Personalized Cancer Medicine

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Personalized Cancer Medicine

Right treatment

Right patient

Right time

Maximise efficacy

Minimise toxicity
Personalized Cancer Medicine
Personalized Cancer Medicine

- Detect cancers earlier
- Analyze cancers more precisely
- Target treatments to individual cancers
- Support patients through their cancer journey
Biomarkers and Personalized Cancer Medicine

• Biomarkers are essential for PCM

  Right treatment

  Right patient

  Right time

• Biomarkers allow us to select the right treatment for the right patient at the right time which leads to maximal efficacy and minimal toxicity
Genetic Epidemiology
Pharmacogenomics
Pharmacogenetics
Cancer Immunology
Molecular Biomarkers and Personalized Cancer Medicine

Host response to cancer
- Predictive for efficacy
- Prognostic

TUMOUR MICROENVIRONMENT

CANCER

BRCA mutations increase risk of breast/ovarian cancer
DPP SNPs predicts increased toxicity from 5FU
BLMH SNPs predicts reduced efficacy from bleomycin

PDL1 expression may predict for benefit from PD1 inhibitors
TIL density is a good prognostic factor in cancer

BRAF mutations are a poor prognostic factor in CRC
KRAS mutations predicts for non-benefit from EGFR mAb

Genetic Epidemiology
Pharmacogenomics
Pharmacogenetics

Somatic molecular aberrations
- Diagnostic
- Prognostic
- Predictive for efficacy

Molecular aberrations
- Risk assessment
- Predictive for toxicity
- Predictive for efficacy
- Prognostic

Cancer Genomics

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Cancer Genomics
Improving our understanding of cancer

• Cancer genomics is the study of the molecular basis behind cancer and consists of three pillars
  1. Technological advances
  2. Discovery of genetic aberrations
  3. Clinical translation to achieve personalized cancer medicine
Personalized Cancer Medicine

Matched therapies

• Personalized cancer medicine involves the use of molecular information regarding each patient’s cancer in making patient care decisions.

• It is based on the premise that
  1. Genetic aberrations exist in human cancers
  2. A subset of these aberrations are drivers of oncogenesis and tumour biology
  3. Tolerable medicines that can effectively modulate these targets exist
**Personalized Cancer Medicine**

*Where are we now?*

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Cancer</th>
<th>Clinical Impact</th>
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</thead>
<tbody>
<tr>
<td>KRAS mutation</td>
<td>Colorectal Cancer</td>
<td>Predicts resistance to EGFR mAb</td>
</tr>
<tr>
<td>HER2 amplification</td>
<td>Breast Cancer</td>
<td>Predicts sensitivity to HER2 targeted agents</td>
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<tr>
<td></td>
<td>Gastric Cancer</td>
<td>Predicts sensitivity to trastuzumab</td>
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<tr>
<td>EGFR mutation</td>
<td>Lung Cancer</td>
<td>Predicts sensitivity to EGFR TKI</td>
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<tr>
<td>BRAF mutation</td>
<td>Melanoma</td>
<td>Predicts sensitivity to BRAF targeted agents</td>
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<tr>
<td>BCR-ABL translocation</td>
<td>CML</td>
<td>Predicts sensitivity to BCR-ABL targeted TKIs</td>
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<td>KIT mutation</td>
<td>GIST</td>
<td>Predicts sensitivity to KIT targeted TKIs</td>
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<td>EML-ALK translocation</td>
<td>Lung Cancer</td>
<td>Predicts sensitivity to crizotinib</td>
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<tr>
<td>BRCA1/2 mutation</td>
<td>Breast Cancer</td>
<td>Predicts sensitivity to PARP inhibitors</td>
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<tr>
<td>MGMT methylation</td>
<td>GBM</td>
<td>Predicts sensitivity to temozolamoide</td>
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<tr>
<td>Microsatellite instability</td>
<td>Colorectal Cancer</td>
<td>Predicts lack of benefit from 5FU in stage 2 disease</td>
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<tr>
<td>ER overexpression</td>
<td>Breast Cancer</td>
<td>Predicts sensitivity to endocrine therapies</td>
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<tr>
<td>Oncotype DX</td>
<td>Breast Cancer</td>
<td>Prognostic biomarker identifies recurrence risk</td>
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</tbody>
</table>
KRAS Mutations
BCR-ABL Translocations
HER2 Amplification

“Gene Expression”
OncotypeDX Breast Panel

“Immunohistochemistry”
ER expression
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The KRAS Story (7)

Cetuximab

Wildtype

Extracellular domain
Plasma membrane
Intracellular domain

PI3K–mTOR pathway
JAK–STAT pathway
PLC pathway

KRAS
BRAF
MEK
ERK

cos
Grb

DNA

• Proliferation
• Metastasis
• Anti-apoptosis
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The KRAS Story (8)

Cetuximab

Mutant

Extracellular domain

Intracellular domain

Plasma membrane

PI3K–mTOR pathway

JAK–STAT pathway

PLC pathway

KRAS

BRAF

MEK

ERK

- Proliferation
- Metastasis
- Anti-apoptosis
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The KRAS story

• Karapetis et al. NEJM 2008
  – Patients with Mutated KRAS do not benefit from EGFR targeted mAb

A Mutated $K_{ras}$

B Wild-type $K_{ras}$

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months after Randomization</th>
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<tbody>
<tr>
<td>Cetuximab plus best supportive care</td>
<td>110</td>
</tr>
<tr>
<td>Best supportive care alone</td>
<td>105</td>
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</table>
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The HER2 Story (1)

Figure 1: Therapeutic Targets in HER2-Positive Breast Cancer—Targets include pathways involved in cell proliferation and survival.

HER2 Amplification

Figure 1: Therapeutic Targets in HER2-Positive Breast Cancer—Targets include pathways involved in cell proliferation and survival.
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The HER2 Story (2)

Breast Cancer – Slamon et al. NEJM 2001

Gastric Cancer – Bang et al. Lancet 2010
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The BRAF Story (1)
Personalized Cancer Medicine
The BRAF Story (2)

Same Drug, same dose, same “target” (BRAF V600E)

Different results!

MELANOMA
Flaherty et al, ASCO 2009

COLORECTAL CANCER
Kopetz et al, ASCO 2010

Courtesy Jayesh Desai
Cancer Genomics  
Facilitating Personalized Cancer Medicine

**Technological advances**

- Greater interrogation of the molecular changes within cancer
- Increased *discovery* of actionable genetic aberrations
- Novel biomarker driven trial design

**Translate** findings in the clinic

- Identify predictive, prognostic biomarkers

**Personalized Cancer Medicine**
Rapidly reducing cost of sequencing

Observation that number of transistors on a circuit doubles every 2 years

Sequencing is increasingly able to provide more data at less cost and in less time
- Facilitates “Discovery” and improved understanding of molecular basis of cancer
Personalized Cancer Medicine
Where are we now?

• We can personalize cancer treatment…

...at the moment, sort of

– Some of us can test for lots of things on a large scale
  • But it can be costly
– There are still only a small number of **validated** biomarkers
  • But lots in development
– Clinical significance of biomarkers **cannot** always be extrapolated across tumour types
  • But sometimes they can
– Molecularly targeted agents are not easily available
  • But they are if you have a strong drug development program
Building a Personalized Medicine Program

Strong Molecular Profiling Program
Patients with known molecular aberrations
“Targets”

Personalized Medicine & Matched Treatments

“Bullets”
Molecularly Targeted Agents
Strong Early Phase Clinical Trials Program
Achieving Personalized Cancer Medicine

• Traditional Path
  1. Discovery of novel actionable genetic aberrations
     • Basic science and translational research
  2. Development of matched targeted therapies
     • Early phase clinical trials
  3. Determining that the activity of a matched targeted therapy is dependent on a companion diagnostic
     • Early/Late phase clinical trials
  4. Proving that targeted therapies provide benefit to the molecularly preselected patient population
     • Late phase clinical trials
  5. Identifying patients with molecular aberrations that can be treated using proven molecularly targeted agents
     • Molecular profiling
Fast Tracking Personalized Medicine

- Technological advances now lead to molecular profiling and identification of molecular aberrations before they are confirmed as actionable and druggable targets, and well before matched treatments are known to provide benefit.

- Today’s Path:
  1. Testing for and identifying molecular aberrations in individual patients
     - Molecular Profiling
  2. Determine if the identified molecular aberration(s) is actionable and druggable
     - Basic Science; Early Drug Development
  3. Consider treating the patient with an unproven molecularly matched treatment
     - Early Drug Development, Off label

- Can we fast track personalized cancer medicine using this approach?
Fast Tracking Personalized Cancer Medicine

• Limitations include
  – Number of genes examined
  – Type of aberrations examined for (mutations +/- amplification)
  – Timeliness of testing
  – Access to off label treatment
  – Access to early phase clinical trials
  – Stage of development of novel targeted therapeutics
  – Performance status of patients
  – Tumour heterogeneity
  – Clonal evolution
Molecular Profiling
Real-time and High-throughput

• Does molecular profiling facilitate personalized medicine?
• Do matched treatments lead to increased patient benefit?

1. TGWS: Ontario Institute for Cancer Research

2. MOSCATO: Insitute Gustave Roussy, Paris France

3. RMH Molecular Profiling Program
Feasibility of real time next generation sequencing of cancer genes linked to drug response: Results from a clinical trial

Ben Tran1*, Andrew M.K. Brown2*, Philippe L. Bedard1, Eric Winquist3, Glenwood D. Goss4, Sebastien J. Hotte5, Stephen A. Welch6, Hal W. Hirst7, Tong Zhang6, Lincoln D. Stein2,7, Vincent Ferretti2, Stuart Watt5, Wei Jiao2,7, Karen Ng7, Sangeet Ghai8, Patricia Shaw6, Teresa Petrocelli2, Thomas J. Hudson2,7,8, Benjamin G. Neel1,8,9, Nicole Onetto2, Lillian L. Siu1*, John D. McPherson7,8*, Suzanne Kamel-Reid1,2,6,8* and Janet E. Dancey2,10

Hospital

Tissue Collection

Pathological Review

Patient

Clinician

Clinical Molecular Diagnostic Lab

Blood & Tumor DNA

OncoCarta Genotyping

Mutation Assessment

Validation

Concordance Novel

Research Sequencing Lab

Targeted Enrichment

Sequencing

Analysis

Somatic Variants

Sample Transfer ——>

Data Transfer — —
56 Patients Approached

- 5 Declined
- 1 Ineligible

51 Patients Consented

50 Patients Enrolled

Patients Biopsied and Archival Specimens Collected

Pathological Processing
- 49 Biopsy Specimens
- 41 Archival Specimens

Pathological Processing
- 1 Insufficient Tumor

DNA Extraction
- 44 Biopsy Specimens
- 40 Archival Specimens

DNA Extraction
- 1 Insufficient Tumor

Molecular Analysis
- 43 Biopsy Specimens
- 40 Archival Specimens

Molecular Analysis
- 1 Insufficient DNA

Mutation Genotyping
- 0 unsuccessful Genotyping
- 1 unsuccessful Sequencing

Mutation Genotyping
- 0 unsuccessful Genotyping
- 3 unsuccessful Sequencing

Targeted Gene Sequencing
- 1 unsuccessful Sequencing

Targeted Gene Sequencing

Molecular Profiling Report
- 16 Mutations in 14 Patients Identified

Molecular Profiling Report
- 13 Mutations in 12 Patients Identified

Impact on Treatment Decision
- 6 Patients had Treatment Decisions Impacted on by Molecular Profiling
TGWS: OICR and PMCC (2011)

- 19 oncogenes included in “panel”
  - Genotyping (Sequenom MASS Array) – 238 known mutations
  - Sequencing (PacBio RS) – exons of the 19 oncogenes

- 16 patients (32%) were found to have mutations
- 6 patients (12%) received matched treatment
- 4 patients (8%) had a response to matched treatment
Molecular Screening for Cancer Treatment Optimization: MOSCATO 01
A prospective molecular triage trial, Interim results

Antoine Hollebecque, Christophe Massard, Thierry de Baere, Nathalie Auger, Ludovic Lacroix, Valérie Koubi-Pick, Philippe Vielh, Vladimir Lazar, Rastislav Bahleda, Eric Angevin, Eric Deutsch, Andreea Varga, Anas Gazzah, Gilles Vassal, Frédéric Deschamps, Catherine Richon, Clément Mazoyer, Maud Ngo-Camus, Alexander Eggermont, Fabrice André and Jean-Charles Soria
• Monocentric

• Target Accrual = 900 patients

Max 21 calendar days
Patients included
N=339

Patients Biopsied
N=295

Screen Failure N=44 (13%)
- Clinical deterioration (++)
- Biopsy technically impossible (++)
- Withdraw consent (n=2)

Biopsy - Tumor Board
21 days (Median)

Actionable Target
N=127 (43.1%)

No Actionable Target
N=168 (56.9%)

Treatment matched to the Target
N=65 (22.0%)

No Treatment
N=62 (18%)

Biopsy
NGS 90%
CGH + NGS 80.5%
**Efficacy**

**Best Response (N=33)**

- **Tumor size variation (%)**

<table>
<thead>
<tr>
<th>Best response (N=33)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>7</td>
<td>21%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>16</td>
<td>48%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>7</td>
<td>21%</td>
</tr>
<tr>
<td>Non Evaluable</td>
<td>3</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Objective response in phase I trials usually ranges from 5 to 10%**

  Italiano et al, Annals Oncol 2007
  Olmos et al, J Clin Oncol 2012

**Radiological Independent review**

- Early clinical progression (n=5)
- Non measurable disease (n=2)
- Early Toxicity (n=3)
MOSCATO: IGR (2012)

• 50 oncogenes included in “panel”
  – Sequencing (Ion Torrent) – exons of 50 oncogenes
  – arrayCGH (Agilent) – whole genome coverage

• 127 of 295 patients (42%) were found to have an actionable target
  – 72% of actionable targets were amplification
  – 28% point mutations

• 65 patients (22%) received matched treatment
• 7 from 33 evaluable patients (21%) had a response to matched treatment

• Increasing the coverage and including amplification, increases the pick up rate of actionable targets
Molecular Profiling at RMH (2014)

• First request 18 September 2013
• Total requests – 160
• **128 mutations** identified in **75 individual patients**
  – 50% of patients tested had at least one mutation
Molecular Profiling at RMH (2014)

- 53 individual patients with “druggable” targets
  - 46% of all successfully completed tests
- 9 (17%) received matched treatment
- 19 (36%) deteriorated
- 5 (9%) did not have access to off-label treatment
- 3 (6%) already received matched treatment
- 17 (32%) still on standard treatment
Molecular Profiling and Personalized Cancer Medicine

• Molecular profiling appears to make a difference
  – Matched treatment does result in patient benefit

• Actionable and druggable mutations identified will increase as molecular profiling becomes accessible
  – Rapid increase over a short period of time

• As the number of mutations identified increases, personalized medicine becomes dependent upon access to clinical trials, rather than access to profiling
Clinical Trial Design in age of Personalized Cancer Medicine

- **In the past:**
  - Biomarkers have been determined in retrospect

- **In the present:**
  - Biomarkers are identified at the preclinical phase of drug development

- **In the future:**
  - Some biomarkers will be discovered incidentally, through widespread use of molecular profiling
Clinical Trial Design

• **Early Phase studies**
  - Increasing trend towards preselecting patients based upon presence of biomarker
    - e.g. BRAF mutation, PIK3CA mutation, FGFR amplification
    - Based upon strong preclinical evidence suggesting benefit predominantly in patients harbouring the selected biomarker
    - Central testing still exists, but increasingly, local testing is required (or expected)
Clinical Trial Design

• Late Phase studies
  – Likely to be increased trend towards preselecting patients based upon presence of biomarker
    • e.g. BRAF mutation, PIK3CA mutation, FGFR amplification
    • Based upon strong early phase clinical trial data
    • Local testing usually required
  – Patients stratified as per normal
Clinical Trial Design

- Basket/Umbrella studies
Personalized Cancer Medicine
Conclusion

• Personalized Medicine makes sense
  – Finding a target (that drives tumour biology) in a patient and giving that patient a drug that impacts that, improves outcomes

• In order to achieve personalized medicine, you need to find the “targets” and have the “bullets”
  – Local molecular profiling capability is essential
  – Large early phase clinical trials program is essential

• Clinical Trial design recognises the promise of personalized medicine
  – Basket and Umbrella trials are becoming more common and will further facilitate personalized medicine
Questions?