



**Institute for Molecular Medicine Finland**  
Nordic EMBL Partnership for Molecular Medicine

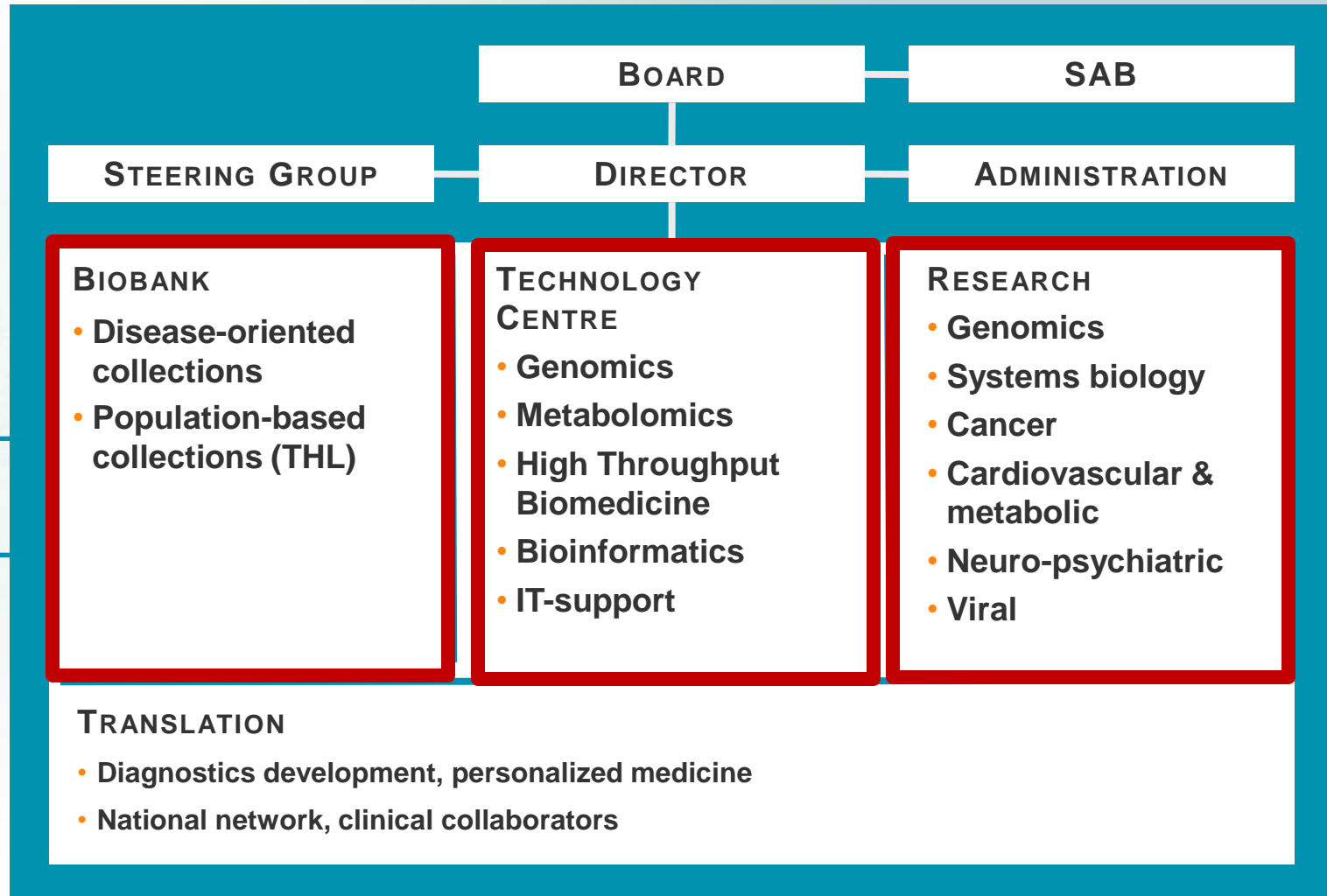
*Building a bridge from discovery to medicine*

# FIMM and the High Throughput Biomedicine (HTB) unit

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# High Throughput Biomedicine Unit

## Current activities:

siRNA  
screening

chemical  
screening

miRNA  
screening

Microarray  
printing

Sharing of chemicals  
with academic  
groups

### Personalized medicine

*ex vivo* testing of  
patient cells with  
oncology drugs:

Leukemia

Ovarian cancer

Glioblastoma



# *High Throughput Biomedicine Unit*

## *Current activities:*



siRNA  
screening

miRNA  
screening

chemical  
screening

- **Project planning, screening format adaptation and assay development**
  - 96- and 384-well (1536-well)
  - Cell viability (CellTiter-Glo and many other well-based readouts)
  - High-content imaging
- **Low medium and high throughput screening**
  - RNAi (siRNA, miRNA)
  - Chemical
- **Secondary assay testing**
- **Analysis and bioinformatics of the results**



# *High Throughput Biomedicine Unit*

## *Current activities:*



siRNA  
screening

miRNA  
screening

chemical  
screening

### **siRNA screens**

- full genome
- subsets (druggable genome, kinases, phosphatases...)
- siRNA library combined with one or a few chemicals
- siRNA screens combined with miRNAs

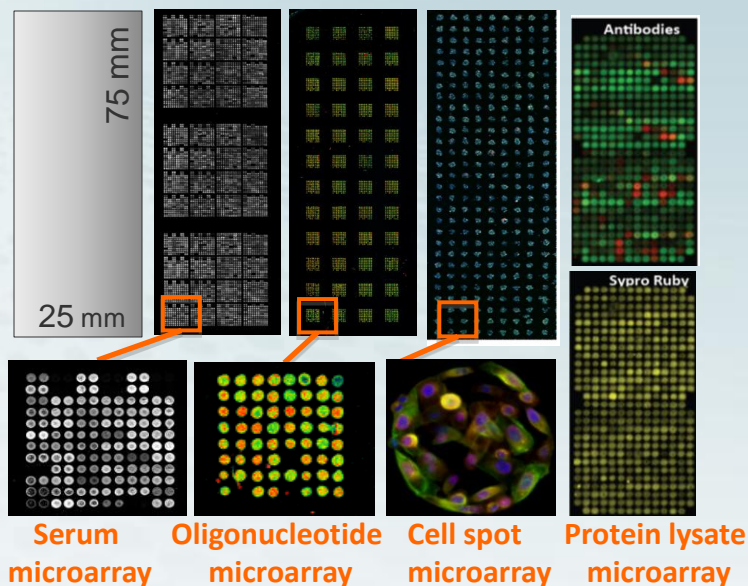
### **Chemical screens**

- Drug sensitivity and resistance testing (DSRT)
- custom screens (mammalian, yeast, prokaryotes)
- Biochemical screens
- Chemical library combined with siRNA KO

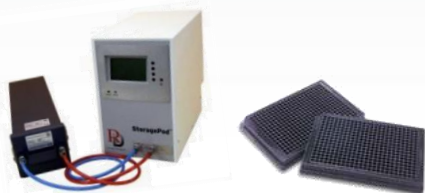
# High Throughput Biomedicine Unit

## Current activities:

### Microarray printing



### Sharing of chemicals with academic groups



- Preplating chemicals on assay plates
- Distributing single aliquotes to different research groups
- Partner in the DDCB network, a national infrastructure for drug discovery and chemical biology research in Finland

# HTB Equipment

## BeckmanCoulter integrated robotic system

- used for splitting libraries on Labcyte ECHO source plates, by pipetting
- running fully automated screens with cell or biochemistry based assays

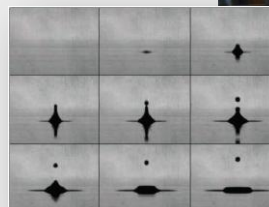
Motoman robotic arm  
Biomek FXp pipetting robot  
Multidrop Combi (x2) and Combi nl (x1)  
Cytomat 6001-plate incubator for cells  
Platelock-plate sealer  
V-spin-centrifuge  
Delidding stations and plate hotels on robot deck  
Paradigm plate reader  
Cytomat 24 plate hotel



## Labcyte Access robotic system

- used for creating assay plates with chemicals and/or siRNAs
- miniaturized cell-based and biochemical screening

Labcyte robotic arm  
Labcyte 550 Omics2 Screening2 (2.5 nl droplet)  
Labcyte LX bulk filler (4 source liquids)  
Xpeel-plate peeler  
Platelock-plate sealer  
V-spin-centrifuge  
Delidding stations and plate hotels on robot deck  
Echo 525 arriving in 2013 (25 nl droplet)





# HTB Equipment- Microscopes and Plate readers



## **Olympus ScanR High content screening system**

10x, 20x, 40x and 60x objectives  
Dapi, Alexa 488, Alexa 555, Alexa 596 and Alexa 647 filters



## **BMG Pherastar FS plate reader**

Luminescence, Absorbance, AlphaScreen, LanthaScreen etc.  
Over 20 different filters



## **Incucyte FLR and Incucyte HD live cell imagers**

Microscopes inside incubators  
20x, objectives and Alexa 488 filters  
Confluence and wound healing assays



## **Molecular Devices Paradigm plate reader**

Luminescence, Absorbance, Fluorescence, TRF etc.

## **HTC1 self service unit**

- Acumen eX3
- BMG Fluostar Optima
- PerkinElmer Topcount
- Flow cytometry

## **Biomedicum Bioimaging Unit and Viikki (UH)**

- Leica
- 2 xCellInsight HT screening microscopes
- Cell-IQ

# Libraries

## siRNA libraries

Ambion Silencer Select genome-wide siRNA library

-whole genome, subsets, cherry picking

Customized RNAi libraries for our users



## Chemical libraries

140 000 screening chemicals

- drugs & known bioactives and chemical diversity libraries

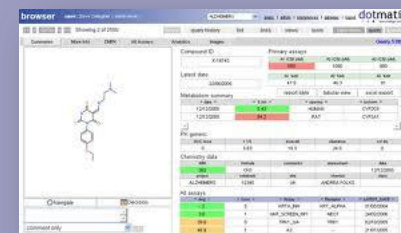
Drug sensitivity and resistance testing

Currently 306 oncology drugs and 355 targeted inhibitors



## Data management

Chemical and data database software – Dotmatics



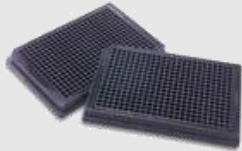
# 384-well based Screen Workflow

Cell culture 384 well assay plates

siRNA libraries on 384 well ECHO plates

siRNA administration (nl)

1) Dispensing of transfection reagent on assay plates  
2) Dispensing of cells on the plates



Luminescence / intensity readout

Dispensing of detection reagent on cells

Incubation 72 h-7 days at 37°C



A



Microscopy readout

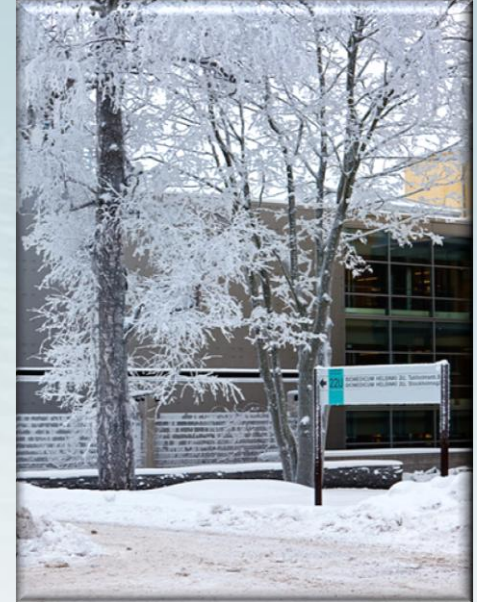
Fixing and staining of cells



B

# Projects 2012

- › **Total of 28 projects (+ongoing projects), 205 screens**
- › **129 oncology screens (~270 drugs in 5 concentrations)**
  - Primary leukemia patient samples (25 screens)
  - HMGB4 (2 sc) (+ 4 follow-up screens)
  - Head and neck squamous cell carcinoma primary cell lines: 3 projects/46 screens (40+3+3 sc)
  - Ovarian granulosa cancer primary cell lines (3 sc)
  - Breast cancer cell lines (49 sc)
  - Glioblastoma multiforme primary cell lines (3 sc)
  - Other cell lines (3 sc)
  - Optimization (1536-format)
- › *Candida* (2)
- › Inhibition of protein-protein interaction (2 sc)
- › Low-throughput chemical screens in follow-up to virtual screening (3 sc)
- › Ongoing chemical screening projects (7) (384/1536-format)
- › **Plate-based siRNA screening**
  - › Finished screens: (1+2 screens)
  - › Ongoing siRNA projects (6)
  - › Ongoing project combining siRNAs+miRNAs+drugs (1)
  - › siRNA + DSRT (10 sc)
- › **siRNA/drug plates** to research groups in Finland: 166+/242+

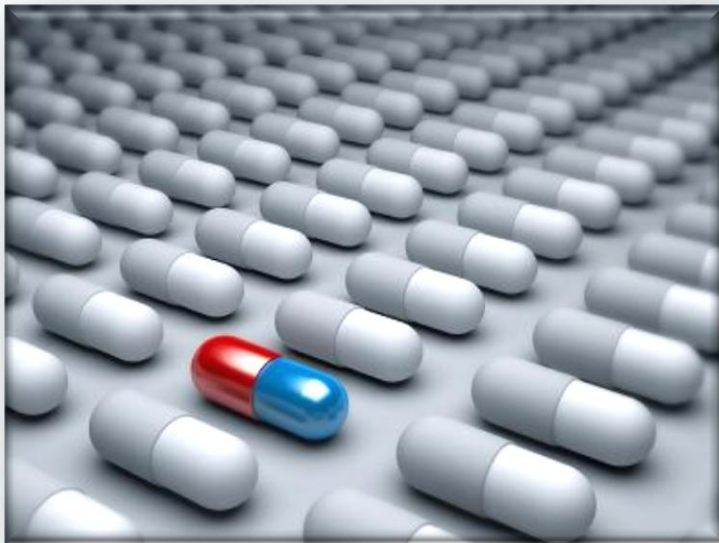


## Methods development

- › **Lysate microarray** optimization ongoing
- › **Cell spot micro array** (EU-project, siRNA): optimization ongoing (BRC, PC)
- › **Plasmid printing using Aushon**: optimization ongoing
- › **Cell seeding using ECHO**: optimization ongoing
- › **qRT-PCR**: optimization ongoing (384-format)
- › **CNV**: optimization ongoing



# Personalized leukemia research at FIMM



**HTB unit**

**Genomics unit**

**Biobank**

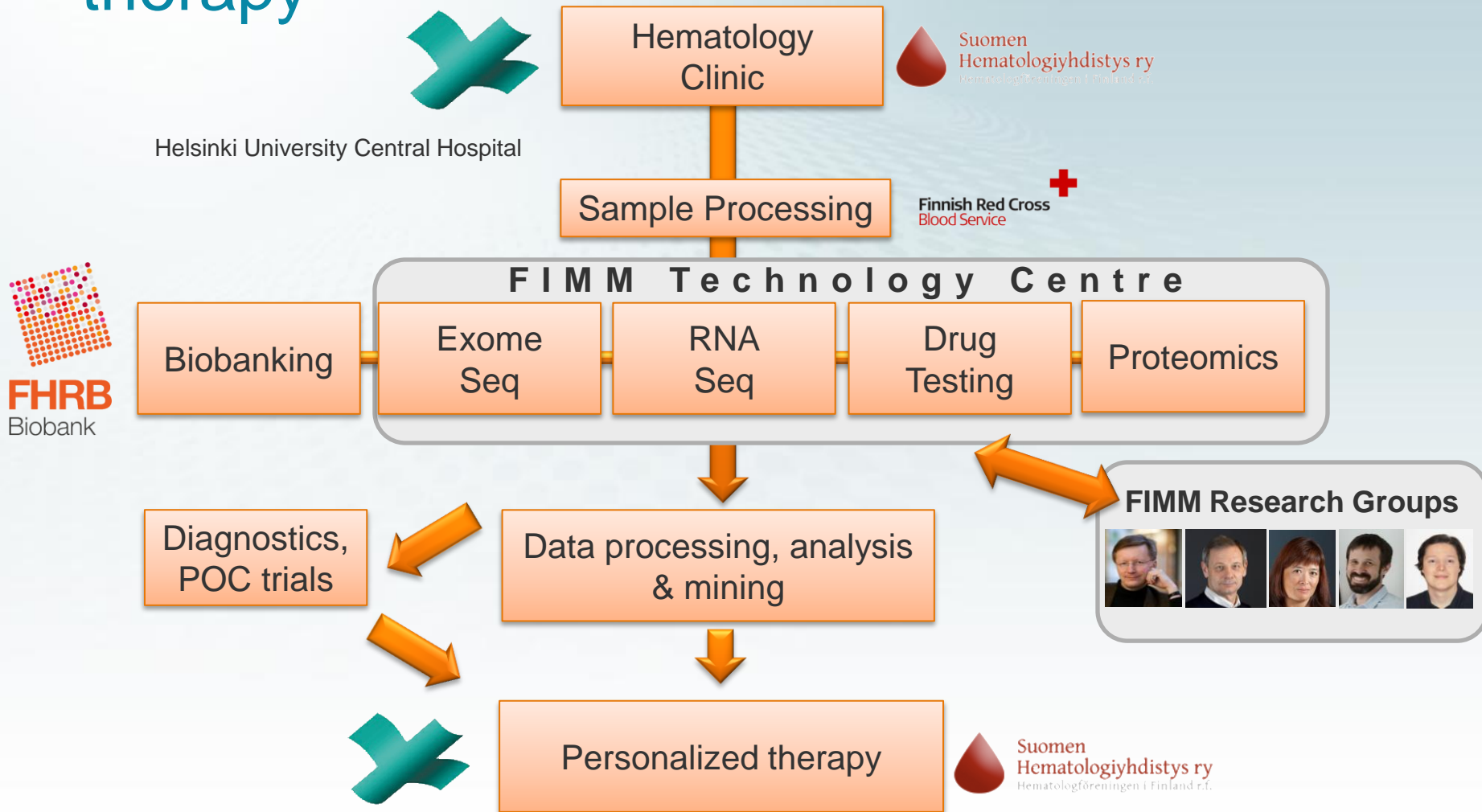
**Kallioniemi**

**Knowles/Heckman**

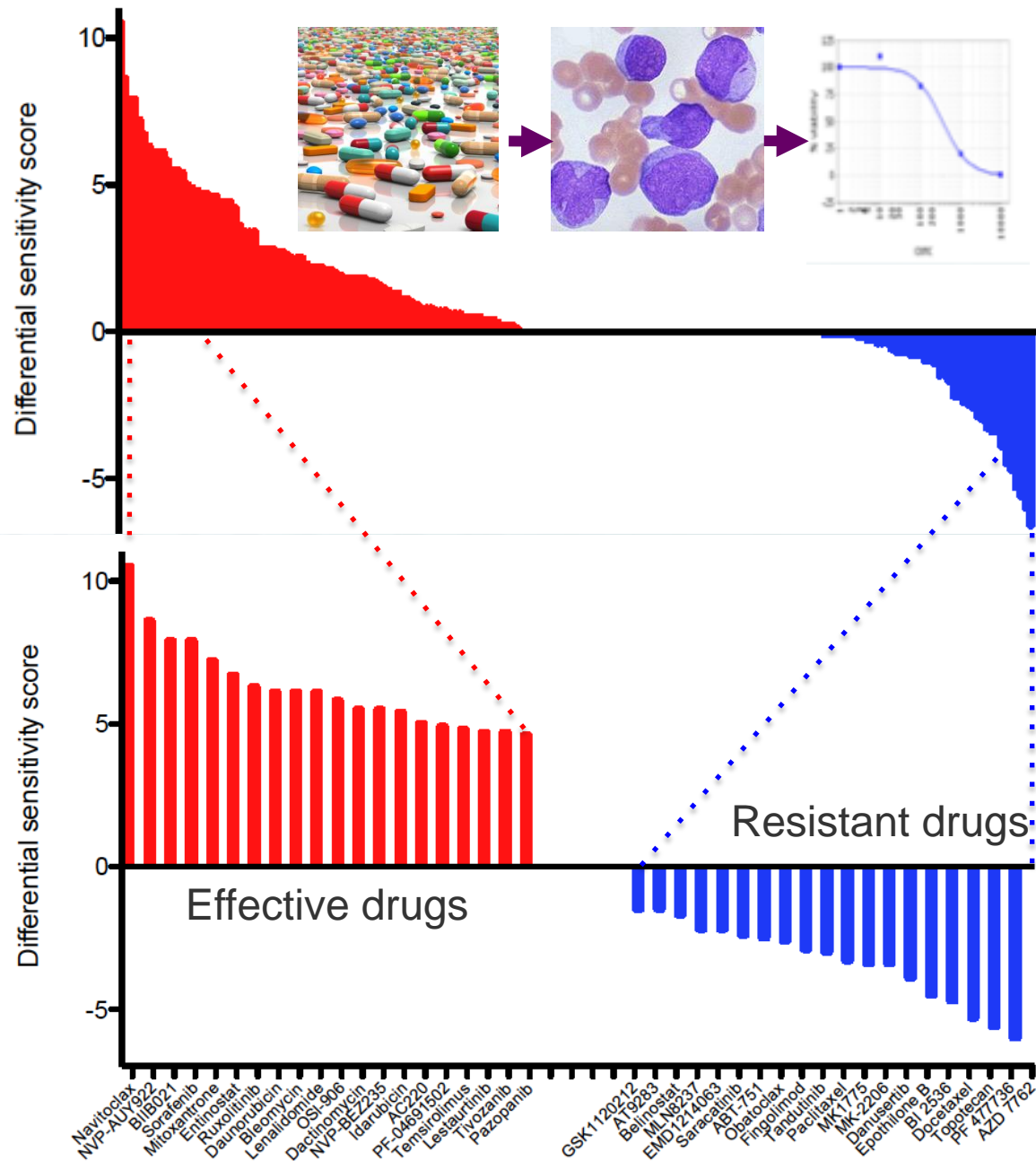
**Wennerberg**

**Aittokallio**

# Personalized leukemia research and therapy



Individual patient-specific treatment “recommendation” based on ex-vivo testing



# Collaborations

**LABCYTE** 



 **biocro**

 **Advanced Microplates**

**Happy Cell**  
ASM



**Happy Cell**  
ASM



**LABCYTE** 

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### Labcyte and FIMM Announce a Collaboration Enabling "Real-Time" Science to Advance Personalized Medicine in Cancer Treatments

Sunnyvale, CA & Helsinki – Labcyte Inc. and the Institute for Molecular Medicine Finland (FIMM) are collaborating to further the development of personalized medicine in cancer treatment. Labcyte acoustic liquid handling technology has already revolutionized small-molecule research. Now, FIMM, a European leader in advanced research for new cancer therapies, will apply the technology extensively in its personalized medicine programs.

"FIMM's groundbreaking use of acoustic liquid handling will demonstrate the technology's role in genetic research," said Mark Fischer-Colbrie, CEO of Labcyte. "FIMM has successfully used Labcyte acoustic liquid handling technology to generate better data and drive down costs in small-molecule screening for the past three years. This collaboration with such a well-regarded institute will facilitate breakthroughs in personalized medicine."

FIMM uses large sample sets with links to detailed patient records and genetic data to discover personalized treatment options at a faster pace.

"We see an enormous potential in expanding our use of Labcyte acoustic dispensing technology to help discover specialized leukemia treatments," said Professor Olli Kallioniemi, director of FIMM. "This research is based on high-throughput drug sensitivity and resistance testing of leukemic cells taken from patients. This new initiative will bring us closer to the clinic and closer to patients."

"Our aim is to find alternate treatment options for patients who simultaneously undergo treatment in the clinic," said Kallioniemi. "We will be doing real-time science, using new scientific insights and technologies to help patients who have failed standard leukemia treatments."

Increasing its throughput enables FIMM to do more rapid and more efficient testing. Researchers at the Institute hope to learn how leukemia cells ex-vivo respond to various types of drugs, and what the resistance mechanisms are. "Larger trials with samples from acute myeloid leukemia patients who have relapsed under standard treatment may quickly suggest individualized treatment options using existing cancer drugs," added Kallioniemi. "We're not saying we can cure leukemia, but for patients who have run out of options, alternative treatments may be available sooner."

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# FIMM EU/ESFRI activities

- › **EU-OPENSREEN:** European Infrastructure of Open Screening Platforms for Chemical Biology
  - FIMM coordinates Finnish participation in the European infrastructure platform planning
- › **EATRIS:** European Advanced Translational Research Infrastructure in Medicine
- › **SysMic:** Systems Microscopy Network of Excellence EU-FP7
- › **EuroBioimaging:** a large-scale pan-European research infrastructure project on ESFRI roadmap; FIMM-HTB is involved in national roadmap application and FiBi network
- › **BBMRI:** Biobanking and Biomolecular Resources Research Infrastructure
- › **ELIXIR:** European Life-Science Infrastructure for Biological Information
- › **Predict:** IMI (Innovative Medicines Initiatives ) -funded partnership between 9 academic, 3 SME and 9 EU pharmaceutical company partners, developing advanced, transferable in vitro models for breast, prostate and lung cancers



# FIMM High Throughput Biomedicine Unit

**Krister Wennerberg (PhD):** Unit head

**Jani Saarela (PhD):** Assay development, coordination of lab operations

**Carina von Schantz-Fant (PhD):** Unit administration, RNAi screening, imaging

**Vilja Pietiäinen (PhD):** RNAi screening, imaging

**Päivi Östling (PhD):** RNAi screening, lysate micro arrays (LMA)

**Evgeny Kuleskiy (PhD student):** Assay development

**Laura Turunen (Lic.Sc.):** HTS coordinator, chemicals

**Karoliina Laamanen (MSc):** HTS technician

**Anna Lehto (BSc):** HTS technician

**Ida Lindenschmidt (MSc):** HTS technician, chemicals

**Ruusu-Maaria Merivirta (MSc):** HTS technician, LMA

**Swapnil Potdar (MSc):** bioinformatics

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# Thanks

## **FIMM HTB Unit & Group Wennerberg**

Tea Pemovska\*  
Evgeny Kuleskiy\*  
Anna Lehto  
Laura Turunen

## **FIMM**

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**Jonathan Knowles**  
Samuli Eldfors  
Riikka Karjalainen  
Muntasir Mamun Majumder

## **Olli Kallioniemi**

Henrik Edgren  
Disha Malani  
John Patrick Mpindi  
Astrid Murumägi

Poojitha Kota Venkata  
Maija Wolf

## **Tero Aittokallio**

Agnieszka Szwajda\*  
Bhagwan Yadav\*

## **Technology centre**

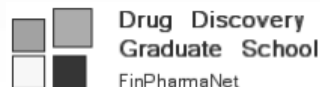
### **Janna Saarela**

Henrikki Almusa  
Pekka Ellonen

## **Division of Hematology, Helsinki University Central Hospital**

### **Kimmo Porkka**

Erkki Elonen  
Mika Kontro,  
Satu Mustjoki



# What's in the collection?

Currently 306 active substances

- › Conventional chemotherapeutics
- › Immunosuppressants
- › Tyrosine kinase-type inhibitors
  - Abl, Src, EGFR, FGFR, VEGFR, JAK, IGF1R, PDGFR, Met, ALK Kit, Flt3....
- › S/T-type inhibitors
  - Aurora, PLK1, MEK, TTK, PDK1, Akt, Wee1, PKCs, Cdks, Chk1...
- › Rapamycin analogs
- › mTOR/PI3K inhibitors
- › PI3K inhibitors
- › HSP90 inhibitors
- › Bcl-2 inhibitors
- › Survivin inhibitor
- › HDACi:s
- › Epigenetic modulators
- › PARP inhibitors
- › Hh inhibitors
- ›  $\gamma$ -secretase inhibitors
- › Farnesyltransferase inhibitor
- › p53 activators
- › Metabolic inhibitors...