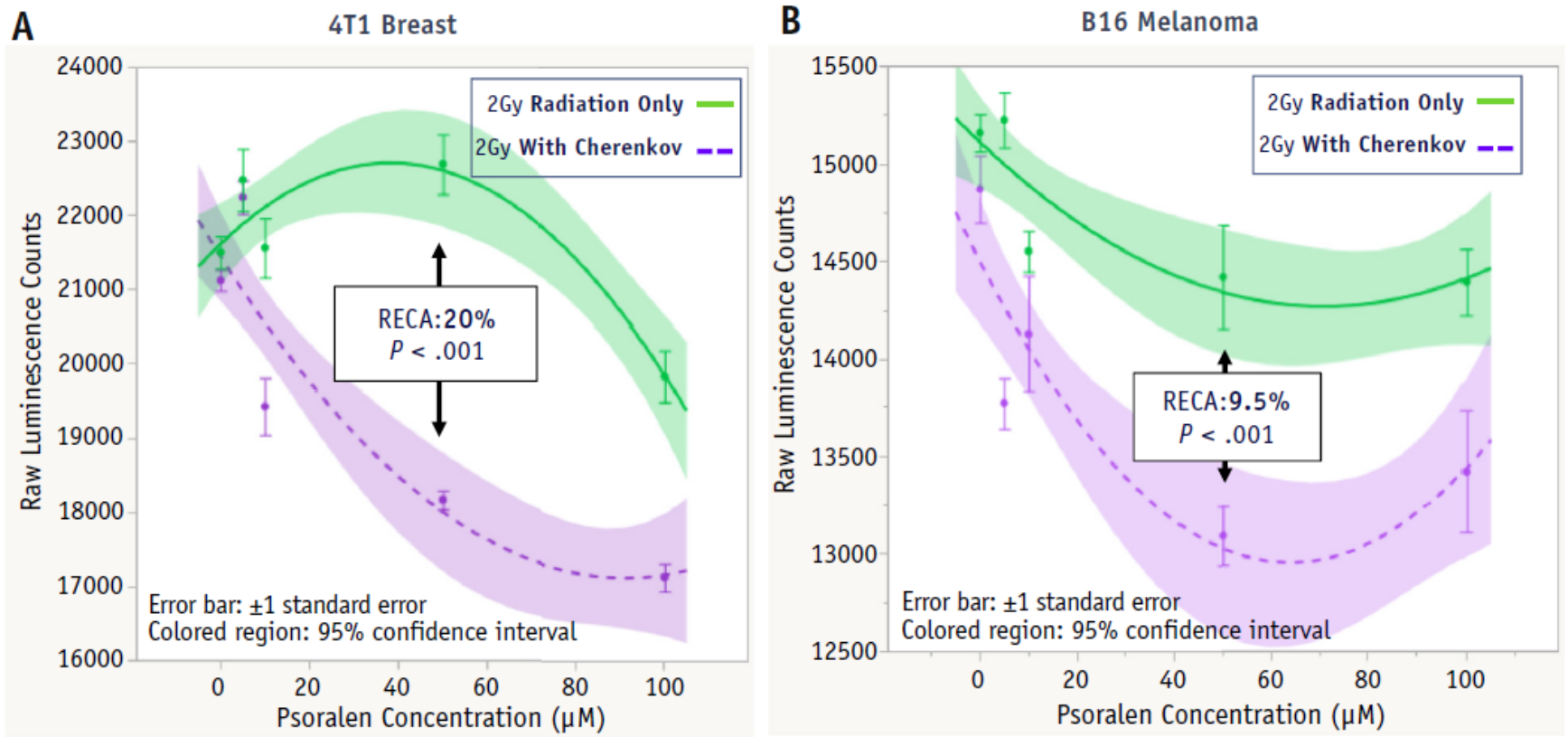
Medical Physics, 2018

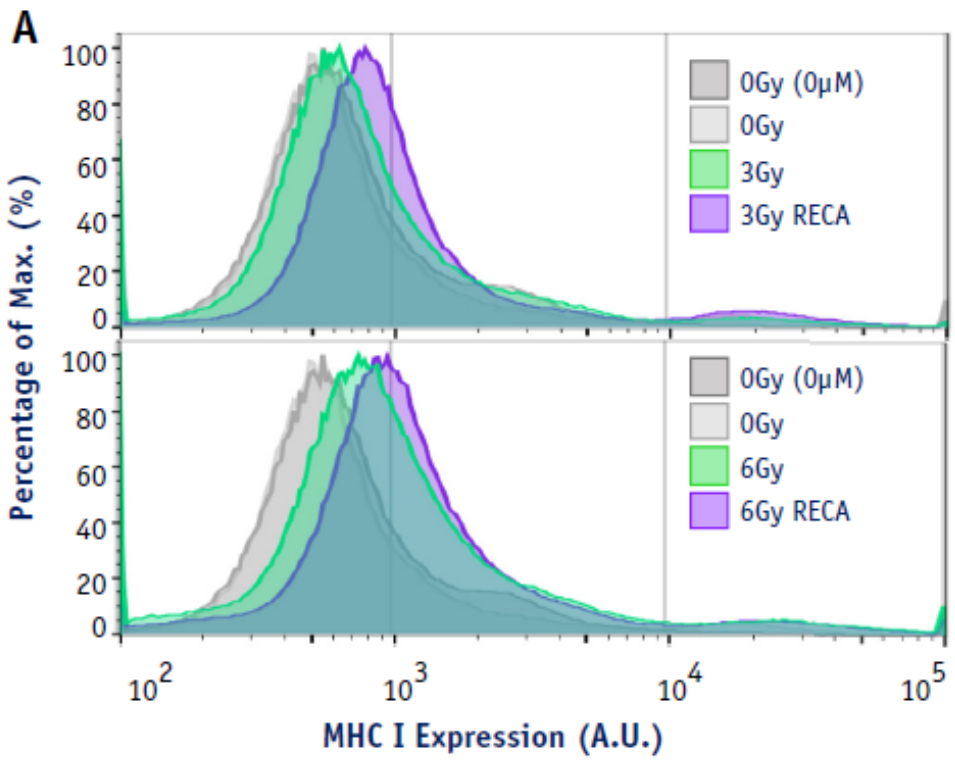
RECA and cell viability
(Cell-Titer Glo Luminescence)

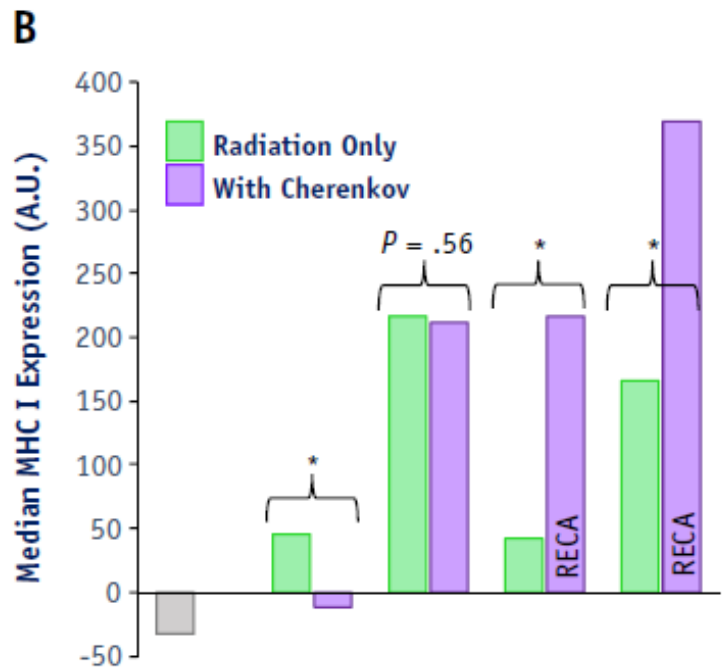


n = 6 wells per data point

n = 24 wells per data point

RECA and MHC I expression (B16)





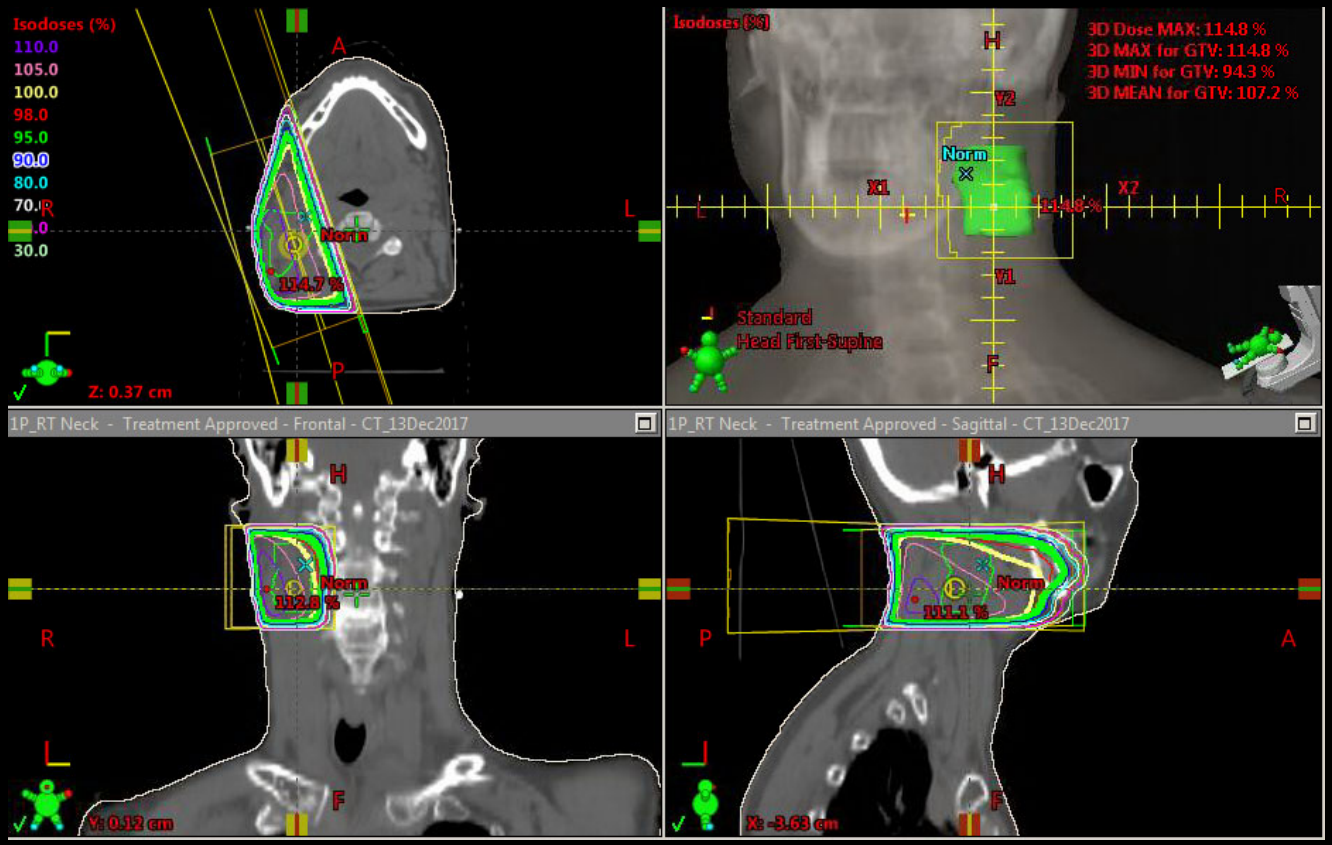
Dose	0Gy	3Gy	6Gy	3Gy	6Gy
Psoralen	+	-	-	+	+

Human patient FDA approved compassionate care MV-XPACT treatment

- 46 yr old Caucasian female
  - Triple negative invasive ductal carcinoma breast (2008)
  - Chemotherapy: 2008, 2009,
    - Metastatic recurrence in 2013, further chemotherapy
    - Metastatic recurrence in spring 2017, further chemotherapy, but disease progression and reluctance to give further chemo due to neuropathy, salvage RT late 2017.
    - MV-XPACT compassionate care treatment Dec 2017

MV-XPACT patient treament

- 4fx over 8 days of 1.35Gy/fx to total dose 5.4Gy
- Phosphor/UVADEX intra-tumoral injection pre-irradatiation
- Latest follow up PET 9 months later – no evidence of active metastatic disease



Dose / Fraction [cGy]	Number of Fractions	Total Dose [cGy]	Target Volume	Primary Reference Point [Volume]	Total Dose at Primary [cGy]	Relative Dose at Primary [%]	Prescribed Percentage [%]	Plan Normalization Mode
135.0	4	540.0	GTV	1P_Rt Neck [BODY]	540.0	100.0	100.0	100% in Reference Point Norm

Conclusions:

X-PACT	RECA
Psoralen required	Psoralen required
kV X-rays	MV X-rays
Very low dose (~1Gy/fx, 10Gy total)	Normal SBRT doses
Phosphors required to activate psoralen	N/A (psoralen activated by Cherenkov produced during the treatment)

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] ,

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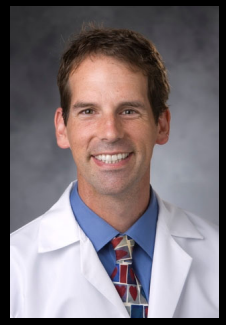

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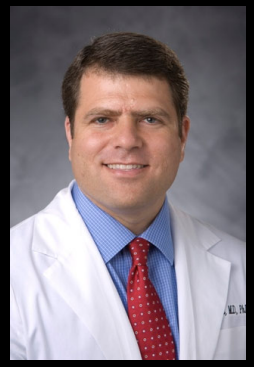

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