Theranostics: Quantitative Diagnostics and Targeted Radio-Therapy in Solid tumors

Frontiers in Oncology

Friday-Saturday, January 27-28, 2017
The Biltmore Hotel, Coral Gables, Florida

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Disclosures

• Financial or Material Support from: Regeneron, Genentech and Bristol Myers
• Shareholder: Voreyda Theranostics, Inc. and Claymore Inc.

Key Concepts

• Theranostics
• Re-differentiation therapy in thyroid cancer
• Therapeutic Index (TI)

Theranostics at MSKCC

• Thyroid Cancer Redifferentiation for $^{131}$I Rx
• Recurrent CNS NB and other GD2 expressing tumors: $^{131}$I,$^{124}$I-8H9; $^{131}$I,$^{124}$I-3F8
• Diffuse Intrapontine Glioma $^{124}$I-8H9
• DOTA-PRIT in solid tumors
Theranostic Drug

• A drug or biologic with intrinsic diagnostic and therapeutic properties
• E.g. Na$^{124}$I/$^{131}$I for Dx/Rx thyroid Ca
• Related concept “Companion Diagnostic”
• E.g. $^{89}$Zr-MSTP (STEAP, Prostate Ca)
  To select patients for Rx who have target antigen

Thyroid Cancer Treatment

Redifferentiation Therapy for $^{131}$I-uptake

The Clinical Problem: RAI-Refractory Thyroid Cancer

• Distant metastases are the most frequent cause of death for patients with differentiated thyroid cancer$^1$
• Decreased RAI incorporation into metastatic sites is associated with higher mortality$^2$
• New therapies for RAI-refractory thyroid cancer are desperately needed

Integrated Genomic Characterization of Papillary Thyroid Carcinoma

MAP Kinase Signaling and Papillary Thyroid Cancer (PTC)

Driver oncogenes are known for ~95% of PTC tumors, and ~75% involve MAPK pathway

BRAF V600E 45%(9/20) patients

Proliferation

Survival

Integrated Genomic Characterization of Papillary Thyroid Carcinoma
Primary Objective

To determine whether RAI incorporation increases in RAI-refractory thyroid cancer metastases after 4 weeks of treatment with a MAPK pathway inhibitor.

Selumetinib (AZD6244 Hyd-Sulfate, ARRY-142886)
Highly selective, allosteric inhibitor of MEK 1/2
Inhibits MEK1 in vitro with an IC\textsubscript{50} of 14.1 +/- 0.79 nM

\textsuperscript{124}I –Positron Emission Tomography (PET)/CT

Advantages of \textsuperscript{124}I –PET
Quantitative, allows lesion dosimetry
Structural correlates for iodine incorporation

Restoring Radiodine Uptake in Thyroid Cancer
124I for lesion specific dosimetry in thyroid cancer

*Selecting for >2000 cGy lesion dose improved response rate for 131I Rx


Simplified dose model

The simplified model relies on the PET information from a single 48hr PET scan.

\[
Dose \ (cGy) = \int A_{\text{max}} \exp \left( -\frac{0.693 \times t}{\tau_e} \right) \Delta \phi \text{ d}t
\]

where \( \tau_e = 48 \text{hr} \) which is an average effective half-life in each lesion and \( \Delta \phi = 0.405 \text{g.cGy/µCi.hr} \) which is the equilibrium dose constant.

It can be shown that SUV > 20 would get > 2000 cGy, per lesion for an administered dose of 250 mCi, the usual maximum outpatient treatment dose.

MEK inhibition restores radioactive iodine uptake

- RET, BRAF, RAS mutant thyroid cancer → MAPK signaling → RAI refractory
- MEK inhibition restores iodine uptake
- 124I effective for 131I dosimetry
- Selumetinib increased 124I uptake in 12/20 pts (4/9 RAF, 5/5 NRAS mutant)
- 8/12 pts reached 131I dosimetry level
- Phase III trial planned

Best Response For Patients Treated with RAI
Summary

- Selumetinib enhances iodine incorporation in patients with RAI refractory thyroid cancer and reverses RAI resistance.
- Selumetinib effects upon iodine incorporation may be dependent upon clinical factors (degree of residual iodine incorporation, FDG avidity, number of previous RAI treatments) and/or tumor genotype.

Mechanism of Action

Nanostring RAI Response Predictor: Thyroid Differentiation Classifier (TDC)

Enhancing the thyroid differentiation score

Pathway/Cell Purity Gene Sets | Source
--- | ---
BRAF/RAS classifier | TCGA, Cell 2014
ERK output | Pratilas et al, PNAS 2009
Tumor purity score | TCGA, Cell 2014
Housekeeping controls | Nanostring + TCGA

J Krauf
Y Senbabaoglu
V Seshan
L Bacusai
J Fagin

eTDS and Vemurafenib in BRAF MUT RAI R Thyroid Cancer Patients

TDS: original thyroid differentiation genes used by TCGA
eTDS(+/+): eTDS(pos)eTDS(reg)
eTDS(all): TDS=eTDS(pos)+eTDS(reg)
Immunoconjugates at MSKCC

- **Radioimmunoconjugate**
  - Diagnostic and or Therapeutic Use
  - PET emitters, Beta Emitters, Alpha emitters
  - 18 clinically active, 2 Pending
- **Drug Conjugates**
  - e.g. STEAP* - Aurestatin E
  - Genetech

**Therapeutic Index for Targeted Radiotherapy**

- Radiation absorbed dose (cGy) in tumor vs radiosensitive tissue (marrow, kidney, lung)

![Image showing AUC values for tumor, blood, and kidney]

- $AUC_{tumor} = 812$
- $AUC_{blood} = 24$
- $AUC_{kidney} = 98$

**TI**

- $TI_{tumor: blood} = 34$
- $TI_{tumor: kidney} = 8$

**Targeted Radiotherapy of Solid Tumors**

- Curative Tumor Dose > 10,000 cGy
- Renal dose < 1500 cGy
  - ~7-10 Therapeutic Index (TI)
- Bone Marrow dose < 150 cGy
  - ~40-100 TI
- Colon mucosa dose < 250 cGy
  - ~40-60 TI

**MSKCC (Finn) Solid Target Assembly**

- $^{124}\text{Te(p,n)}^{124}\text{I}$ (incident energy 15 MeV)
- Ronald D. Finn, Ph.D.
Neuroblastoma and Glioma Theranostics with Radioimmuno-conjugates

- Nai Kong Cheung et al in Pediatric Oncology
- Unmet clinical need: better therapy for CNS recurrence of NB and primary Rx of Glioma
- 3F8 and 8H9 excellent antibodies
- PET scanning of iodine-124-3F8 for tumor dosimetry during treatment planning for radioimmunotherapy
- Long term collaboration including development of novel antibody forms

Sagittal section from serial $^{124}$I-3F8 PET images of pediatric patient with neuroblastoma

4 hours 24 hours 48 hours John Humm

Quantitative PET images used to estimate the radiation dose from 50mCi of $^{131}$I-3F8. Tumor dose estimates 12000 to 90000. Blood dose is 75 cGy. TI = 250-1200

Leptomeningeal Disease Uptake of $^{124}$I-8H9 (48 hours)

cRIT: Outpatient intraOmmaya injections at the bedside
Demographics N=188

3F8

- Assessment n=154
- Treated n=113
- Diagnoses
  - Neuroblastoma 81
  - Ependymoma 9
  - Medullo 9
  - Melanoma 4
  - RMS 3
  - CPC 2
  - Chordoma 1
  - Retinoblastoma 1
- Median age
  - 5.3 yrs (10 mo - 53 years)

8H9

- Assessment n=154
- Treated n=113
- Diagnoses
  - Neuroblastoma 81
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Recurrent neuroblastoma metastatic to the CNS

MSKCC
- Phase I Study of Convection-Enhanced Delivery of $^{131}$I-8H9 for Patients with Non-Progressive Diffuse Pontine Gliomas Previously Treated with External Beam RT Therapy

(PIs: Drs. Mark Souweidane/Ira Dunkel/Kim Kramer)

Kim Kramer  Naeta Pandit Taskar  Jorge Carraquillo  Jason Lewis
Conventional Radioimmunotherapy
e.g. $^{131}$I-Bexxar or $^{90}$Y-Zevulin

Pre-targeted Radioimmunotherapy
DOTA-PRIT
A33 (GPA33)
3F8 (GD2)
Herceptin (Her2)
Separate the antigen targeting step and the radioactivity targeting step

Targeting Challenge: Radiation directly bound to an antibody

Collaborators
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K. Dane Wittrup, Ph.D. CP Dubbs Professor of Chemical Engineering and Biologic Engineering; Assoc. Director, Koch Institute of Technology

Key Personnel
Sarah Cheal, Ph.D. Senior Scientist Molecular Pharmacology Program; Radio chemist, pre-Doc under Claude Meares and Post-Doc in Larson Lab

Hong Xu, Ph.D., Senior Scientist, Robert Steele Lab.
Immunobiologist, Memorial Sloan Kettering Cancer Center
huA33
GPA33 antigen
Junctional Membrane Complex Ag
Metastatic Colorectal Cancer

A33 extensively studied in colorectal cancer patients in vivo:
• huA33 is a humanized mAb which binds to GPA33 antigen
• At MSKCC: 124I-huA33 in patients with advanced colorectal cancer
  • GPA33+ cancers:
    95% of colon carcinomas

124I-huA33 PETCT

OS’Donoghue et al. JNM (2011) 52: 1878-1885
Zanoni et al. EJNMMI (2015) 42: 1700-1706
Curative therapy for SW1222 Colon Cancer
Twin Benefits of High Therapeutic Index:
Safe Treatment (A) and Superior Diagnosis (B)

Anti-GPA33 DOTA-PRIT: theranostics

Step 1: Inject huA33-C825 @ t = 0
Step 2: Inject clearing agent (CA) @ t = 24 h
Step 3: Inject $^{177}$Lu-Benzy1-DOTA or $^{90}$Y-Benzyl-DOTA @ t = 28 h

MW ~ 210 kD
MW 15.4 ± 2.0 pM
MW 10.8 ± 2.5 pM

Tissue Absorbed Dose

Minimum Effective or Maximum Permissible Dose (rad)

Blood

GPA33+ tumor

Kidney

Curative Anti-GPA33 DOTA-PRIT is below estimated MTD

At 96 days post treatment, 5/10 examined for normal organ toxicity
No toxicity detected*

*Examined for:
Bone marrow hypocellularity
Renal Damage (tubular damage, sub-cortical atrophy, glomerular proliferation)
CBC’s and blood chemistry abnormalities
SPECT/CT imaging for Dosimetry of cycle 1-3

Fitted exponential decay curves on three-cycle treatment regimen. Units for activity concentration (y-axis) are μCi/mL. Of the total dose of ~100 Gy, the first dose contributes 30%; the second dose 60%; and the third dose 10%.

Harnessing Atomic Energy to Cure Cancer : DOTA PRIT*

- Novel Immuno-oncology Rx
- Improve therapeutic index >10-fold over conventional Radioimmunotherapy
- Potential to greatly Reduce toxicity for ADC
  - Radioactive payloads
  - Toxins
  - Chemotherapies
- A platform technology, Applicable to the Common Solid Tumors: Colon, Ovary, Breast, Gastric, Lung (SCLC), Sarcoma

Support

- Ludwig Center for Radioimmunotherapy and Theraonotics
- ICMIC NCI  P50 SM Larson PI
- Thyroid SPOR P50 J Fagin PI
- NCI P30 Cancer Center Support Grant
  G. Thompson, PI>