Sheikh Khalifa bin Zayed Al Nahyan Institute for Personalized Cancer Therapy

John Mendelsohn  Gordon Mills
Funda Meric-Bernstam  Kenna Mills  Shaw

DELIVERING ON THE PROMISE OF PERSONALIZED MOLECULAR MEDICINE
• Financial Relationships
  – **SAB/Consultant:** AstraZeneca, Catena Pharmaceuticals, Critical Outcome Technologies, ImmunoMET, Ionis, Medimmune, Nuevolution, Pfizer, Precision Medicine, Signalchem Lifesciences, Symphogen, Takeda/Millennium Pharmaceuticals, Tarveda,
  – **Stock/ Options/Financial:** Catena Pharmaceuticals, ImmunoMET, Spindle Top Ventures, Tarveda
  – **Licensed Technology**  HRD assay to Myriad Genetics
  – **Sponsored Research:** Abbvie, Adelson Medical Research Foundation, AstraZeneca, Breast Cancer Research Foundation, Critical Outcomes Technology, Horizon Diagnostics, Illumina, Ionis, Karus Therapeutics, Komen Research Foundation, Nanostring, Takeda/Millennium Pharmaceuticals, Tesaro

I will discuss off label use and/or investigational use of drugs
Targeting the Genetic Changes Specific to Each Patient’s Cancer
Small molecules and immune therapy

Capitalizing on the vulnerabilities (Achilles Heel) of cancer
## Most Effective Targeted Agents Are Linked to Response Prediction Biomarkers

<table>
<thead>
<tr>
<th>Imatinib mesylate</th>
<th>CML</th>
<th>BCR-ABL translocation</th>
<th>Oncogene addiction</th>
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<td>GIST</td>
<td>c-KIT mutation</td>
<td>Oncogene addiction (1982)</td>
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<td>protuberans</td>
<td>HER2 amplification</td>
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<td>Cetuxumab</td>
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<td>FLT-3 mutation, tandem</td>
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<td>Breast</td>
<td>BRCA1/2 mutation</td>
<td>Synthetic lethality (2005)</td>
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<td>PLX4032</td>
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<td>BRAF (8 years)</td>
<td>Oncogene addiction (2002)</td>
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<td>Lung</td>
<td>EML-4 ALK (4 years)</td>
<td>Oncogene addiction (2007)</td>
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<td>BTK expression</td>
<td>Lineage (1993)</td>
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<tr>
<td>Tamoxifen, Alts</td>
<td>Breast cancer</td>
<td>ER expression</td>
<td>Lineage (1800s)</td>
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*Except VEGFR and proteosome inhibitors

Combination of mutation, co mutation and lineage
Khalifa Institute for Personalized Therapy

MDACC patients without curable disease 20,000
5-9000 per year

Actionable mutations
Targetable
Predict patient outcomes
(Paraffin compliant)

Targetable aberration present

Standard of care
N of 1 trials
Clinical trial cohorts

No Targetable Aberration
Deep characterization
High throughput biological validation

Deep learning from each patient; Real time adaptive treatment
Efficacy of targeted therapy conditioned by mutation, comutation and tissue lineage BRAF in melanoma and bowel

**Patients**

- Colorectal
- Small intestine
- Ovarian
- Endometrial
- Cervical
- Breast

* Clinical progression
+ Continuing response

Janku et Mol Can Ther
CAN WE ACHIEVE TRULY PERSONALIZED THERAPY?
N of one problem
Precision Medicine?

Stratified Medicine
Homogenous patient groups
Ductal Breast Cancer
8 subclasses
A set of orphan diseases

Rare aberration populations
AKT mutant tumors
2-3% in any major lineage
0.7% in trial sets

Multiplex analysis of multiple aberrations allows “amortization” of costs across multiple trials
IPCT CLEARING HOUSE PROGRAM

Patient identified by physician  Over 10,000 patients now registered
(Likely to enter clinical trial)

Block Requested

Biopsy if clinically indicated or part of trial

Research

T200.2

CLIA testing in P and LM

Oncomine: Hot spot, full length, fusions

Actionable events

Database development and updates for trials
Querriable database of patients and mutations

Decision support: Tumor board

Data capture

Mutation frequency
Outcomes: patients on trials
Biomarker of benefit of prior regimen

Active Pending

Phase I, II, III Umbrella trials

Ultradeep analysis

Mutations InDel
Copy number (cost effective)
Can be used to request CLIA confirmation
Patient identified by physician  
Over 10,000 patients now registered  
(Likely to enter clinical trial)

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Biopsy if clinically indicated or part of trial

Philanthropy  
Non Sustainable

Research  
T200.2  
Ultradeep analysis  
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Active Pending  
Phase I, II, III Umbrella trials

Data capture  
Mutation frequency  
Outcomes: patients on trials  
Biomarker of benefit of prior regimen
19000 (2000 in set) patients likely to enter trials
Hot Spot Mutation CMS46 (Ion Torrent)
Potentially actionable 39%
TP53 not counted (31%) KRAS counted (11%)

Most targetable aberrations are rare across cancers
All testing covered by philanthropy:
Not sustainable
19000 (2000 in set) likely
Hot Spot Mutation CI
Potentially actionable
TP53 not counted (31%) KRA

AKT mutant tumors respond to AKT targeted drugs

Endometrioid ovarian primary, 480mg BD 4d on/3d off Confirmed RECIST PR (maximum reduction 55%). Ongoing in study (more than 600 days on drug).
How do we determine whether rare mutations indicate vulnerability?

AKT1 1.4% 2% in breast cancer

Want 50 patients on trial
50% positive will not be eligible
Test 5,000 patients at $3000 per patient
15 million dollars in testing

Multiplex across many aberrations
THERAPEUTIC INDEX IS LIMITING FACTOR

COULD WE IMPLEMENT MUTATION SPECIFIC DRUGS (1-2% frequency)

ie PIK3CA H1047R vs pan PIK3CA drug

Hotspot frequency might allow mutation specific drugs
Outcomes for first 2000 patients

Underwent Genomic Testing
N = 2000

Potentially Actionable Mutations

Yes (789)  No (1211)

Genomically-matched trial after genomic testing?

Yes (83)  No (706)

Genomically-Selected Trial N = 54  Genomically-Relevant Trial N = 29

4% of patients tested were ultimately treated with “matched” agent

39% of patients had aberration in actionable gene

11% of pts with mutations in actionable genes went on genotype-matched trials
What did we learn  Goal 25% of patients to trials

• Increasing scope of testing increases rate of actionable events modestly (39-53%):
  • 90% of actionable aberrations are in limited set of genes
• Time to results critical in Phase I due to patient deterioration
  • Test when likely to need information and have therapeutic options
• Physician decision support is critical
  • Aberration level information
  • Not all alterations in actionable genes are actionable
  • Clinical trials alert to curated results and eligible clinical trials
• The utility of genomic testing is dependent on availability and efficacy of therapeutic agents
  • Increase number of molecular marker driven trials
  • Develop basket trials to deal with rare events AKT, TRK
• Move from single aberrations to pathways and networks
• Circulating DNA allows for proximal analysis of metastases
Value of Molecular Testing

• Directing patients to standard of care or off label use is important outcome

• Rapid approval of effective drugs

• Reputational event to recruit patients

• Recruit high quality information rich trials

• Consider testing a “loss-leader”
  • Added cost of multiplex testing modest

• Critical to convince payors of value
  • Philanthropy non sustainable
ENTRY INTO CLINICAL TRIALS UNDERESTIMATES UTILITY OF MOLECULAR TESTING

Types of Genotype Matched Treatment Received

- Standard of Care: 36%
- Clinical Trial: 58%
- Off Label Use: 6%

Gene Alterations for Which Patients Received Treatment

- BRAF: 30%
- PIK3CA: 32%
- CDKN2A: 2%
- NRAS: 10%
- PTEN: 10%
- SMO TP53: 2%
- EGFR: 2%
- KRAS: 2%
- ERBB2: 6%
- FGFR3: 2%

ENTRY INTO CLINICAL TRIALS UNDERESTIMATES UTILITY OF MOLECULAR TESTING
• Cancer genomes are extremely complex!
• Which genomic events are “Drivers” vs. “Passengers”?
• Significant challenge: bioinformatic annotation is not sufficient
  – Are specific aberrations in cancer genes drivers or passengers
  – What are the functional consequences of rare driver aberrations?
    – Are they hypomorph, hypermorph, neomorph
  – Do they indicate therapeutic liabilities or resistance mechanism?
    - Are the aberrations actionable?
• Functional Annotation Critical

Genome Science  Targeted Therapeutics
Scope of the problem
Now more than 1 million variants without functional annotation

Are these passengers or drivers and are drivers hypomorphs, hypermorphs or neomorphs
IDH1 and IDH2 MUTATIONS ARE NEOMORPHS
Wild type produces alpha ketoglutarate from isocitrate
Mutant produces 2 hydroxyglutarate from alpha ketoglutarate
alpha-ketoglutarate and hydroxyglutarate have markedly different functions

AML 20%
GBM 6%
Melanoma 6%
Construct lentiviral vector carrying wild type or mutated genes
Introduce into addicted sensor cells line Ba/F3 or MCF10A cells
Integrate analysis for function, mechanism and therapy
Iterative algorithm to identify POTTENTIAL DRIVER ABBERRATIONS
Current 50 per month: Point indel fusion Readily scalable
High throughput generation of mutant ORFs

Cell viability assay

Select potential drivers

Establish stable driver addicted cell lines

Context dependent in vivo screen for potential drivers.

Sensitivity to informer targeted therapeutic library

Data sets
MDACC
TCGA
ICGC

Drivers and Therapies

Integrative analysis for function, mechanism and therapy

RPPA to define signaling network

Aberration based functional genomics
Over 1000 aberrations functionally annotated
70% novel 1035 mutants 95 wild type

Annotation in oncoKB
- 223 Yes (21.26%)
- 826 No (78.74%)

Annotation in PCT
- 193 Yes (18.84%)
- 856 No (81.16%)

Inhibitory (5)
Non-inhibitory (29)
Non-informative (92)
Inactivating (96)
Activating (303)
Neutral (519)

Predictive Algorithms

Functional Calls

ONCOKB

Kwok Xing Ng

C

% mutations

- Strong activating
- Moderate activating
- Weak activating
- Neutral

Candra_plus: AUC: 76.4%
CHASM: AUC: 72.8%
vest3: AUC: 72.8%
mutpred: AUC: 67.6%
revel: AUC: 67.0%
Doc, you must know everything!

Nonsense... just relax and lie back on the bar code scanner.
Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy. In addition, patient genetic factors can be associated with drug metabolism, drug response and drug toxicity. Personalized tumor molecular profiles, tumor disease sites and other patient characteristics are then potentially used for determining optimum individualized therapy options.

Tumor biomarkers can be DNA, RNA, protein and metabolomic profiles that predict therapy response. However, the most recent approach is the sequencing of tumor DNA, which can reveal genomic alterations that have implications for cancer treatment. This Personalized Cancer Therapy website was specifically developed as a tool for physicians and patients to assess potential therapy options based on specific tumor biomarkers.
27 potentially actionable genes fully annotated

- Mutations
- Copy number changes
- Fusions
- Germline alterations if relevant

- Interactive: Physician determines level of information

- Therapeutic implications and the level of evidence for each therapy

- Clinical trials available by location
Decision Support in Real Time Improves ‘Matching’ to ‘Right’ Drug

Approximately 25% of patients with mutations in actionable genes were enrolled on clinical trials using matched therapies (~12% can be potentially enrolled - still awaiting progression)
‘Matching’ to ‘Right’ Drug Improves Patient Outcomes

Incidental Results in non-CLIA Research Testing

Potential for germline findings on CLIA and research testing

What to tell patient before and after testing

• Hereditary cancer risk?
  – Autosomal dominant eg BRCA, p53, PTEN
  – Slightly increased relative risk eg FGFR
  – Implications for trial enrollment: eg BRCA, PTEN, TSC1/2

• Pharmacogenomics

• Risk of preventable problems---Hypercoagulable state

• Risk of unpreventable disease---Eg Alzheimer’s
Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol

99% requested return of incidental results

43 germline mutations in 19 cancer related genes recommended for testing

23 previously unknown
UNEXPECTED HIGH RATE OF FAILURE OF TARGETED THERAPEUTICS

Even for patients with the biomarker only subpopulations of patients benefit from monotherapy:
Usually short term

Resistance is almost universal
Intrinsic (Genetic)
Selected (Genetic)
Adaptive (Homeostatic loops, cross talk and bypass)
Heterogeneity

Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy
Yossi Yarden Arthur Lander
GENOMIC EVENTS INTEGRATE INTO A LIMITED NUMBER OF PROTEIN SIGNALING PATHWAYS

SENSOR
Mutated Amplified

AMPLIFIER
Mutated Amplified

INTEGRATOR/EFFECCTOR
Rarely mutated

FUNCTION

RNA

MTOR
p70S6K
PS6
4EBP

TSC1/2

LKB1
AMPK

RNA INTEGRATOR/EFFECTOR

EGFR

PIK3CA
PIK3R1
PTEN
AKT

RAS

BRAF
MEK
MAPK
P90RSK

Mutated
Amplified

Mutated
Amplified

Rarely mutated

Solid Frequently mutated
Intratumoral heterogeneity in renal cancer

A Biopsy Sites

R1 (G3)  R2 (G3)
R3 (G4)  R4 (G1)
R5 (G4)  R6 (G1)
R7 (G4)  R8 (G4)
R9        Hilum

10 cm

B Regional Distribution of Mutations

Ubiquitous

Shared primary

Shared metastasis

Private

Gray present  Blue is absent

Swanton NEJM 2013
Many tumors have trunks and branches

However, actionable events are frequently dominant

Metastasis more divergent than primary
Convergent Evolution of Intratumoral Heterogeneity RCC: Futreal

Many tumors have trunks and branches
However, actionable events are frequently dominant

Metastasis more divergent than primary
Convergent evolution (SETD2, KDM5C and PTEN)
PI3K pathway ie mTOR and PTEN late
Somatic mutations
- 97 of 112 (86.6%) somatic mutations were concordant

Copy number alterations
- 136 of 159 (85.5%) were concordant
- 37 (23.3%) were concordant, but below the reporting threshold in one of the matched samples
- 23 (14.5%) discordant

Of the 38 discordant, only 13 are potentially actionable

Meric-Bernstam, Mol Can Ther 2014
Acquisition of a Constitutively Active ESR1 Mutation
Only major difference in primary and recurrent tumor

Liquid Biopsy Opportunities

Ready for exploration:
• Detecting actionable alterations in metastatic cancer
• Monitoring response in metastatic cancer
• Monitoring for acquired resistance mechanisms

Maybe with better sensitivity:

• Early detection
• Monitoring of response in neoadjuvant therapy
• Determination of pathologic complete response after neoadjuvant therapy
UNEXPECTED HIGH RATE OF FAILURE OF TARGETED THERAPEUTICS

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Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Yossi Yarden Arthur Lander
Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Systems are robust to individual perturbations but are susceptible to multiple perturbations. Yossi Yarden and Arthur Lander

Mathematical modeling indicates that by chance during phylogeny, many/most molecules in cell/organism will be blocked by mutation or environmental stress.

Thus, response to single targeted therapy is expected to be short and transient as observed!

Interdict a critical pathway mediator.
Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Systems are robust to individual perturbations but are susceptible to multiple perturbations Yossi Yarden and Arthur Lander

Cells adapt by using an alternative pathway

Chance that both the original target and the adaptive response will be “hit” randomly (mutation or environmental stress) is vanishingly low

Adaptation can occur at the protein level which is best assessed by post translational modification
Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Systems are robust to individual perturbations but are susceptible to multiple perturbations

Yossi Yarden and Arthur Lander

Optomistic that drug combinations will be effective: but convinced that they will be necessary to fulfill the promise of personalized therapy
Initial Evidence that Extracellular Matrix Protects from Drug-Induced Killing

Cells in 2D, 3D, in vivo, or patient tumors

Add drug

- Early time points: target engagement
- Medium time points: adaptive responses
- Late time points: genomic resistance

Harvest cells for Omic analysis
- DNA, RNA, protein metabolomics

A PLATFORM TO FACILITATE TARGETING ADAPTIVE RESISTANCE TO INCREASE UTILITY OF TARGETED THERAPEUTICS
HUMAN PROTEOMICS ATLAS: RPPA

Quantitative high throughput multiplexed inexpensive ELISA

300 validated antibodies

Dot blot: less sensitive to degradation

Requires high quality validated antibodies and robotics

No Spatial orientation: combined tumor and stromal signature

>10,000 TCGA and internal patient samples with extensive DNA, RNA, miRNA, and clinical data

Tcpaportal.org

Search Cancer Proteome Atlas

Cell lines with RNASeq and drug data

700 lines in house

http://tcpaportal.org/mclp/#/

Broad Cancer Cell Line Encyclopedia

130,000 samples in total

CCSG Core Web Site

Functional proteomics

Duplicate Spotting Reliability
PARP inhibitors induce synthetic lethality in homologous recombination-deficient (HRD) cancer cells

DNA damage occurs constantly

DNA damage induces cell cycle checkpoints to allow DNA damage repair

Normal cells have many DNA Repair Pathways

PARP inhibitors induce DNA damage

HRD cells do not accurately repair damage

PARP inhibitors induce synthetic lethality

Three PARP inhibitors have been approved for ovarian cancer and OLYMPIAD Phase III trial in breast cancer has met its goals

Despite high response rate, duration of response remains short
Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red. >50,000 data points.

Data is ratio of treated to untreated

Samples are ordered based on adding all antibody scores

Only significant changes presented

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Yiling Lu Xiaohua Chen
5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red.
BKM and Olaparib demonstrate marked responses

77% OvCa gBRCA
57% BrCa gBRCA
Non mutant BRCA1/2 2 PR
One biopsy: ATR mutant

N=46
N=24

Ursula Matulonis
Shannon Westin

PI3K Dream Team
http://pi3k.org
Time on Treatment

Olaparib, BKM120 Pan PI3K

PI3K alpha, mTOR and AKT in progress

Up to 24 months response: 50% of endometrial cancers

Ovarian Cancer

Breast Cancer

* On study

Partial Response
Stable Disease
Progressive Disease
Unevaluable

Time on treatment (days)
Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red.

Yiling Lu Xiaohua Chen
SERENDIPITY

KRAS mutation is a marker for BMN673 resistance: markedly improved HR DNA repair in RAS mutant lines

Chaoyang Sun
Synergistic effect of PARP and MEK/ERK inhibition is lineage independent and observed with KRAS/NRAS/BRAF mutations.

35/37 models

Dong Zhang
Yong Fang
Chaoyang Sun

MEKi active as monotherapy
Acquired PARPi resistance is associated with RAS MAPK pathway activation, acquisition of RAS mutations and sensitization to combination therapy.

Chaoyang Sun
PARP plus MEK inhibitors are synergistic in vivo
Operating Model

DNA damage checkpoint

DSB Damage repair

Apoptosis

Hypoxia
SOLAR study: selumetinib and olaparib in RAS activated tumors

- Endometrial Tumors with RAS Pathway Activation
  - N=15

- Ovarian Tumors with RAS Pathway Activation
  - N=15

- Ovarian Tumors with Progression on Prior PARP Inhibitor Treatment
  - N=15

- Solid Tumors with RAS Pathway Activation
  - N=15

Shannon Westin
Funda Meric-Bernstam

CRC Approved, IRB 3/1/17
FDA no Objection
SIV May 30 2017
Anticipate FSI Aug 2017
Rational Strategy for Combination Therapies

Blocking critical signaling nodes "rewires" signaling pathways

Rewired networks contribute to cellular resistance to targeted therapeutics

Induced signaling events represent "vulnerabilities" that can be exploited leading to synthetic lethality

Adaptive responses can be restricted to specific tumor subpopulations

Combinatorial Adaptive Resistance Therapy CART
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