Functional precision cancer medicine
- from leukemia to solid tumors

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Molecular and Systems Level Data on Disease

Personalized Medicine

Individualized Medicine

Precision Medicine

January, 2015
the Precision Medicine Initiative
in State of the Union address

June 2015
The PerMed SRIA: ‘Shaping Europe’s Vision for Personalised Medicine’
Are we not already practicing precision medicine?

Clinician:
“I am always treating my patients in an individualized way”

Pathologist:
“I am always providing an individualized diagnosis, IHC, sometimes gene tests”

Researcher:
“We have established a biobank”
“We do genomics profiling of tumors”

What is typically lacking today (in oncology)
- Comprehensive molecular data & understanding (-omics)
- Reference databases & resources for molecular medicine
- Few targeted treatments and drug combinations
- Follow-up and real-time monitoring
- Predictive / preventive approaches
First –omics wave: Genomics of Cancer

- The Cancer Genome Atlas (TCGA)
- Dec 13, 2005: NIH launches comprehensive effort to explore genomic alterations in human tumors
- June 6, 2016: The Genomic Data Commons (GDC)
The International Cancer Genome Consortium (ICGC)

ICGCmed, linking clinical data to genomics
Clinical Utility of Precision Medicine?

The ALCHEMIST (NCT02194738)
LungMAP (NCT02154490)

NCI-MATCH (NCT02465060)
MyPathway (Genentech Inc., NCT02091141)

Adaptive trial
TAPUR
Targeted Agent and Profiling Utilization Registry (NCT026935359)

AstraZeneca
Bayer
Bristol-Myers Squibb
Eli Lilly and Company
Genentech, Inc.
Pfizer

Umbrella trial
Basket trial

Biankin et al., Nature 2015
Chakradhar, Nature Medicine 2016
The precision–oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says Vinay Prasad.

Limits to Personalized Cancer Medicine

Ilan F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.

“There should also be a clear message to patients that personalized cancer medicine has not led to gains in survival or its quality and is an appropriate strategy only within well designed clinical trials.”
Precision Systems Medicine

Deep molecular profiling

TCGA Weinstein et al., Nature Genetics 45, 1113–1120, 2013

Deep functional profiling

Pemovska T et al., Cancer Disc 3:1416-1429, 2013
Saeed K et al., Eur J Urol., May 5, 2017
Ojamies P et al., Leukemia, 31 Oct 31, 2017
Malani D et al., Leukemia, May 31, 2017
Oncology Drugs not Available for All Driver Mutations

NCI-MATCH Interim analysis May 2016

EXaCT-1: detected genomic alterations

Pauli et al., Cancer Discov 2017

Letai Nature Med 2017
Functional Precision Systems Medicine

Molecular profiling

Deep functional profiling
Clinical translation was performed in 35% of cases based on drug testing (18/52 relapsed and refractory samples)

Each patient was given different targeted drugs or drug combinations

In few cases, the same patient was given different targeted drugs in sequential therapies

7/18 (39%) led to complete remission or morphologic leukemia-free state
**Flow to a personalized drug sensitivity and resistance profile**

**Drug testing data**
Leukemia, prostate, renal, ovarian, pancreatic cancer, conventional cell lines  
> 1500 profiles

**Patient-specific drug profile report:**
Leukemia: ready in 4 days  
Solid tumors: 6-8 weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>sDSS</th>
<th>IC50 (nM)</th>
<th>Curve fit</th>
<th>QC</th>
<th>Mechanism/Targets</th>
<th>class</th>
<th>phase status</th>
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<tr>
<td>1 UCN-01</td>
<td>9.3</td>
<td>10.04</td>
<td>4</td>
<td>2</td>
<td>PKCbeta, PDK1, Chk, Cdk2 inhibitor</td>
<td>B. Eruse inhibitor</td>
<td>Investigational (I)</td>
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<tr>
<td>2 SL-6047</td>
<td>9.3</td>
<td>10.6</td>
<td>4</td>
<td>2</td>
<td>EGFR, HER2, VEGFR, Eph receptor inhibitor</td>
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<tr>
<td>3 Dasatinib</td>
<td>7.3</td>
<td>16.5</td>
<td>2</td>
<td>2</td>
<td>BCR/ABL, Src, Epi, Eph... inhibitor</td>
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<tr>
<td>4 Imatinib</td>
<td>7.3</td>
<td>16.6</td>
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<td>MEK/ERK2 inhibitor</td>
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<tr>
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<td>6.9</td>
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<td>1550</td>
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<td>1</td>
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<td>Probe</td>
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<tr>
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<td>15.7</td>
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<tr>
<td>8 Erlotinib</td>
<td>6.25</td>
<td>212</td>
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<td>4</td>
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<tr>
<td>9 STX79771</td>
<td>6.2</td>
<td>210</td>
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<td>6.9</td>
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<td>2</td>
<td>EGFR inhibitor</td>
<td>B. Eruse inhibitor</td>
<td>Investigational (III)</td>
</tr>
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**Quality Control, curve fitting, DSS, sDSS**

**Sensitive drugs vs. control**

**Less sensitive than control**

**Calculate sensitivity to controls**

**Drug testing data**
Leukemia, ovarian, bladder, conventional cell lines  
> 70 profiles

**Viability / Toxicity**

**5 doses: 1 – 10 000 nM**

**Less sensitive than control**

**Calculate sensitivity to controls**
Translation (n=1), PoC with guidance from ex vivo DSRT in advanced serous ovarian cancer

Samples for –omics and drug profiling

April.2014

Genomics: CDKN2A deletion
RNA-Seq: NRG1 fusion gene
→ nrg1-erbB3 activation loop
→ HER2 and EGFR pathways active

April.2017

Jan.2018

Serum CA125 U/ml tumor marker levels

0 10 20 30 40

OC2_2014 DSS

OC2_2017 DSS

Murumägi, Bützov et al., in preparation 2018

1) Gemcitabine + erlotinib: 3 months
2) Erlotinib: 2 months
3) Gemcitabine + erlotinib: 6 months
4) Gemcitabine + afatinib: 2 weeks
5) Afatinib: 1 year, 3 months
6) Vinorelbine: 2 weeks
7) Vinorelbine + afatinib: 3 months
8) Afatinib: 6 months + ongoing

Murumägi, Bützov et al., in preparation 2018
Elements needed to take precision systems medicine to the clinical setting

- Genomics & other technologies
- Individualized and improved cancer therapy
- Patient-derived primary ex vivo models
- Clinical expertise & data
- Clinical laboratory
- Companies
- Clinical trials
- Bioinformatics / decision support
- Biomedical expertise
- Ethical, Legal, Regulatory
- Team science
- Real-time translation
- Patient

Slide by Olli Kallioniemi
Functional Precision Systems Cancer Medicine

• PCM should not be just about genome sequencing

• Primary cell reprogramming provides enables functional testing

• Cells in *ex vivo* culture will drift in their geno- and phenotype, care needs to be taken to ensure representation of original disease

• Multiple sampling from primary and metastasis provides for a ways to profile the tumor burden of the patient

• Functional PCM facilitates drug repositioning, clinical trials, drug development programs
Challenges to Precision Medicine

- PCM Hype: “everyone is doing it” = dilution of concept
- Technology-enabled and data-driven: how to avoid data and technology silos and allow for common data collection & integration?
- Data infrastructure, linking research and clinical data
- Cultural change: challenge-driven team science = Fearless collaborations and trust in multidisciplinary teams
- Biology-technology-bioinformatics-clinic-industry-patients
- A clear need to find champions to work outside of business as usual
- Patients and relatives are aware: How to allow for compassionate cases?
- How to expand the field from 10-100s to more/all patients?
- How to turn hype to hope? Clinical trials will be needed
- Novel drugs targeting novel pathways and smaller and smaller subpopulations
"How smooth! An elephant is like a wall."
"How sharp! An elephant is like a spear."
"How wide! An elephant is like a fan."
Translational research:
Crossing the valley of death

Technologies: national center for molecular life sciences

- **Quick numbers**: 40 national facilities, 1200 scientists, 700 publications, 3073 projects
- **Unique and enabling infrastructures for national life science research**
- **Collaborative research within a community of excellent scientists**
- **Translation towards lasting societal benefits**
Technology platforms

Clinical Genomics
Genomics Medicine Sweden

Mass spectrometry-based proteomics
- proteogenomics
- mass cytometry

Richard Rosenqvist-Brandell

Janne Lehtiö

Zhu Y et al., Nature Comm 2018
Uhlen et al., Science 2017
Thul et al., Science 2017
Barmanis et al., Cell Rep 2016
Volk et al., Sci Rep 2016
Boekel et al., Nature Biotech 2015
Brodin et al., Cell 2015
Uhlen et al., Science, 2015