Personaalmeditsiin onkoloogias

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HiLIFE
HELSINKI INSTITUTE OF LIFE SCIENCE

FIMM

Agenda:

- Funktsionaalne personaalmeditsiin - mis see on?
- Funktsionaalne personaalmeditsiin leukeemiate ravis
- Funktsionaalne personaalmeditsiin tahkete vähkide ravis
- Järgmised sammud

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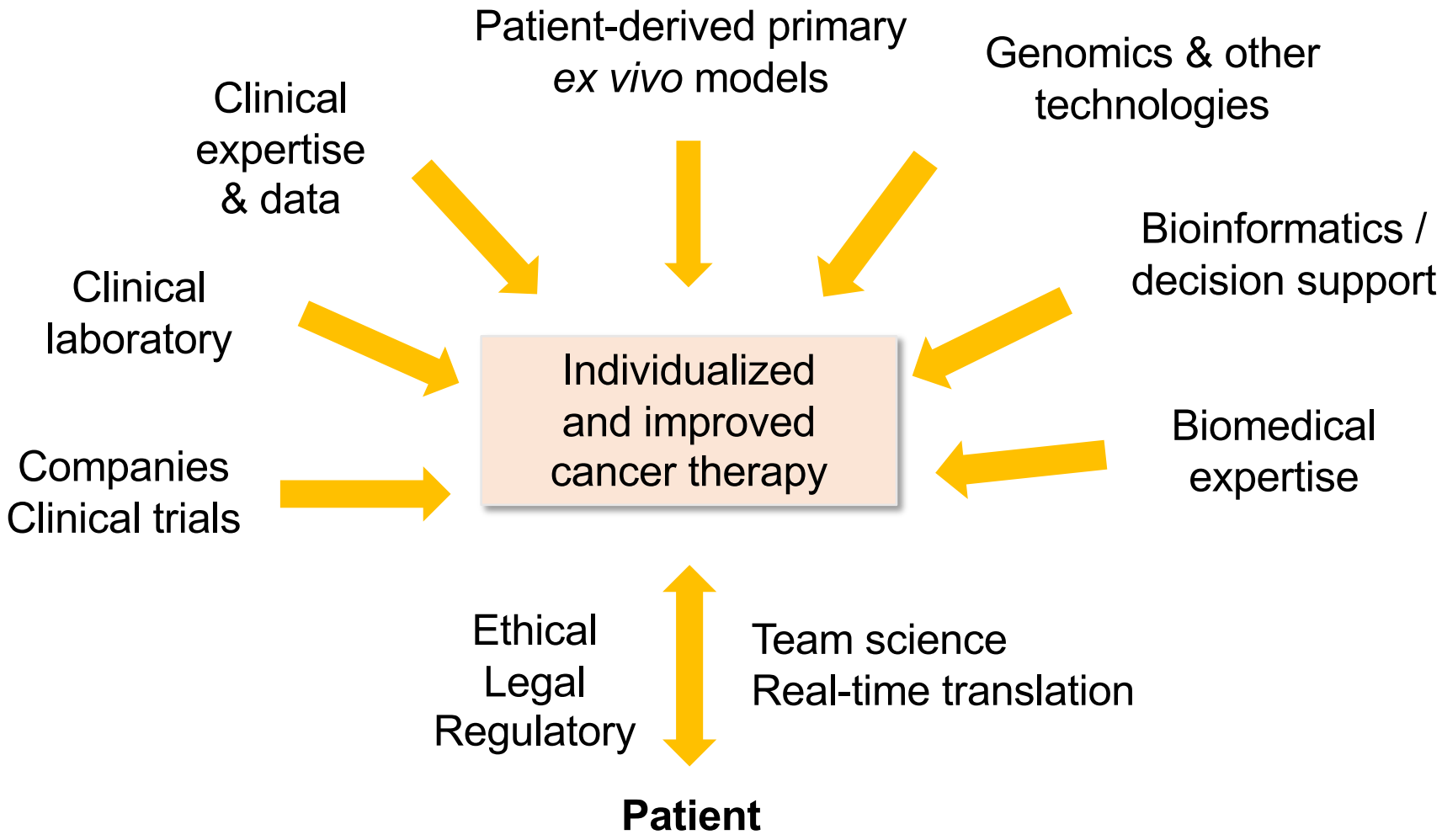
Elements needed to take precision systems medicine to the clinical setting



Slide by Olli Kallioniemi

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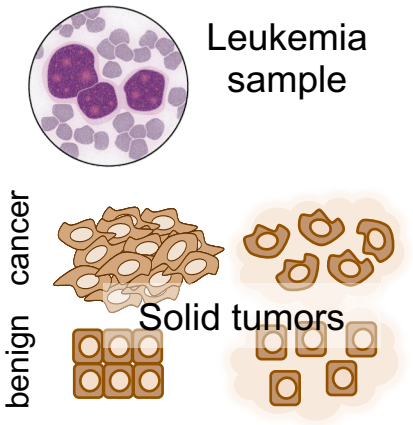
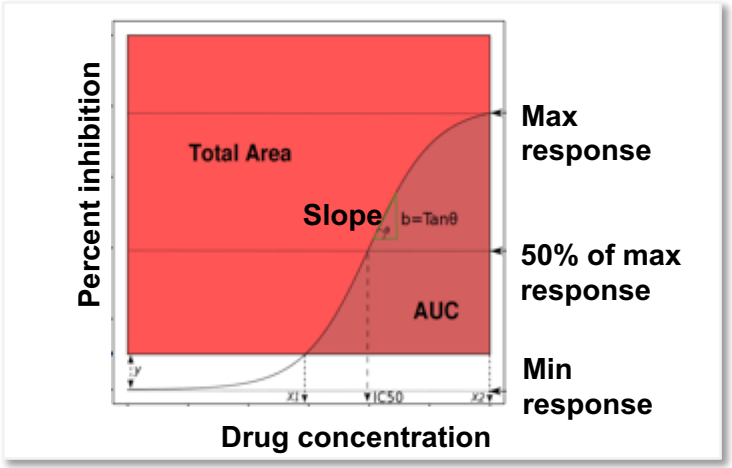
Functional Drug Testing Platform at FIMM

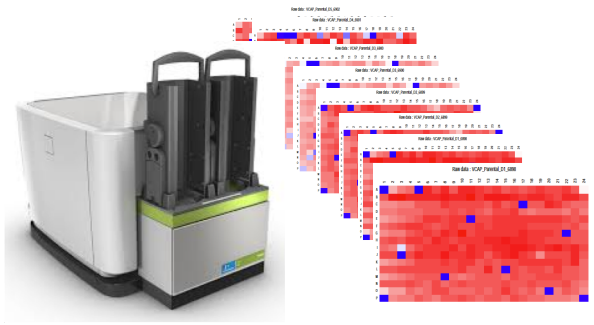


525 oncology drugs
149 approved drugs
376 investigational drugs
- conventional chemotherapeutics
- hormone therapy drugs
- kinase inhibitors
- epigenetic/differentiating drugs
- other targeted drugs
- immunosuppressants

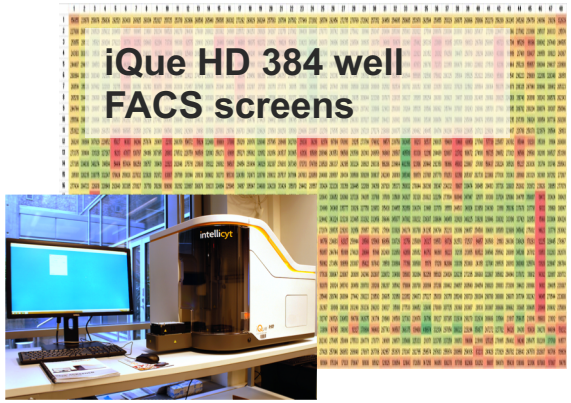


Fresh material, expansion, single cell suspension

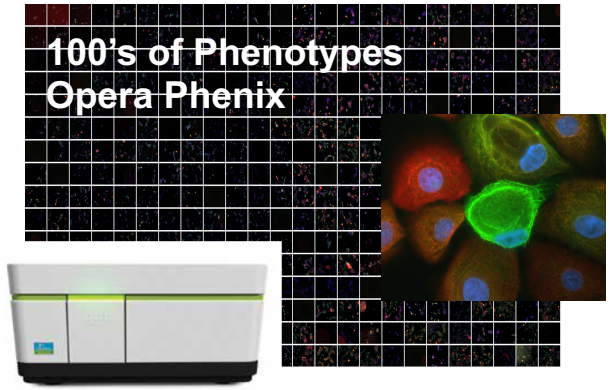
Cell Viability / Toxicity by CellTiter-Glo / CellTox



Multiplexed high throughput flow cytometry



High throughput high-content image-based screens



Slide by Päivi Östling / Olli Kallioniemi

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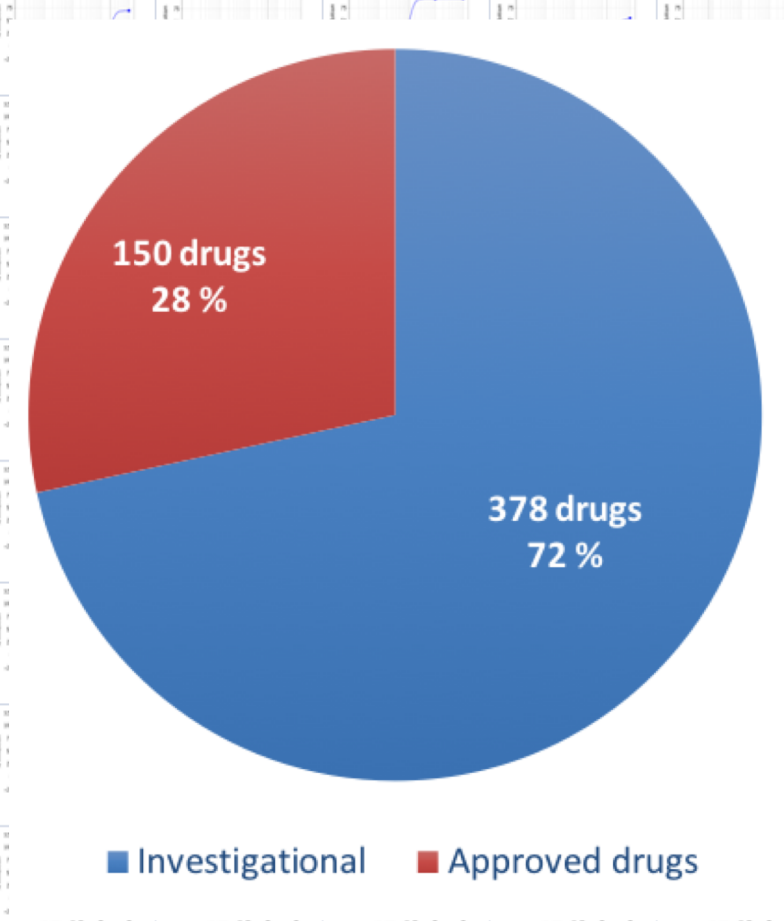
Pharmacopeia-wide drug sensitivity and resistance testing with dose-response curves for each drug

Detailed dose-response curves for all oncology drugs and many emerging cancer compounds for individual patient cell samples

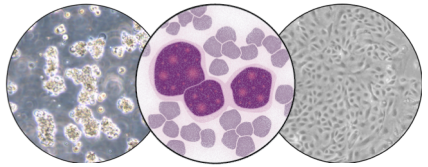
- Conventional chemotherapeutics
- Tyrosine kinase inhibitors
- S/T-type inhibitors
- PI3K inhibitors
- mTOR inhibitors
- HDAC inhibitors
- HSP90 inhibitors
- BCL2 inhibitors and other apoptosis modulators
- p53 activators
- PARP inhibitors
- Hh inhibitors
- g-Secretase inhibitors
- Farnesyltransferase inhibitors
- Proteasome inhibitors
- Immunomodulatory drugs



1-10000 nM
➔ dose response curves

Drug sensitivity and resistance testing (DSRT)

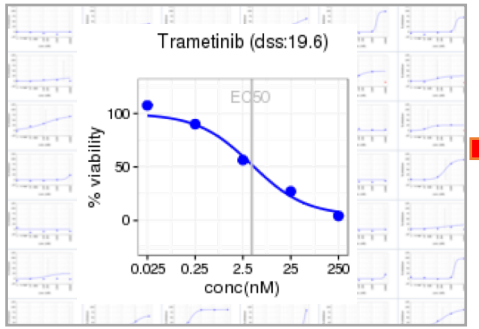
Patient cells



Assay & detection reagents

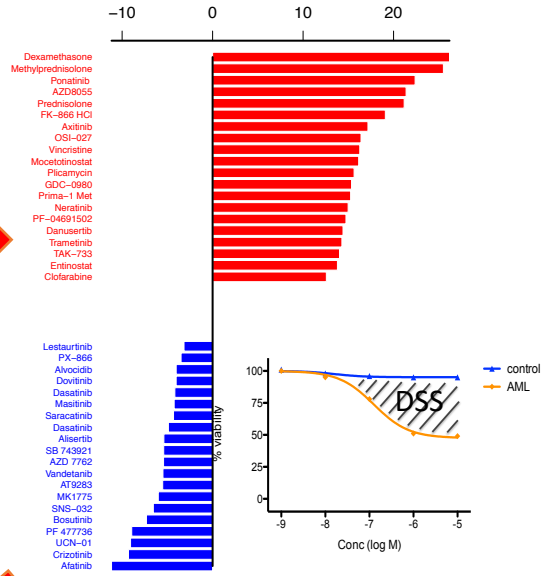
37°C
72 h

525 dose response curves



Results in 4 days

Calculate activity and compare to controls



Labcyte Access Workstation (www.labcyte.com)

The FIMM oncology drug collection is pre-plated:
525 drugs, 5 concentrations,
10,000-fold concentration range

Novel biological understanding of the disease

Translate directly to patients

Find responding cells/patients - drug repositioning

Pemovska et al, Cancer Discovery 2013, Yadav B et al, Scientific Reports 2014

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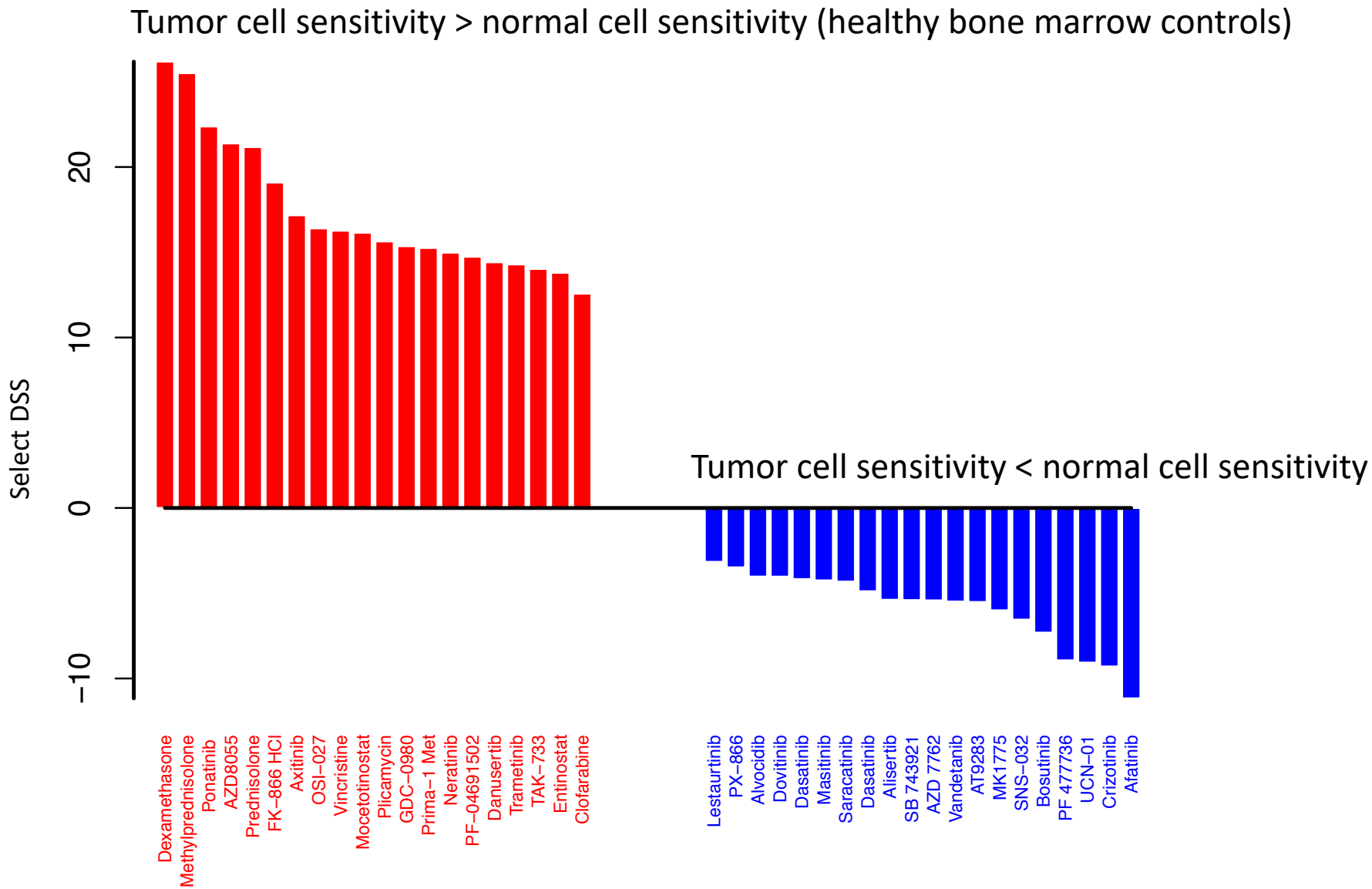
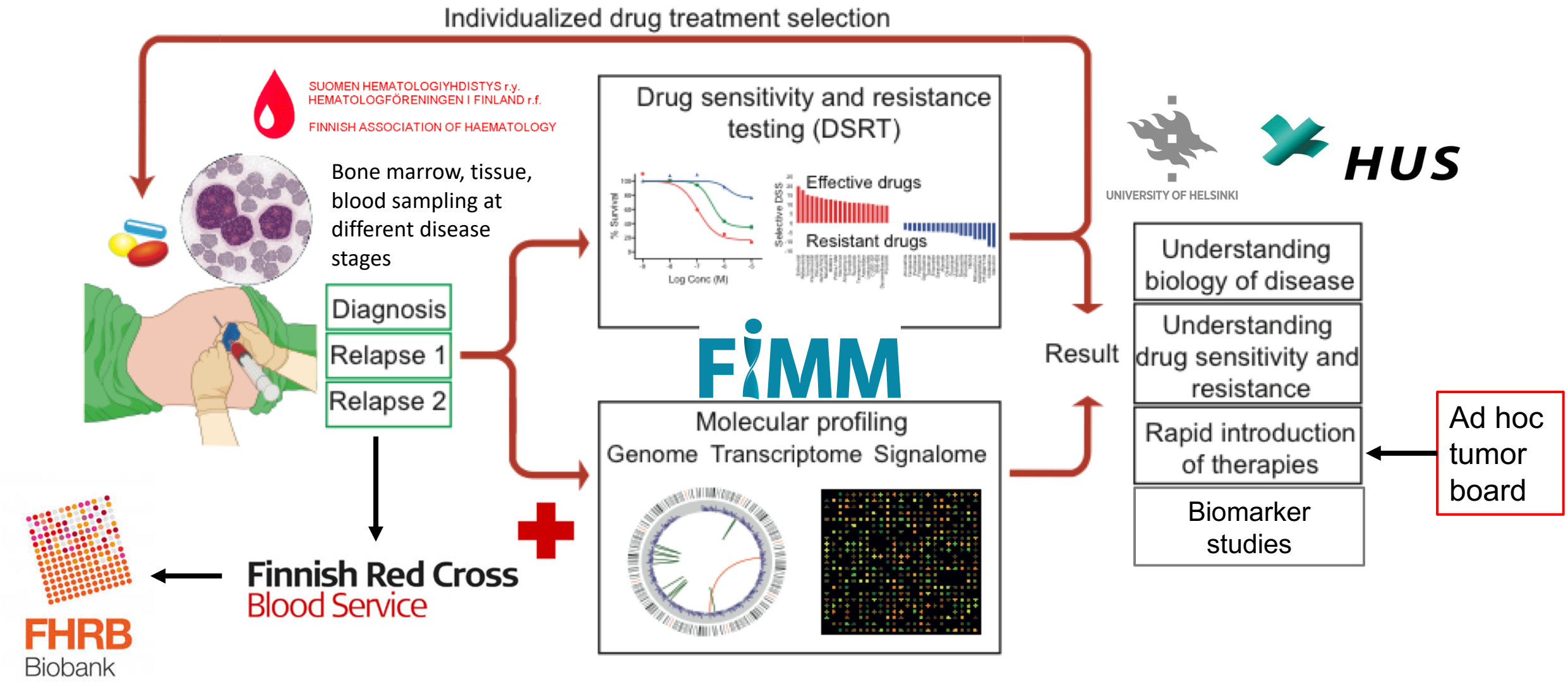
Prioritizing drugs based on tumor specific sensitivity

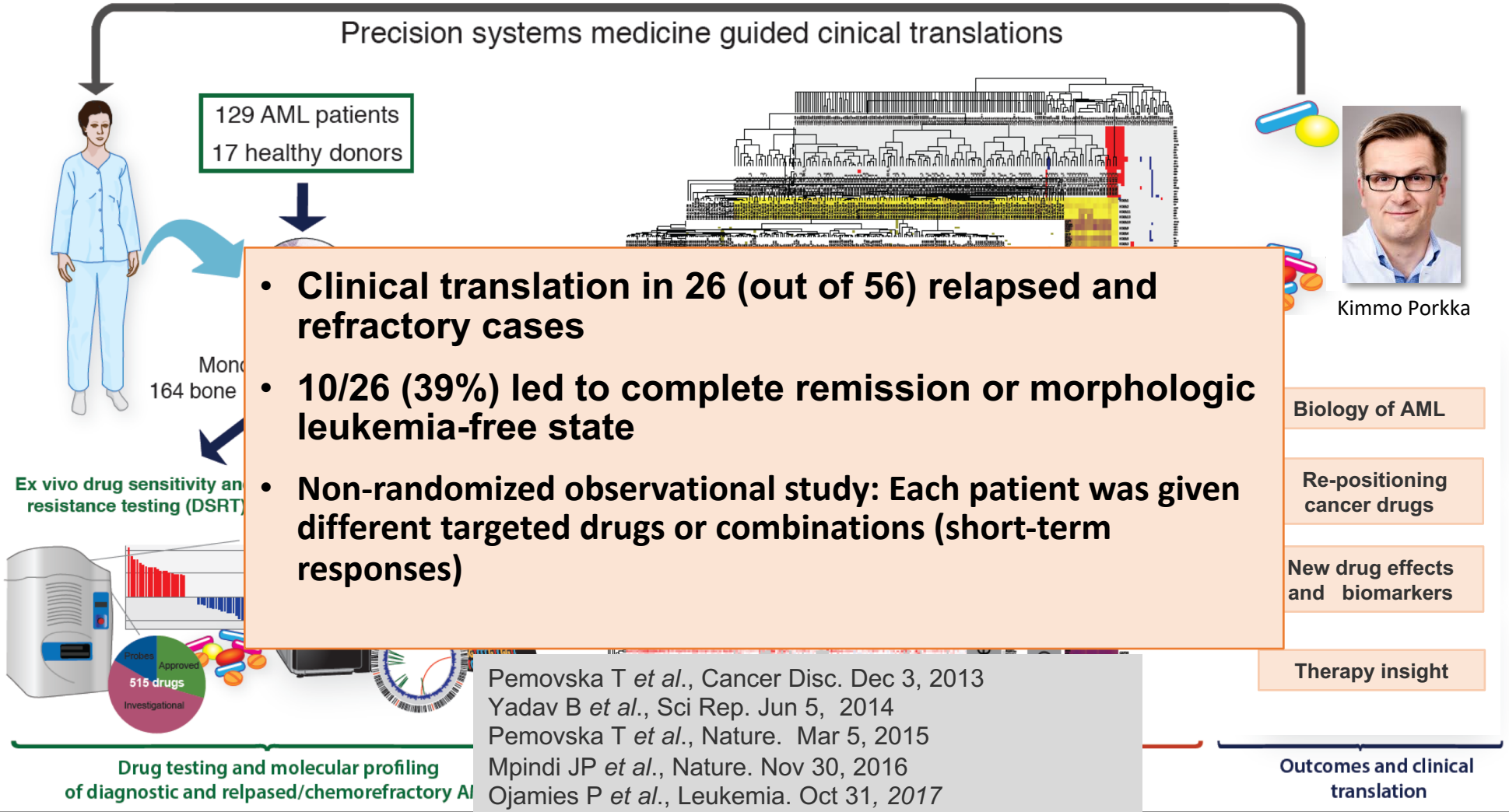


Individualized Systems Medicine (ISM) for rapid translation in treatment of leukemia



Slide by Caroline Heckman

Precision Systems Medicine study of 164 consecutive AML samples



- **Clinical translation in 26 (out of 56) relapsed and refractory cases**
- **10/26 (39%) led to complete remission or morphologic leukemia-free state**
- **Non-randomized observational study: Each patient was given different targeted drugs or combinations (short-term responses)**

Pemovska T *et al.*, Cancer Disc. Dec 3, 2013
Yadav B *et al.*, Sci Rep. Jun 5, 2014
Pemovska T *et al.*, Nature. Mar 5, 2015
Mpindi JP *et al.*, Nature. Nov 30, 2016
Ojamies P *et al.*, Leukemia. Oct 31, *2017*
Malani D *et al.*, Leukemia. May 31, 2017
Ojamies P *et al.,* Leuk Lymphoma. Apr 4, 2018

Kimmo Porkka


Disha Malani


Bhaqwan Yadav


Ashwini Kumar

Slide by Disha Malani

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nature International weekly journal of science

NATURE | LETTER

Axitinib effectively inhibits BCR-ABL1(T315I) with a distinct binding conformation

Tea Pemovska, Eric Johnson, Mika Kontro, Gretchen A. Repasky, Jeffrey Chen, Peter Wells, Ciarán N. Cronin, Michele McTigue, Olli Kallioniemi, Kimmo Porkka, Brion W. Murray & Krister Wennerberg

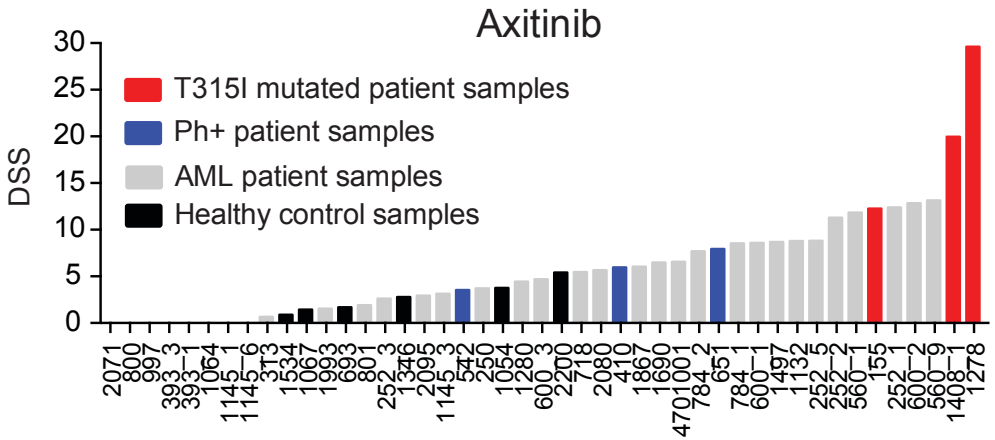
Nature. 2015 Mar 5;519(7541):102-5

Krister Wennerberg

Axitinib - Currently approved for relapsed renal cell carcinoma

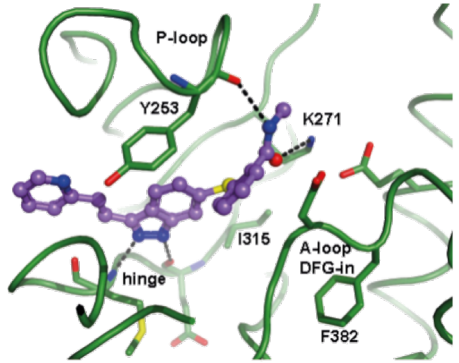
Primary targets -> VEGFR-1, -2, -3, PDGFR and KIT

1. Drug efficacy in a subgroup ex-vivo:
   - T315I gate-keeper mutation in BCR-ABL
   - Resistance to ABL inhibitors

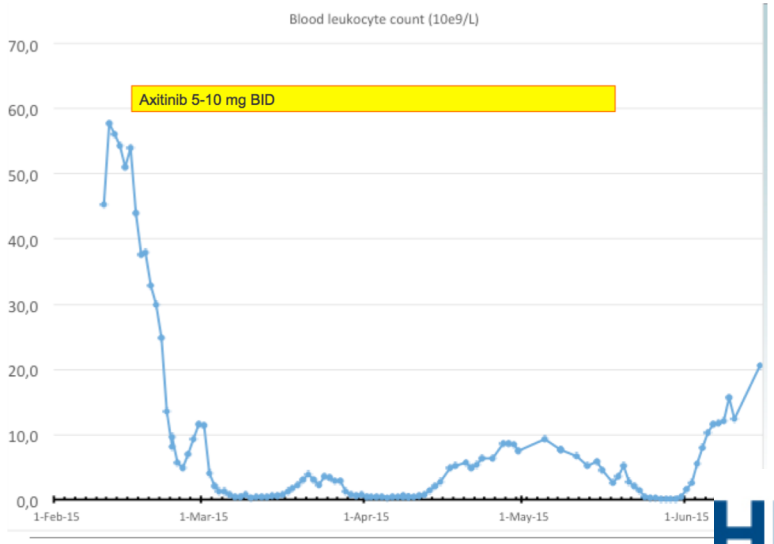


2. Molecular mechanisms

Kinase	Axitinib Kd (nM)
ABL1	36
ABL1(T315I)	**1.5**
ABL1(H396P)	20
ABL1(M351T)	36
ABL1(E255K)	63
ABL1(Y253F)	230
ABL1(F317I)	800
VEGFR2	**5.9**



3. Clinical proof of concept



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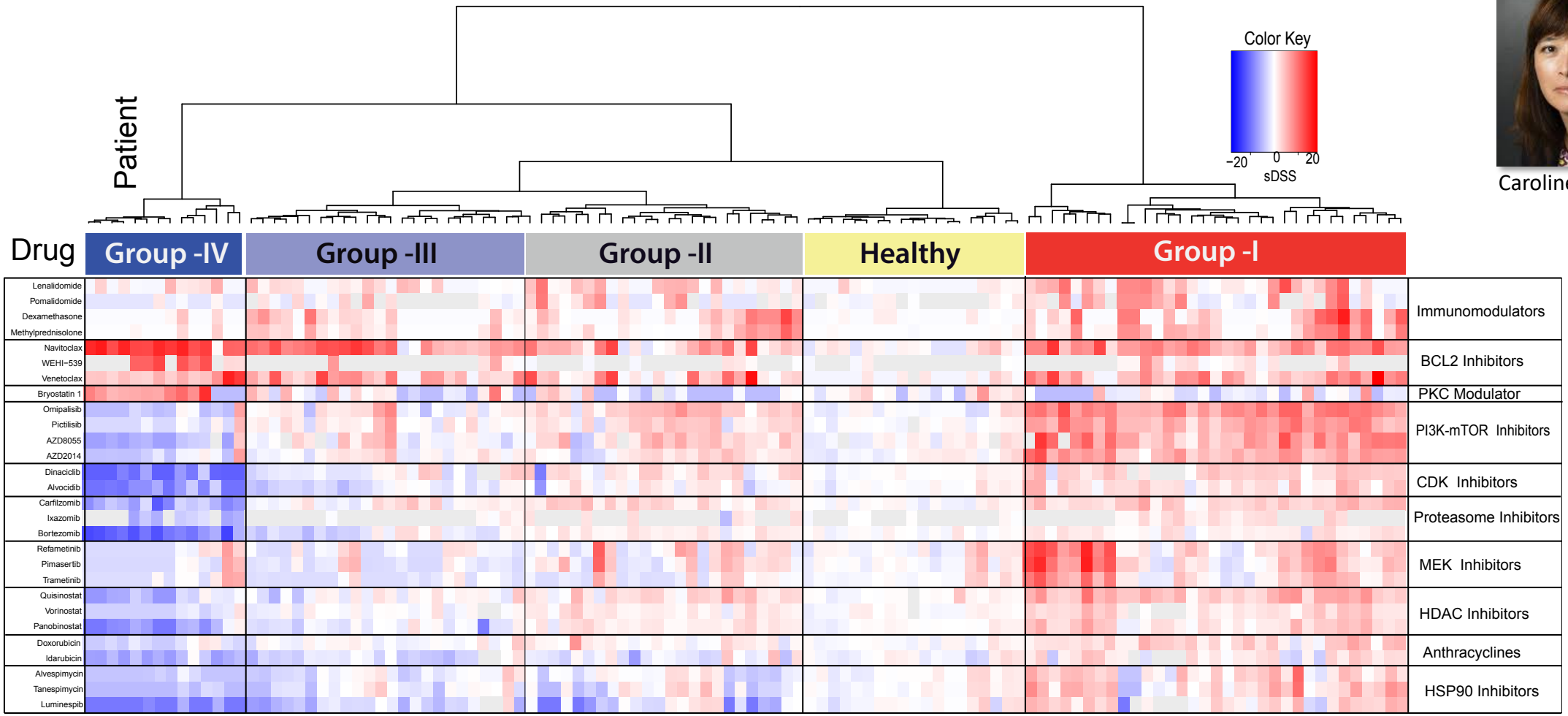
Multiple Myeloma patients can be stratified based on their drug sensitivity profile

Muntasir Mamun Majumder

Caroline Heckman



Majumder et al. Oncotarget 2017

Multiple Myeloma patients can be stratified based on their drug sensitivity profile

Muntasir Mamun Majumder

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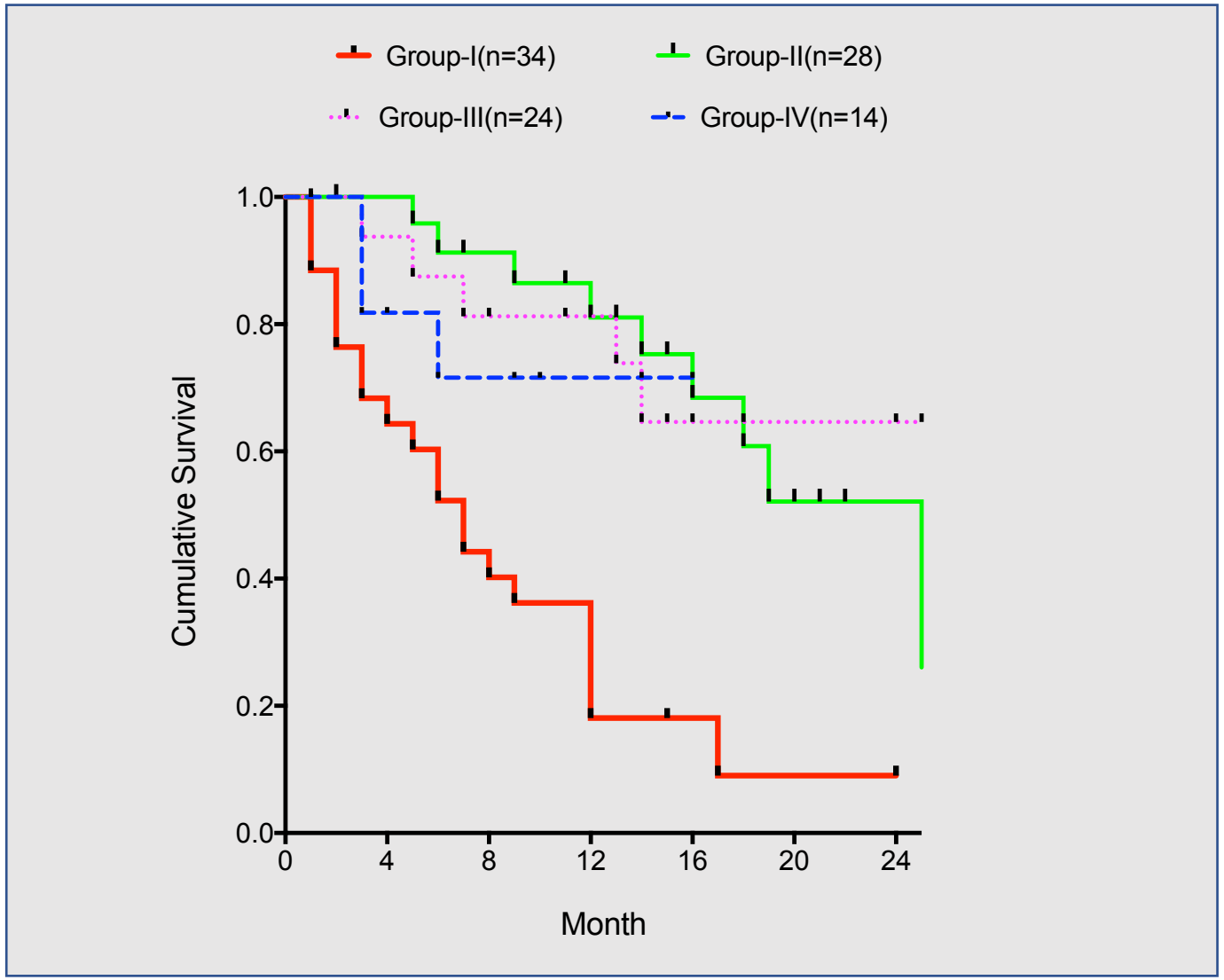
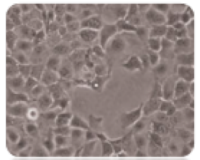


Majumder et al. Oncotarget 2017

Ovarian cancer Individualized Systems Medicine platform

Models

In vivo
(Patient tissue samples)



Ex vivo
(Primary cell models)

In vitro
(Cell lines)

Methods

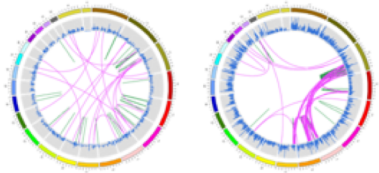
Molecular profiling
- Genome
- Transcriptome
- Signalome

Drug sensitivity and resistance testing (DSRT)
- 664 anti-cancer agents and targeted inhibitors

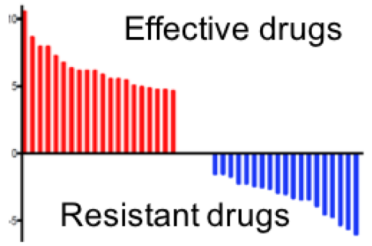
Bionformatics and models
- pipelines for DNA, RNA, data analysis
- data integration
- predictive models

Results

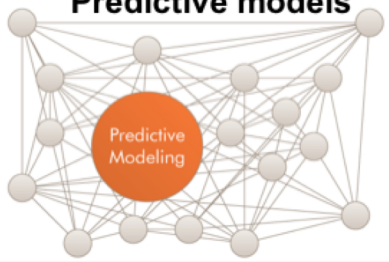
Driver mutations, deregulated genes



Patient specific treatment recommendations



Predictive models

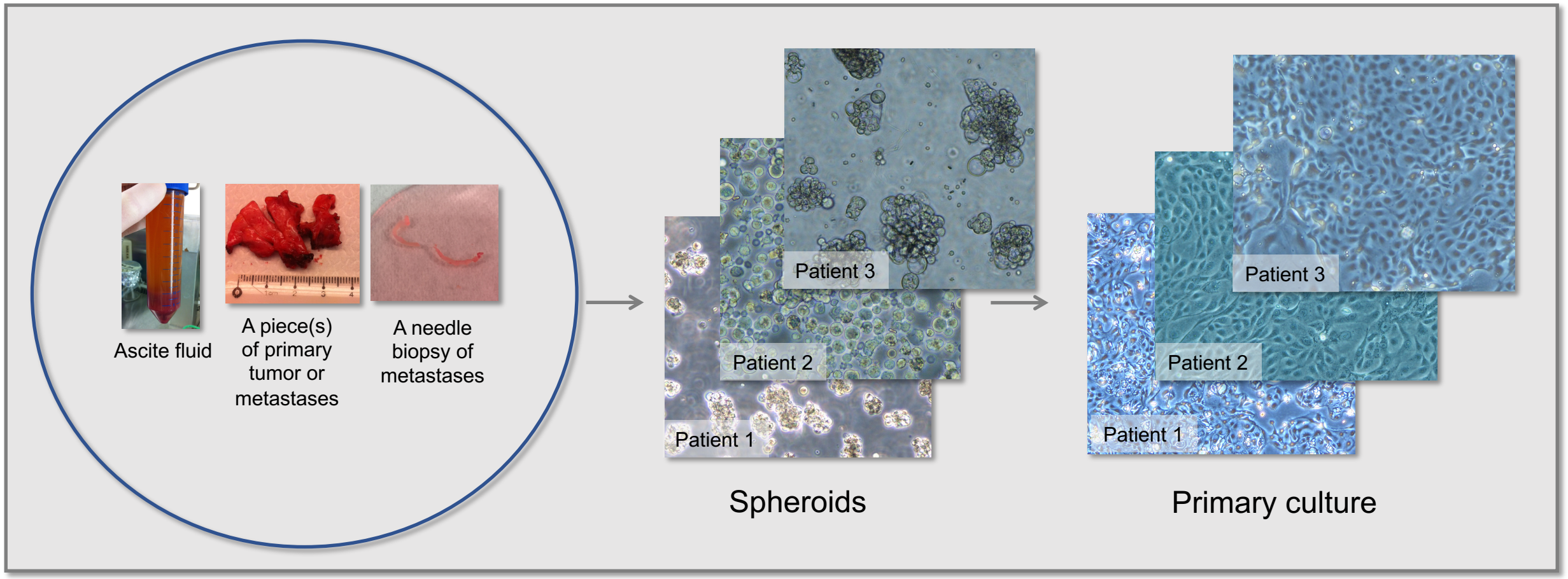


Outcome

Integrated view of chemorefractory ovarian cancer

Translational impact via drug repositioning and combinations

Ovarian cancer Individualized Systems Medicine platform



Caroline Heckman Group

Hematology Research Unit (Satu Mustjoki, Kimmo Porkka)
Helsinki University Hospital

Olli Kallioniemi Group

Tero Aittokallio Group

Patients & Funders

HUS

Mothers ♥ Daughters ♥ Sisters ♥ Friends
We're In This Together

Krister Wennerberg Group

HUS/ Women´s Hospital

Johanna Tapper
Riitta Koivisto-Korander
Päivi Pakarinen
Heini Lassus
Ralf Bützow

Tartu University Hospital

Andrus Mägi
Tiina Kuum
Peeter Padrik

BMT /Tampere

Daniela Ungureanu
Harlan Baker

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Sequencing unit
Bioinformatics unit
Digital and molecular pathology unit

Jing Tang Group