Shaping the future of cancer research from the end of the beginning

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MRC | Cancer Unit

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1994-2019


MINISTRY OF HEALTH
SINGAPORE

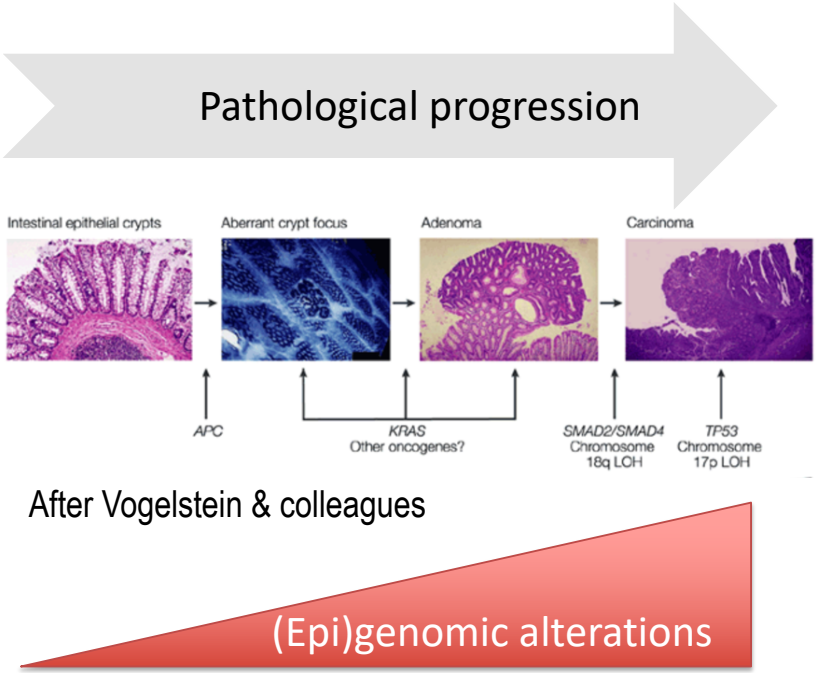

NMRC
National Medical
Research Council
Singapore

Shaping the future of cancer research from the end of the beginning

Cancer will affect ~1 in 4 of us. Its incidence is increasing worldwide with aging populations. Cancer has a larger economic impact than any other disease.

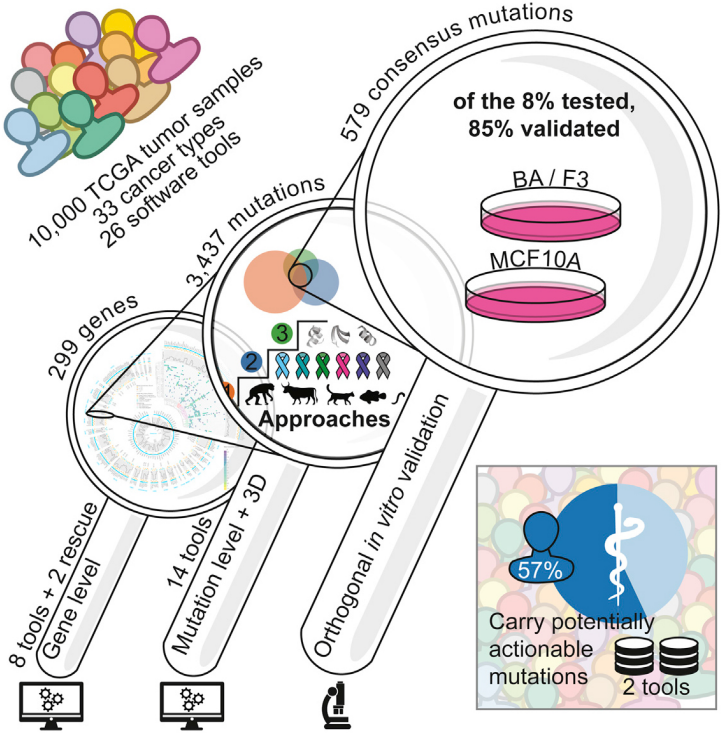
- Why are we at the 'end of the beginning' in understanding and treating cancer?
- What are the future horizons for cancer research?
- What will it take to reach them – in Singapore and elsewhere?

Cancer: the end of the beginning

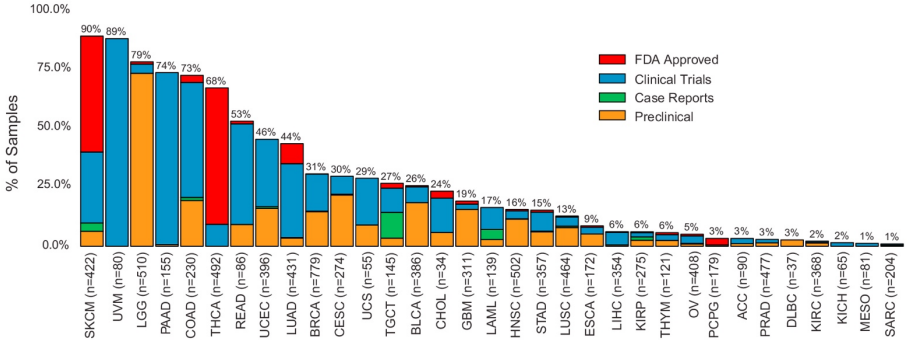


- 2005 – first cancer genome
- 2010 – about a hundred cancer genomes, information used for scientific research & discovery
- 2018 – 1000s of cancer genomes – translation to the clinic underway (eg., stratification of patients in clinical trials based on ‘actionable’ genotypes)

Cancer: the end of the beginning



Bailey et al., *Cell* (2018)



- The Cancer Genome Atlas (TCGA) reported in 2018 the analysis of 10,300 cancers from 33 different tissues
- About 300 genetic alterations collude to drive the most common cancers
- ~60% are potentially 'actionable' in the clinic ***if*** new treatments can be devised

The end of the beginning: approaching the premise of personalized medicine

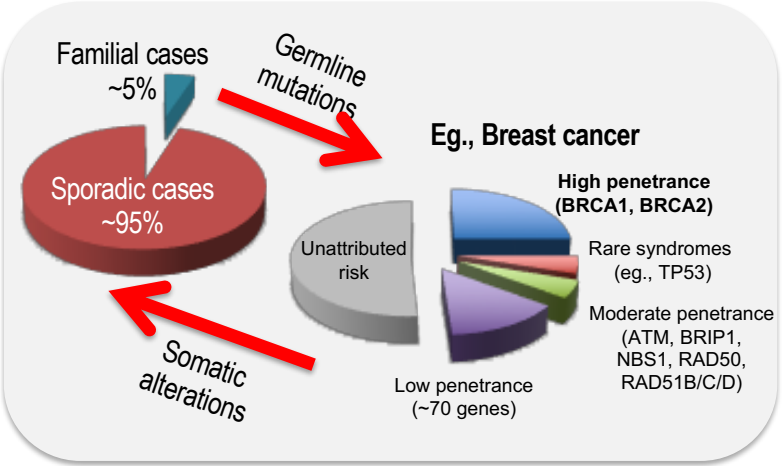
Integration of molecular research with clinical data from individual patients to develop a more accurate **molecular taxonomy of diseases** that enhances diagnosis and treatment and **tailors disease management to the individual** characteristics of each patient.
(US Nat Acad of Sciences, 2011)

Matching therapies with specific patient population characteristics **using clinical biomarkers**.
(Trusheim et al, 2007)

Shaping the future: delivering the clinical impact of personalized cancer medicine

- Formulation of a new taxonomy of human cancers, based on the integration of their molecular and clinical features
- Discovery and validation of robust, clinically applicable biomarkers to individualize patient management
- Creation of an enhanced repertoire of drugs and clinical interventions suited to individual patients
- Beyond personalized therapy ….. towards EARLY intervention in cancer

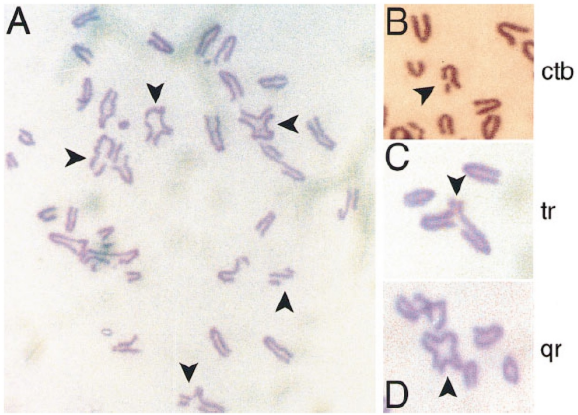
From taxonomy to treatment: germline mutations in the breast cancer gene, *BRCA2*



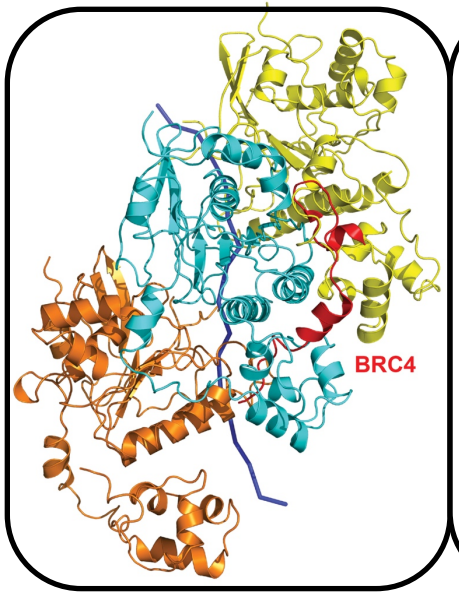
Reviewed in Venkitaraman *Science* (2014)

- Germline *BRCA2* mutations affecting a single allele predispose to breast, ovarian, pancreatic, prostatic and other cancers
- Carriers exhibit a cumulative risk of ~70% for breast cancer, and ~25% for ovarian cancer, by age 80 yrs. (ie., ***highly penetrant***)
- Cancer risk increases rapidly until ~45 yrs. (ie., ***early onset***)

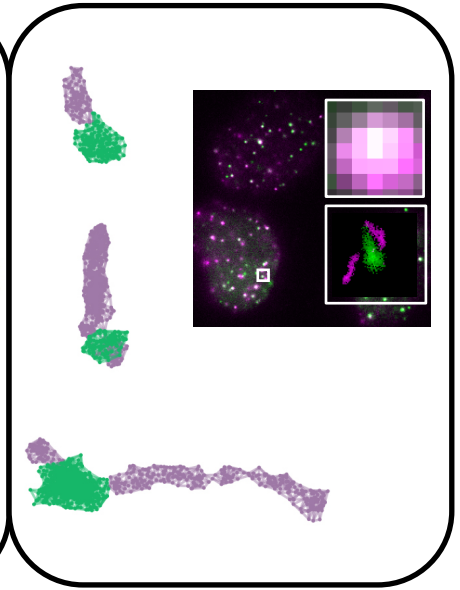
From taxonomy to treatment: germline mutations in the breast cancer gene, *BRCA2*



Patel, Yu et al. (1998)



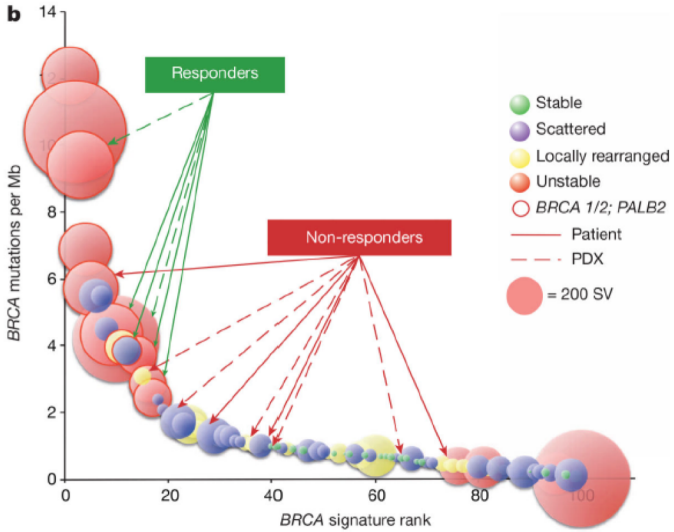
Jude Short, Yang Liu (2016)



Kalina Haas, Ale Esposito (2018)

Reviewed in Venkitaraman *Science* (2014)

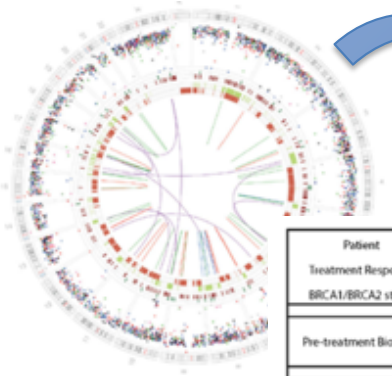
From taxonomy to treatment: germline mutations in the breast cancer gene, *BRCA2*



Modified from Waddell et al, *Nature* 2014

Responsiveness to DNA damaging agents

Reviewed in Venkitaraman *Science* (2014)



The "HR Detect" biomarker predicts responsiveness

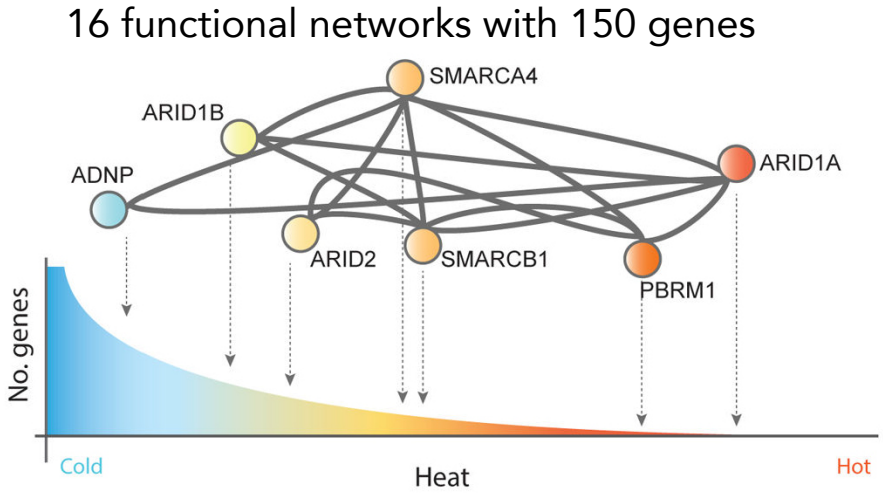
Modified from Davies et al, *Nat Med* 2017

Patient	PD9768	PD9769	PD9770	PD9771	PD9777	PD9772	PD9774	PD9775	PD9776
Treatment Response	RD	RD	RD	RD	RD	CR	CR	CR	CR
BRCA1/BRCA2 status							BRCA1		BRCA1
Pre-treatment Biopsy 1	PD9768c 0.02	PD9769c 0.22	PD9770c 0.01	PD9771c 0.00	PD9777c 0.55	PD9772a2 1.00	PD9774c 1.00	PD9775c 1.00	PD9776c 1.00
Pre-treatment Biopsy 2			PD9770d 0.14	PD9771a 0.01	PD9777a 0.03			PD9775a 1.00	PD9776a 1.00
Post-treatment specimen from surgical block		PD9769a 0.16	PD9770a 0.39	PD9771d 0.03	PD9777d 0.07				

RD = residual disease
CR = complete response
Numbers indicate HRDetect probability score for each specimen

But translating cancer taxonomy to mechanism generally remains challenging

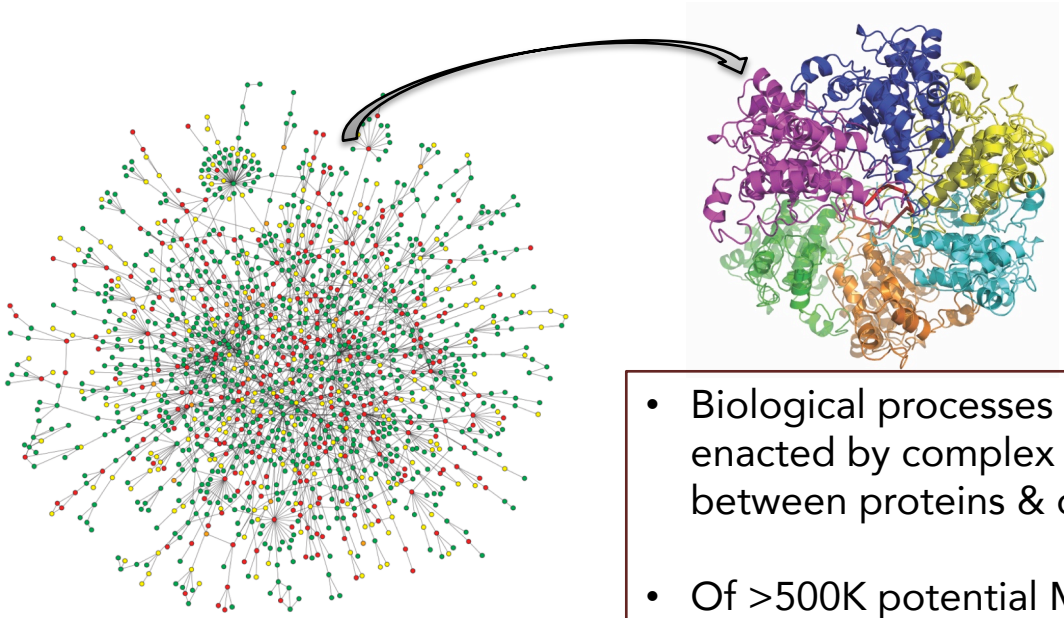
Venkitaraman *Science* (2014)



Leiserson et al. *Nature Gen* (2015)

- Many genomic alterations that characterize cancer are rare, and difficult to distinguish from "background"
- Multiple genes in multiple functional networks are affected even in the most significant clusters of alterations
- These features pose challenges in translating taxonomy to treatment …..

As is the translation of mechanism to cancer therapy …..



S. cerevesiae protein interaction network
(Jeong et al., *Nature* (2011))

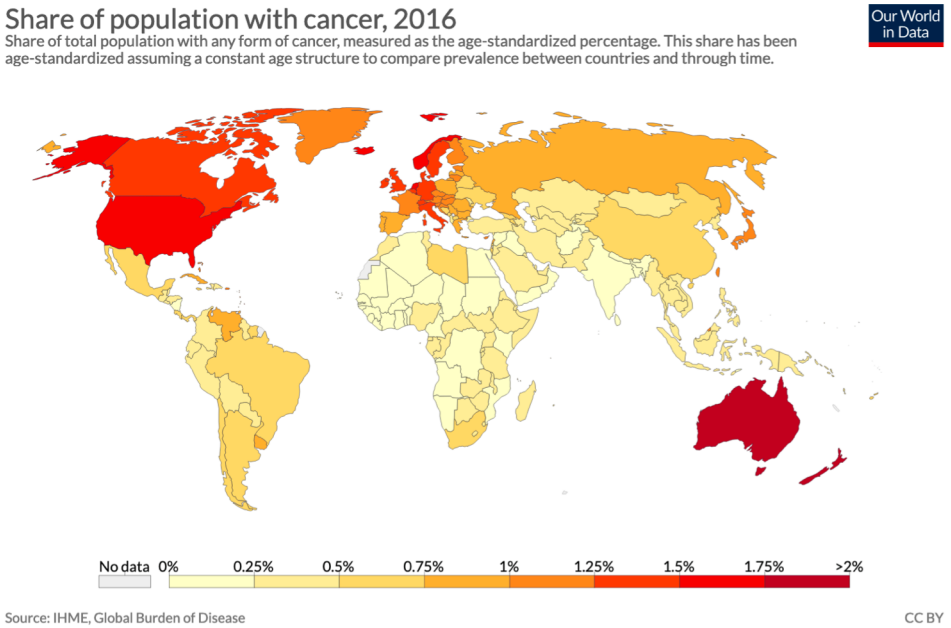
- Biological processes altered in human disease are enacted by complex networks of interactions between proteins & other macromolecules (MMIs)
- Of >500K potential MMI targets, only a handful have been successfully ‘drugged”
- Our limited ability to parse MMI networks using selective chemical tools impedes chemical biology & the development of new therapies

The *status quo* is not an option

- The cost of bringing a new medicine to market is estimated by pharma companies to exceed $1BN. The time taken exceeds 10 years. Yet, the failure rate may approach 70-90%.

- *The status quo is not an option* ….We need to more rapidly and cheaply develop ‘next generation’ drugs to fuel the personalized treatment of diseases like cancer.

Yet the global unmet need is acute

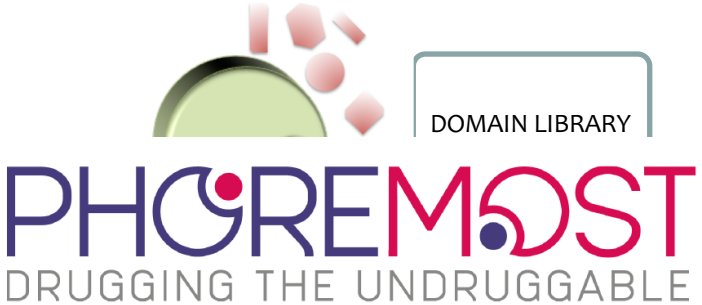


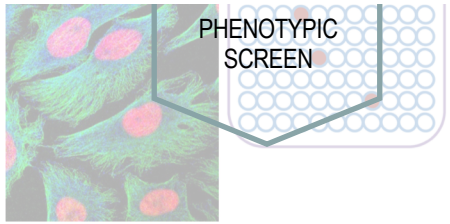
Accelerating next-generation medicines – our work at the MRC Cancer Unit in Cambridge

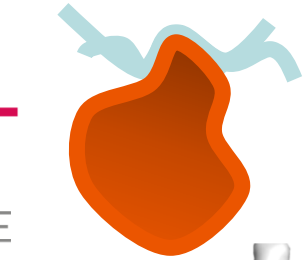
New genetic tools to identify rate-limiting steps

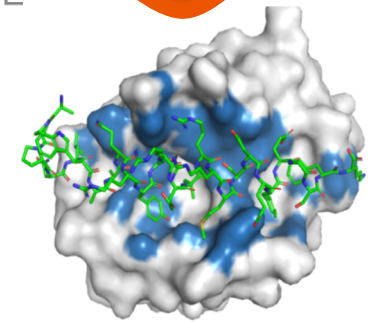
Structure-guided chemical lead discovery as a starting point for new drugs

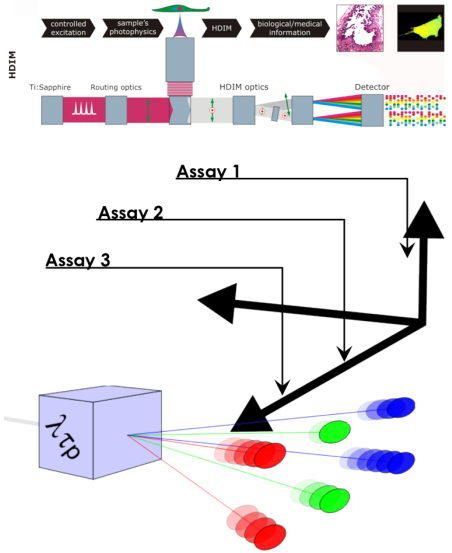
Systems microscopy to reveal how new drugs work



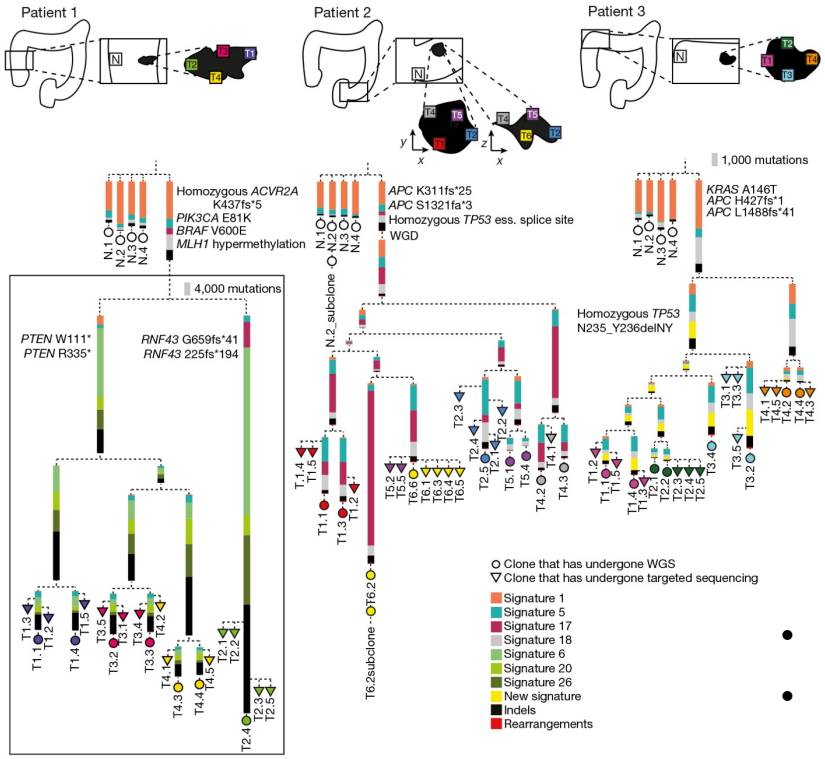


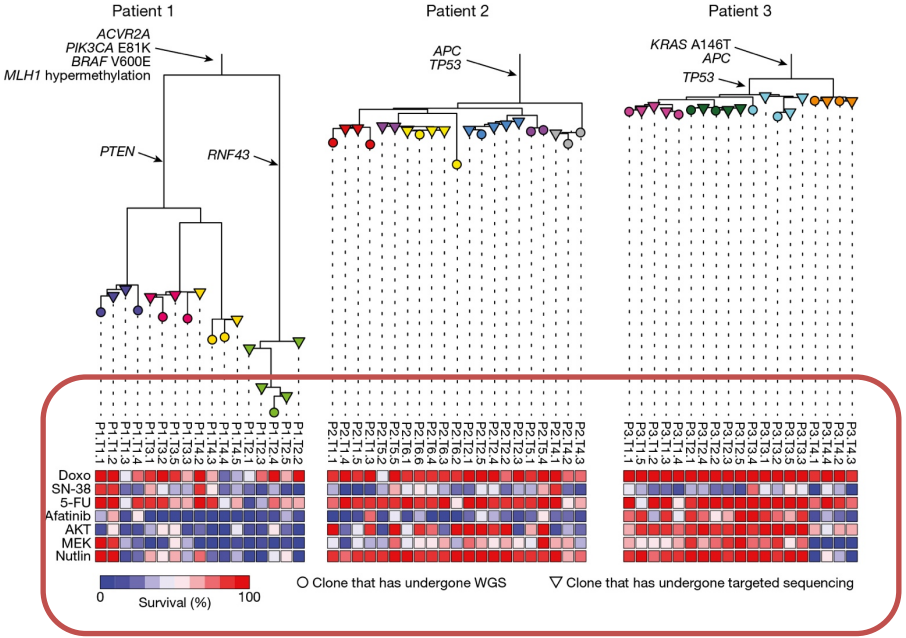






Clonal heterogeneity & therapy resistance

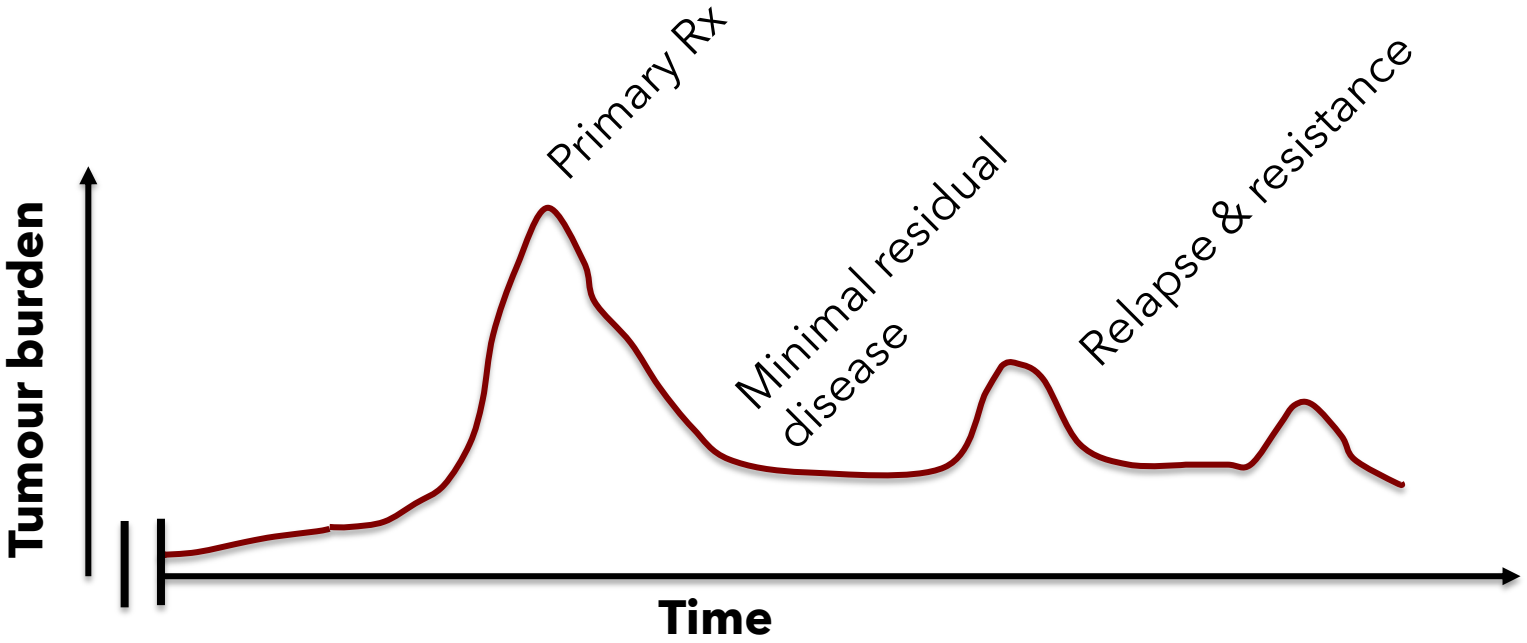




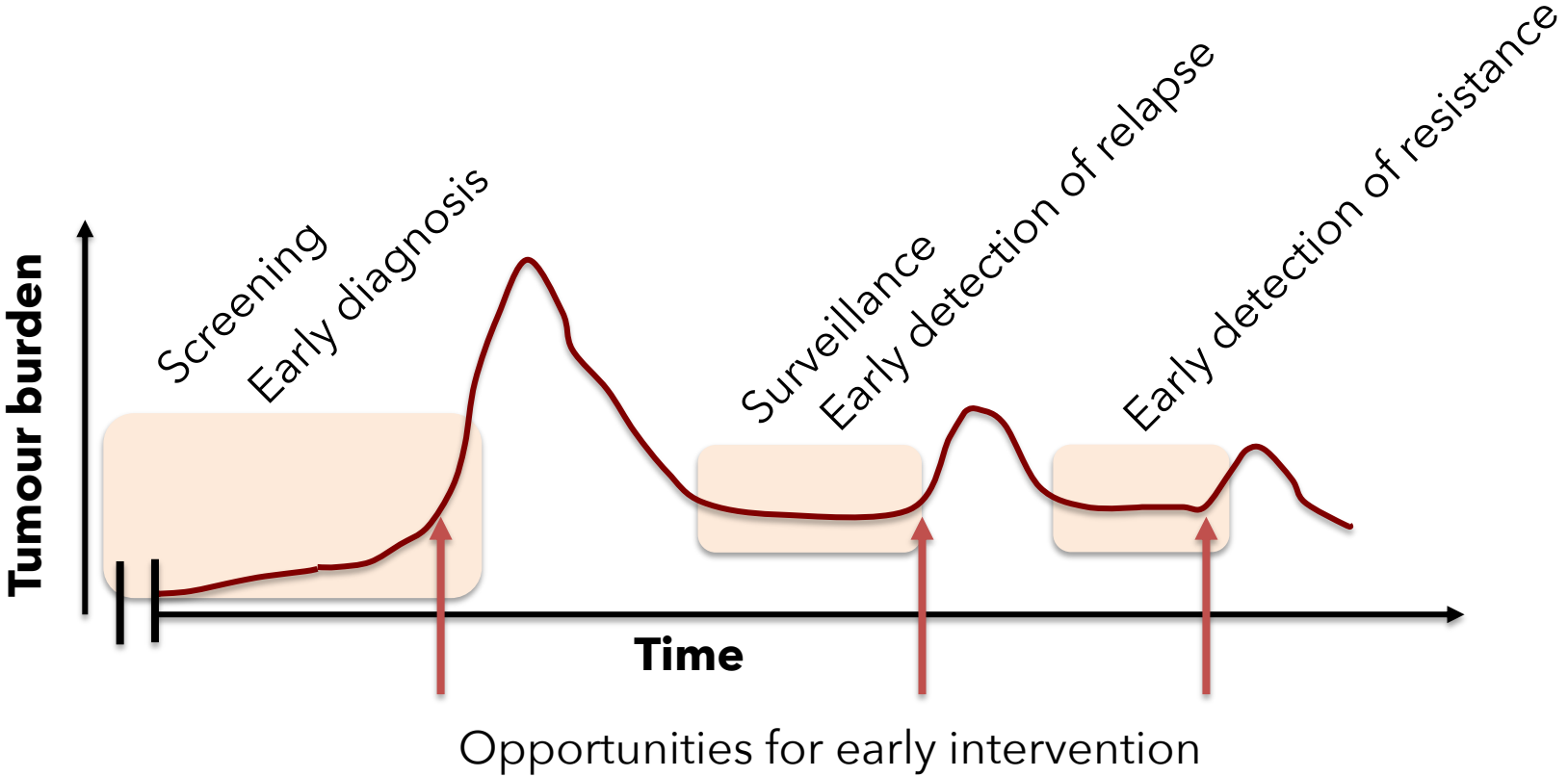
Roerink et al., *Nature* (2018)

- Combination therapy vital – <u>new agents</u> needed!
- Extreme responders / resistors may yield novel insight into mechanisms & new targets
- Needs a change in clinical *mindset*? Cancer as a chronic disease

Beyond personalized therapy?



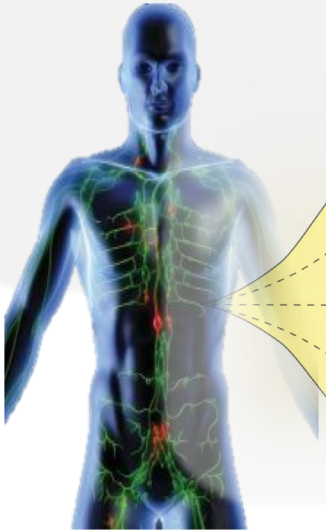
Beyond personalized therapy? Early intervention across disease progression



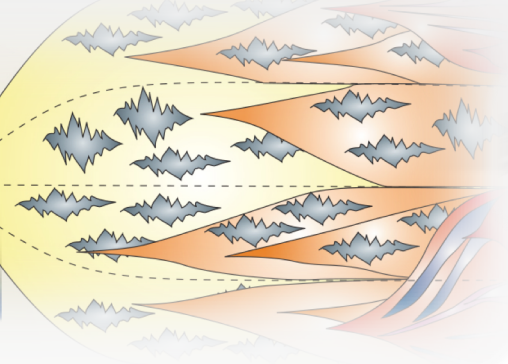
The MRC Cancer Unit: Advancing early intervention in cancer

- **Early detection**
- **Risk stratification**
- **New approaches for therapy and prevention**

Genetic & environmental risk



Molecular & cellular events during carcinogenesis

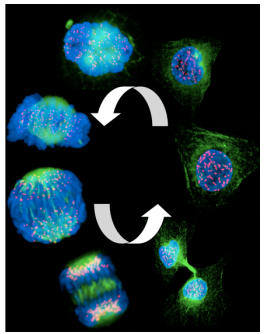


Enabling technologies

MRC Cancer Unit

Brief reflections – What will it take in Singapore and elsewhere?

Paradigm-shifting clinical translation is impossible without fundamental research



Aaron Klug

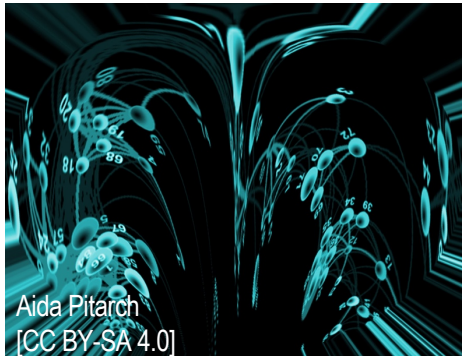
Fred Sanger

John Sulston

MRC Medical Research Council

Richard Doll, A.B. Hill

Cesar Milstein, Greg Winter

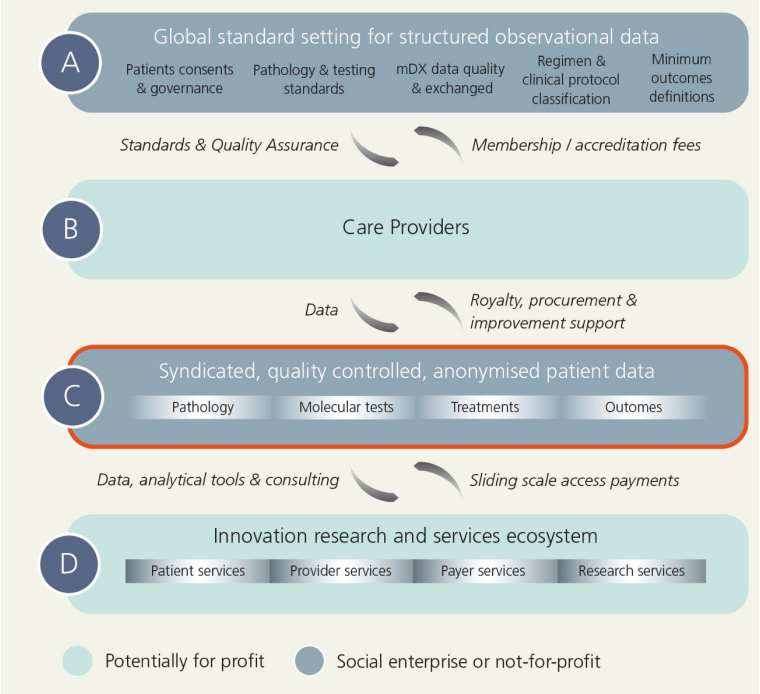


Peter Mansfield

The growing need for “game changing” information bases

“Game changing” information bases may potentially require:

- 100K to 1000K cancer genomes including l*ongitudinal* collections
- Deep linkage to clinical phenotypes and associated samples (eg., blood)
- Standardized mechanisms for collection, analysis and reporting



Mahon & Tenenbaum *J Precis Med* (2015)
Andrew Morris, Health Data Research UK

Singapore: does size matter?

Millions of patients tested to identify 250 cases/year assuming X% biomarker prevalence

Incidence Rank	Site	Incidence (per m)	Mortality	X=30%	X=10%	X=5%	X=1%
3	Lung	530	83%	1.6	4.7	9.4	47
8	Pancreas	111	94%	7.5	23	45	226
14	Kidney	82	46%	10	31	61	306
17	Ovary	62	62%	13	40	81	405
25	Brain	38	81%	22	66	131	657

Mahon & Tenenbaum *J Precis Med* (2015)

Singapore needs an integrated clinical infrastructure, with managed points of entry into clinical trials, to compete globally in academic or industrial cancer research that requires clinical material

Singapore

- Strong clinical base
- Multiethnic genetics
- Good research infrastructure

BUT

- ~5.8M population
- ~15K cancer cases/yr
- Insufficient integration between clinical centers

Leveraging the 4th Industrial Revolution

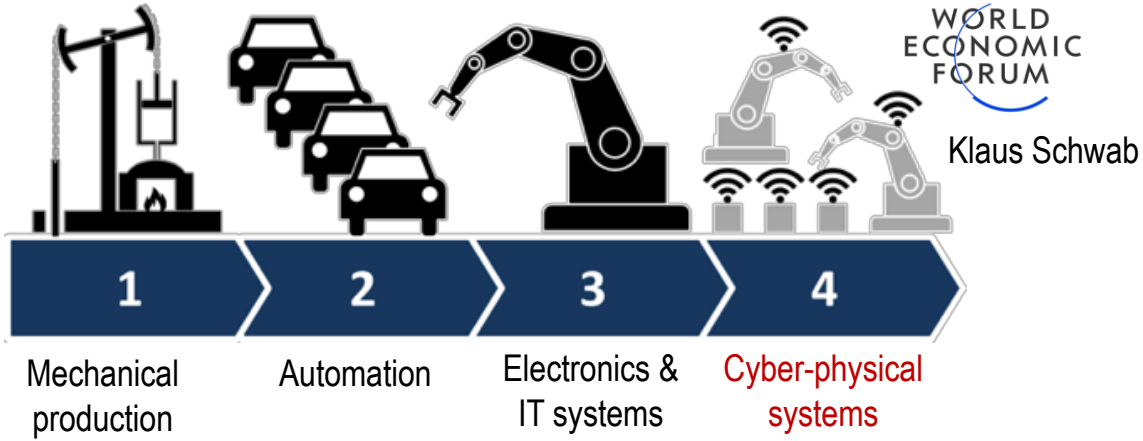
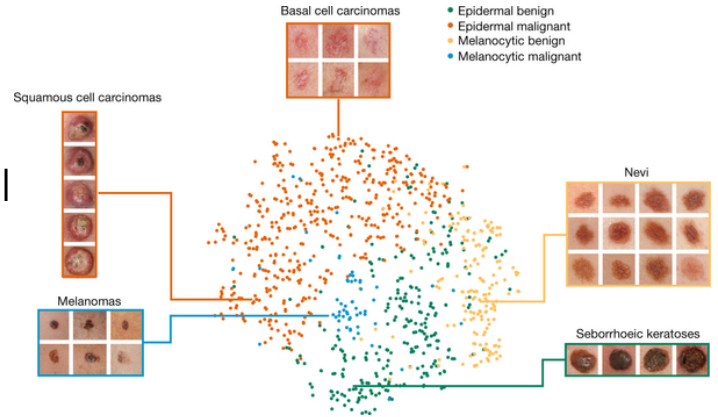


Image courtesy Christopher Rossner



Cancer diagnosis by mobile phone …..

- ~130K images of skin lesions analysed using deep neural networks; algorithm outperforms specialist dermatologists in diagnosis of malignancy
- >6 billion mobile telephones by 2020

Shaping the future of cancer research from the end of the beginning

- What are the future horizons for cancer research?
  - Disruptive technologies to discover clinically stratified new therapeutics
  - Deep fundamental understanding & innovation for early intervention across all disease stages
- What will it take to reach them?
  - Build disease-centric multidisciplinary communities of fundamental, applied & clinical researchers addressing key challenges together
  - Devise assessment metrics that encourage paradigm shifts
  - Support the creation, accessibility & analysis of multidimensional, *longitudinal* clinical datasets
  - Nurture mutually beneficial external collaborations

The Medical Research Council Cancer Unit

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The mission of the MRC Cancer Unit is to discover the fundamental mechanisms underlying early steps in carcinogenesis, and to exploit this knowledge for early intervention in the clinic, using innovative enabling technologies.