Precision Medicine

Precise Landing for a Cancer Moonshot

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Disclosure

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- Supported from Marian Falk Foundation
- Supported from State of Pennsylvania Department of Health
- Founder and CSO of AAA Phoenix and ProstaGene
- External Advisor to 7 NCI cancer centers
Precise Medicine

- Definition
- Resourcing
- Ethics
- FDA Approved Drug - Retasking
Precision Medicine

- Medical Model
- Customizes Healthcare
- Decision practice and products
- Tailored to the individual patient
Precise Medicine - evolution of medical culture

**Blockbuster Model**

- Narrow
- Mass Phenotype
- Disease State
- 1 Drug - 1 Disease State
- Scale
- Few "Large" Runs
- Few, Large

**Product Portfolio**

- Wide

**Markets**

- Targeted Genotype

**Focus, Patient Relationships**

- Disease Life Cycle

**Treatments/Drugs**

- Continuity of Treatments Over Disease Life Cycle

**Economics**

- Knowledge

**Manufacturing**

- Many "Small" Runs

**Sales Forces**

- Multiple, Small
I’m Alive Thanks to Precision Medicine ... and Other Patients

Stage 3a NSCLC 05/2011
Stage 3b/4 10/2011
Metastatic 09/2012

No Evidence of Disease since 12/31/2012

Clinicians

Request pathology results
Submit slides for gene panel
Visit U of Colorado Hospital request ROS1/RET tests enroll in clinical trial

Interact online with lung cancer patients and follow research developments
<table>
<thead>
<tr>
<th>CANCER THERAPY TYPE</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>5-Flourouracil Carboplatin</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>Abiraterone acetate Fulvestrant</td>
</tr>
<tr>
<td>Epigenetic modifiers</td>
<td>Azacitidine Decitabine</td>
</tr>
<tr>
<td>Immune stimulators &amp; Checkpoint inhibitors</td>
<td>Aldesleukin Pembrolizumab</td>
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<tr>
<td>Angiogenesis inhibitors</td>
<td>Bevacizumab Regorafenib</td>
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<tr>
<td>Vaccines</td>
<td>Sipuleucel-T DCVax-L</td>
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<tr>
<td>Adoptive immunotherapy</td>
<td>Anti-CD19 CAR-T cell therapy CART-Meso</td>
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<tr>
<td>Therapeutic antibodies</td>
<td>Cetuximab TDM-1</td>
</tr>
<tr>
<td>Cell signaling inhibitors</td>
<td>Ibrutinib Imatinib Ceritinib</td>
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</table>

Within each category, some therapeutics are more precise than others.
Precision Medicine

- 2015 Precision Medicine Initiative
- Public trust
- Accountability
- Data sharing, quality integrity
Moon Shot Initiative

- 2016 moon shot initiative
- $1B initiative
- Discovery
- Delivery

- Cancer Vaccine
- Early cancer detection
- Immunotherapy/combination
- Genomic profiling- microenvironment
- Pediatric Cancer
- FDA- virtual center of excellence

And the goal of this initiative—this “Moonshot”—is to seize this moment. To accelerate our efforts to progress towards a cure, and to unleash new discoveries and breakthroughs for other deadly diseases.

-Vice President Joe Biden, January 13, 2016
Barriers to Precision Medical Care

- Financial barriers
  - Reimbursement,
- Discrimination
  - Medical insurers, employers
- Legal barriers to innovation and development
  - Patent protection -Federal court- (Myriad ruling), Patent,
- Incumbent inertia
  - Current dogma, financial incentive to status quo.
1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. CCR5
1. Cyclin D1 kinase inhibitors
1. Cyclin D1 kinase inhibitors

Cyclin D1 gene deletion reduces tumor formation

Anti-sense reduces tumor formation


Hulit, J, Pestell, R, (MCB) 2003
1. Cyclin D1 kinase inhibitors
1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. CCR5
2. Nuclear Receptor Acetylation Governs tumor growth

- WT K630T
- [14C] Ac-p300
- [14C] Ac-ERα
- GST-ERα
- p300
- GST
- kDa

<table>
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<th>Veh</th>
<th>DHT</th>
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<tr>
<td>Vector</td>
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<tr>
<td>K630Q</td>
<td></td>
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<tr>
<td>K630T</td>
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</tbody>
</table>

- % Colonies >100 cells
- 0 10 20 30 40 50 60 70 80 90

- [14C] Ac-p300
- [14C] Ac-ERα (aa282-420)

- K630T
- WT
- pDNA3
- Veh
- DHT
2. Nuclear Receptor Acetylation Governs tumor growth
1. Cell-cycle and cyclin D1 kinase
2. Nuclear receptor acetylation
3. CCR5 – HIV co-receptor
3. CCR5 Receptor is expressed in Breast Cancer
Breast oncogene induction of CCR5 Receptor Signaling and Invasion

MCF-10A:Vector  Neu-T  Ras  Src

Invasion

Control

CCL5

P>0.05
P<0.05  P<0.05
P>0.05
CCR5 Receptor Expression Promotes Breast Cancer Cell invasion

Cell number at 240 μm

P=0.004
The HIV CCR5 Receptor Signaling and Function

- **CD4 Binding**
  - BMS-cpds
  - TNX-355
  - PRO 542
  - gp41
  - gp 120
  - V3 loop
  - CD4

- **Coreceptor Binding**
  - CCR5/CXCR4
  - (R5/X4)
  - CCR5 Inhibitors
    - maraviroc
    - PRO 140
    - TAK 652
    - vicriviroc
  - CXCR4 Inhibitors
    - AMD-070
    - KRH cpds

- **Virus-Cell Fusion**
  - enfuvirtide
  - TRI-999
  - TRI-1144
CCR5 Receptor Inhibition blocks Breast Cancer invasion

Control  Maraviroc 100 nM  Vicriviroc 100 nM
CCR5 Receptor Inhibition blocks Breast Cancer Metastases lung metastasis in vivo
CCR5 Receptor Inhibition blocks Breast Cancer Metastases in vivo

P < 0.0001
CCR5 Receptor Inhibition blocks homing step of Metastases in vivo
Clinical Trial Breast Cancer

Study Diagram

Phase 1 (9-12 patients)
Maraviroc 300-500 mg QD
Carboplatin AUC 2 q week x 3 weeks (28 days cycle)

Phase 2
Maraviroc 300-600 mg QD
Carboplatin AUC 2 q week x 3 weeks (28 days cycle)

Endpoints
1) OS
2) PFS
3) CTCs decline
4) CTCs-CCR5
5) TTNM

Images:
- Merged
- DAPI
- Cytokeratin
- EpCAM
- CD45
- Merged
- DAPI
- PD-L1
- CCR5
- PD-1
CCR5 function in Breast cancer

- CCR5 signaling induced in human basal breast cancer
- Oncogenes induce CCR5 signaling
- CCR5 overexpressed in basal breast epithelial cells
- CCR5 induces invasion and metastasis
- CCR5 inhibition blocks basal breast cancer metastasis in pre-clinical models
- FDA approved safety- expedited Phase I/II clinical trial (in progress)
Prostate Cancer

- Most common cancer in American men (ACS 2012) (1/6 men)
- 241,740 men will acquire this year
- 28,170 deaths/per year
- 2.5 M current survivors - no reliable predictors of survivors
- Increasing incidence globally
- Death from metastasis (bone, brain)
- No reliable pre-clinical testing metastasis models
Development of immune-competent metastatic prostate cancer model

- Immune system participates in human prostate cancer
- Immune competent systems (transgenics)- unreliable metastasis
- Transgenic of Probasin-c-Myc- reflect human disease
- Pre-clinical need for therapy testing in immune-competent animals
Lung Metastases of Prostate Cancer lines

c-Myc
NeuT
Ha-Ras
v-Src

30 days 16 days 30 days 30 days

25 µm 25 µm 25 µm 25 µm

30 days 16 days 30 days 30 days

2mm 2mm 2mm 2mm
Vicriviroc blocks lung metastasis

- Vicriviroc blocks lung metastasis

- Preclinical testing demonstrates efficacy
Isogenic Prostate Cancer Lines Reliably Metastasize to Brain in Immune-competent Mice
Maraviroc blocks brain metastasis
Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice
CCR5 Receptor inhibition reduces bone metastasis in vivo
Maravirocin blocks bone metastasis.
Maraviroc blocks bone metastasis
CCR5 in Prostate Cancer

- CCR5 signaling activated in vivo in immune competent animals
- Reliable metastasis of isogenic prostate cancer lines
- CCR5 inhibitors reduce metastasis in immune-competent mice in vivo (total body, lung, bone and bone)
- FDA approved safety- expedited Phase I/II clinical trial
CCR5 in Human Cancer

- Expressed in broad array of human cancers (breast, prostate, lung, brain, lymphoma)
- Expressed in significant proportion of patients with cancer (>50% of BCa, PCa)
- Expressed on CTC (surrogate for clinical trial/management)
- Enhances DNA damage of chemotherapy in tumor
- CCR5 inhibitors reduce metastasis in immune-competent mice in vivo (total body, lung, bone and bone).
- FDA repurposing
Acknowledgements
Spend more time with your family and friends, eat your favorite foods, visit the places you love.
CCR5 Receptor In Breast and Prostate Cancer Metastases
Isogenic Prostate Cancer Lines Reliably Metastasize to Liver in Immune-competent Mice

Liver

% mice with tumors

Ras Src NeuT

Photon flux (p/sec/cm²/sr)

Ras Src NeuT

Kidney

% mice with tumors

Ras Src NeuT

Photon flux (p/sec/cm²/sr)

Ras Src NeuT

C

D

E

F
Oncogene Signature Distinguishes Normal vs. Tumor
Prostate Cancer
Isogenic Lines- conserved oncogene signature
3. CCR5 Receptor Signals In Breast Cancer

![Images showing the effects of CCL5 and FBS on the MDA-MB-231 cell line.](Image)

- **CCL5**
  - 0 s
  - 81 s
  - 391 s

- **FBS**
  - 0 s
  - 81 s
  - 391 s

![Graph showing RFI over time with peaks for CCL5 and FBS.](Image)

**Time (s)**

- 0
- 150
- 300
- 450

**RFI**

- 0
- 1
- 2
- 3
- 4
Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice
Vicriviroc blocks lung metastasis 2 weeks

- Vicriviroc blocks lung metastasis
- Preclinical testing demonstrates efficacy
Prostate Cancer CCR5 Receptor Signaling activated in vivo
Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice

**B**

<table>
<thead>
<tr>
<th></th>
<th>% mice with tumors</th>
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<tbody>
<tr>
<td>Ras</td>
<td>100</td>
</tr>
<tr>
<td>Src</td>
<td>100</td>
</tr>
<tr>
<td>NeuT</td>
<td>100</td>
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**C**

<table>
<thead>
<tr>
<th></th>
<th>Photon flux (p/sec/cm²/sr)</th>
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<tbody>
<tr>
<td>Ras</td>
<td>100</td>
</tr>
<tr>
<td>Src</td>
<td>100</td>
</tr>
<tr>
<td>NeuT</td>
<td>100</td>
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</table>

![mice with tumors](image)

![bone metastasis](image)
Isogenic Prostate Cancer Lines Reliably Metastasize to Bone in Immune-competent Mice
CCR5 Signaling induction in Breast Cancer

Correlation in healthy samples:
- CCL5: R = 0.26, p = 0.07349
- CCR5: R = 0.17, p = 0.095335
- CCR1: R = -0.28, p = 0.038666

Correlation in tumor samples:
- CCL5: R = 0.66, p = 5.2809e-271
- CCR5: R = 0.40, p = 6.4999e-132
- CCR3: R = -0.16, p = 3.7945e-013
CCR5 Receptor and Breast Cancer Outcome

% samples in quadrant

Upper right
Upper left
Lower right
Lower left

Survival probability

p = 6.1204e-008

met-free survival (yrs)
Spend more time with your family and friends, eat your favorite foods, visit the places you love.


Antisense

Cyclin D1 genotype

-/+  +/-  +/-

0 1 2 3

Number of Polyps

proximal distal

Colonic tumor distribution

PALOMA-1: Randomized open-label phase II trial

- FDA Breakthrough Designation
  April, 2013
- Accelerated FDA approval
  February 3, 2015

Medicinal Research

Presented by Joseph Sparano at 2015 ASCO Annual Meeting

Jefferson Kimmel Cancer Center NCI-designated
Maraviroc blocks brain metastasis