BSA Concept Presentation
Physical Sciences-Oncology Centers

(Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology)

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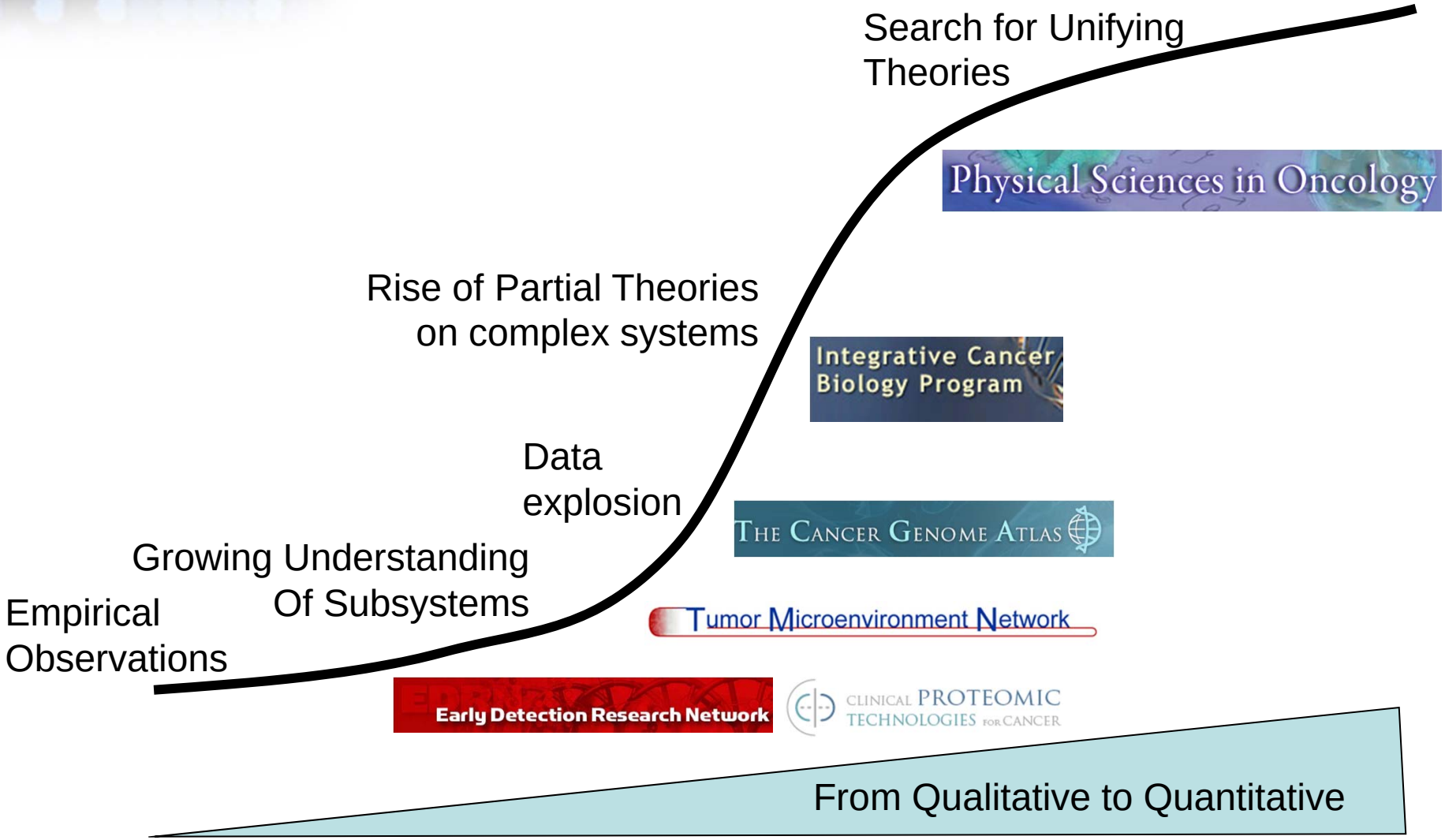
Some Observations

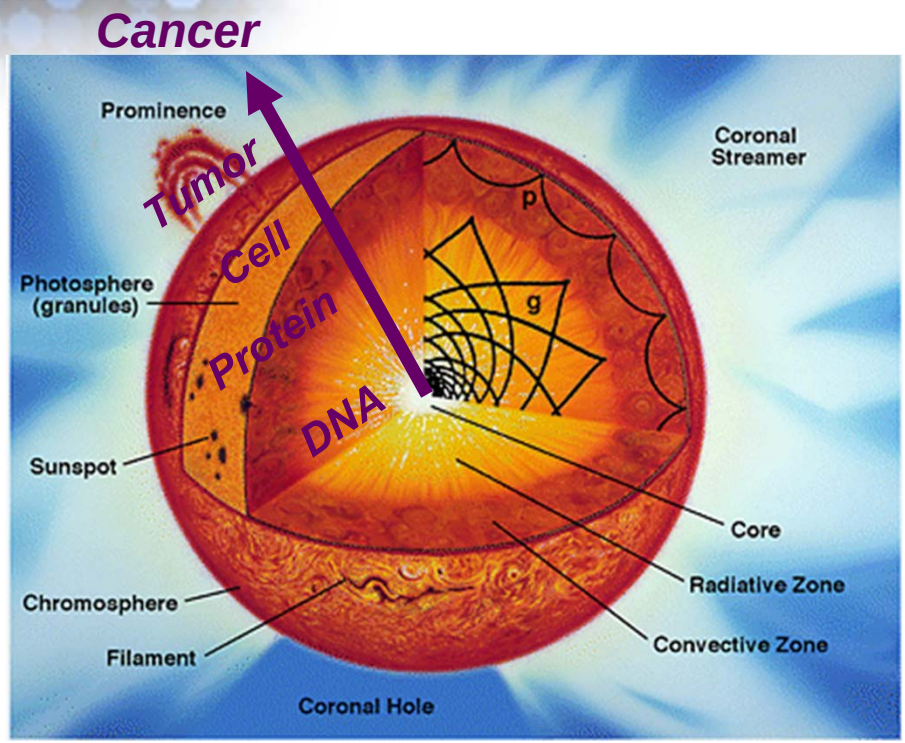
- Stunning advances in defining a wide range of changes in cancer vs. normal cells over the past decade – beginnings of signaling-pathways biology and the microenvironment, etc.
- All of these discoveries and advances are pointing us toward a need to understand the physics of these highly complex systems…
- To ultimately control cancer we need to go well beyond knowing pathways – speculating on signals – we must understand how cancer differs in terms of the physics of these systems at the molecular and sub-molecular levels with consideration to space and time
- This is the new frontier in cancer science – and perhaps the most promising

The “S” Curve of Science

Adapted from E. Zerhouni



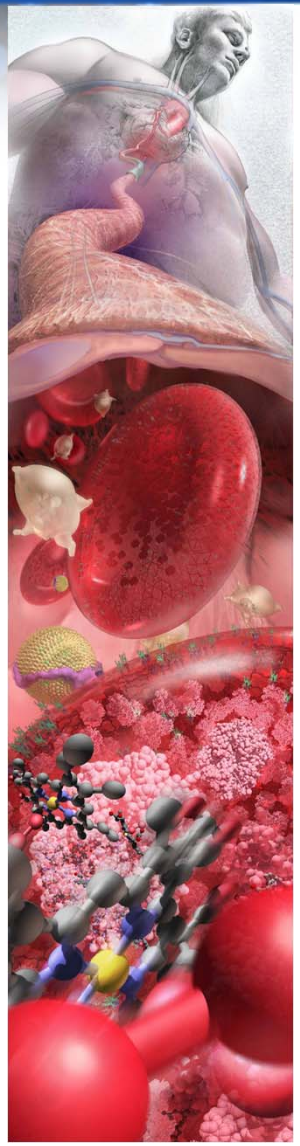
Integrating Cancer Biology with the Physical Sciences – New Ideas New Directions – Comprehensive Understanding



Depending on the 'length scale', the physics of how the sun works is different. Physicists working at these different length scales came together to develop a working model that describes the overall process of energy generation, transfer and explains much of what we observe and measure

- **The physics of the sun is different at the core (nuclear fusion) than near the surface (e.g., thermal gradients) – cancer represents a similar construct at different scales**
- **Developing a similar 'seamless' understanding of cancer will require the integration of current knowledge with new information from physics, mathematics, chemistry and engineering – viewing cancer as a dynamic evolving system in time space**
- **What we know about cancer can only be really understood in the context of the physical, spatial, chemical – and temporal aspects of this highly complex system**

Length-scale, Complexity, Emergence



Length Scales	Players	*Interactions*	Emergent 'Objects'
10^{-2} m	Organs	→	Organism
10^{-4} m	Cellular	→	Organ
10^{-6} m	Organelle	→	Cell
10^{-8} m	Molecular	→	Organelle

For decades, cancer biologists have been trying to understand the complicated systems of cancer by understanding each part at its most basic level. However, we have overlooked how the interactions of all the 'players' (within a length-scale) lead to emergent 'objects'/properties that work together in complex tasks.

Background

- A series of meetings with the extramural communities – physicists, mathematicians, physical chemists and engineers –cancer biologists and oncologists working in - or appreciative of - the physics of cancer
- First meeting of this "new frontiers" series - "Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology" in February – followed by "A New Look at Evolution and Evolutionary Theory in Cancer" – in July. A third think tank in late October convened around "Information Coding, Decoding, Transfer, and Translation in Cancer".

….overall, a near-universal theme to come out of all of these think-tanks to date is that the physical sciences have unique knowledge and expertise that may well be a prerequisite to address some of the most pressing research questions in cancer – and ultimately understand and control this complex disease….

Integrating and Leveraging the Physical Sciences to Open a New Frontier in Oncology

*"…bringing together physical scientists and cancer researchers will provide new directions…that will lead to **new conceptual approaches** to understanding complexities of cancer…"*

- John E. Niederhuber

"Life is not a self-organizing system. It is a supervised organizing system, under software control…When the supervision is flawed, life 'goes wrong.'…Life involves a web of information flow, but the information is not just "bits" – it depends on the context."- Paul Davies

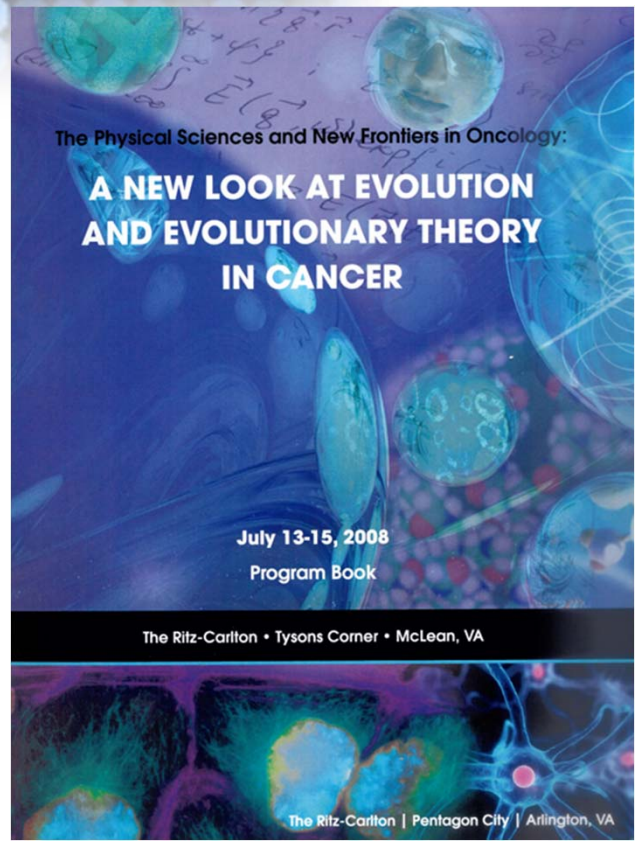
Consensus Scientific Themes

- Laws/Principles of Physics Apply to Cancer Biology (Understanding the Physics of Cancer)
- Evolution and Evolutionary Theory in Cancer
- Coding, Decoding, Transfer, and Translation of Information in cancer
- De-convoluting the complexity of cancer

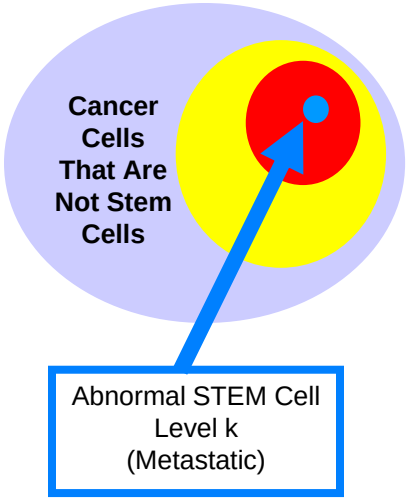
Recommendations

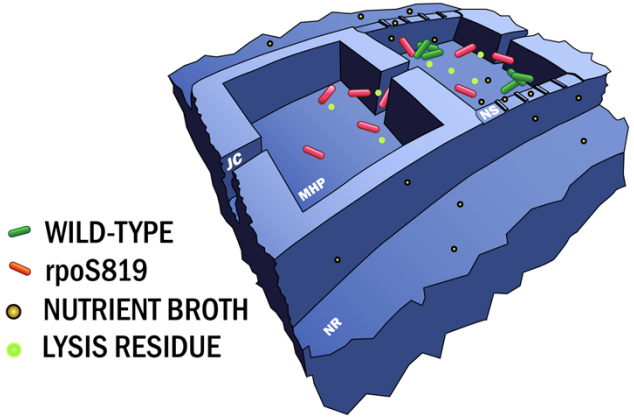
- Establish transdisciplinary physical sciences-oncology centers
- Composed of integrated physical sciences-oncology teams
- Focus on theme(s) for center framework
- Centers led by physicists with co-principal investigator from oncology

Physical Sciences and New Frontiers in Oncology: A New Look at Evolution and Evolutionary Theory in Cancer



"If only a subset of the cancer cells have metastatic capacity, how does molecular profiling work?"- Larry Norton

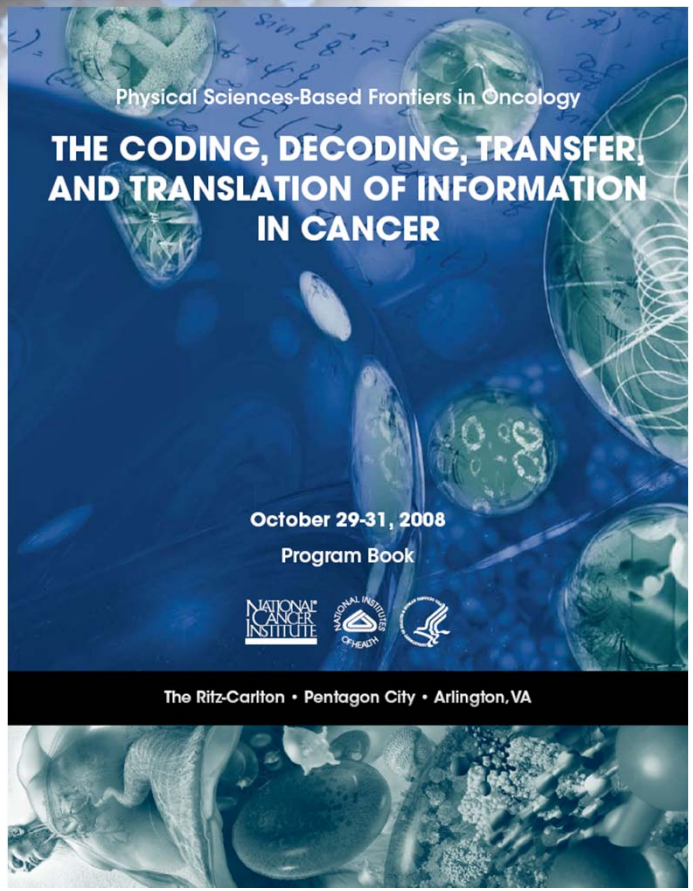




"Worldwide, no more than 15 percent of all cancers may be caused by viruses [Pervues] <u>What causes the other 85%</u>?"- Paul Ewald

"I wonder if metastasis is just a logical decision by a metapopulation of complex cells to survive, actually driven by the body's misguided (or medicine's) effort to destroy that metapopulation?"- Robert Austin

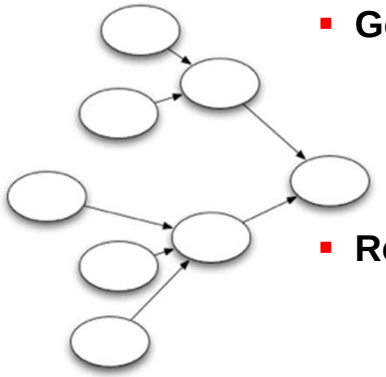
Physical Sciences and New Frontiers in Oncology: The Coding, Decoding, Transfer, and Translation of Information in Cancer



"I challenge you to tell me exactly what a gene is?" – Phillip A. Sharp

Think Tank Questions Posed:

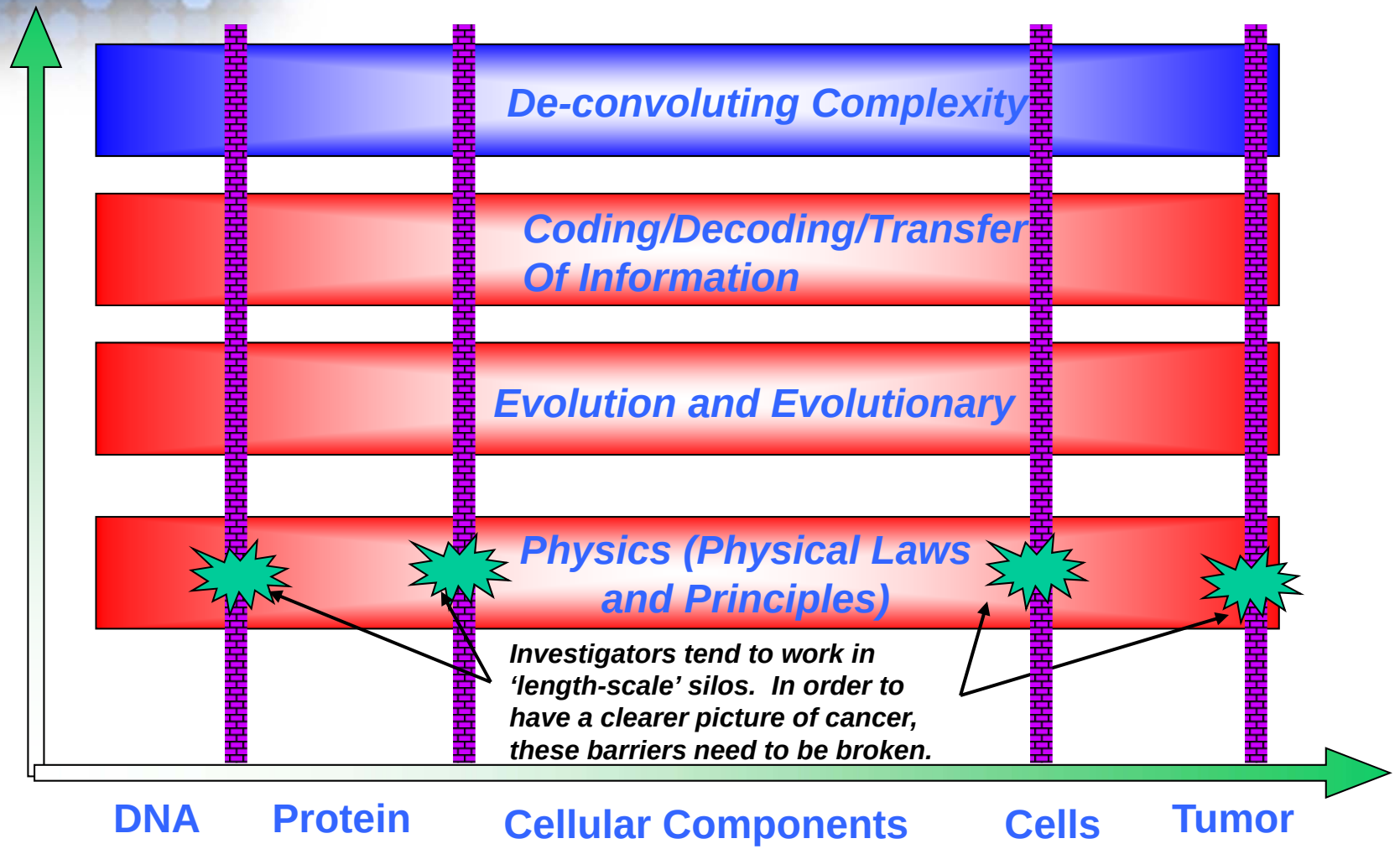
- What does "information" mean in terms of the genetic code and its translation in cancer relative to context and certain specific aspects that characterize cancer?
- What is the "state of the science" of information and information theory in terms of understanding of cancer at all scales?
- What are critical research questions from information and information sciences in cancer that could represent major areas for transdisciplinary research and lead to the development of new cancer interventions?



- **Goal is control (vs. detailed understanding)**
  – understanding is a tool
- **Robustness Hides Information**
  – Many variations of inputs must lead to the same output
  – Just controlling the outputs cannot work

"The level we understand is often not the best level to control" – W. Danny Hillis

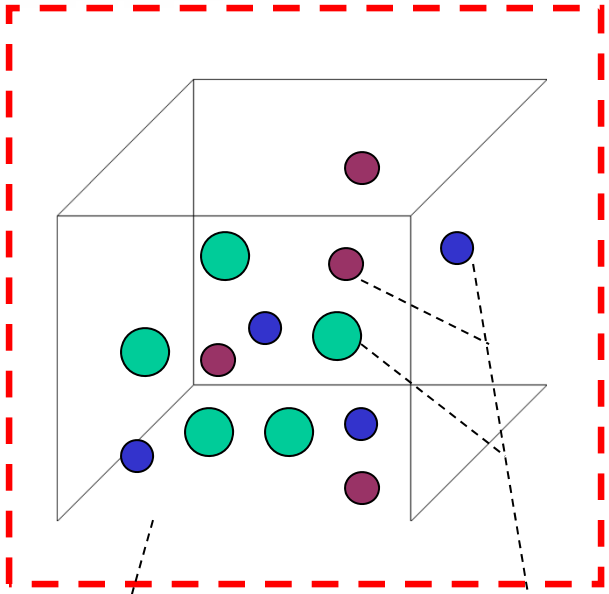
Summary of Theme Areas



Length Scale – In Reference to Size (Ranging from 1 nm – 1 mm)

Physics/Engineering Approach: System versus "Systems"

The System



1. **Define the System** by drawing boundaries and setting length-scale
2. **Identification of** known and unknown variables set by length-scale
3. **Determine** change of variables based on conservation laws
4. **Measure** variables with different robust techniques
5. **Develop** robust equations of state to describe state of system

Relevant Length-scale
- meters (Organisms)
- cm (Organs/Tissues)
- mm- μm (Cells/organelles)
- nm (DNA/proteins)

Relevant Variables
- Organism
- Organs/Tissues
- Cells/organelles
- DNA/proteins

Conservation Laws
- Mass/Momentum balance
- Energy balance
- Entropy balance

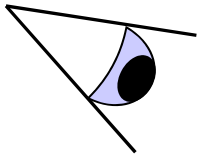
Living Systems – Obey the laws of physics but these laws **do not** explain their behavior/properties. They are "*complex systems*".

"Complex System" – Behavior/properties which are not fully explained by an understanding of its component parts.

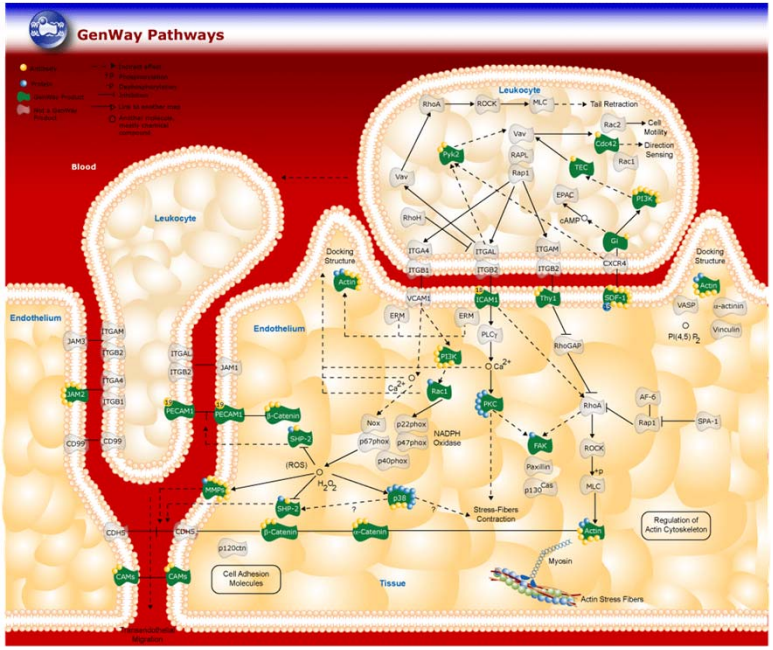
Emergent Properties – Each component part of a complex system participates in many different interactions that generate (unforeseen) behavior

Comparing “Perspectives”

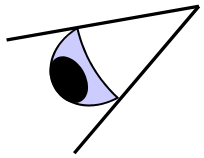
Physicist



- How much energy is needed to do this?
- How much force does it take to cross this barrier?
- Are reactions rates altered during this process?
- How much time does it take?
- What are the spatial effects?



Biologist

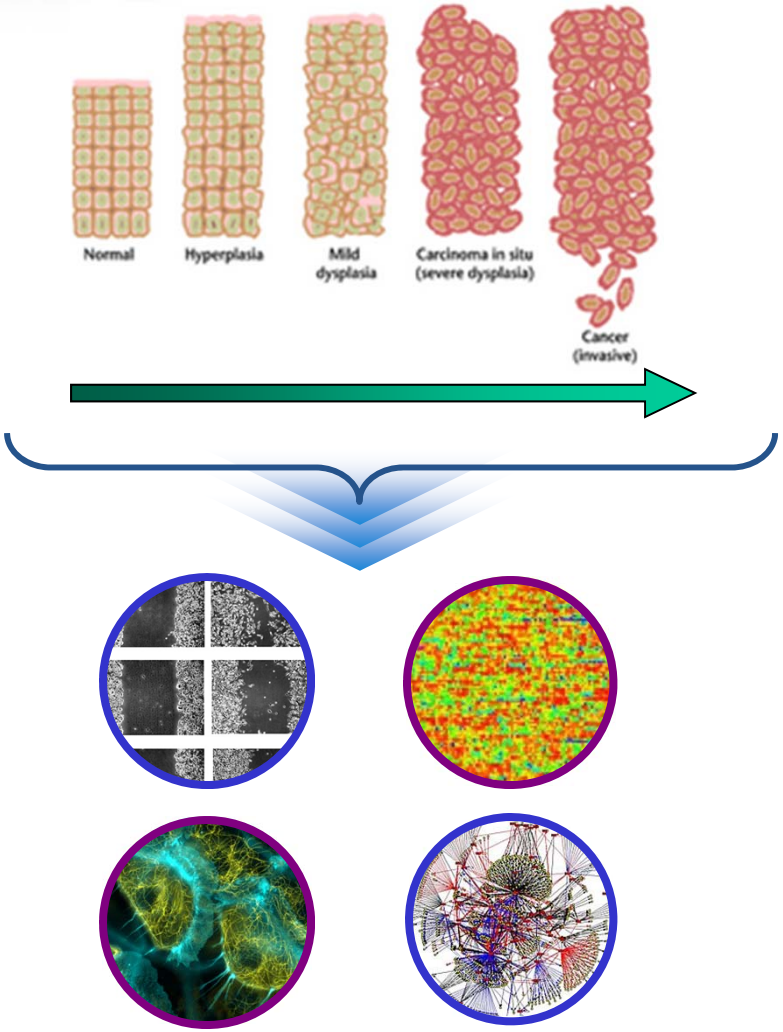


- What cell, molecule, tissue is it?
- What changed?
- Where does this fit?
- Do I see the same thing in several tumors?

Both ‘view’ the same picture differently, but

<u>Having both</u> perspectives yields a more comprehensive (clearer) picture of what cancer is and how it functions at all levels – especially at the sub-molecular/atomic scales

Adding Critical Dimensions to Traditional Cancer Research



- **Conclusions in cancer biology based heavily on "observations" –morphologic changes - today moving to "omics" –expression**
- **Characterization of "molecular interactions" – "signaling cascades" (tissue level, cell-matrix level, intracellular level)**

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Cancer (molecules – organelles – cells – tissues….occur in 3-dimensioanal space over a time scale – how do we consider those facts in our understanding and control strategies?

How do we integrate critical knowledge of the forces, gradients, thermodynamics, etc. that impact cancer at all scales?

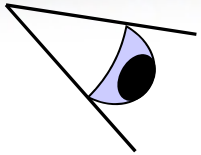
What are signals at the molecular and sub-molecular levels?

How do the emergent properties of cancer evolve?

Theme: The "Physics" of Cancer – Laws/Principles that Govern All Matter

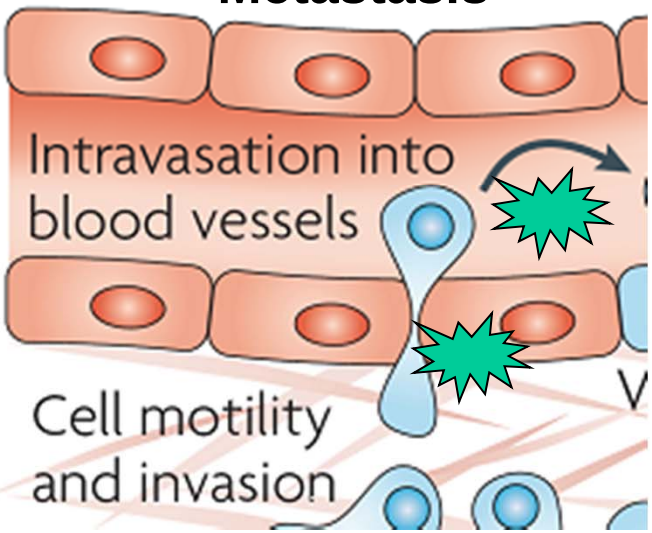
- Forces - short-range, hydrostatic forces etc.
- Thermodynamics - energy flows
- Chemical/energy gradients
- Spatial – time constraints - considerations
- Cell and biomechanics

Theme: Physical Laws and Principles – New Conceptual Approaches



Physical Science Perspective

Metastasis



- **Biology is not exempt from physical laws and principles**
- **Forces (shear, compressive, pressure, etc.) are experienced by metastatic cells**
- **Quantify, catalog, and determine impact and outcomes of forces**

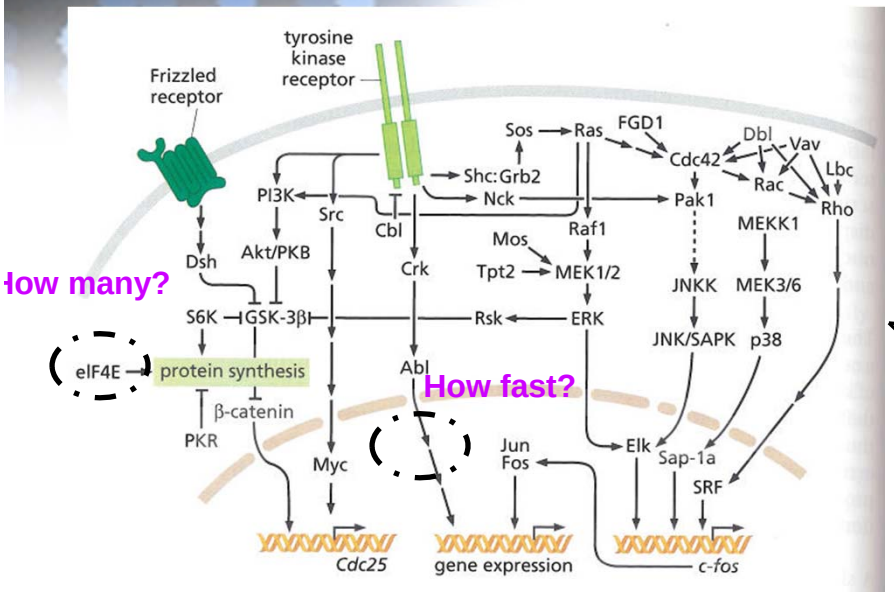
Conservative Estimates of Force

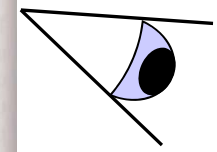
Shear Force **~0.1 picoN/μm^2**

Pressure Change

Arteriole **Capillary: ~2300 picoN/μm^2** (~ 50 lbs/ft^2)
Venule **Capillary: ~1000 picoN/μm^2**

Theme: New Conceptual Approach Coding-Decoding and Transferring Information; e.g. "Signaling"

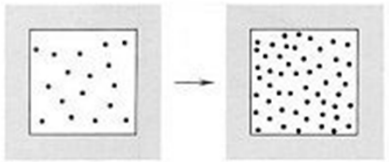




Physical Sciences in Information Transfer:

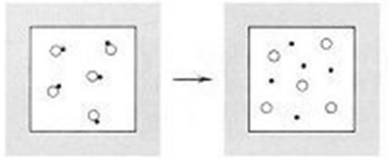
- *Determine "**energy budget**" of the system (cell, organ, organism).*
- ***Quantify** additional metrics to change entropy of the system*
- *Determine **best length-scale** to **effectively control** based on robustness of the system*

Traditional Perspective



Add/subtract coding elements

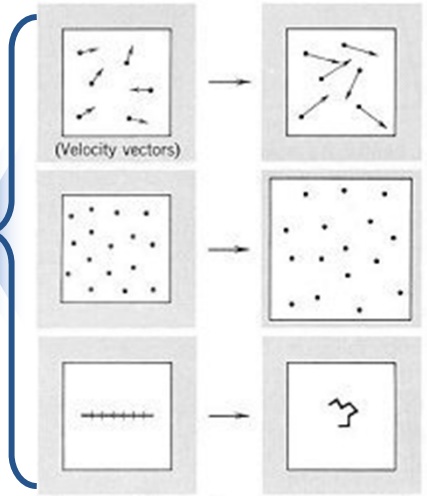
(DNA, Proteins, Pathways)



Alter elements

(Degradation of genes, proteins)

Physical Sciences Perspective



Additional Ways to Increase Entropy

Add energy enable movement

(Gradients)

Increase space

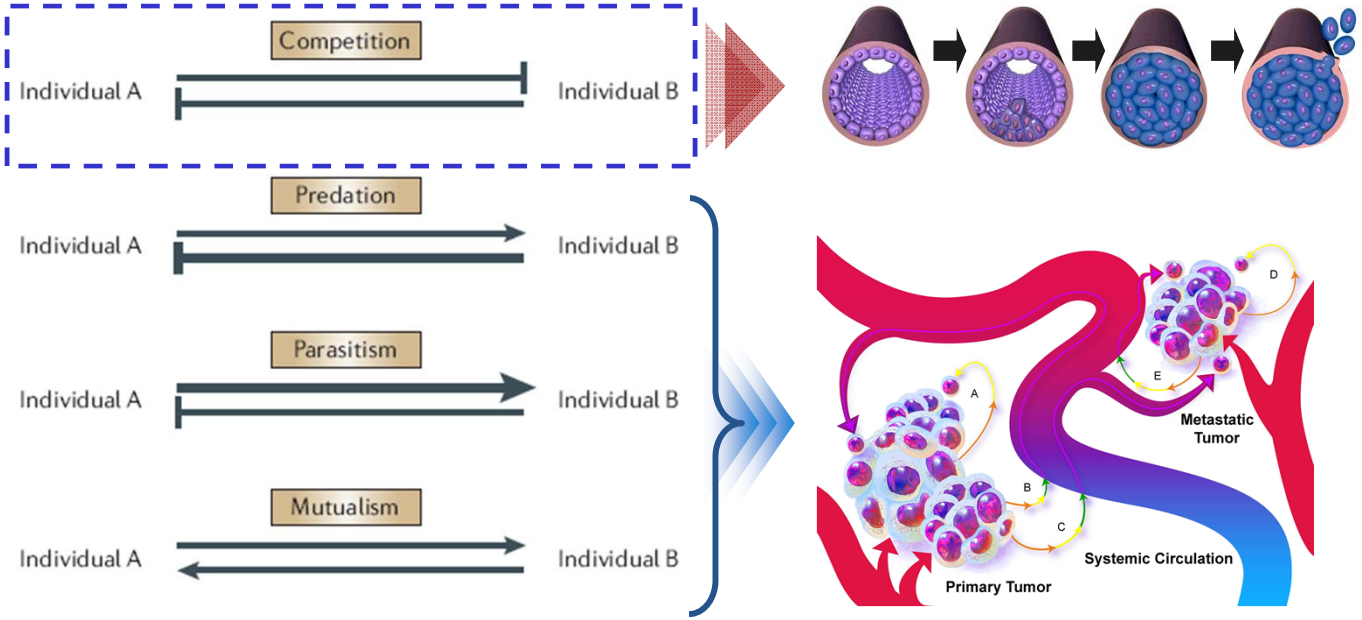
(Proximity of interacting proteins/organelles)

Reorganize elements in space

(Spatial/temporal heterogeneity in 3D)

Theme: Evolution and Evolutionary Theory in Cancer

Physical Science Perspectives

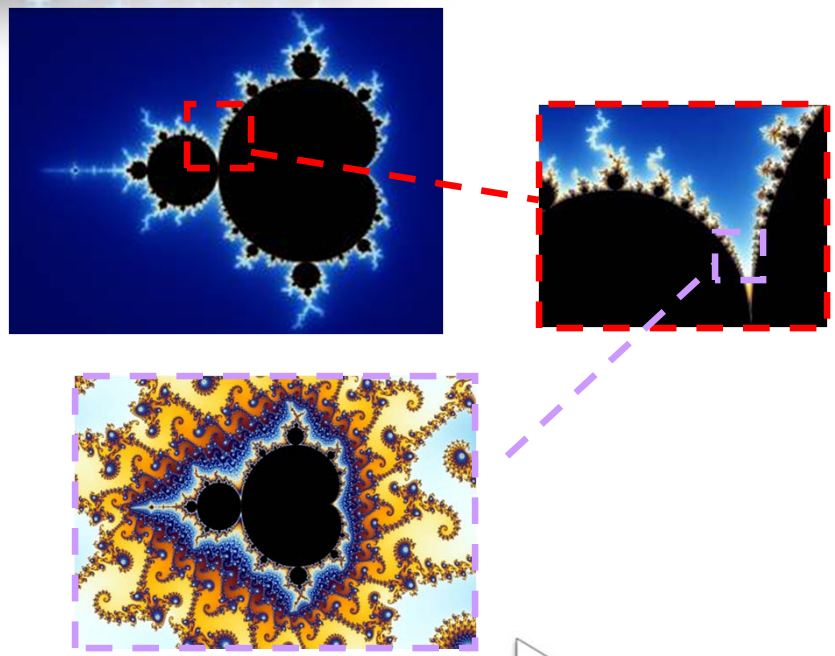


- **Are there key approaches to controlling cancer inherent in understanding its evolution?**
- **Is cancer stochastic – deterministic – what emergent properties will be critical to measure and understand in terms of evolutionary principles?**
- **Can an evolutionary framework be developed that includes physical laws and principles?**

What drives “we” to “me”?

Themes: Organizing Universal Physical and Biological Principles – De- convoluting Complexity of Cancer

Complex **Patterns** that Repeat



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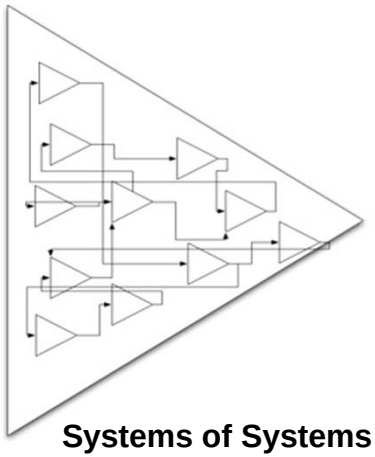
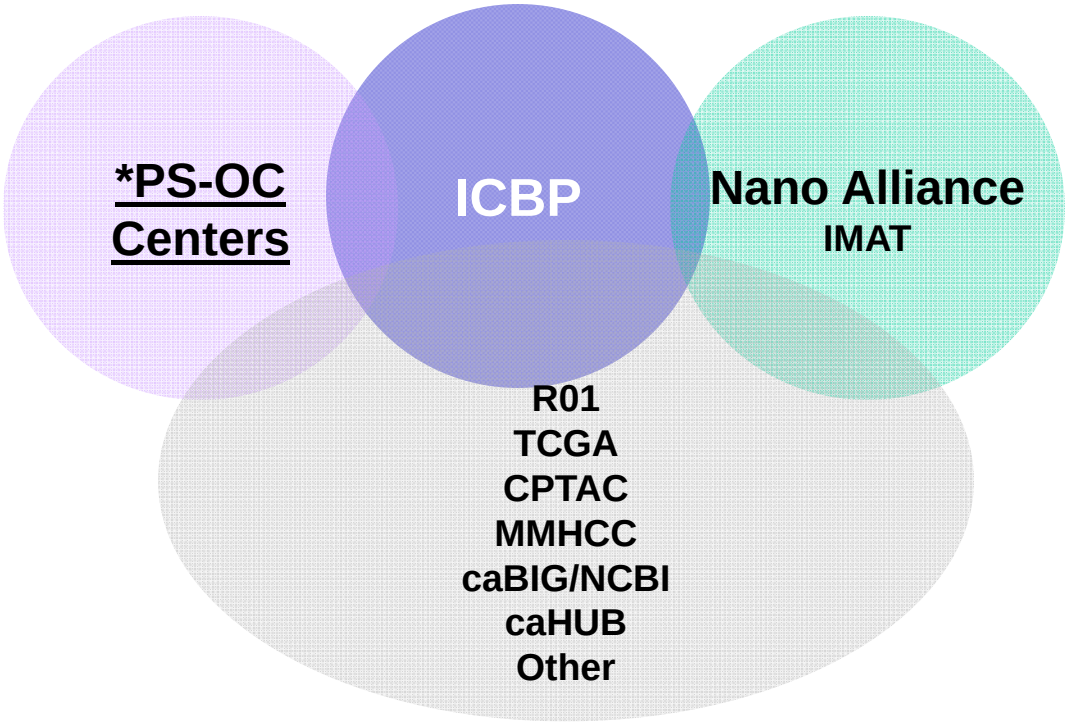


Systems of Systems

- Critical need for reproducible frameworks and constructs that can be tested and verified through experimentation
- Determine irreducible complexity and reducible complexity for "normal" and cancer cells
- Intersection & culmination of evolution processes, information transfer theory, and physical laws and principles
- Need a field of theoretical cancer biology

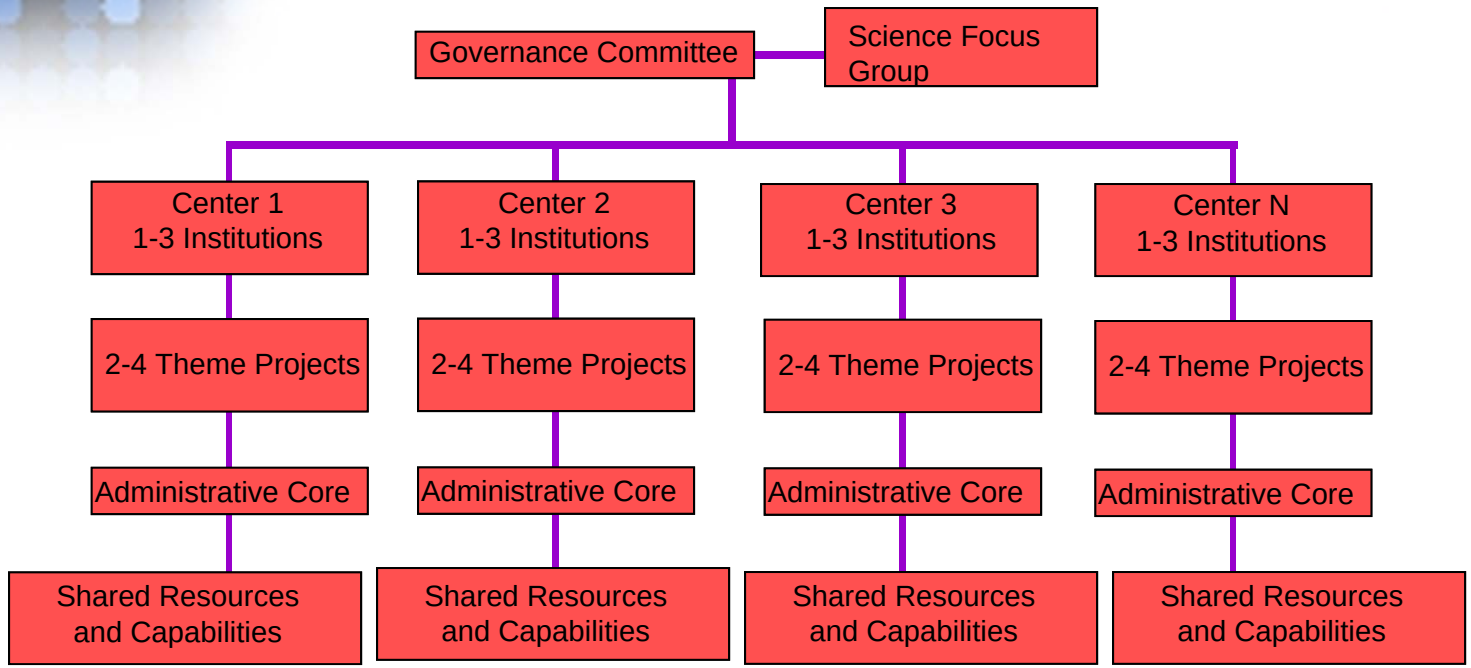
Future NCI Programs Linkages: Continuum

New Knowledge/Physical Sciences ⇔ Cancer Systems ⇔ Nano-Based High Dimensional Interventions



*** The Missing Component**

Proposed Center Structure



Proposed Center Requirements

- **Overarching conceptual physical sciences - cancer theme/approach**
- **Physical scientist PI with basic/clinical cancer researcher co-PI(s)**
- **Transdisciplinary teams – and team environment**
- **Adopt 2-4 synergistic theme projects (*i.e.*, complexity, coding, decoding, transferring information, evolution/evolutionary theory, physical science principles/laws)**
- **Shared Research Capabilities collaboratively linked through multiple centers including training, education, and outreach**
- **External advisory board provides scientific input to the program**

Proposed Mechanism and Budget

Mechanism:

- U54 (Cooperative Agreement Specialized Center)
  - Facilitate and enable the convergence of the physical sciences with cancer biology to understand cancer at a fundamental level – and create new opportunities for intervention and control
  - Need for several disciplines and teams to form a network and governance structure
  - Active coordination by program managers trained in physical and cancer sciences - and input from scientific focus groups
  - Accelerate leverage gained from resource sharing
  - Provide linkages to key NCI programs and resources

Budget:

- 4-6 Centers
- $3.0-3.5M per year per center
- Annual budget – $15-21M, Total budget – $75-105M

Evaluation Criteria

- Development of this unique infrastructure and transdisciplinary teams focused on established physics-centric themes
- Regular evaluation of progress in the context of stated objectives
- Track progress of the novel experimental and theoretical approaches in theme areas: physical laws and forces, evolution/evolutionary theory, coding, decoding and transferring information, and de-convoluting complexity –and others
- Collaborative cross-network team building and resource sharing
- Development and experimental testing of dogma-challenging hypotheses on cancer initiation and progression
- Training transdisciplinary scientists through their work in Center teams and across the network
- Community communications and outreach

*"Biology is a very interesting field...[because of] the vastness of its structure and the extraordinary variety of strange facts...**but to the physicist it is also a depressing subject**, because...the analysis seems to have **stalled around in a semi-descriptive manner** without noticeably progressing towards **a radical physical explanation**..."- Max Delbruck, A Physicist Looks at Biology, 1949*

*"**Bringing physics**, **not just the physicists, to biology**…what physicists brought to biology was not any skills acquired in physics, but rather an attitude: the conviction which few biologists had at that time, that mysteries can be solved…I now encourage physicists to work collaboratively with biologists as we strive to achieve Delbruck's 'radical physical explanation' for biological systems"- Harold Varmus, 1999*

*"Tool-making leads to new knowledge…the **ability to measure accurately at different scales is why scientific progress occurs**…accurate measurements do **change your perspective** on reality…the work in front of us is to understand the biology behind all of these…Resistance to new knowledge is a constant…The greatest risk in science is to stop taking risks…and finally, **Don't be a me-too**, **that's not the way to succeed**…"- Elias Zerhouni, 2008*