Opening New Frontiers: Physical Sciences in Oncology

Physical Sciences-Oncology Centers (RFA CA09-009)
Pre-Application Meeting

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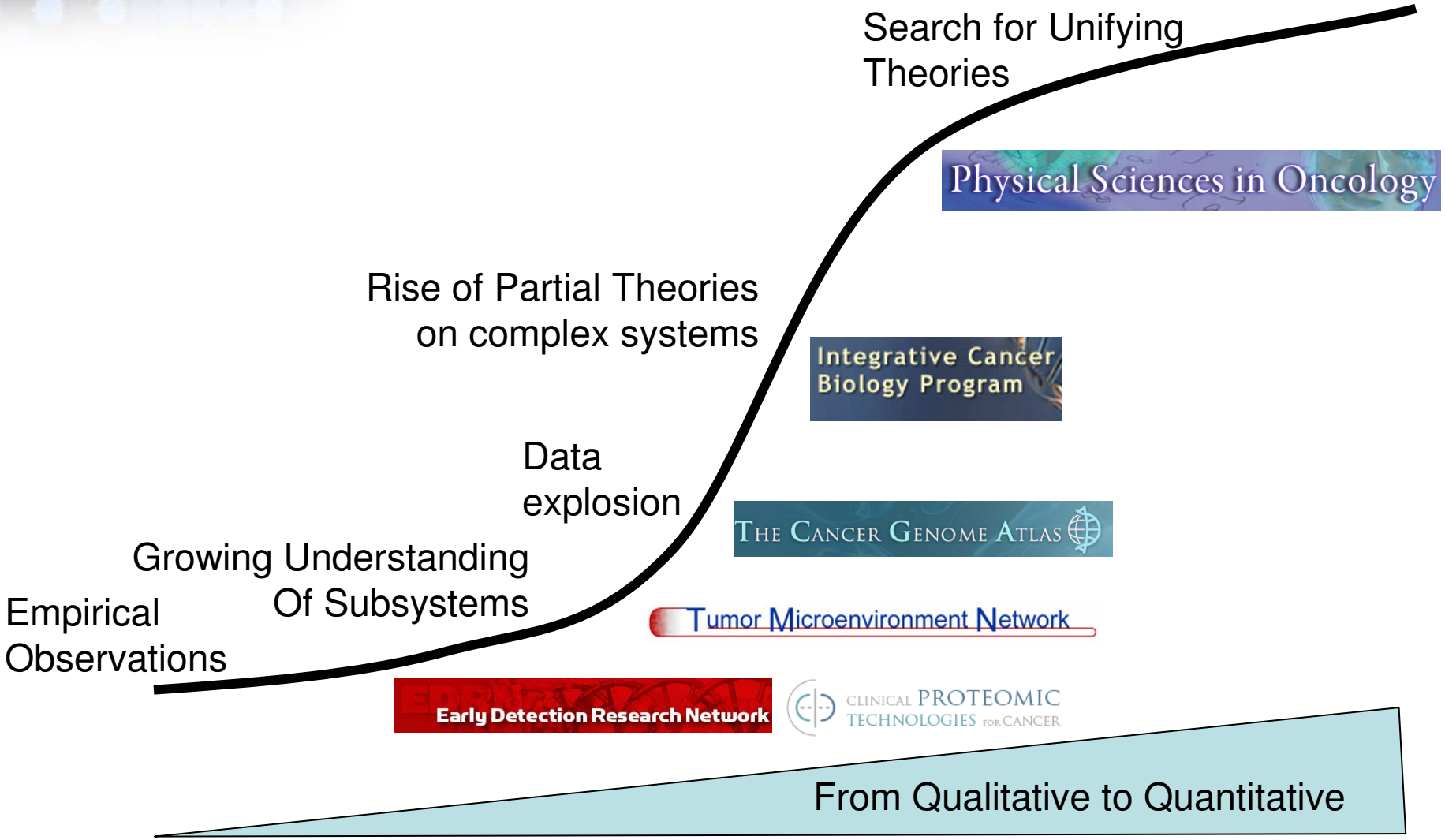
Some Observations

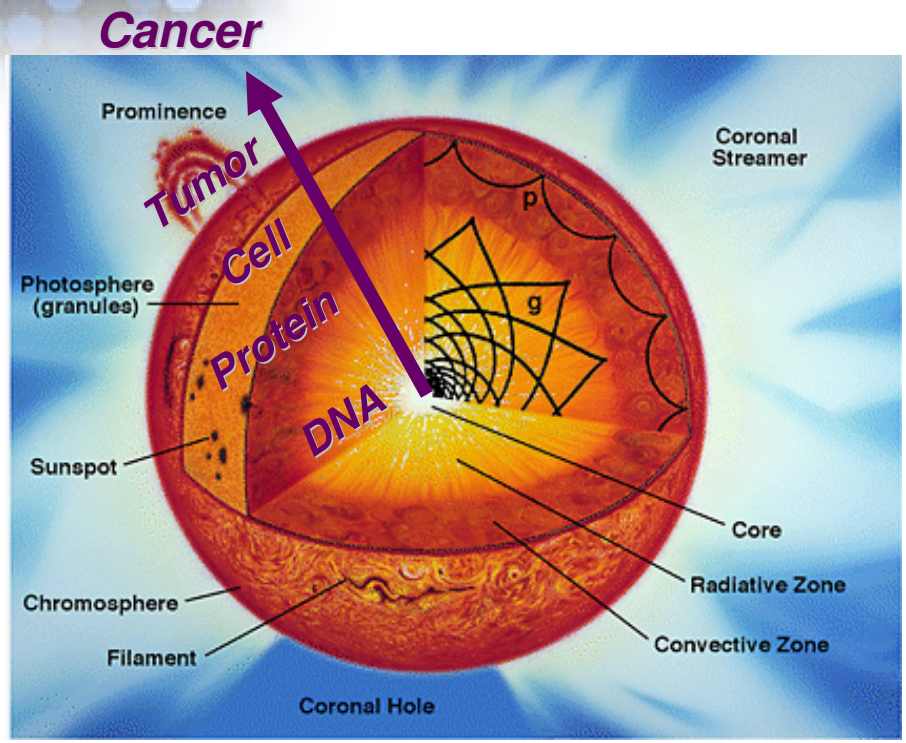
- Stunning advances in defining a wide range of changes in cancer vs. normal cells over the past decade – beginnings of pathway biology – signaling – microenvironment, etc.
- All of these discoveries and advances are pointing us toward a need to understand the physics of these highly complex systems…
- 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 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



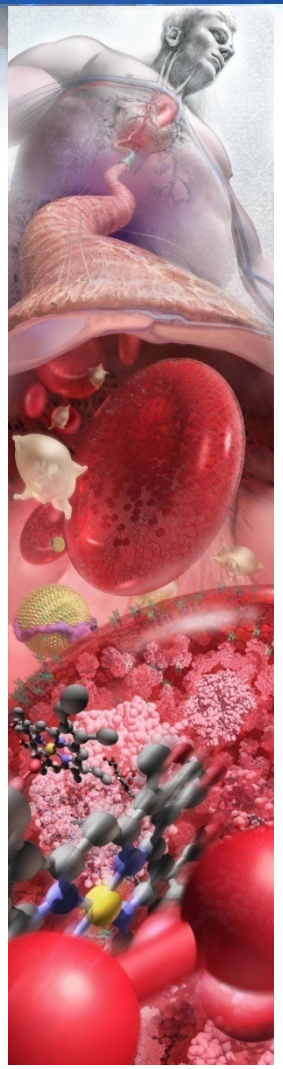
Physical Sciences and Cancer Biology– New Ideas New Directions – Comprehensive Understanding (An Interesting Example)



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

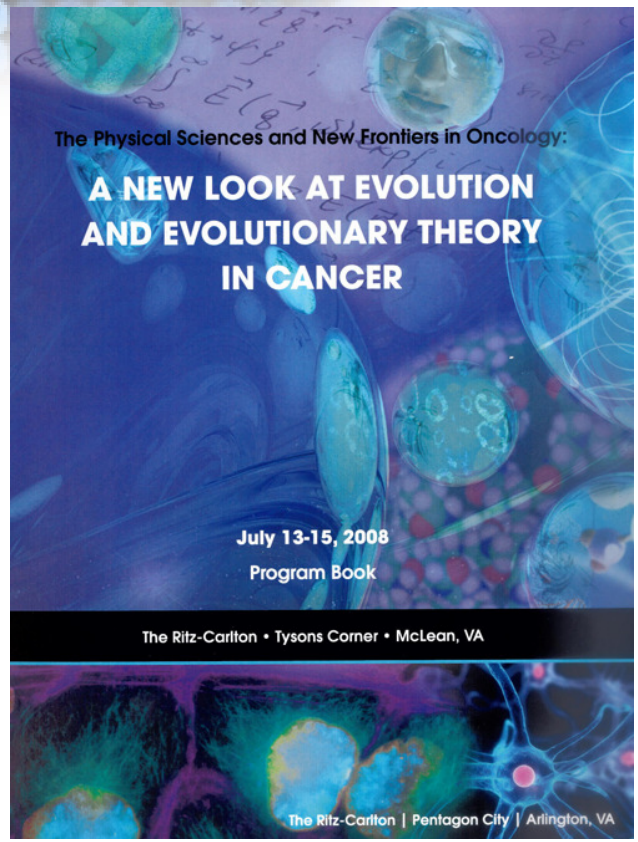
Consensus Scientific Themes

- 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

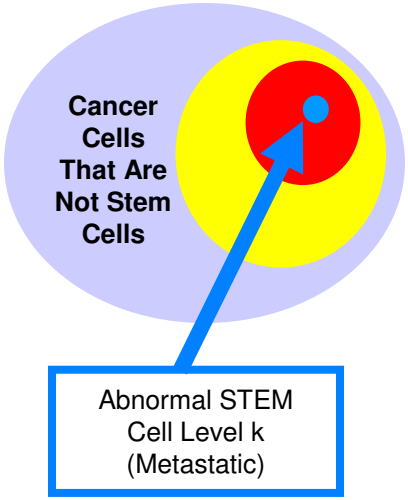
Recommendations

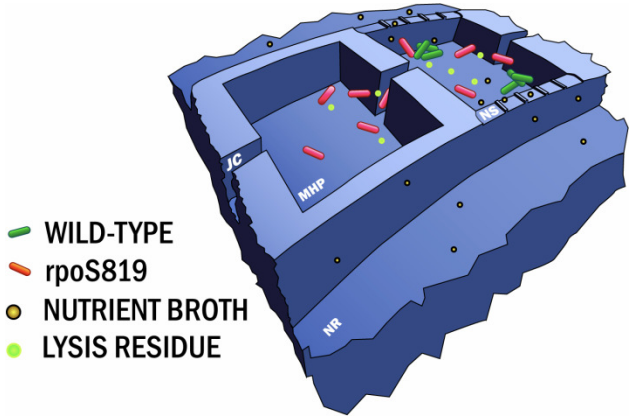
- Establish transdisciplinary physical sciences-oncology centers
- Composed of integrated physical sciences-oncology teams
- Focus on theme(s) for center framework
- Centers led by physicists with co-principal investigator from oncology

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



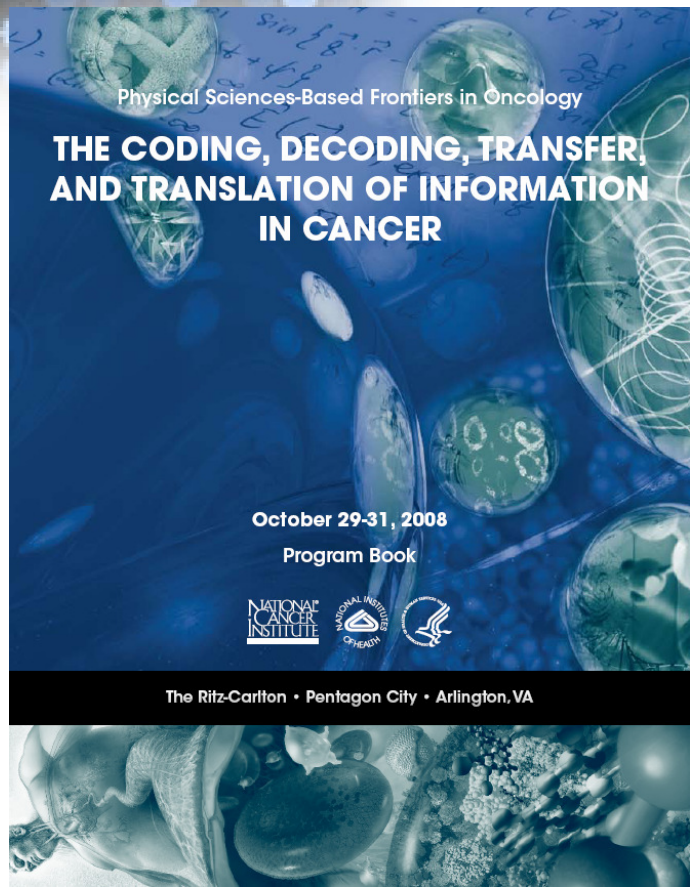


"Worldwide, no more than 15 percent of all cancers may be caused by viruses.

What causes the other 85%?"- 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

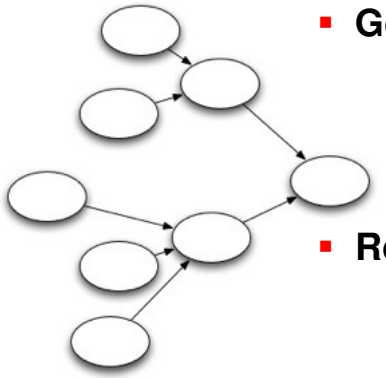


"I challenge you to tell me exactly what a gene is?" – Dr. Phillip A. Sharp

Think Tank Questions Posed:

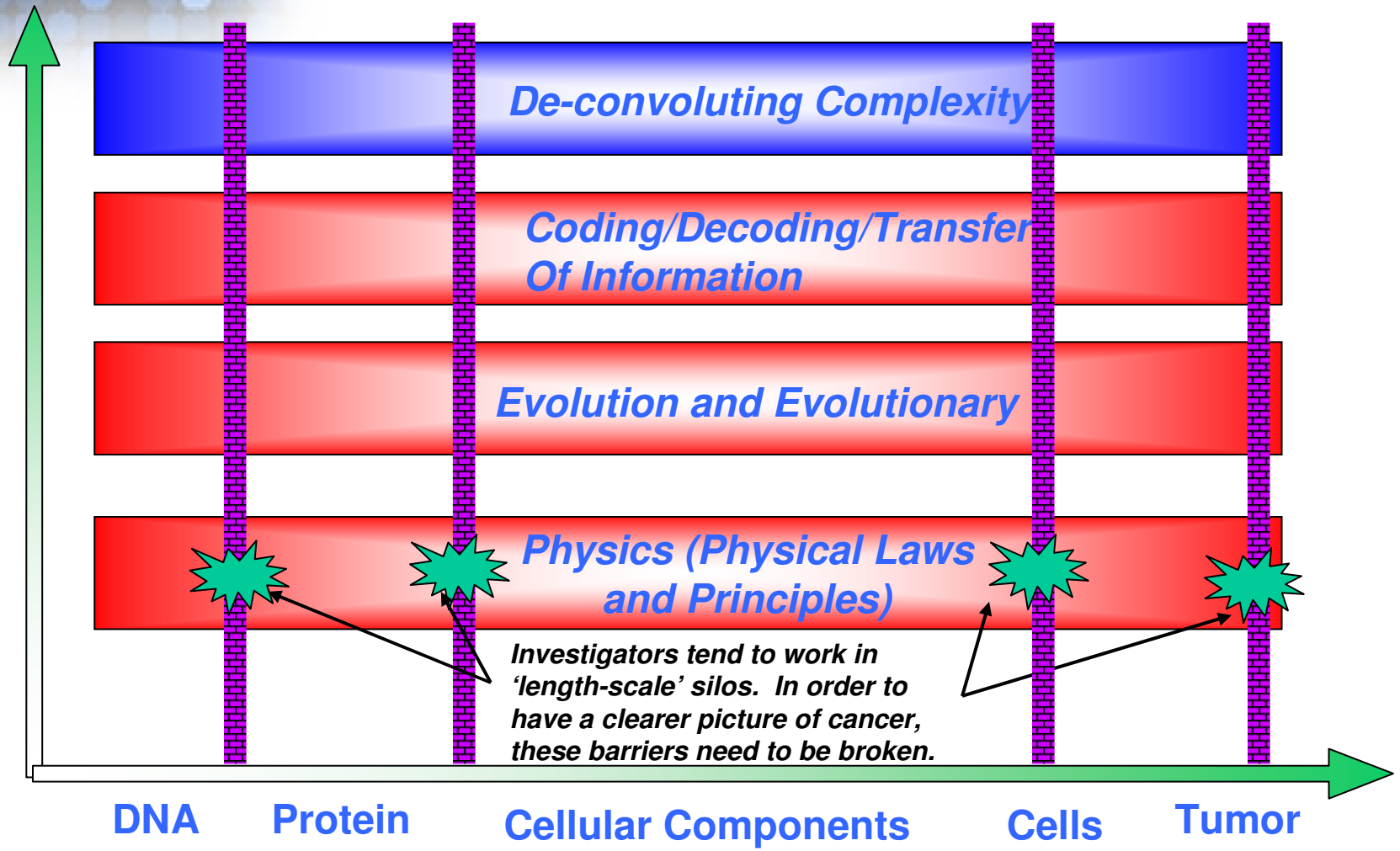
- What does "information" mean in terms of the genetic code and its translation in cancer relative to context and certain specific aspects that characterize cancer?
- What is the "state of the science" of information and information theory in terms of understanding of cancer at all scales?
- What are 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?

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



- **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

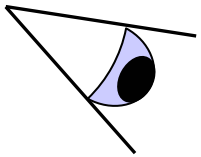
Summary of Theme Areas



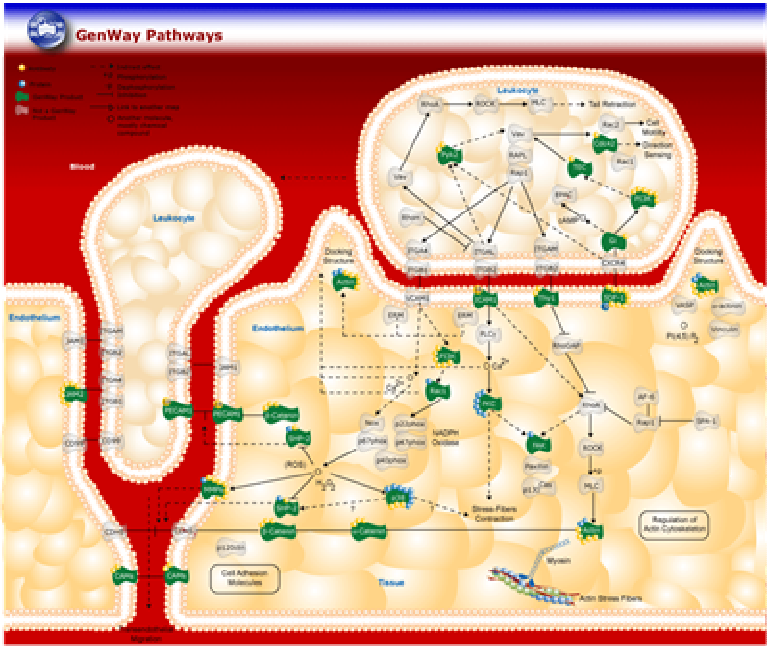
Length Scale – In Reference to Size (Ranging from 1 nm – 1 mm)

Comparing "Perspectives"

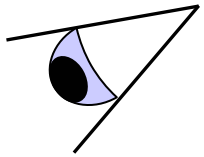
Physicist



- 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?

Different 'views' of the same picture

Having both 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

*"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 clues…It's like drinking from a fire hydrant…Don't be afraid of failure or bad ideas. Give it a try, take the risk…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. **Go for it—let's ride!**"- Elias Zerhouni, 2008*