

# Treating Cancer in the Era of Omics

Effie Liakopoulou MD, PhD, FRCPath, CMM

# Transforming Lives

## Stem Cell Transplantation

### Aim of treatment for Cancer

- To cure the disease
- Prolong survival
- Improve quality of life

# Removal of T cells



- GvHD
- Early mortality



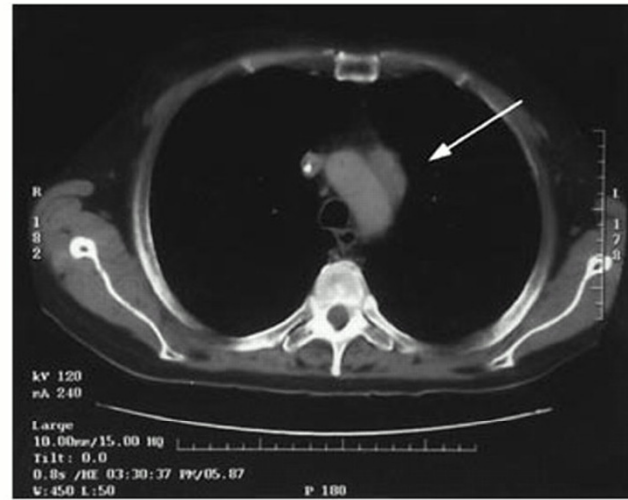
- Infection
- Engraftment



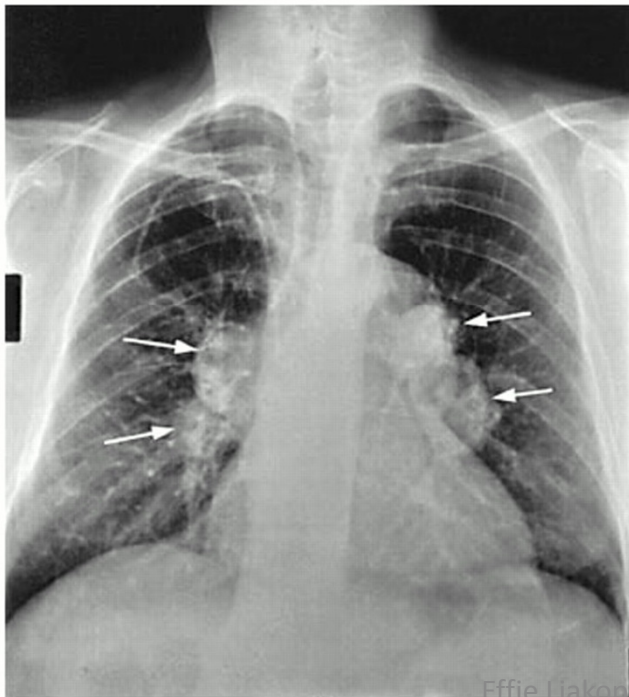
Pre  
SCT



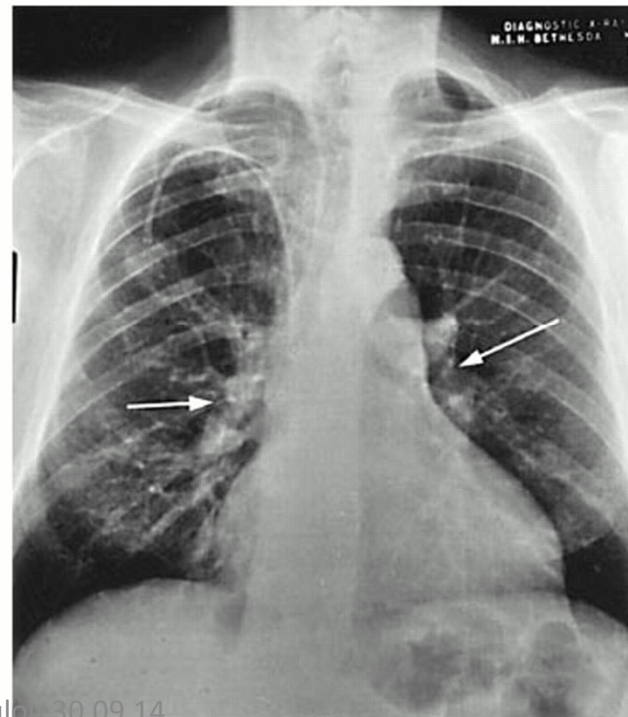
A



B



C



D

Day +276  
Post SCT

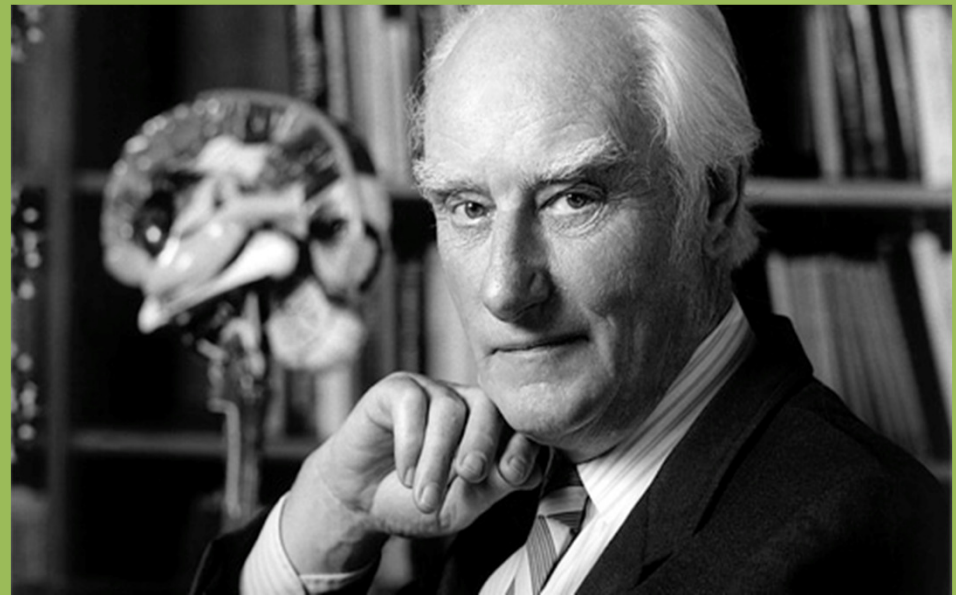
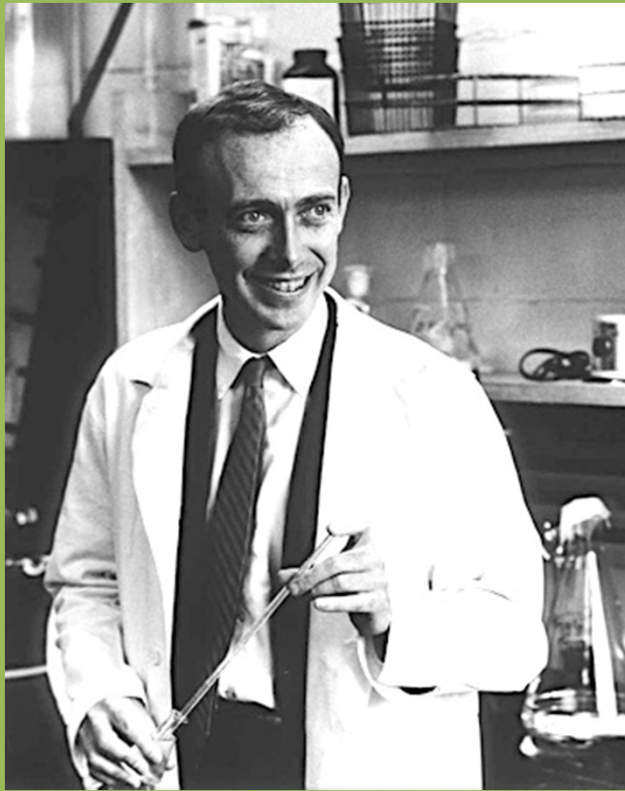




## 2011: 40 Years War on Cancer



# 2012: 50 Years Genetic Revolution

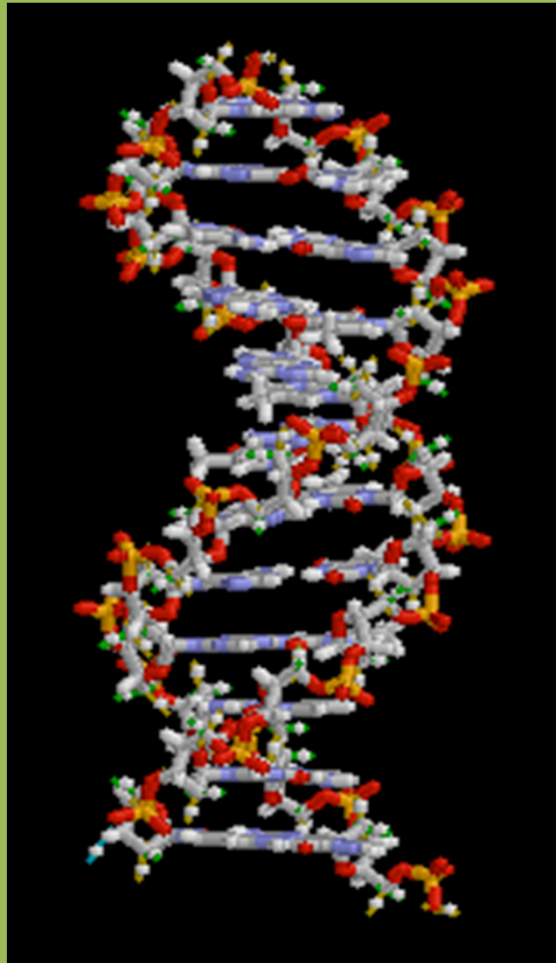




# 2012: National Science Award



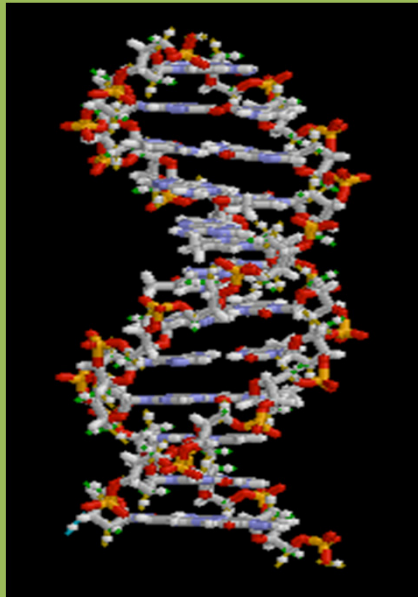
# Watson, Crick & Wilkins Achievement



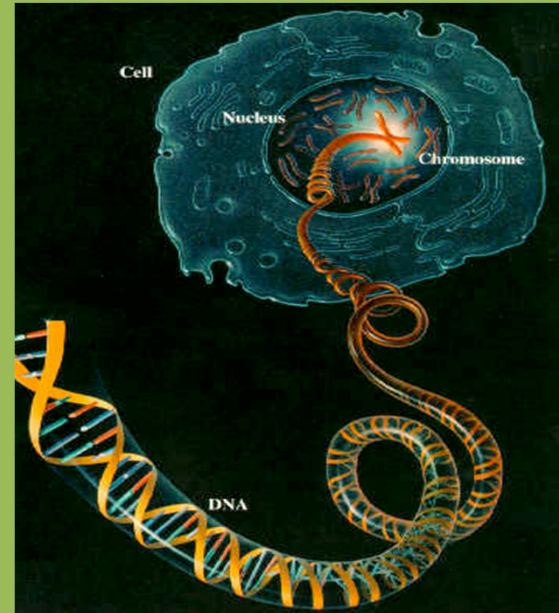
**Molecular Structure  
of DNA**

# Hood's Achievement

## DNA Molecular Structure



## Structure of Human Genome





# ENCODE in Numbers

- 30 Km (22miles) long
- 16 m (48 ft) wide

paper to print the data generated !!

There is No Junk!



# Genetic Revolution

Will we need another 50 Years to make sense of the data?

# Genetic Revolution

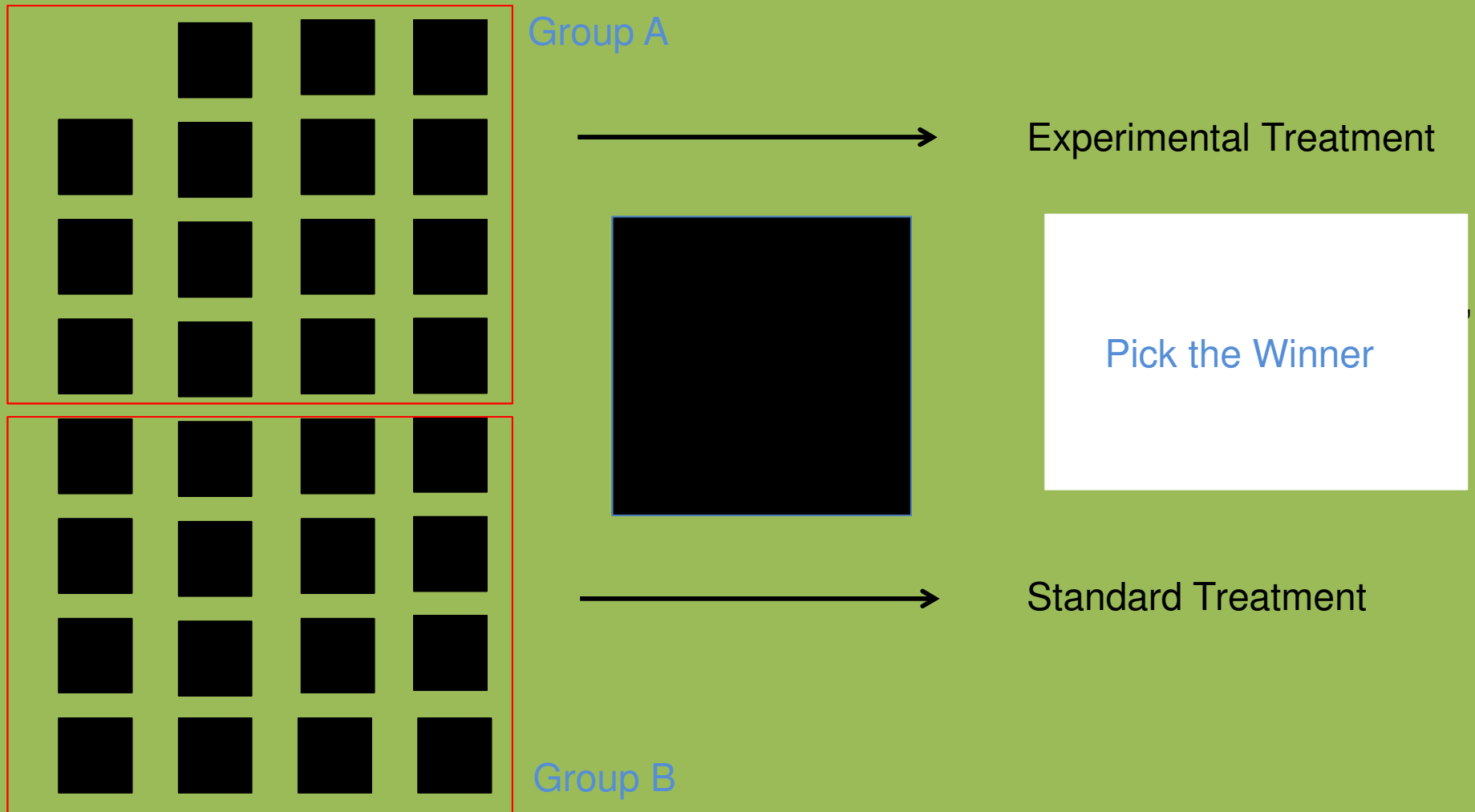
Will we need another 50 Years to make sense of the data?

- From Fragmented data  Global information
- From Biological Mechanisms  Medicines

From Sublime insight  Infinite Library of Life

**NEED**  
for technological applications  
to facilitate progress

# Cancer as a Black Box



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TARGET CANCER

## New Drugs Stir Debate on Rules of Clinical Trials



Monica Almeida/The New York Times, left

**Two Cousins, Two Paths** Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it.

By **AMY HARMON**

Published: September 18, 2010

Growing up in California's rural Central Valley, the two cousins spent summers racing dirt bikes and Christmases at their grandmother's on the coast. Endowed with a similar brash charm, they bought each other matching hardhats and sought iron-working jobs together. They shared a love for the rush that comes with hanging steel at dizzying heights, and a knack for collecting speeding tickets.

RECOMMEND

TWITTER

E-MAIL

SEND TO PHONE

PRINT

Ernie Liakopoulos 30.09.14

**Can we do better?**



# Partners in Personal Oncology

Aligning the interests of cancer patients and science

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If everyone is thinking alike, then somebody isn't thinking.

*-George S. Patton*

[www.personaloncology.org](http://www.personaloncology.org)

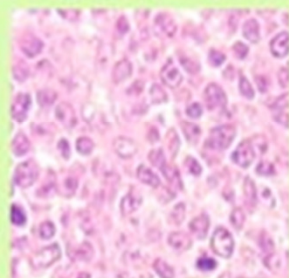
“It’s far more  
important to know  
what person the  
disease has than  
what disease the  
person has.”

*Hippocrates*

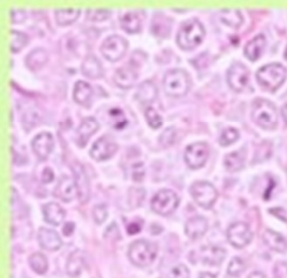
# Can Genome-Wide Profiles Help Diagnose Cancer?

Diffuse large B-cell lymphoma under the microscope

Pathology  
sees one  
cancer



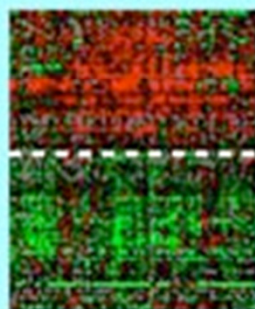
Patient 1



Patient 2

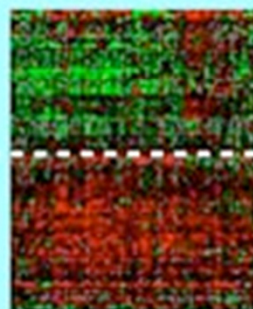
Diffuse large B-cell lymphoma after genome-wide profiling

Molecular  
diagnosis  
sees two  
cancers



Region A

Region B



Adapted by Jeanne Kelly © 2008

NATIONAL  
CANCER  
INSTITUTE





# How Many Different Kinds of Lung Cancer ?



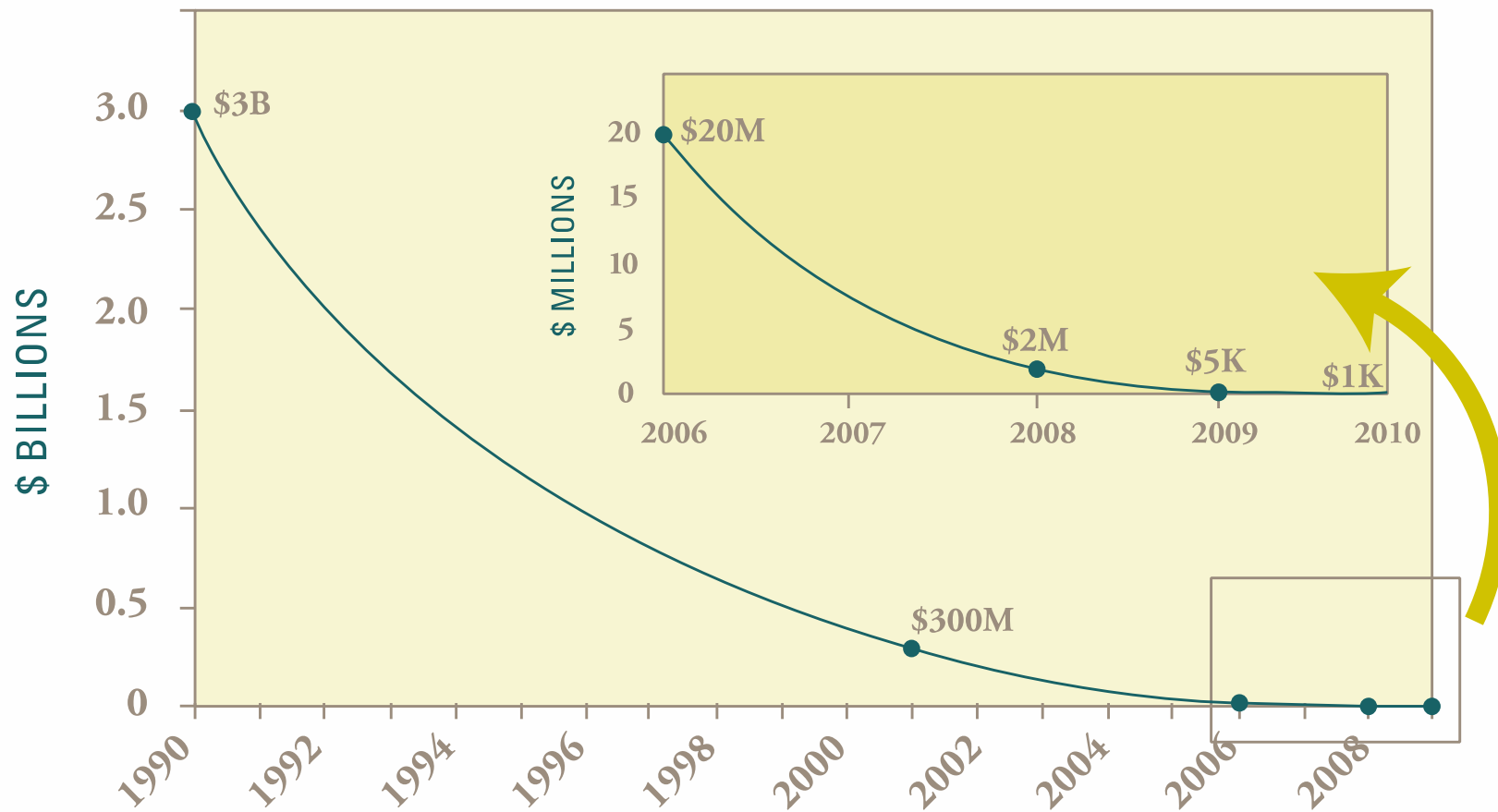
# Transforming Medicine

## 4 Main Drivers

# Transforming Medicine #1

## The Shrinking Cost of DNA Sequencing

*Towards the \$1000 Genome*

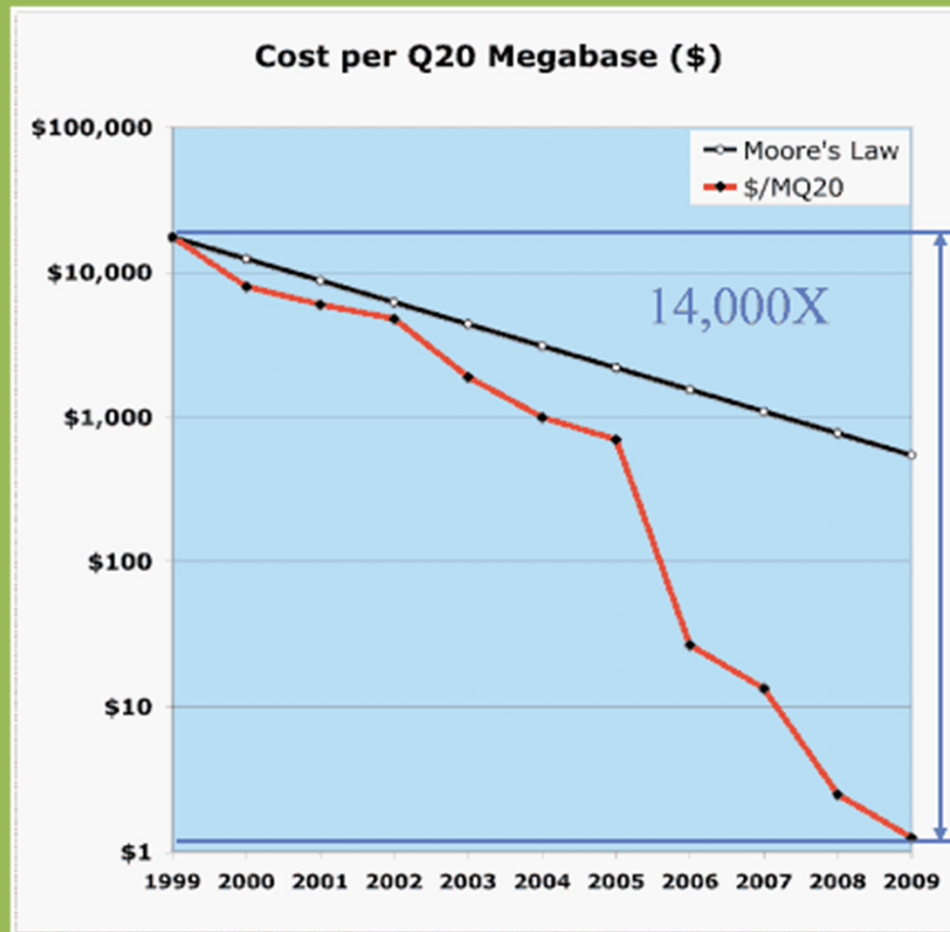




# Transforming Medicine #1

## Moore's Law put to shame

### Moore's Law put to shame



Courtesy of Eric Lander, Broad Institute  
Effie Liakopoulou 30.09.14

# Every Cancer is Different

nature

Vol 456 | 6 November 2008 | doi:10.1038/nature07485

## ARTICLES

### DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley<sup>1,2,3,4\*</sup>, Elaine R. Mardis<sup>2,3\*</sup>, Li Ding<sup>2,3</sup>, Bob Fulton<sup>3</sup>, Michael D. McLellan<sup>3</sup>, Ken Chen<sup>3</sup>, David Dooling<sup>3</sup>, Brian H. Dunford-Shore<sup>3</sup>, Sean McGrath<sup>3</sup>, Matthew Hickenbotham<sup>3</sup>, Lisa Cook<sup>3</sup>, Rachel Abbott<sup>3</sup>, David E. Larson<sup>3</sup>, Dan C. Koboldt<sup>3</sup>, Craig Pohl<sup>3</sup>, Scott Smith<sup>3</sup>, Amy Hawkins<sup>3</sup>, Scott Abbott<sup>3</sup>, Devin Locke<sup>3</sup>, LaDeana W. Hillier<sup>3,8</sup>, Tracie Miner<sup>3</sup>, Lucinda Fulton<sup>3</sup>, Vincent Magrini<sup>2,3</sup>, Todd Wylie<sup>3</sup>, Jarret Glasscock<sup>3</sup>, Joshua Conyers<sup>3</sup>, Nathan Sander<sup>3</sup>, Xiaohi Shi<sup>3</sup>, John R. Osborne<sup>3</sup>, Patrick Minx<sup>3</sup>, David Gordon<sup>8</sup>, Asif Chinwalla<sup>3</sup>, Yu Zhao<sup>1</sup>, Rhonda E. Ries<sup>1</sup>, Jacqueline E. Payton<sup>5</sup>, Peter Westervelt<sup>1,4</sup>, Michael H. Tomasson<sup>1,4</sup>, Mark Watson<sup>3,4,5</sup>, Jack Baty<sup>6</sup>, Jennifer Ivanovich<sup>4,7</sup>, Sharon Heath<sup>1,4</sup>, William D. Shannon<sup>1,4</sup>, Rakesh Nagarajan<sup>4,5</sup>, Matthew J. Walter<sup>1,4</sup>, Daniel C. Link<sup>1,4</sup>, Timothy A. Graubert<sup>1,4</sup>, John F. DiPersio<sup>1,4</sup> & Richard K. Wilson<sup>2,3,4</sup>

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

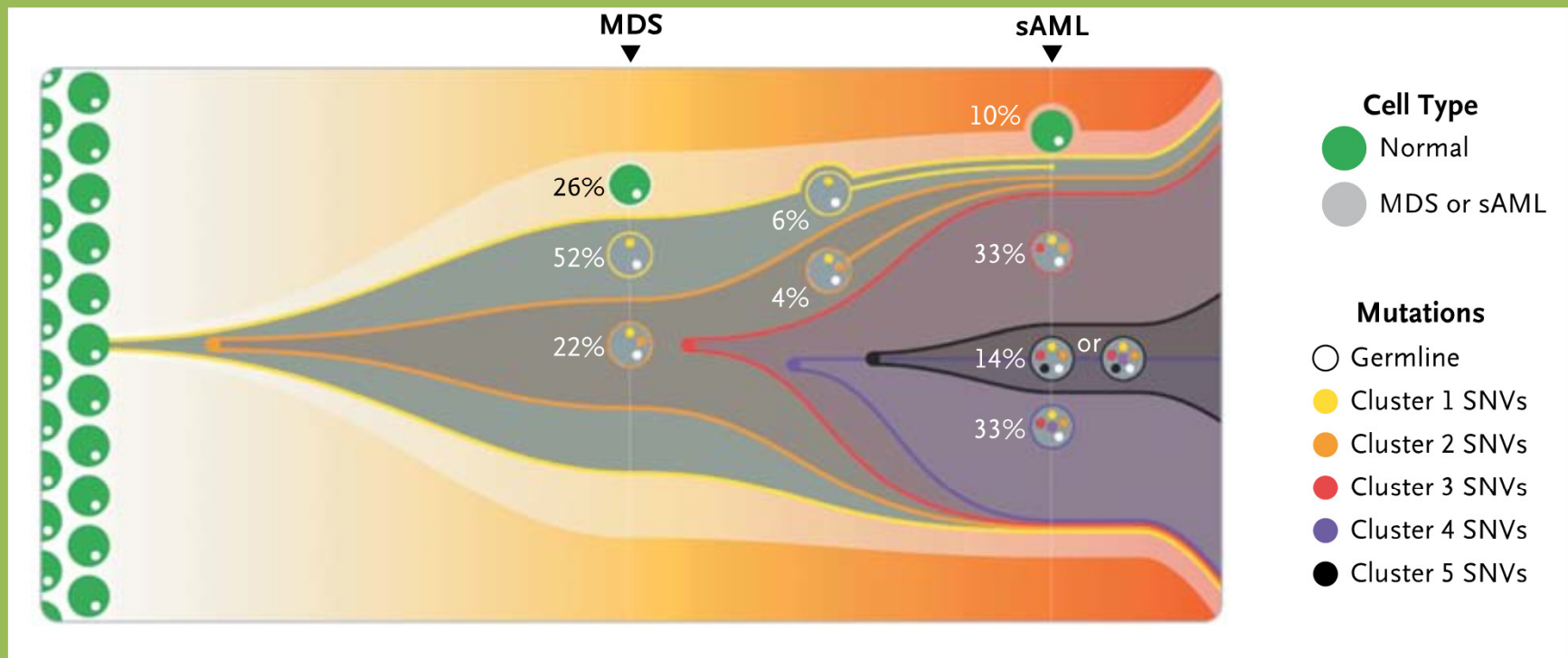
ORIGINAL ARTICLE

### Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

Elaine R. Mardis, Ph.D., Li Ding, Ph.D., David J. Dooling, Ph.D., David E. Larson, Ph.D., Michael D. McLellan, B.S., Ken Chen, Ph.D., Daniel C. Koboldt, M.S., Robert S. Fulton, M.S., Kim D. Delehaunty, B.A., Sean D. McGrath, M.S., Lucinda A. Fulton, M.S., Devin P. Locke, Ph.D., Vincent J. Magrini, Ph.D., Rachel M. Abbott, B.S., Tammi L. Vickery, B.S., Jerry S. Reed, M.S., Jody S. Robinson, M.S., Todd Wylie, B.S., Scott M. Smith, Lynn Carmichael, B.S., James M. Eldred, Christopher C. Harris, B.S., Jason Walker, B.A., B.S., Joshua B. Peck, M.B.A., Feiyu Du, M.S., Adam F. Dukes, B.A., Gabriel E. Sanderson, B.S., Anthony M. Brummett, Eric Clark, Joshua F. McMichael, B.S., Rick J. Meyer, M.S., Jonathan K. Schindler, B.S., B.A., Craig S. Pohl, M.S., John W. Wallis, Ph.D., Xiaohi Shi, M.S., Ling Lin, M.S., Heather Schmidt, B.S., Yuzhu Tang, M.D., Carrie Haipek, M.S., Madeline E. Wiechert, M.S., Jolynda V. Ivy, M.B.A., Joelle Kalicki, B.S., Glendoria Elliott, Rhonda E. Ries, M.A., Jacqueline E. Payton, M.D., Ph.D., Peter Westervelt, M.D., Ph.D., Michael H. Tomasson, M.D., Mark A. Watson, M.D., Ph.D., Jack Baty, B.A., Sharon Heath, William D. Shannon, Ph.D., Rakesh Nagarajan, M.D., Ph.D., Daniel C. Link, M.D., Matthew J. Walter, M.D., Timothy A. Graubert, M.D., John F. DiPersio, M.D., Ph.D., Richard K. Wilson, Ph.D., and Timothy J. Ley, M.D.

N ENGL J MED 361:11 NEJM.ORG SEPTEMBER 10, 2009

# Clonal Evolution from MDS to sAML



*M.J Walter et al, NEJM, March 22, 2012*

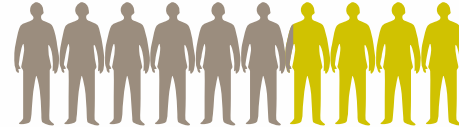
Effie Liakopoulou 30.09.14

# One Size Does Not Fit All

## PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE

ANTI-DEPRESSANTS  
(SSRI's)

38%



ASTHMA DRUGS

40%



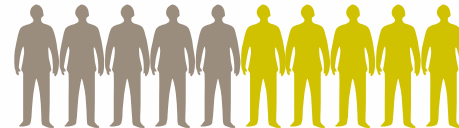
DIABETES DRUGS

43%



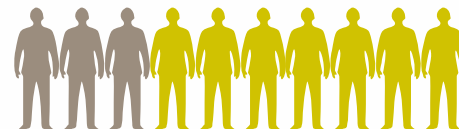
ARTHRITIS DRUGS

50%



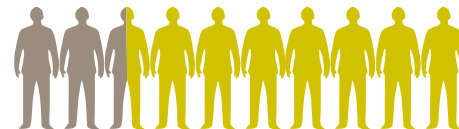
ALZHEIMER'S DRUGS

70%



CANCER DRUGS

75%



Percentage of the patient population for which a particular drug in a class is ineffective, on average

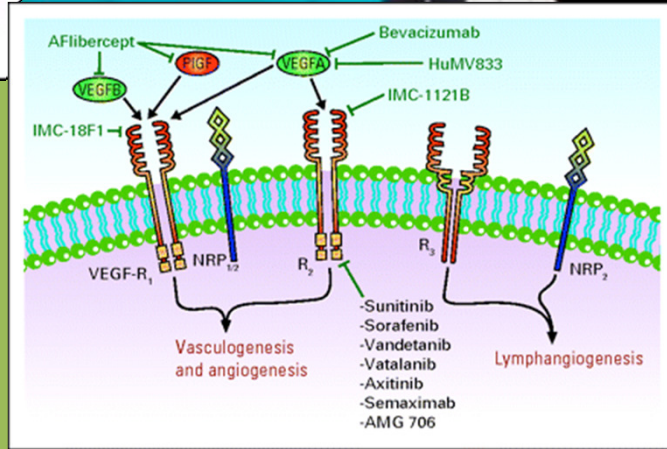
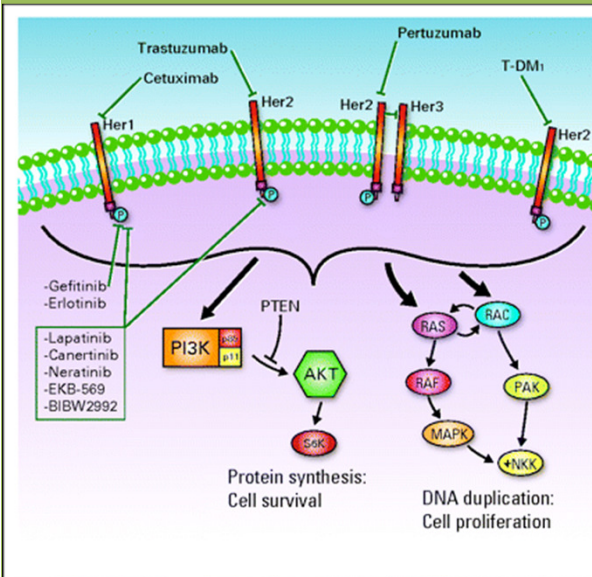
Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, Pages 201-204."  
ΕΠΕΛΙΑΚΟΠΟΙΟΥΜΕΝΟ 30.09.14



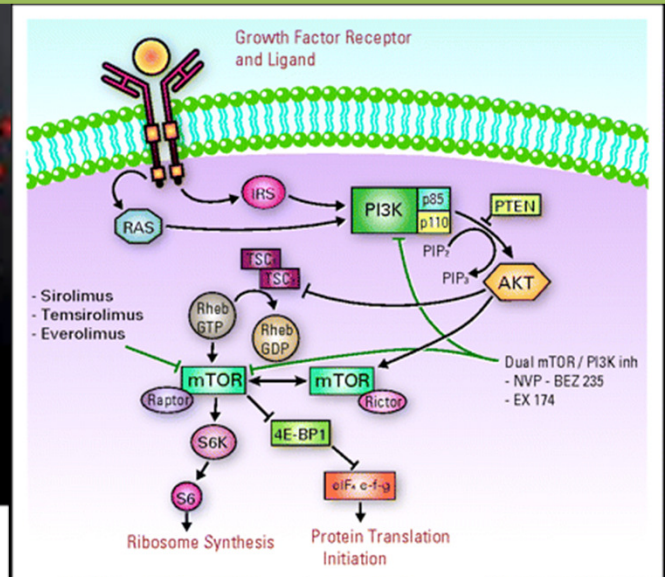
# Transforming Medicine #2

## Targeted Therapies

### EGFR



### PI3K/AKT/mTOR



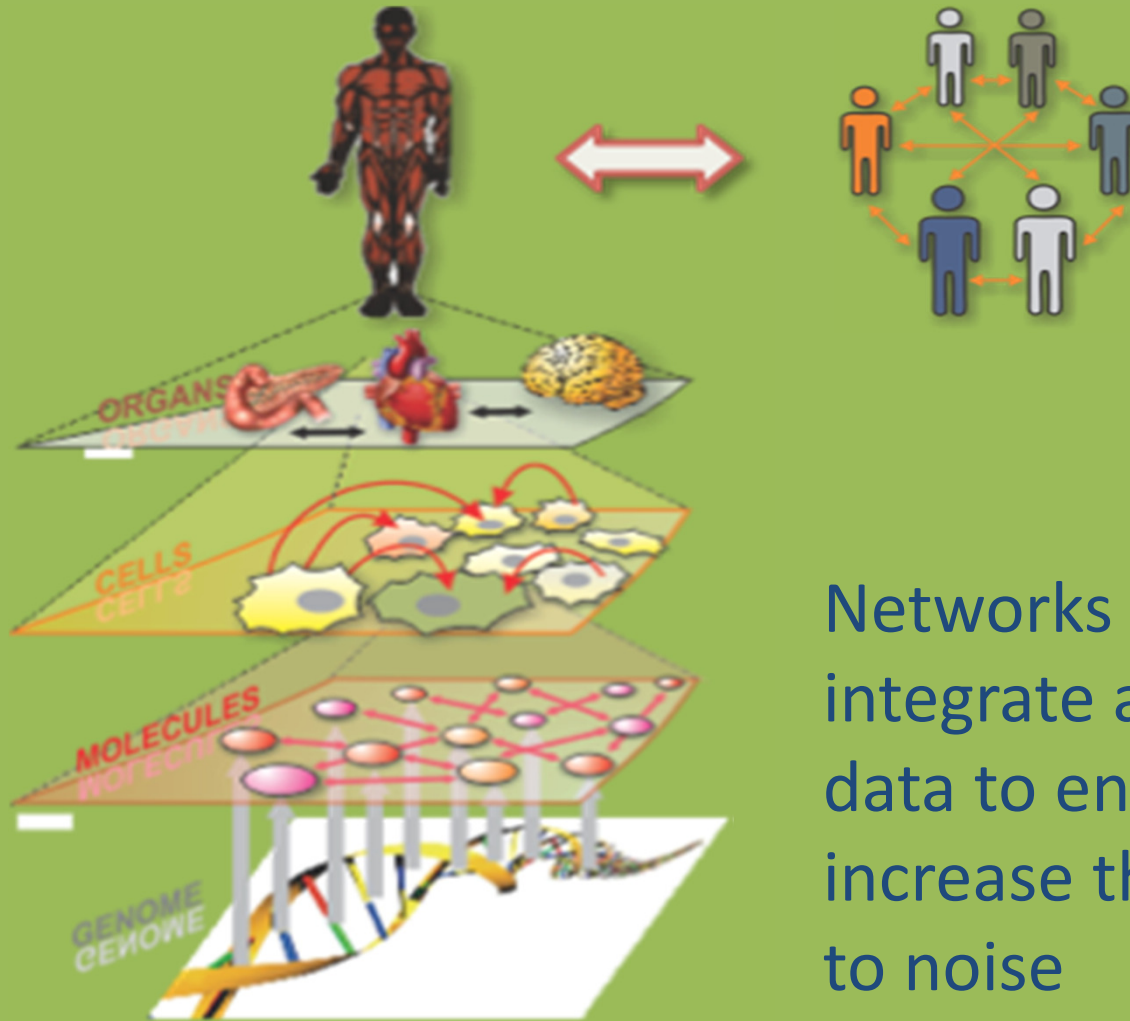
### Other RTKs

# Some Rationally Designed Cancer Therapies

- Chronic myelogenous leukemia (Bcr-Abl)
- c-Kit – positive gastrointestinal stromal tumor
- Her2 – positive breast cancer
- EGFR - mutated lung and colorectal cancer
- Alk – mutated lung cancer
- BRAF - mutated melanoma

# Transforming Medicine #3: Systems Biology

## The Network of Networks

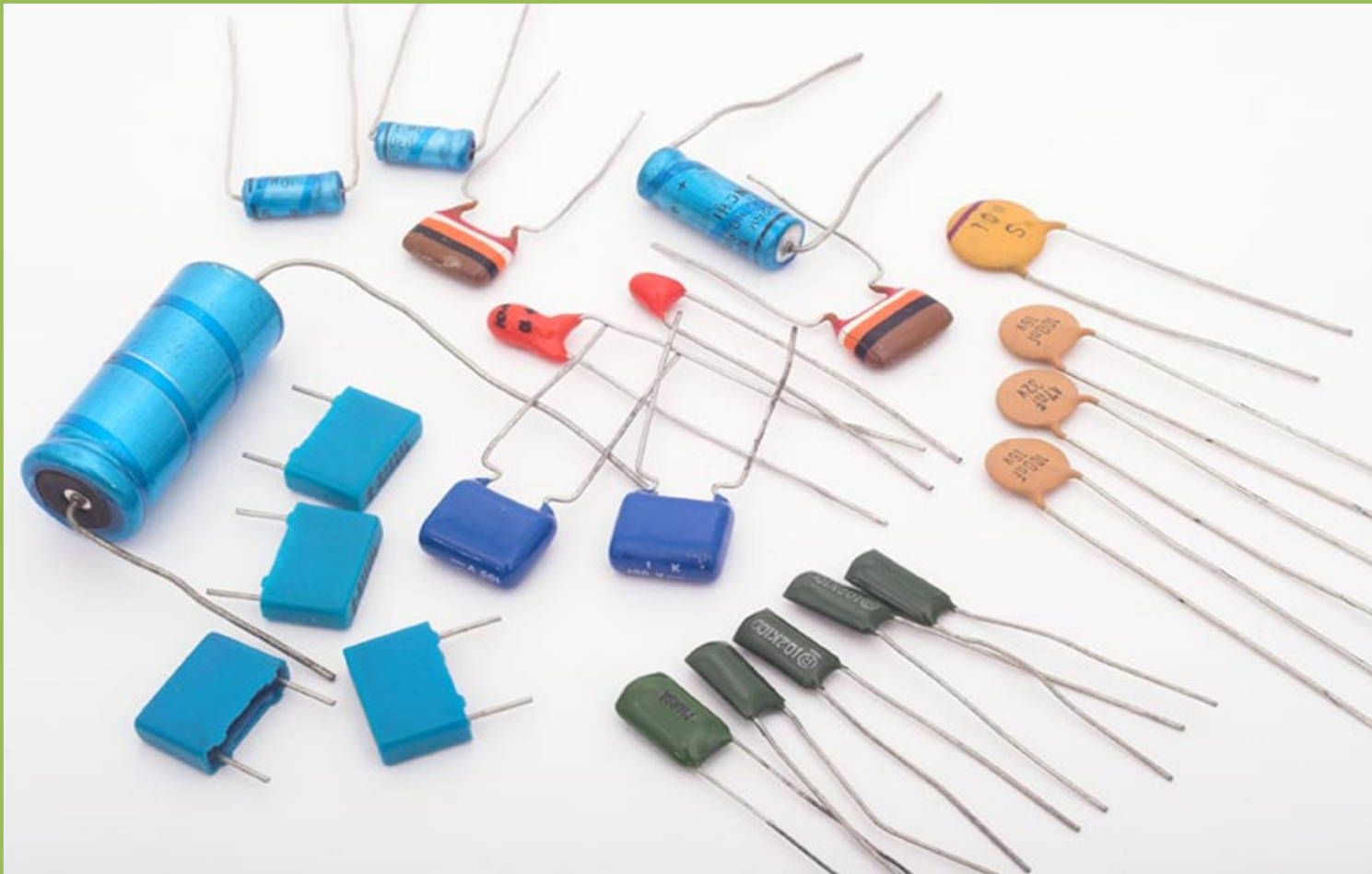


Networks organize,  
integrate and model  
data to enormously  
increase the signal  
to noise

Radio Waves



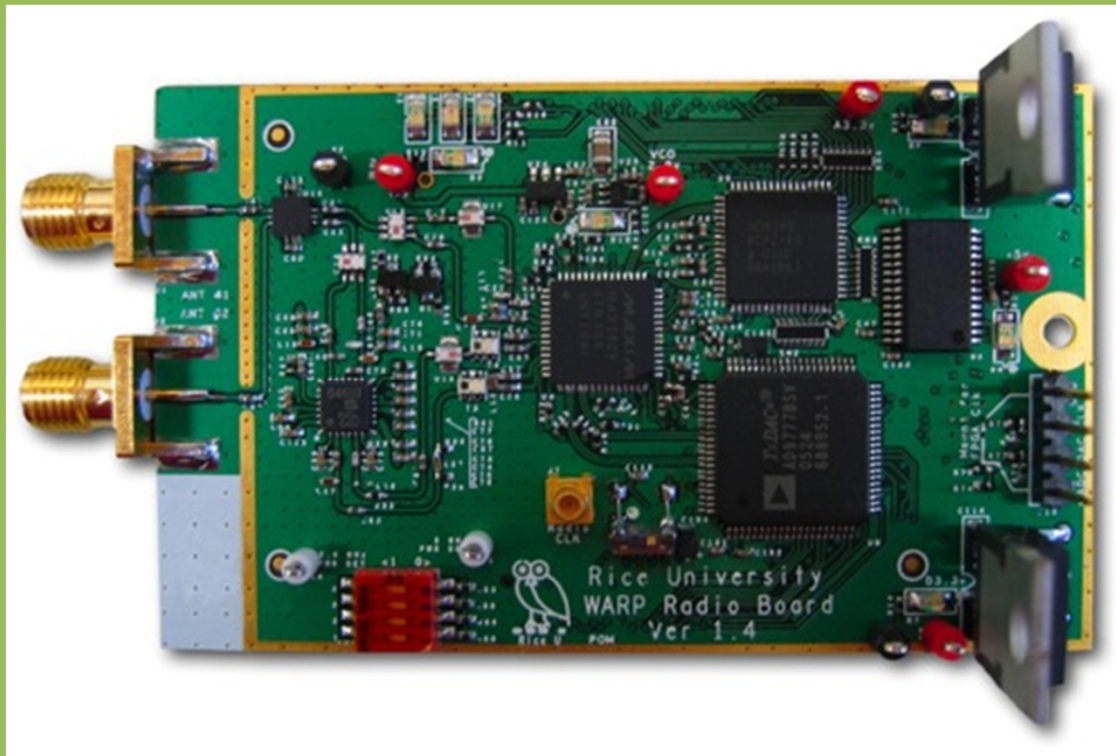
Sound Waves



Effie Liakopoulou 30.09.14

*Courtesy Dr. Leroy Hood*





Effie Liakopoulou 30.09.14

*Courtesy Dr. Leroy Hood*

Health

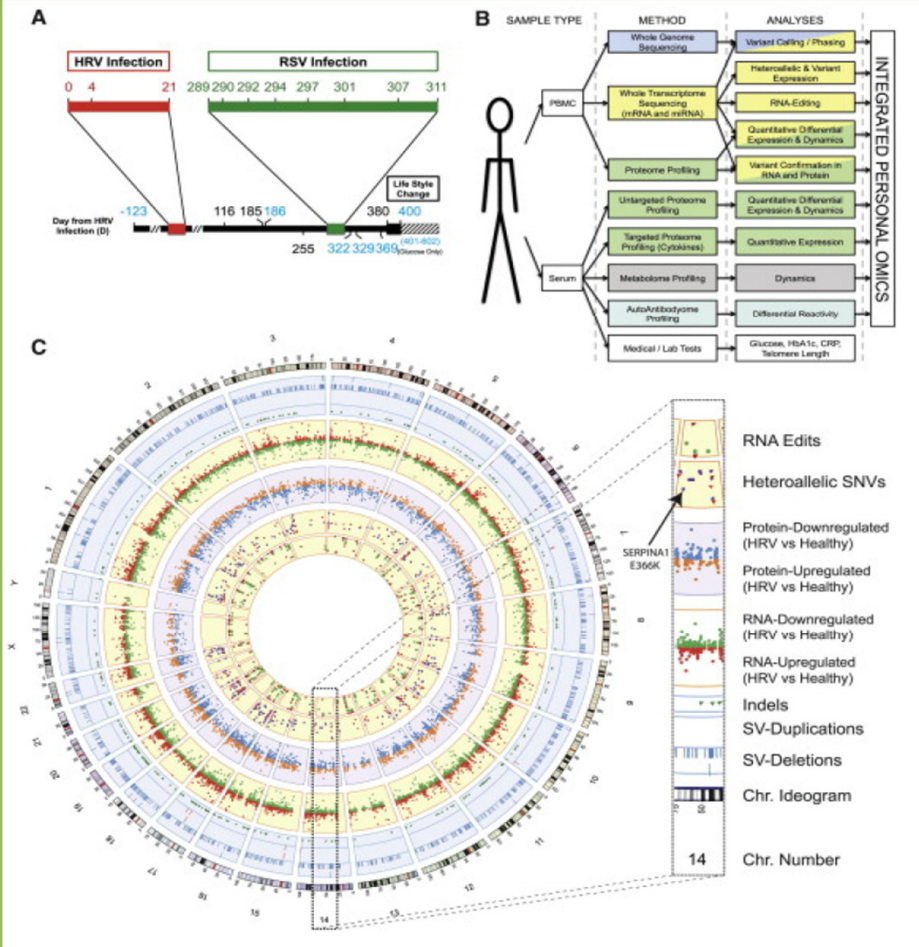


Disease

“networks of  
networks”

# Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

1 Patient, 400 days, 3 billion data points



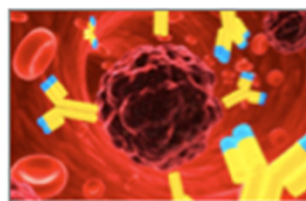


# Transforming Medicine #4: The Internet



A screenshot of the PubMed.gov website interface. The top navigation bar is blue and contains the NCBI logo, "Resources" with a dropdown arrow, and "How To" with a dropdown arrow. On the right side of the bar are "My NCBI" and "Sign In" links. Below the navigation bar is a search area with the PubMed logo on the left, which includes the text "U.S. National Library of Medicine" and "National Institutes of Health". The search area features a search box with "PubMed" entered, a "Search" button, and a "Clear" button. To the right of the search box are links for "Limits", "Advanced search", and "Help". Below the search area is a promotional banner for PubMed. The banner has a dark blue background on the right side with the text "PubMed" in white, followed by a description: "PubMed comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites." The left side of the banner shows a close-up image of the pages of a book.

**How to Use This Tool**

 Learn More:  
[Patients](#) | [Physicians](#)
**Breaking News:**  
 Ipilimumab/Yervoy  
 Approved for Melanoma

 Ipilimumab/Yervoy, an  
 antibody that blocks

**Provide Melanoma Information**
**Melanoma Stage** ?
  Early  
Stage 0, I, II
 Stage III  
 Stage IV  
Advanced Stage
**Primary Origin** ?
  Skin/Other
  Eye
  Acral/Mucosal
 
**Metastatic Sites** ?  
(For statistical purposes only)
 Lymph Nodes
  Liver  
 Brain/CNS
  Other
 
**Mutation Information** ?
   
 BRAF 
  
 C-KIT 
  
 GNAQ 
  
 GNA11 

clear form

SEARCH

**Learn the Science Behind the Targeted Therapy Finder at Cancer Commons Melanoma**

**Targeted Therapy Finder Advisors\***

 David E Fisher MD PhD  
Department of

 Keith T Flaherty MD  
Department of

# Partners in Personal Oncology



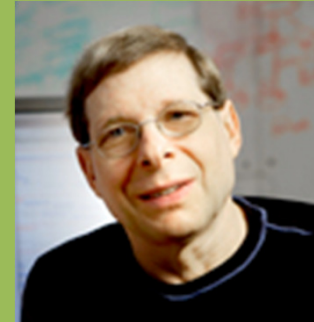
Tony Blau



Greg Foltz



Effie Liakopoulou



Marty Tenenbaum



Lee Hood



Brian Druker



Mike Bisesi



Houda Hachad



Bruce Avolio



Sibel Blau



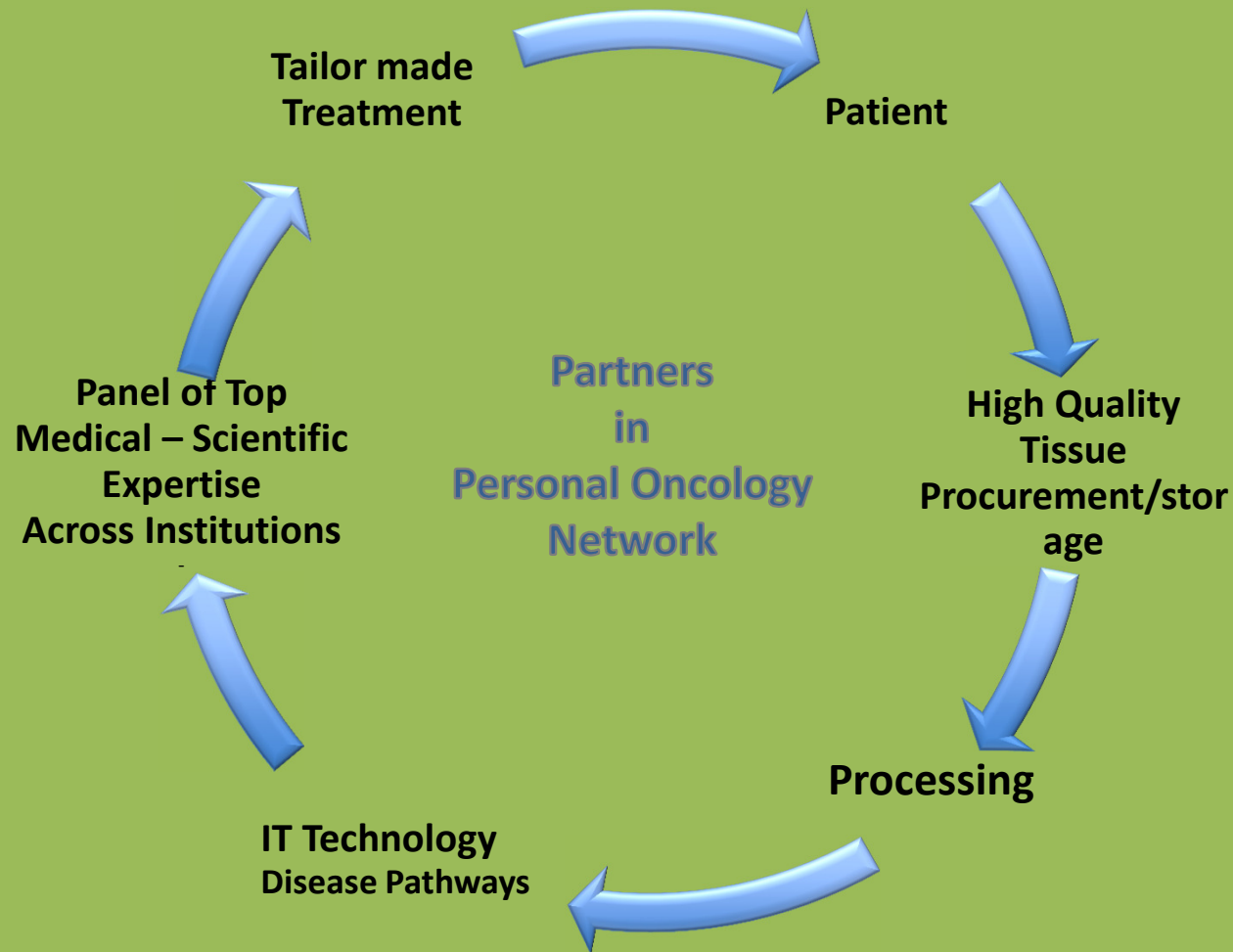
David Beatty



Robin Jones

Effie Liakopoulou 30.09.14

## Partners in Personal Oncology



*How to Deconstruct Cancer One Patient at a time*  
T. Blau & E. Liakopoulou  
*Trends in Genetics 2013 &*  
*Cell Press Reviews: Cancer Therapeutics, 2014*

# Fundamental Idea of Personalized Medicine

- Coupling established clinical–pathological indexes  
with
- State-of-the-art molecular profiling  
to create
- Diagnostic, prognostic, and therapeutic strategies precisely tailored to patient's requirements





## Two Clinical Trials

### Triple Negative Breast Cancer

### AML (Pam Becker)

- Enroll patients with cancers not generally considered curable.
- Seek to better match patients to drugs.
- To do this, both use HTS and Omics.
- Both represent grass roots efforts.

# Protocol 8132: ITOMIC-001: Intensive Trial of OMics In Cancer

October 28, 2013: Trial Launch

Highlights:

- 1) Multiple samplings from multiple different sites of disease.
- 2) Standardized protocols for tissue acquisition, handling, and storage.
- 3) Coordinate analyses across multiple different labs, platforms & institutions.
  - 1) Convene ITOMIC tumor board (X4).
  - 2) Respond rapidly to a change in a patient's clinical status.
  - 3) Obtain data from all patients examined thus far.
  - 4) Prepare reports.
  - 5) Assist with accessing drugs.
  - 6) Perform repeated biopsies.
  - 7) Culture tumor cells, test in drug screen (1 patient).
  - 8) Serially monitor circulating tumor cells (CTCs) (1 patient).
  - 9) Patient Surveys

# AML - A Practical Approach

- Examining the relationship between gene expression and sensitivity to chemotherapy.
- Immediately address drug sensitivity, with treatment based on high throughput drug sensitivity testing.

UNIVERSITY OF WASHINGTON

# Institute for Stem Cell & Regenerative Medicine

## QUELLOS HIGH THROUGHPUT SCREENING CORE

### ABOUT THE CORE



The Quellos High Throughput Screening (HTS) Core specializes in Functional Genomics as well as Drug Discovery and Small-Molecule Optimization through chemical screening. It is located within the UW's Institute for Stem Cell and Regenerative Medicine at the South Lake Union Campus of the University Of Washington School Of Medicine serving Academic Institutions (e.g., Fred Hutchinson Cancer Research Center) as well as BioTechs and Pharma organizations in Washington State and nationwide. A team with industrial and academic experience is available to aid investigators in their assay optimization and screening activities. The Quellos HTS Core was created to provide "state of the art" high throughput and lab automation approaches that were once only available in large pharmaceutical organizations.

# AML Trial

HTS Screen

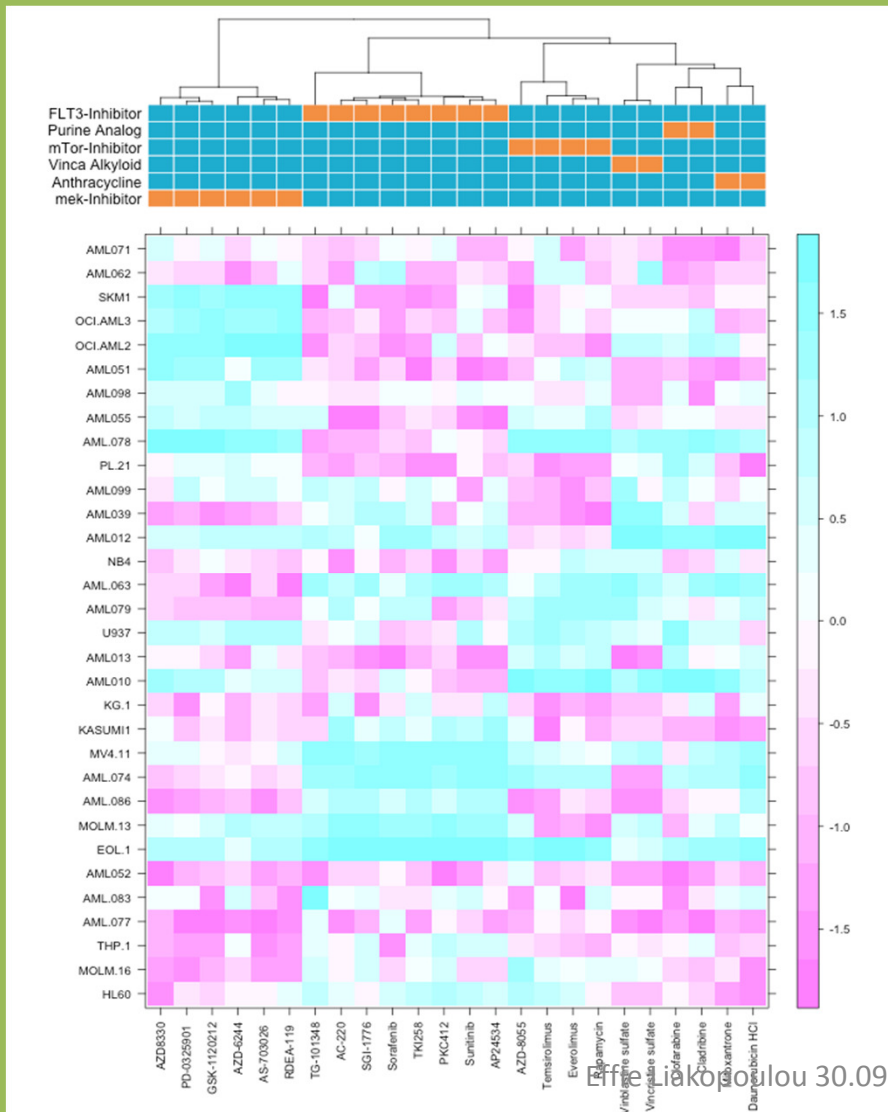
160 Drugs - 45 FDA Approved, 115 Investigational

Ability to use cryopreserved cells

Use of adherent culture conditions



# 14 AML cell lines, 30 patient samples



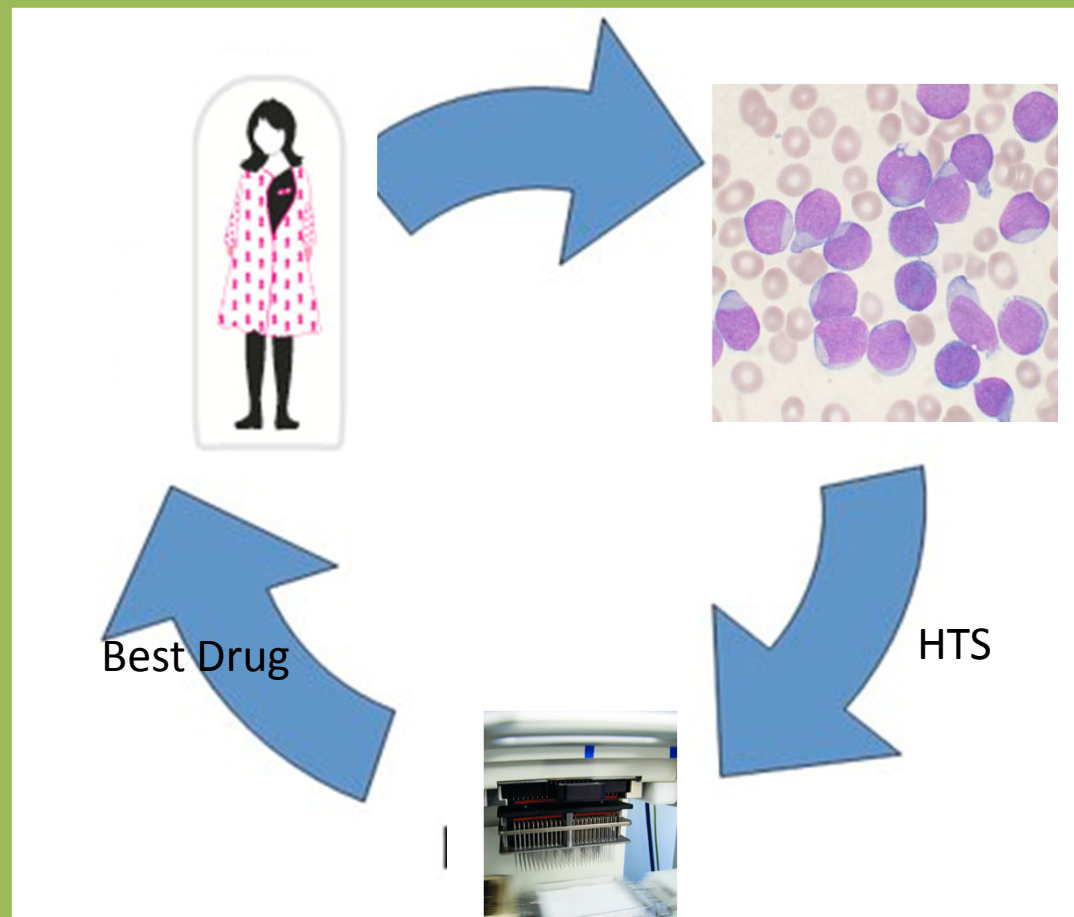
Sensitive

Each patient exhibits unique result.  
Clustering of similar drugs.

Resistant

## AML Trial

Collect Leukemia Cells



## AML Trial

**Primary Objective:** Demonstrate feasibility of the assay as a potential means to predict response

**Secondary Objective:** Cytoreduction with chosen drugs

**Subjects:** Multiply relapsed or refractory AML patients  
Declines in blast count in all 11 patients treated.

**Actual:** Drug sensitivity test results 5-7d (mean 5.2d).  
All pts treated within 7-21 days.

# Take Home Message

Recent biotechnological advances have led to an explosion of disease-relevant molecular information, with the potential for greatly advancing patient care.

## Personalized Medicine

No longer a blip on the horizon

Brings new challenges and success is based:

- establishing frameworks for regulating,
- compiling, and
- interpreting the influx of information that can keep pace with rapid scientific developments

## 2<sup>nd</sup> international Conference on Hematology and Blood Disorders

Session 4 : 10.20, 1 October 2014

*Whole genome methodology for in silico quantification of  
intra tumor heterogeneity: Model for clinical applications  
in the treatment of patients with hematological  
malignancies*





Tony Blau



Greg Foltz



Tony Blau  
Effie Liakopoulou 30.09.14

*Thank you*