CANCER & EVOLUTION SYMPOSIUM

"The Next Challenge in Precision Medicine: Evolutionary Cancer Biomarkers"

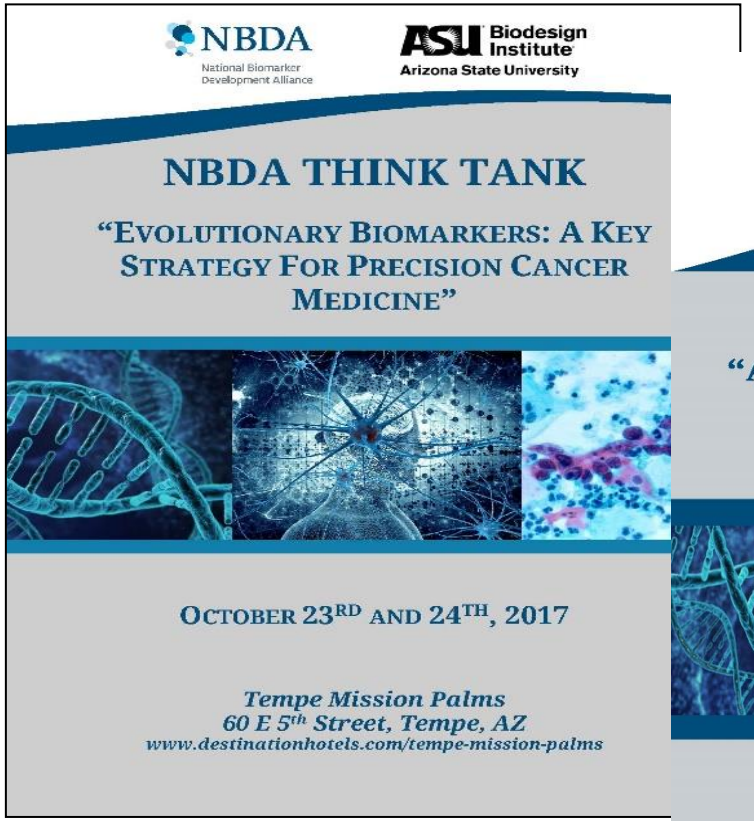
(Making evolution relevant in advancing precision cancer medicine)

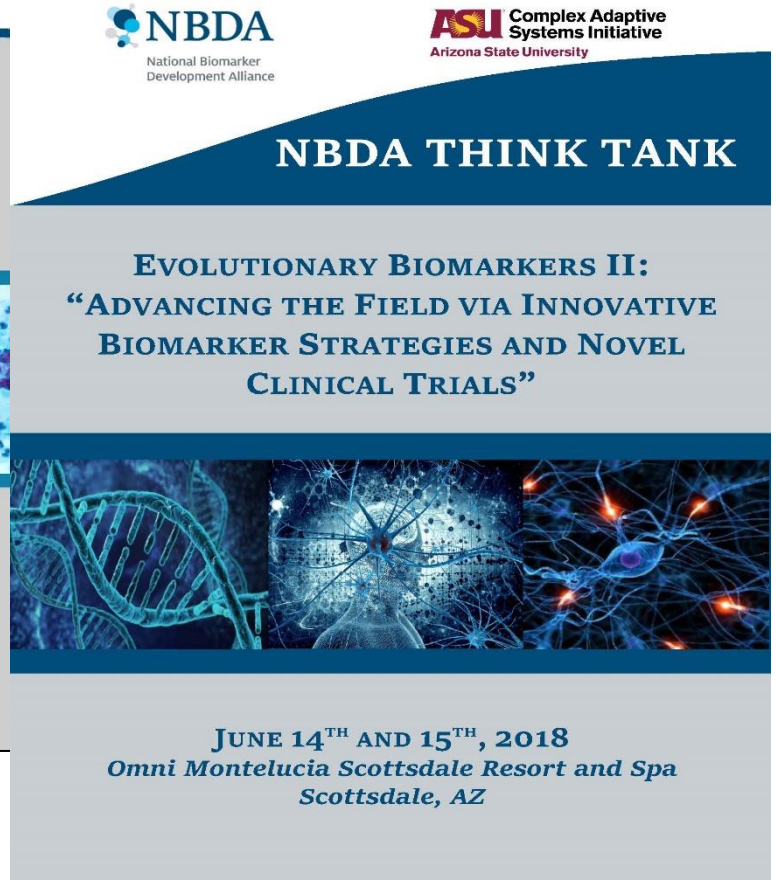
Anna D. Barker, Ph.D.
Chief Strategy Officer
Lawrence J. Ellison Institute for Transformative Medicine
University of Southern California (USC)
Distinguished Visiting Fellow, Complex Systems
Arizona State University (ASU)

Lawrence J. Ellison Institute for Transformative Medicine of USC

Efforts to Make Evolution Mainstream in Oncology: Timing is Everything!!

2008



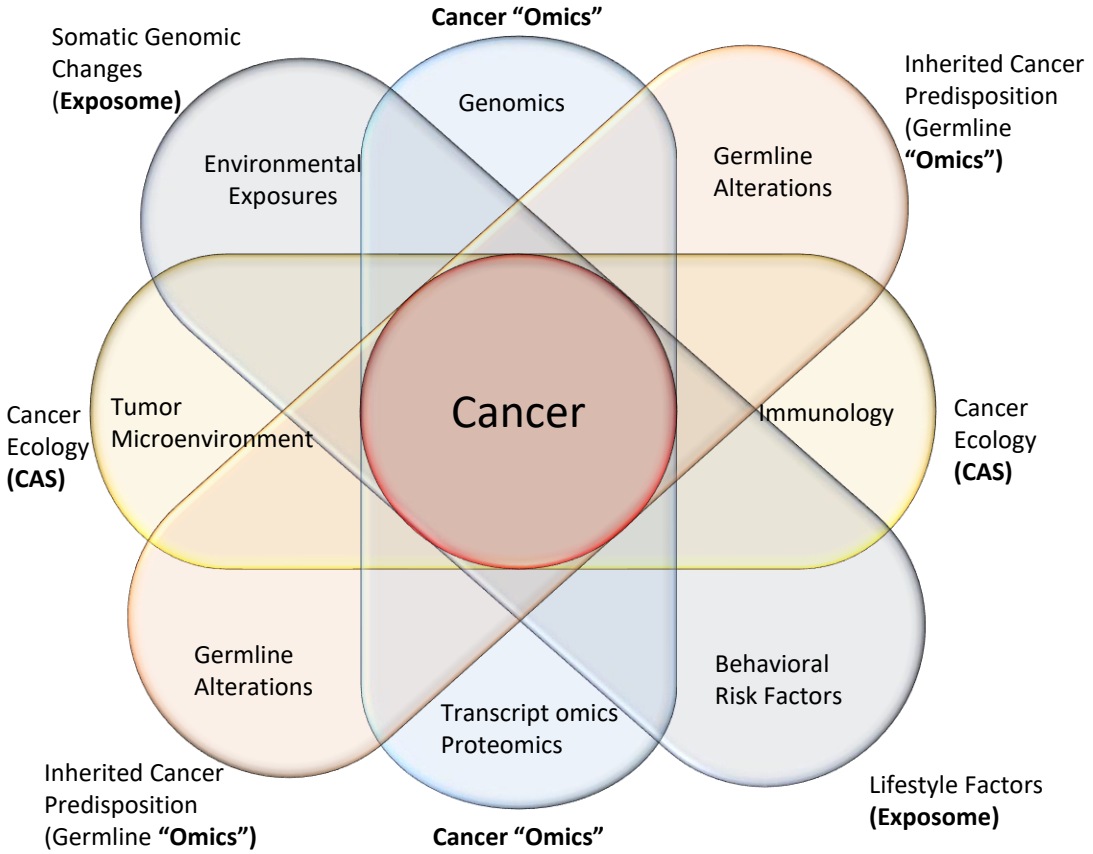


2017-2018

Lawrence J. Ellison Institute for Transformative Medicine of USC

2020 – Although Still Studying the "Parts", Timing for Applying Evolution in Cancer Could Just be NOW!

- **We are currently defining the "parts" and producing a data "Tsunami" – but data are not information**
- One cancer patient can generate a terabyte of data
- Annually, genomics research generates ~ 1 exabyte (10^6 terabytes) of data
- Complex biomedical data does not necessarily suggest how variables affect outcomes
- Biomedical data complexity has outpaced our analytics capabilities
- Large amounts of noisy or "scruffy" data complicates analyses – but the scruffy data matters
- **Isolated understanding of "parts" is helpful, but cancer is a complex adaptive (evolving) system (CAS)**
- **To make evolution both measurable and relevant, we need to understand how evolution impacts cancer at specific scales - including both the parts and the ecological context**

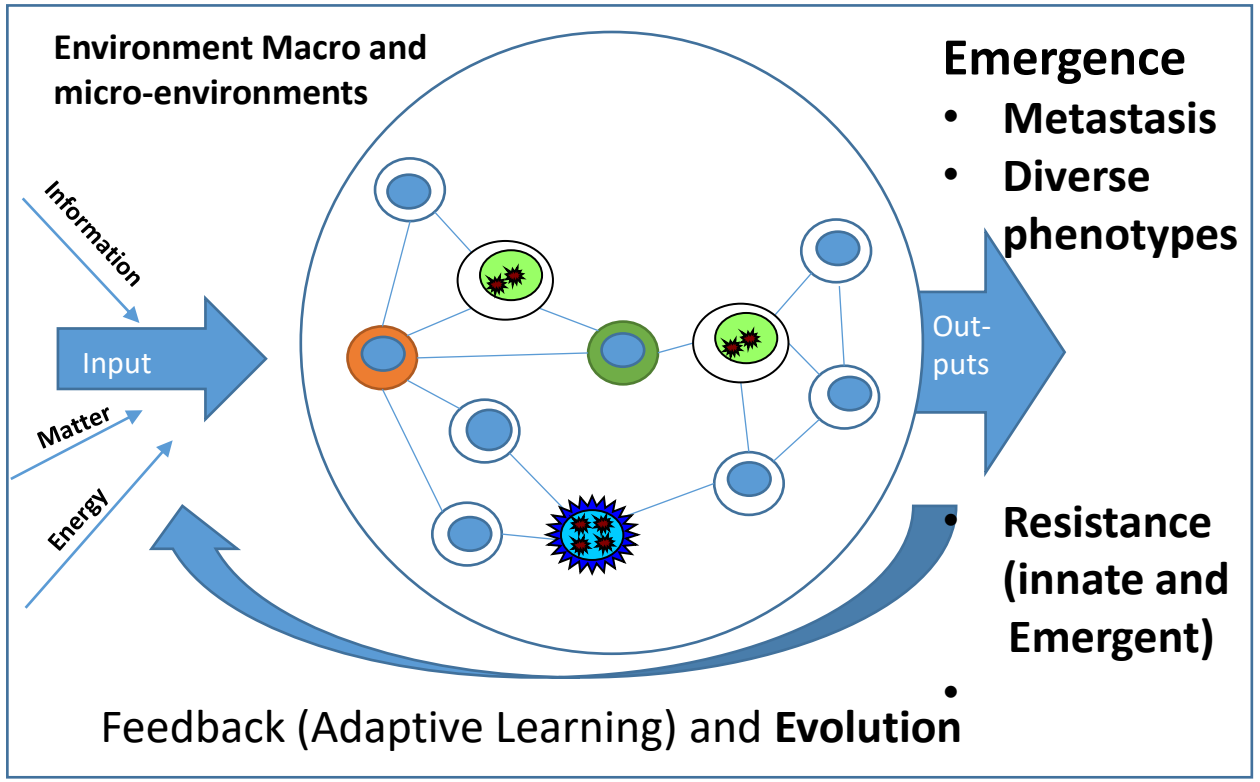


Adapted from: https://www.canwelivebetter.bayer.com/innovation/finding-cure-cancer-big-data-solution

Lawrence J. Ellison Institute for Transformative Medicine of USC

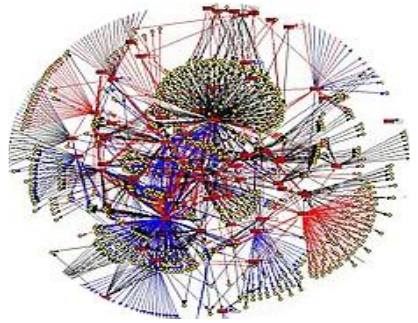
Reality: Cancer is a Complex Adaptive System (CAS) – Actually a Combined Cancer- Immune System CAS

- Composition - **diverse interacting agents -** no central control.
- **Self-organizing, non-linear** systems - operate **far from equilibrium**
- Ordered system states – system organization across scales - operate within **excursion boundaries.**
- **Emergent properties** – Interaction of agents within/across scales can produce different/unique properties **(HALLMARKS).**
- **Robust (redundancy)** –changes can cause major shifts in system states (fragility) and emergent properties.
- Exhibit **complex information processing** and management.
- **Adaptable, evolvable, Multiple clones and subclones evolve in the context of the environment.**



Coarse Grained Model of Cancer as CAS

Lawrence J. Ellison Institute for Transformative Medicine of USC



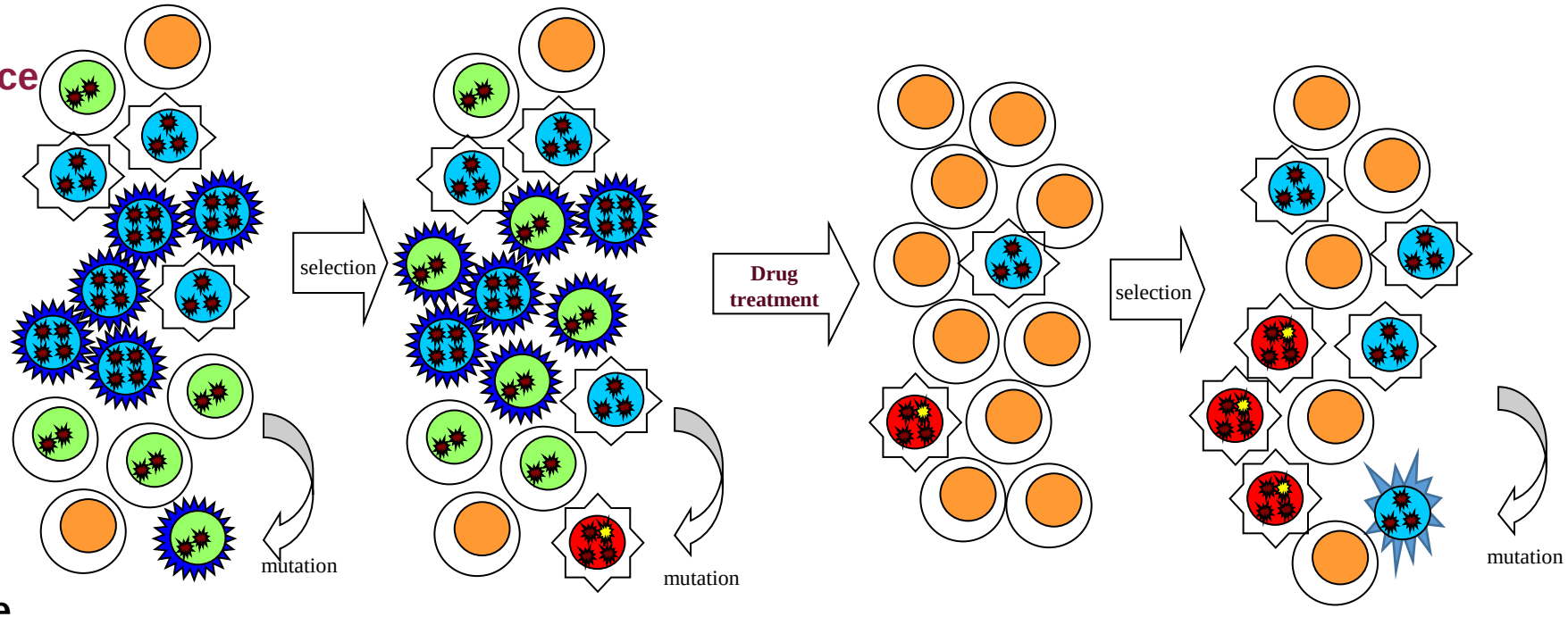
Problems/barriers where both applications of evolutionary theory and applied evolution could make a difference:

- ***Bringing context to the big data "omics" tsunami integration problem.***
- ***Addressing acquired resistance in cancer treatment via chemotherapy (targeted and non-targeted) (intrinsic and induced)***
- ***Combing therapies to address cancer homogeneity***
- ***Increasing the success of clinical trials***
- ***And more……***

Lawrence J. Ellison Institute for Transformative Medicine of USC

Therapeutic Interventions Drive Cancer Evolution - Resistance

- Most cancer **evolve through spontaneous somatic cell mutation** and selection as a consequence of **fitness changes.**
- **Information drives emergence** and **selection** within cancer subsystems.
- **Fitness changes imply changes in information content.**
- **Spontaneous mutation** promotes increased genetic **heterogeneity** over time
- **Drug treatments** select for specific **resistant cancer cell subpopulations** (clones).
- **Relevant information for use in patients to potentially predict resistance will depend on identifying and validating biomarkers of cancer evolution!!**

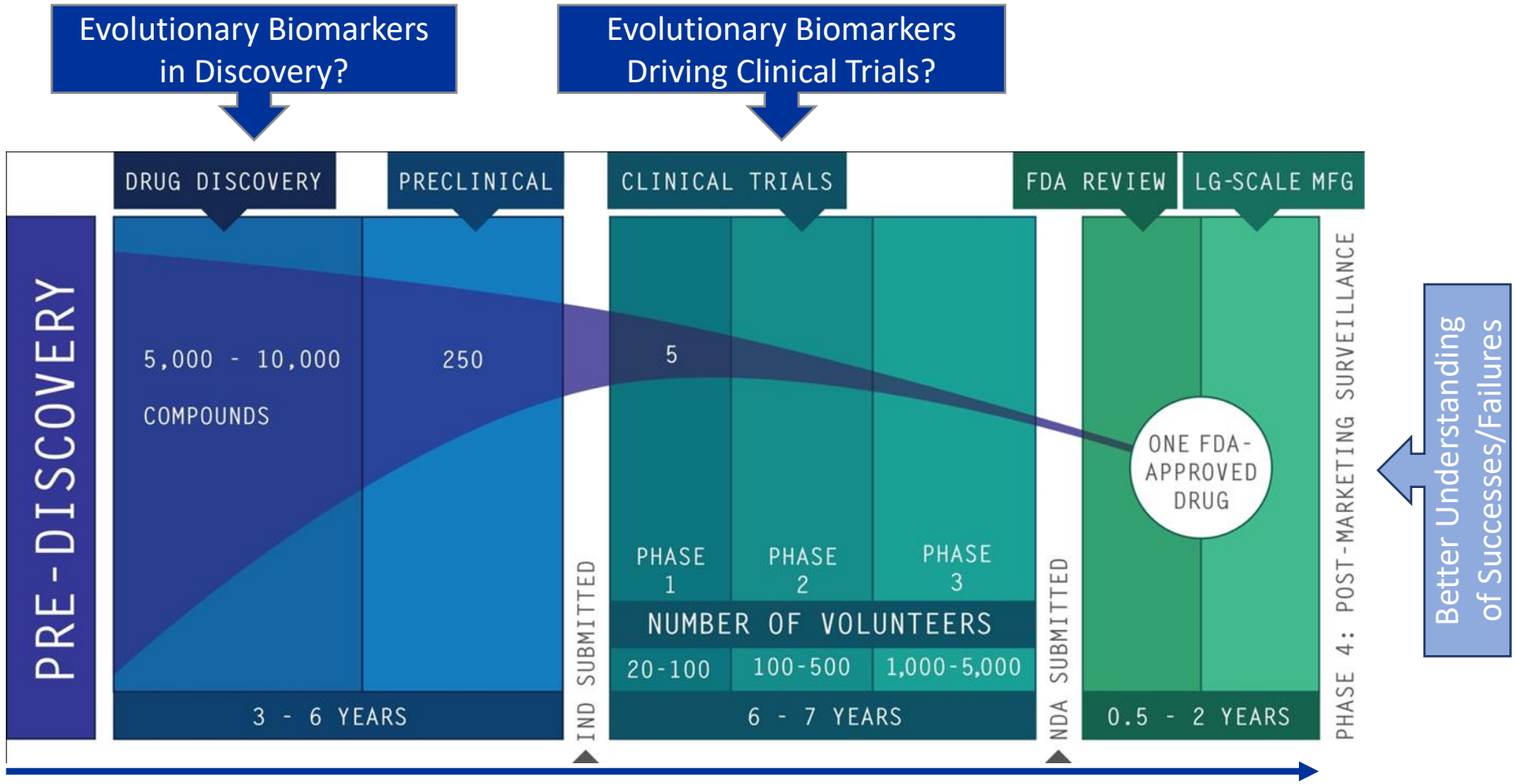


This is not a linear process, but rather a complex of processes and subsystems involving tumor cell subsystems and the microenvironment

Lawrence J. Ellison Institute for Transformative Medicine of USC

Reality - Oncology Biomarker Clinical Trials : Massive Attrition, Long Duration, High Costs (High Failure Rate)

What if instead o the current paradigm evolutionary biomarkers played a major role ?

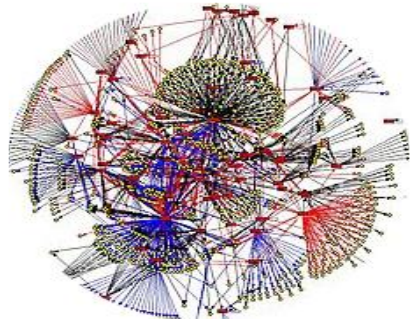


5-10,000:1 chance of success 12-15 years (Cost 1-2 Billion)

Time and attrition are directly related to lack of validated clinically important biomarkers – where is evolution in this process?

Lawrence J. Ellison Institute for Transformative Medicine of USC

ARE WE CHASING THE WRONG BIOMARKERS?



Biomarkers today generally focus on genomic alterations (singular) or in panels of genes (molecular profiles), images and a few complex biomarkers. Increasingly cancer is viewed as occurring in context – and evolves within (and in response to) its environment – genotype to phenotype (across scales from molecular to human) and evolution plays a role at every scale.

Could evolutionary biomarkers be as (or more) important than the "omics"-centric and other biomarkers in advancing precision cancer medicine – especially areas such as therapy and drug discovery?

Lawrence J. Ellison Institute for Transformative Medicine of USC

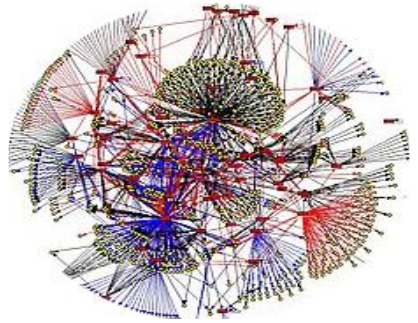
Biomarker: As Officially Defined

*Biomarker (New Definition)***

"A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are examples of biomarkers. A biomarker is not an assessment of how a patient feels, functions or survives

** Joint FDA-NIH Working Group, 2015

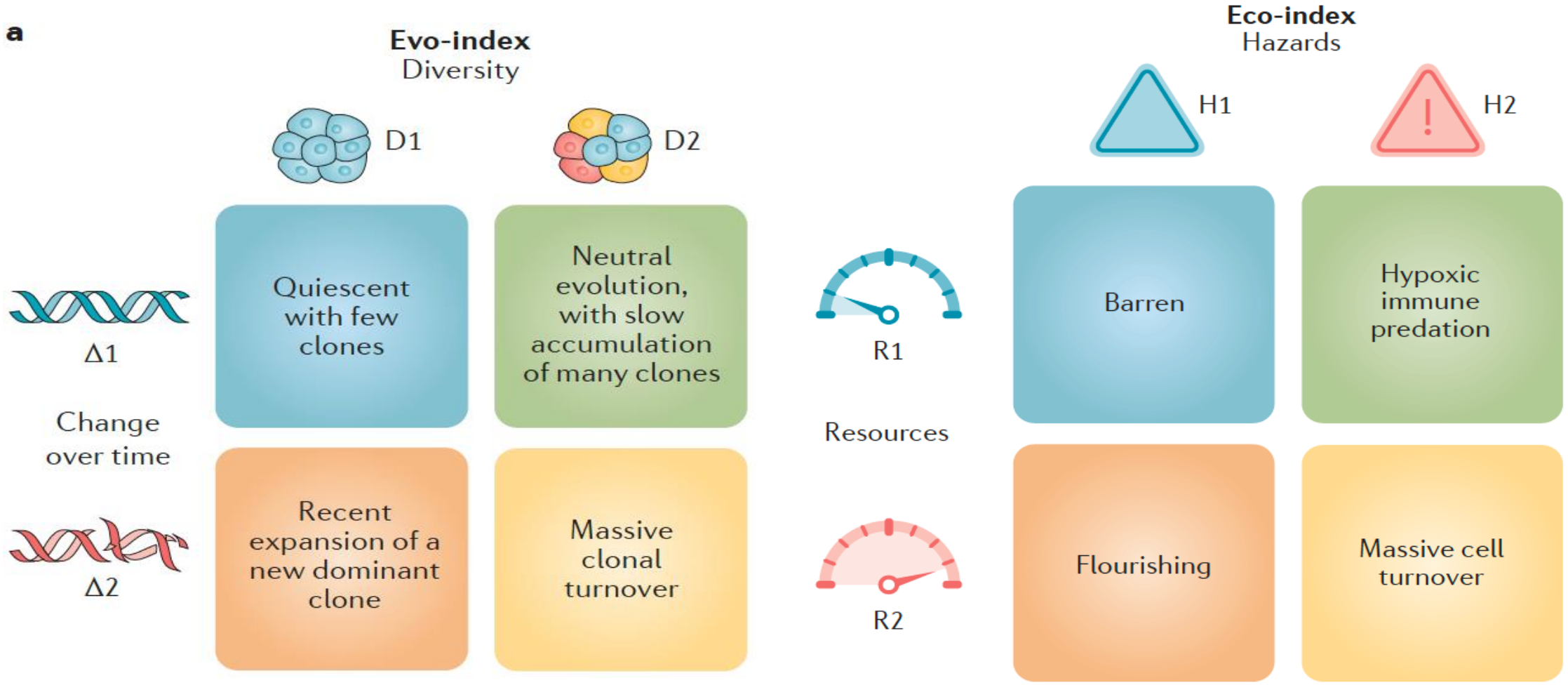
Lawrence J. Ellison Institute for Transformative Medicine of USC



- ***Do we have models for developing evolutionary biomarkers”?***
- ***Are their clinical trials models for validating biomarkers?***
- ***Will the regulators approve evolutionary biomarkers?***

Lawrence J. Ellison Institute for Transformative Medicine of USC

Evo- and Eco-Indices:Proposed as a Classification System but Could it Also be a Platform for Biomarker Identification)



Nature Reviews Cancer **volume 17**, pages 605–619(2017):

Wellcome Consensus Statement, was to develop a framework that would enable quantifiably describing, and eventually classify, the evolutionary distinctions between tumors

Lawrence J. Ellison Institute for Transformative Medicine of USC

Candidate Evolutionary Biomarkers

- **Evolvability (Maley et al.)* reached consensus that it should include 4 factors**

"The *evolutionary index* considers diversity within the tumor and the change of that diversity over time

The ecological index considers the prevalence of various hazards and the availability of resources"

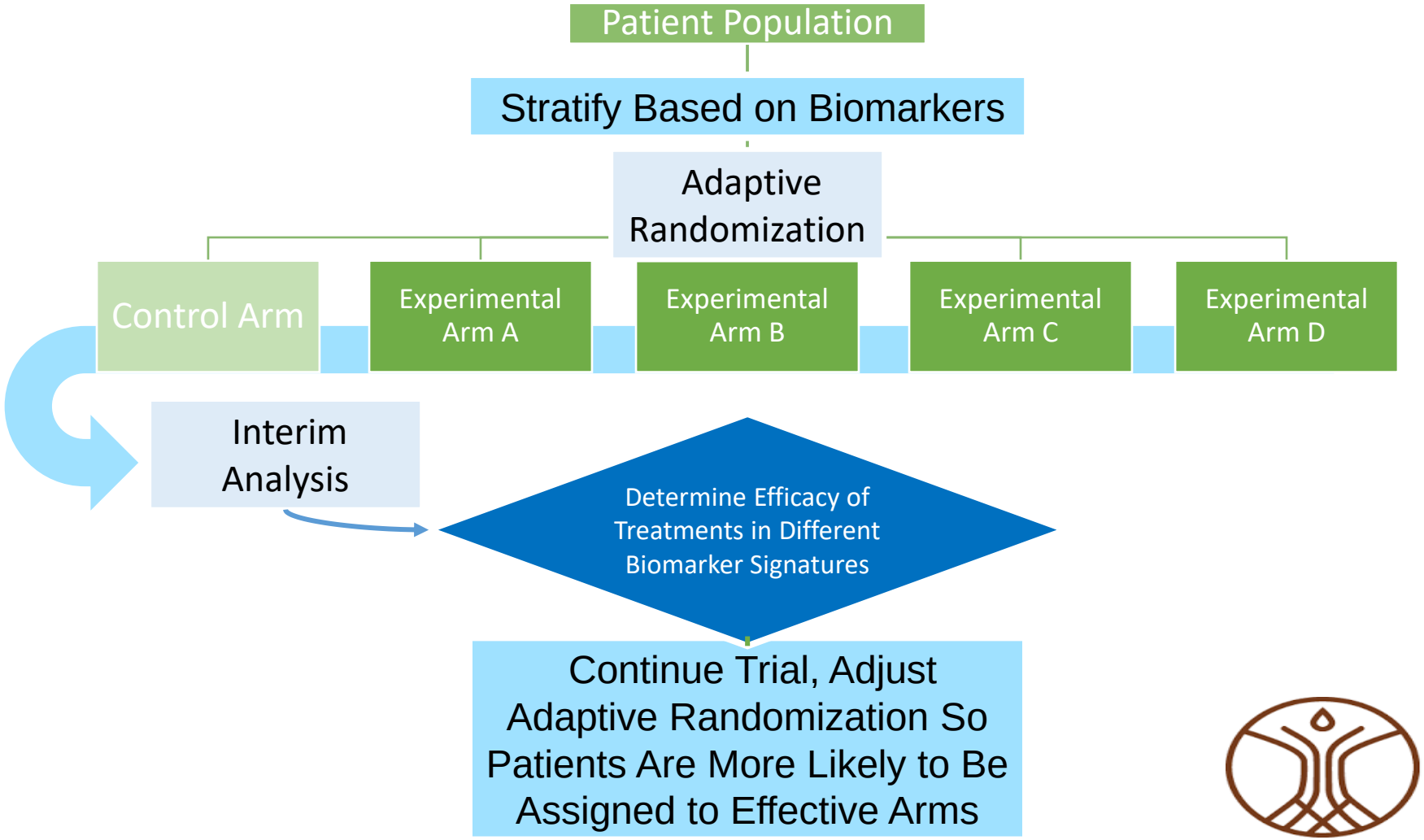
(Could this concept potentially create a discovery engine for evolutionary/ecological biomarkers?)

- **Examples of Other biomarker concepts (Depends on the question):**
- *Clonal expression*
- *Rate of evolution*
- *Change in diversity over time*
- *Stress responses*
- *Combination of genotypic and phenotypic responses*
- *Fitness changes*

*Nature Reviews Cancer **volume 17**, pages 605–619(2017)

Lawrence J. Ellison Institute for Transformative Medicine of USC

Bayesian Driven Adaptive Platform Trials



Lawrence J. Ellison Institute for Transformative Medicine of USC

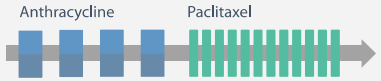
Greater Personalization: Driving Toward Optimal Early Endpoints

I-SPY 1

Measure outcomes by subtype

- Standardize imaging, pathology, biomarkers, data collection

GOAL: create collaborative framework



1

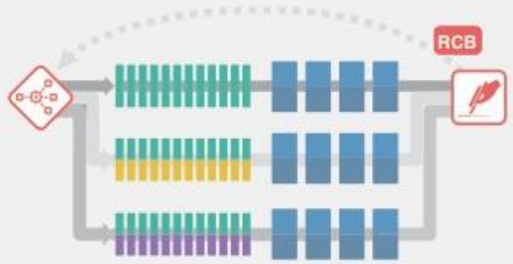
- Absence of tumor after neoadjuvant chemo (pCR) is optimal early endpoint
- for molecularly high risk disease
- Better by subtype

I-SPY 2

Adapt therapy within trial

- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation

GOAL: Increase pCR in each biomarker signature



2

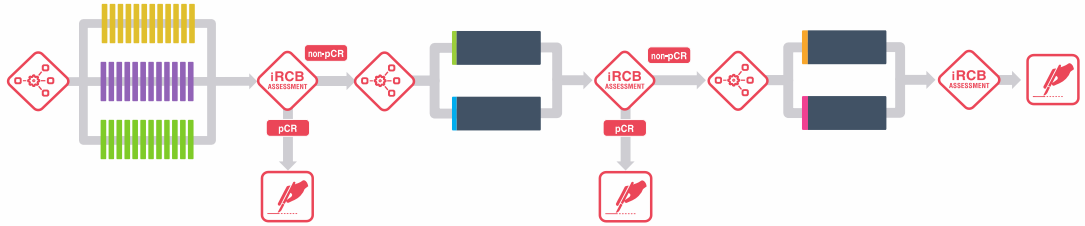
- pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB stratifies outcome
- MRI and biopsy predict pCR
- Many agents identified that improve subtype specific pCR
- Molecular markers better classifiers than receptors

I-SPY 2+

Adapt therapy within patients

- iRCB, Imaging as a regulatory endpoint for poor responders
- SMART approach
- Compare pathways vs receptors to select agents

GOAL: Increase chance of pCR for each patient

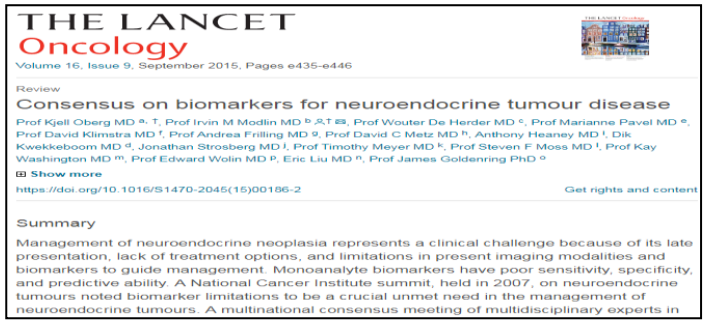


2+

- Optimize pCR for each patient
- Stop at pCR, continue if not
- Accelerated approve for agents that generate optimal pCR rates
- Confirm DRFS at 3 years ≥92% for full approval

Lawrence J. Ellison Institute for Transformative Medicine of USC

Paths for Regulatory Biomarker Approval



THE LANCET
Oncology
Volume 16, Issue 9, September 2015, Pages e435-e446

Review

Consensus on biomarkers for neuroendocrine tumour disease

Prof Kjell Oberg MD [a, †], Prof Irvin M Modlin MD [b, §, †, ✉], Prof Wouter De Herder MD [c], Prof Marianne Pavel MD [e], Prof David Klimstra MD [f], Prof Andrea Frilling MD [g], Prof David C Metz MD [h], Anthony Heaney MD [i], Dik Kwekkeboom MD [d], Jonathan Strosberg MD [j], Prof Timothy Meyer MD [k], Prof Steven F Moss MD [l], Prof Kay Washington MD [m], Prof Edward Wolin MD [p], Eric Liu MD [n], Prof James Goldenring PhD [o]

Show more

https://doi.org/10.1016/S1470-2045(15)00186-2 Get rights and content

Summary

Management of neuroendocrine neoplasia represents a clinical challenge because of its late presentation, lack of treatment options, and limitations in present imaging modalities and biomarkers to guide management. Monoanalyte biomarkers have poor sensitivity, specificity, and predictive ability. A National Cancer Institute summit, held in 2007, on neuroendocrine tumours noted biomarker limitations to be a crucial unmet need in the management of neuroendocrine tumours. A multinational consensus meeting of multidisciplinary experts in

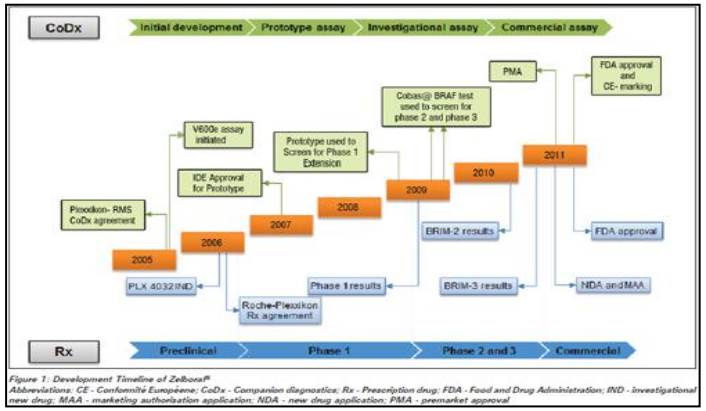


Figure 1: Development Timeline of Zelboraf®
Abbreviations: CE - Conformité Européene; CoDx - Companion diagnostics; Rx - Prescription drug; FDA - Food and Drug Administration; IND - Investigational new drug; MAA - marketing authorisation application; NDA - new drug application; PMA - premarket approval

Stage 1: Initiation

Submit Letter of Intent (LOI)

FDA determines acceptability of LOI

Stage 2: Consultation and Advice

Submit briefing package

Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review

Submit full qualification package

FDA reviews package and makes yes/no decision to qualify

FDA drafts guidance document

Publication of Guidance

Draft guidance document posted to Federal Register for public comment

FDA publishes final guidance document

Lawrence J. Ellison Institute for Transformative Medicine of USC

If There Candidate Evolutionary Biomarkers, Is this the Right Time to Launch an Initiative. Timing Yes – But Some Realities!

- There is no cancer evolution community – writ large – no constituency advocating for the critical research that could be transformative to cancer
- Evolution in cancer is not a major focus for either government or private funding; beyond our investments through the NCI Physical Sciences Oncology Centers, resources are limited
- Evolutonary Biomarker Initiatives must demonstrate that they produce better outcomes for patients. We need to review and assemble examples – e.g., Bob Gatenby, adaptive therapy model; Charlie Swanton, TRACERx
- Validating evolutionary biomarkers (e.g., EVO/ECO) in Clinical trials will require new trial models (longitudinal samples and data) and new networks
- Bottom line we need a revolution in cancer evolution! A “community” that focuses on something tangible (evolutionary biomarkers) – identification, development, standards, clinical trials and regulatory review and approval

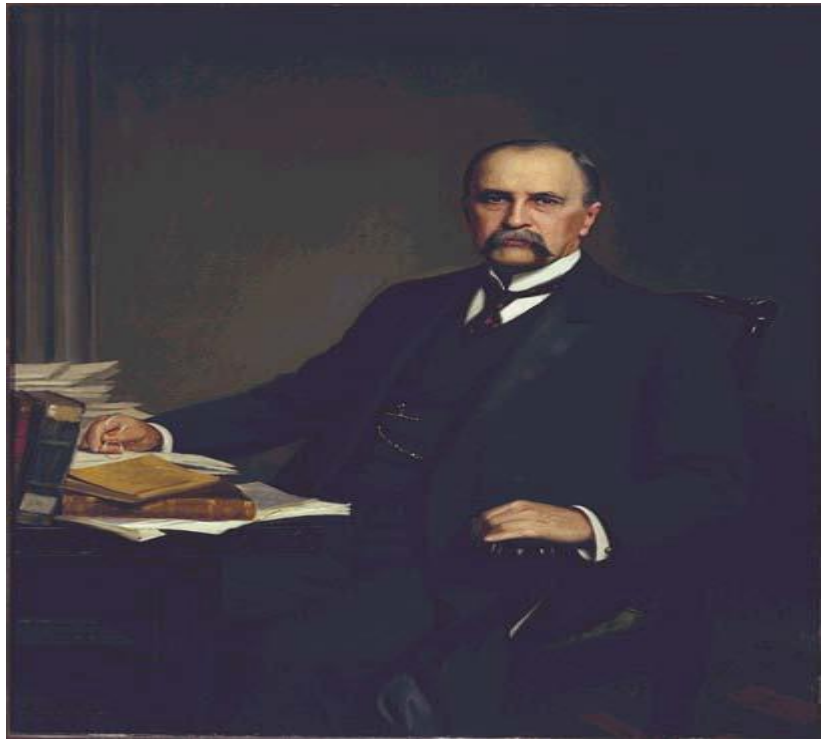
Lawrence J. Ellison Institute for Transformative Medicine of USC

Some Issues/Questions where Evolutionary Biomarkers May Make a Difference for Cancer Patients

- Focus on understanding malignant tumors through characterization of targeted clones and fitness landscapes
- Identify what the selection pressures are – and where they have impact
- De-convolute the role of the numbers and types of mutations in different clones – and how they interact
- Tumors are organ specific – and malignant clones find their way to specific organs – could evolutionary biomarkers determine if the fitness is programmed occurs in the organ, the cancer cells, or both?
- Can we use evolutionary biomarkers to design cancer therapies that consider selection pressures?
- Could evolutionary biomarkers inform the development of combinations of agents that target various aspects of tumor evolution within an environmental context?

Lawrence J. Ellison Institute for Transformative Medicine of USC

Post Script: Need to Move from Evolutionary Theory to Applications that Demonstrate the Value of Evolution in Understanding and Controlling Cancer



Sir William Osler (1849-1919)

"If it were not for the great variability among individuals, medicine might as well be a science and not an art"

Lawrence J. Ellison Institute for Transformative Medicine of USC