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, vitiligo
  - Proliferative and photodermatose disorders

From Edelson R, et al.
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)

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Psoralen in Extra-Corporeal Photopheresis (ECP)

• 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.”

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

Oldham et al. PLOS ONE, 2016
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

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

X-PACT canine pilot study at NC State Vet School

6 dogs, compassionate care study:
- 9 fx over 3 weeks
- 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)
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 Glaser¹, Rongxiao Zhang², Jacqueline M Androzzi¹, David J Gladstone¹,³,⁴ and Brian W Pogue¹,²

Radiotherapy Enhanced by Cherenkov photo-Activation (RECA)

Cherenkov spectrum well-matched to psoralen
Linac MV generated Cherekov imaging experiments:

Top‐View

Gantry angle 270

134.5cm

Black box on couch

Lead bricks

Line profile through the sample
MV generated Cherenkov from tissue samples

A. Sample
B. 120kV
Pork
Chicken
Beef
Solid Water
Picture

C. Sample
D. 6MV
15MV
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
RECA and cell viability
(Cell-Titer Glo Luminescence)

**4T1 Breast**

- 2Gy Radiation Only
- 2Gy With Cherenkov

RECA: 20%

$P < 0.001$

**B16 Melanoma**

- 2Gy Radiation Only
- 2Gy With Cherenkov

RECA: 9.5%

$P < 0.001$

$n = 6$ wells per data point

$n = 24$ wells per data point
RECA and MHC I expression (B16)
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 treatment

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

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

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