Disclosures

Consultant: Bayer, Roche
Scientific Advisory Board: Orano Med
Founder: Radiopharmaceutical Imaging and Dosimetry (Rapid), LLC
## Current cancer therapies

### 5-year survival by stage*

<table>
<thead>
<tr>
<th>Site</th>
<th>localized</th>
<th>distant</th>
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<tbody>
<tr>
<td>Breast</td>
<td>99%</td>
<td>30%</td>
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<tr>
<td>Colorectal</td>
<td>90%</td>
<td>14%</td>
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<tr>
<td>Lung</td>
<td>56%</td>
<td>5%</td>
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<tr>
<td>Ovary</td>
<td>93%</td>
<td>29%</td>
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<tr>
<td>Pancreas</td>
<td>32%</td>
<td>3%</td>
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<tr>
<td>prostate</td>
<td>100%</td>
<td>30%</td>
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*SEER.Cancer.gov
Current cancer therapies

After the cancer has spread/metastasized

- **Chemotherapy**
  - Kill rapidly proliferating cells

- **Targeted Biologic Therapy (hormonal Tx)**
  - Inhibit signaling pathways that tumor cells are addicted to (i.e., rely on to maintain cancer phenotype)

- **Immunotherapy**
  - Overcome immune tolerance to cancer
Radiopharmaceutical Therapy

**Molecular Radiotherapy (MRT), Targeted Radionuclide Therapy (TRT), Radioimmunotherapy (RIT)**

- Agent distributes throughout body
- Reacts with/binds to target cells
- Cleared from non-target cells
- Prolonged exposure to target cells gives larger radiation dose to target cells than to normal cells

**Where (else) does the drug concentrate, and for how long?**
Radiopharmaceutical therapy

- RPT provides targeted delivery of radiation
- Not susceptible to resistance mechanism seen in chemotherapy
- Kills target cells vs inhibiting growth/survival pathways; precludes adaptation
- Can measure delivery of the therapeutic agent to tumor targets and to normal organs
- Guide escalation protocols and plan treatment
## Radiopharmaceutical therapy

<table>
<thead>
<tr>
<th>RPT agent</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I-radioiodine</td>
<td>Jubilant Draximage</td>
<td>Thyroid cancer</td>
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<tr>
<td>$^{131}$I-MIBG</td>
<td>Progenics</td>
<td>Adrenergic+ tumors</td>
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<tr>
<td>$^{212}$Pb-trastuzumab</td>
<td>OranoMed</td>
<td>HER2+ tumors</td>
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<tr>
<td>$^{212}$Pb-PRIT</td>
<td>OranoMed/Roche</td>
<td>Undisclosed</td>
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<tr>
<td>$^{212}$Pb-antisomatostatin</td>
<td>OranoMed/Radiomedix</td>
<td>Somatostatin+ tumors</td>
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<tr>
<td>$^{212}$Pb-aTEM1</td>
<td>OranoMed/Morphotek</td>
<td>TEM1+ tumors</td>
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<tr>
<td>$^{212}$Pb-aCD37</td>
<td>OranoMed/NordicNanovector</td>
<td>Leukemia</td>
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<tr>
<td>$^{131}$I-aCD45</td>
<td>Actinium Pharmaceuticals</td>
<td>BM xplant prep</td>
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<tr>
<td>$^{225}$Ac-aCD33</td>
<td>Actinium Pharmaceuticals</td>
<td>Leukemia</td>
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<td>Varian/Sirtex</td>
<td>Hepatic malignancies</td>
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<td>$^{90}$Y-microspheres</td>
<td>BTG</td>
<td>Hepatic malignancies</td>
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<tr>
<td>Lutathera (^{177}\text{Lu})</td>
<td>Novartis/AAA</td>
<td>Somatostatin(^{+}) tumors</td>
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<tr>
<td>(^{177}\text{Lu})-aPSMA-R2</td>
<td>Novartis/AAA</td>
<td>Prostate, tumor neovasc.</td>
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<tr>
<td>(^{177}\text{Lu})-NeoBOMB1</td>
<td>Novartis/AAA</td>
<td>Bombesin(^{+}) tumors</td>
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<tr>
<td>(^{177}\text{Lu})-PSMA-617</td>
<td>Endocyte</td>
<td>Prostate, tumor neovasc.</td>
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<tr>
<td>Xofigo (^{223}\text{Ra})</td>
<td>Bayer</td>
<td>Bone mets</td>
</tr>
<tr>
<td>HER2-TTC (^{227}\text{Th})</td>
<td>Bayer</td>
<td>HER2(^{+}) tumors</td>
</tr>
<tr>
<td>PSMA-TTC (^{227}\text{Th})</td>
<td>Bayer</td>
<td>Prostate, tumor neovasc.</td>
</tr>
<tr>
<td>MSLN-TTC (^{227}\text{Th})</td>
<td>Bayer</td>
<td>Mesothelin(^{+}) tumors</td>
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<tr>
<td>aCD22-TTC (^{227}\text{Th})</td>
<td>Bayer</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>FPX-01 (^{225}\text{Ac})</td>
<td>J&amp;J/Fusion Pharma</td>
<td>NSCLC, pan-cancer target</td>
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</table>
Radiopharmaceutical therapy

- 21 RPTs (abridged list)
- 5 commercially available/FDA approved
  - $^{131}$I thyroid malignancies
  - Xofigo ($^{223}$Ra) castration resistant prostate cancer bone mets
  - Lutathera ($^{177}$Lu) somatostatin$^+$ tumors
  - Sirtex ($^{90}$Y) hepatic malignancies
  - Therapsheres ($^{90}$Y) hepatic malignancies
- 3 beta-emitters – $^{131}$I, $^{177}$Lu, $^{90}$Y
- 4 alpha-emitters – $^{225}$Ac, $^{227}$Th, $^{212}$Pb/$^{212}$Bi, $^{223}$Ra
Linear Energy Transfer (LET)

Tracks in chromatin fibre

Clustered ionizations from low-energy electron

Single ionization

Low LET tracks

High-LET track

DNA

Alpha-particle

25 nm

Delta-ray electron

-- high probability of damage when alpha-particle hits DNA.

Even better. High LET radiation!

- 250 KeV
- Co-60
- 6 MV
- 15 MV
- Protons
- High LET

% Dose vs. Tissue Depth in Centimeters
**Bifunctional Chelator**

CHX-A\(^{\text{N}}\)-DTPA

- **Antibody** (i.e.: trastuzumab)

- **Peptide** [i.e.: cyclo(Arg-Gly-Asp)]

- **Biovector**

  - \( ^{64}\text{Cu} / ^{68}\text{Ga} / ^{86/90}\text{Y} / ^{89}\text{Zr} \)

- **Chelate**

  - \( \text{NCS} \)

  - \( \text{H}_2\text{N} \)

  - \( \text{HO-C}_{\text{aryl}} \)

  - \( \text{CO}_{2}\text{H} \)

- **Target**
FIGURE 1. $^{68}$Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of $^{225}$Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C).
Tumor-response evaluation in RPT

A

B

C

D

2 x $^{177}$Lu-PSMA

2 x $^{225}$Ac-PSMA

$^{225}$Ac-PSMA

6/2015

9/2015

2/2016

4/2016

PSA = 294 ng/ml

PSA = 419 ng/ml

PSA = 3.5 ng/ml

PSA < 0.1 ng/ml

Kratochwil, et al. JNM 2016
DNA double-strand breaks

BT474, 4Gy XRT @1h

BT474, 370kBq (10 uCi) $^{213}$Bi-trastuzumab @1h
Relative Biological Effectiveness (RBE)

- dose for cell kill w/ betas $\approx 3-7 \times$ alphas, \textit{in vitro}

\[
RBE(x) = \frac{D_r(x)}{D_t(x)}
\]

$x =$ biological effect,
$r =$ reference radiation,
$t =$ test radiation

- RBE influenced by:
  - Biological end-point
  - Reference radiation
  - Dosimetry methodology
### Radiosensitivity (D₀) and Relative Biological Efficacy (RBE) of the MDA-MB-231 Cell Line under Different Exposure and DNA Repair Pathway Inhibition Conditions

<table>
<thead>
<tr>
<th>Agent, manipulation</th>
<th>D₀ (Gy)</th>
<th>RBE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>²¹³Bi-Rituximab (irrelevant Ab)</td>
<td>0.84</td>
<td>3.8</td>
</tr>
<tr>
<td>²¹³Bi-Cetuximab</td>
<td>0.87</td>
<td>3.7</td>
</tr>
<tr>
<td>²¹³Bi-Cetuximab, siRNA scrambled control</td>
<td>0.69</td>
<td>4.7</td>
</tr>
<tr>
<td>²¹³Bi-Cetuximab, siRNA DNA-PKcs-/DNA-PKcs-</td>
<td>0.37</td>
<td>8.6</td>
</tr>
<tr>
<td>²¹³Bi-Cetuximab, siRNA BRCA1-/BRCA1-</td>
<td>0.21</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*RBE is reported using 37% cell survival as the biological endpoint and Cs-137 gamma rays as the reference radiation.
The European Medicines Agency (EMA) has concluded its review of the cancer medicine Xofigo (radium-223 dichloride), and has recommended restricting its use to patients who have had two previous treatments for metastatic prostate cancer (prostate cancer that has spread to the bone) or who cannot receive other treatments.

Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases.
Early phase trials – opportunity to collect data
Don’t propose altering treatment
Show that dosimetry would have predicted toxicity or lack of efficacy
Assess patient variability
Apply rigorous, consistent methods
  - 3 time-points; 1\textsuperscript{st} and last cycle
  - Pre-therapy tracer study
  - SPECT/CT
Use collected data to validate simpler schemes
Be prepared to accept conclusions
  - Prior patient history, dose-range can impact dose-response relationship
Biomarkers

- Select patients most likely to respond
- Avoid toxicity
- Tumor biopsy
- Serum sampling
- Genetic and epigenetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials
Dosimetry

- Select patients most likely to respond
- Avoid toxicity
- Quantitative Imaging
- Blood Sampling
- Genetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials
Admin Activity (AA) vs Abs Dose

Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

Is small fraction of patients that will be undertreated worth the dosimetry effort/cost?

131I-anti-CD20 Ab; NHL patients Bexxar

Wahl, RL Semin Oncol ‘03
Tumor-Absorbed Dose Predicts Progression-Free Survival Following (131)I-Tositumomab Radioimmunotherapy.

Dewaraja YK\textsuperscript{1}, Schipper MJ\textsuperscript{2}, Shen J\textsuperscript{3}, Smith LB\textsuperscript{4}, Murgic J\textsuperscript{5}, Savas H\textsuperscript{6}, Youssef E\textsuperscript{6}, Regan D\textsuperscript{6}, Wilderman SJ\textsuperscript{7}, Roberson PL\textsuperscript{2}, Kaminski MS\textsuperscript{8}, Avram AM\textsuperscript{6}.

Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 (177Lu)–Dotatate in patients...
Red Marrow Dose vs Response: Literature

Platelet Toxicity Grade

A (N = 109)

B (N = 57)

C (N = 91)

D (N = 56)

O'Donoghue, et al., CBR ‘00
Red Marrow Dose vs Response: MSKCC (N=36)

Platelet Toxicity Grade

(A) Activity (GBq)

(B) Activity (GBq/m2)

(C) RM dose (Gy)

(D) WB dose (Gy)

O'Donoghue, et al., CBR '00
Effect of Chemotherapy: Mitomycin

- w/ mito
- w/o mito

RM dose (rad)

WB dose (rad)

Admin. Activity/SA (mCi/m²)
RM Dose Correlation Coefficients (r)

- **P-G**
- **W-%DC**
- **W-G**
- **P-%DC**
- **W-ADC**
- **W-TTN**
- **P-TTN**
- **P-ADC**

Legend:
- **w/o mitomycin**
- **w/ mitomycin**
Importance of organ volume in self irradiation

Correlation between kidney dose (Gy) and creatinine clearance loss/year (% baseline) N=18

Barone, et al. JNM ‘05
Correlation between BED and creatinine clearance loss/year

3D-RD Flowchart

1. Input
   - Activity data: SPECT or PET
   - Anatomic data: CT (or MRI)

2. Processing
   - Registration
   - VOIs definition
   - Generation of data volumes

3. Monte Carlo Calculation
   - Activity (x,y,z,t)
   - Density (x,y,z)
   - Composition (x,y,z)

4. Output
   - Abs. dose rate (x,y,z,t)
   - Processing
     - Mean dose
     - Isodose
     - DVH
     - BED (BVH)
     - EUD

MIRD Pamphlet 23: Quantitative SPECT for Patient-Specific 3-D Dosimetry in Radionuclide Therapy, JNM 2012
$^{153}\text{Sm}$-EDTMP – Xbeam Therapy

Pediatric patient population
$^{153}\text{Sm}$ emits $\beta^-$ with a half-life of 46.7 h and 103 keV photon.

Escalation protocols – patients treated with 1.2 mCi/kg and 5.0 mCi/kg (myeloablative) and imaged with planar images for dosimetry.

Median survival was 79 days – 2 patients (out of 14) had longer survival times (990 and 1472 days)

Loeb et al. Cancer ’09
Hobbs et al. Phys Med Biol ’10
Loeb et al. Cancer ’10
Senthamizhchelvan et al. J Nucl Med ’11
Sm-135 osteosarcoma RPT

Absorbed Dose, EUD vs Response

Absorbed Dose (21 Gy), EUD (6 Gy) threshold for PD vs SD

$p < 0.05$

Srinivasan, et al JNM ’12
Sm-135 osteosarcoma RPT

% Tumor Volume Reduction vs AD, EUD

Conirms PD vs SD results

Srinivasan, et al JNM ’12
Combined modality Therapy

- Osteogenic Sarcoma
- XRT for inoperable tumors
- XRT limited if close to spinal cord (SC)
- Combine w/ $^{153}$Sm (RPT)
- ↑ tumor dose, ↗ SC dose
- Adjust for dose-rates

\[
D_{RPT}^{dGF} = \frac{D_{RPT} \left( \frac{\alpha}{\beta} + G(\infty) \cdot D_{RPT} \right)}{\left( \frac{\alpha}{\beta} + \mu \right)}
\]

\[
G(T) = \frac{2}{D_{RPT}^2} \cdot \int_0^T \dot{D}_{RPT}(t) dt \int_0^t \dot{D}_{RPT}(w) \cdot e^{-\mu(t-w)} dw
\]

Hobbs, et al IJROBP '10
3. Combined RPT-XRT

Idea
- XRT can deliver precise amounts of radiation to regions of interest (ROIs) but limited by adjacent organ at risk (e.g. spinal cord).
- RPT highly conformal - delivers dose to all tumor sites including micro-metastases.

How?
- The combination XRT with RPT requires accurate 3-D dose calculations to avoid toxicity and evaluate potential efficacy.
- Deliver RPT (1.2 mCi/kg) and make 3D dose map in 3D-RD, convert to external beam AD values and import into XRT software and include in treatment plan.

Hobbs et al. IJROBP '10
Protocol

(a.) $^{18}\text{F}-\text{MISO PET/CT}$ for baseline
b. Stem cell collection for autologous transplant
c. CT-sim used for both XRT and RPT treatment planning
d. Low dose $^{153}\text{Sm-EDTMP}$ (1 mCi/kg)
e. SPECT/CT imaging at 4, 24 and 48 h, image reconstruction and dosimetry calculations.
f. High dose $^{153}\text{Sm-EDTMP}$ determined by dosimetry (max 20 mCi/kg)
g. High dose imaging at 4, 24 and 48 h, image reconstruction and dosimetry calculations
h. Autologous stem cell transplant (recovery)
i. IMRT plan, add fusion of low + high dose maps
(j.) $^{18}\text{F}-\text{MISO PET/CT}$ for treatment response
RPT-XRT AD equivalence

AD from XRT fractionated
AD from RPT over time
What about biological equivalence?
Use BED as a bridge
(Equivalent linear dose compared to the linear-quadratic absorbed dose with a repair term)
Equivalence depends on dose per fraction, $d$

$$BED_i = D_i \left(1 + \frac{D_i}{\alpha_i / \beta_i} \cdot G_i(\infty)\right)$$

$$BED_i = D_i \left(1 + \frac{d}{\alpha_i / \beta_i}\right)$$

$$EQD_2 = \frac{D_{RPT}(\alpha / \beta + D_{RPT} \cdot G_i(\infty))}{\alpha / \beta + 2}$$

Hobbs et al. IJROBP ’10
Combined treatment

Xbeam and PTV

Xbeam and Sm-153
Conclusions

- RPT dosimetry is the ideal biomarker
- Mechanism of action is well understood
- Needed measurements are known
- Patient-specific dosimetry tools are available
- Response data from radiotherapy
- Can measure delivery of the therapeutic agent to tumor targets and to normal organs
- Calculate radiation dose to tumors, normal organs
can guide escalation protocols and plan treatment

Need to overcome prior history—2nd chance
Implement standardized, validated activity quantification and dosimetry methods in early phase clinical trials to gather rigorous evidence that dosimetry will improve patient care.
## Acknowledgments

<table>
<thead>
<tr>
<th>Rob Hobbs</th>
<th>Ivan Guan</th>
<th>Eric Frey</th>
<th>NIH</th>
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<tr>
<td>Senthamil Srinivasan</td>
<td>Kevin Yeh</td>
<td>Richard Wahl</td>
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