National Cancer Institute

Physical Sciences-Oncology Centers (PS-OC) Think Tank

Integrating the PHYSICAL SCIENCES PERSPECTIVE to Open a New Frontier in Oncology

MEETING REPORT

February 6-8, 2012

Hyatt Regency Bethesda
Bethesda, Maryland

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Executive Summary

In February 2008, the National Cancer Institute (NCI) held the first of a series of three Think Tanks designed to explore how the fields of physics, mathematics, chemistry, and engineering could advance cancer research and clinical oncology by bringing fresh insights and new tools to some of the most challenging problems in cancer. Those workshops led to the creation of the Physical Sciences-Oncology Centers (PS-OC) program and the funding of 12 transdisciplinary Centers in September 2009. By all accounts, the PS-OC program has made strong progress in producing innovative research and has resulted in developments that are not only reshaping how we look at cancer as a disease, but also clinically relevant.

At the midpoint of this 5-year program the NCI convened another Think Tank in February 2012 to reflect on progress made and, more importantly, to identify additional aspects and problems in cancer biology and clinical oncology that would benefit from a physical sciences perspective. For this Think Tank, the NCI brought together a mix of current PS-OC investigators along with cancer biologists, clinicians, and physical scientists who have no involvement in the program. Over 2 days, the invited scientists listened to talks from thought leaders and heard the perspectives and advances of scientists working at the intersection of physical sciences and oncology. However, most of the time was spent brainstorming emerging areas and formulating questions that leverage a physical sciences perspective and would, if answered, greatly advance cancer research.

Throughout the meeting, three areas were highlighted as examples where the PS-OC Network has made significant progress in understanding cancer using a physical sciences perspective. The first was the progress made by researchers in applying computational physics approaches to facilitate advances and allow new insights into complex problems in cancer biology across time and length scales. For example, at the nanometer scale, scientists at the Massachusetts Institute of Technology PS-OC used approaches from polymer physics to mathematically model the 3D organization of the human genome and used this information to predict the distribution of somatic copy number alterations. The second area highlighted was work examining the evolutionary dynamics of cancer. At the Dana-Farber Cancer Institute PS-OC, mathematical models incorporating evolutionary dynamics have been used to design alternative chemotherapy schedules that could reduce the emergence of drug resistance. Additionally, new technologies being developed at the Cornell and Scripps PS-OCs to capture circulating tumor cells now offer the opportunity to repeatedly sample a tumor in a non-invasive manner and collect time course data that can help researchers, and potentially clinicians, more accurately follow the evolution of late-stage tumor progression. The third highlight was the role of mechanical forces in tumor development and progression. Presentations discussed a variety of forces and mechanical properties that have implications for understanding cancer including hydrostatic pressure, shear flow, tension, compressive force, stretching, and substrate rigidity. PS-OC supported research has contributed significantly to the progress in this emerging field. For instance, work at the University of California at Berkeley PS-OC has demonstrated how malignant cells can modify the stiffness of their environment by pulling on collagen fibers and promoting the formation of high-density bundles. Intriguingly, this effect allows cells to communicate over long distances (mm), and the ability of cells to remodel the extracellular matrix can create a persistent pro-tumorigenic environment.

In addition to highlighting recent progress, the Think Tank participants identified five directions for future research that could benefit greatly from integrating the physical sciences, mathematics, and engineering with cancer research:

- **Developing theoretical frameworks to understand cancer.** In comparison to the physical sciences, cancer research suffers from a lack of overarching theories that guide experimentation. Could a greater emphasis on theory allow us to understand and ultimately predict the emergent

properties of cancer? Further application of principles from computational physics as well as fields such as advanced high-performance computing, engineering, weather prediction, and other complex dynamical systems could dramatically move the field forward.

- **Exploring the links between cancer and other physiological systems from a physical sciences perspective.** Over the past decade, significant knowledge in other biological processes, such as development, tissue regeneration, and immunology, has been gained by using physical sciences perspectives. This work has, for example, demonstrated the importance of electrical, spatial, and mechanical properties in regulating these systems. Could insights drawn from applying the physical sciences in these other systems lead to breakthroughs in our understanding of cancer? For example, understanding the role of forces during embryogenesis could inform research into the role of forces in tumor progression. Incorporating physical science approaches from these fields into the PS-OC Network could increase the impact of this program.

- **Defining the state space of cancer.** Is cancer a dynamic system that can be described by a "state space" function – a set of parameters that can accurately describe the system at any instant? If so, what are the parameters – genetic, physical, metabolic, and others – that define these states and could this information be used to predict changes over time or characterize "phase transitions," such as from "normal" to malignant or from treatable to resistant? Thinking about cancer in these terms could lead to novel strategies to control the "phase transitions" that occur in cancer progression. Instead of seeking to kill cancer cells, could it be possible to drive neoplastic cells into benign or indolent states? Theoretical and analytical frameworks from the physical sciences, such as thermodynamics, will be fundamental to this effort.

- **Developing approaches to control the physical parameters and architecture of tumors.** Given the changes to the physical parameters of cells and the increased understanding of the role that mechanical forces, geometry, and topology play in the initiation and progression of cancer, could techniques or therapies that modulate physical parameters or target cells with specific physical properties help to combat cancer? Being able to target the physical properties of cells and the tumor microenvironment (e.g., stiffness, cell modulus, adhesion strength, pH) would draw on disciplines such as control theory, bioengineering, synthetic biology, and material science, and could open new therapeutic avenues.

- **Employing physical sciences perspectives for cancer diagnosis.** Throughout the Think Tank, several ideas for using physical sciences perspectives to develop novel methods to diagnose cancer were proposed. Measurements of physical properties such as elasticity, nuclear morphology, chromatin compaction, cell shape, tissue stiffness, and architecture have the potential to aid pathologists in more accurately detecting and staging cancers. Future research should focus on exploring the range of physical parameters that can be measured, developing the technologies to measure these factors noninvasively where possible, and identifying the measurements that can best detect cancer and predict disease outcomes.

The Think Tank discussions also emphasized the importance of the transdisciplinary nature of the PS-OC program's work. The ability to generate new ideas and perspectives through integrating the many disparate fields that make up physical sciences and oncology is dependent on the free exchange of ideas occurring across institutions and academic silos. Though great progress has been made, the meeting's participants emphasized that these interactions are at an early stage. Initiatives such as the PS-OC program are critical for the long-term convergence of the life and physical sciences, and the ability of scientists to pursue high risk-high reward projects that explore new fields of study.

Day 1: February 7, 2012

Welcome

Douglas Lowy, M.D., National Cancer Institute

In his introductory talk, Dr. Lowy noted that NCI has a history of holding Think Tanks, including a set of three that led to the creation of the Physical Sciences-Oncology Centers (PS-OC) program in 2008 and its funding in 2009. He remarked that because this program is young, he expects that the best is yet to come from this effort. He also expects that the perspectives generated by the PS-OC program are most likely to be transformative in basic cancer research, but that he would not be surprised if some of this work is applied in the clinic. Four areas of cancer research that lend themselves to a physical science orientation were cited: single cell analysis; three-dimensional systems; tumor cell/microenvironment interactions; and biomechanical forces, hypoxia, and other external factors that can be manipulated in a rigorous manner.

Dr. Lowy then discussed a few issues that NCI and the PS-OC program still need to settle. Should the program, for example, focus on one or two overarching themes or a range of questions? His opinion was that there are a range of questions that need addressing with a physical science perspective. Is the PS-OC network functioning well and what should its role be in terms of catalyzing new collaborations and sharing information with the larger research community? Is it most productive to pair a physical science principal investigator with a senior investigator, or is there a different model that might better ensure bidirectional influences between the physical sciences and oncology communities? In particular, it is important for the physical sciences perspective to influence the senior investigator's work, not just for the senior investigator to make sure that the principal investigator's research stays focused on cancer problems.

The relationship between the physical sciences and NCI is not limited to the PS-OC initiative. NCI's Provocative Questions request for applications (RFA) has several items that could take enormous advantage of a physical science approach. In addition, NCI will issue an omnibus R21 RFA later this year that would welcome applications from the physical sciences community.

Orientation

Robert Mittman, M.S. M.P.P., Facilitation, Foresight, Strategy

To set the stage for the Think Tank, the moderator explained that the purpose of the meeting was to formulate recommendations to the Office of Physical Sciences-Oncology (OPSO) on future directions for the Office's research programs, including the PS-OC program. These recommendations could identify new domains of work that might emerge and that might bring new investigators into this effort.

The agenda for the Think Tank called for a series of discussions that would weave together two broad topics. The first part of the agenda, encompassing a set of presentations and panels, was meant to provide background and generate discussion on some of the work that has been done by the PS-OC network. The second part of the agenda then called for the participants to provide input on a research agenda that is based on bringing a physical sciences perspective to problems in cancer research. The style of the meeting was such that formal remarks would be kept to a minimum and conversations and discussions would be the main venue for generating new ideas and research questions.

Opening Roundtable

The Think Tank participants were seated at tables in small groups and were asked to introduce themselves to one another. They were then asked to discuss ideas for one or two problems that are amenable to a physical science perspective or that are now being tackled but would not have been without a physical science approach. The list of ideas that the participants generated included:

- Explore the relationship between evolution, stress, and cancer and develop testable models that encompass the phenotypic changes and responses to therapy observed in cancer.
- Understand differentiation and organization of tissues and how cancer cells integrate into and disrupt the overall architecture of a tissue.
- Develop new tools that can generate novel ways of thinking about data and how to approach the major challenges in cancer.
- Apply semiconductor science to oncology.
- Bring mathematical models to cancer and new approaches to generate data in order to develop and test models; without data, there is no value to a model.
- Create new theoretical frameworks and new tools to test frameworks that result from new bi-directional collaborations between modelers and experimentalists.
- Characterize the three-dimensional organization of chromatin in normal, proliferating, and malignant cells and the role this plays in the progression of cancer.
- Identify factors in the microenvironment that allow cancer cells to develop.
- Catalog the physical properties of a cell that play a role in tumor progression.
- Use the multiscale approach of physics to determine which details of cancer are truly important when trying to understand this disease and develop treatments for it.
- Determine the extent of diversity in tumors at the genomic and transcriptional levels.
- Construct models of drug delivery, intravasation, and action that account for the physical barriers that prevent drugs from reaching their targets.

In addition to these suggestions, the participants made a few general comments worth noting. One participant said that this effort is not just about the physical sciences, but must include mathematics and engineering. Another said that the proximity of researchers involved in team science plays an important role in determining the scientific impact of the resulting papers generated by the team. This idea was countered by a participant who noted that the impact of this network has been amplified by the persistent handshake across institutions, as well as across intellectual silos, and remarked on the large number of productive multi-institutional collaborations that have developed over the short lifetime of the PS-OC program. Several participants remarked that developing tools apart from developing informatics methodology and models will not generate the breakthroughs needed to advance cancer research. This was followed by a comment that the PS-OC network needs to remember the patient, and to focus the knowledge and skills of this multidisciplinary collection of investigators on the development of new treatments for cancer.

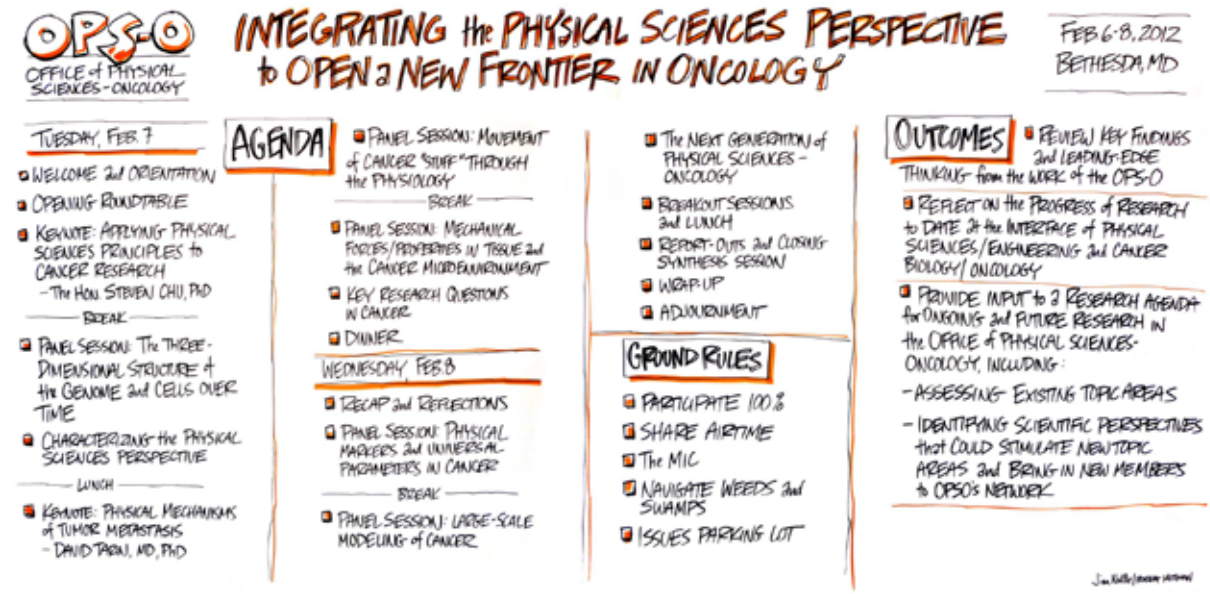

Figure 1: The agenda, ground rules, and expectations for the Office of Physical Sciences-Oncology Think Tank.

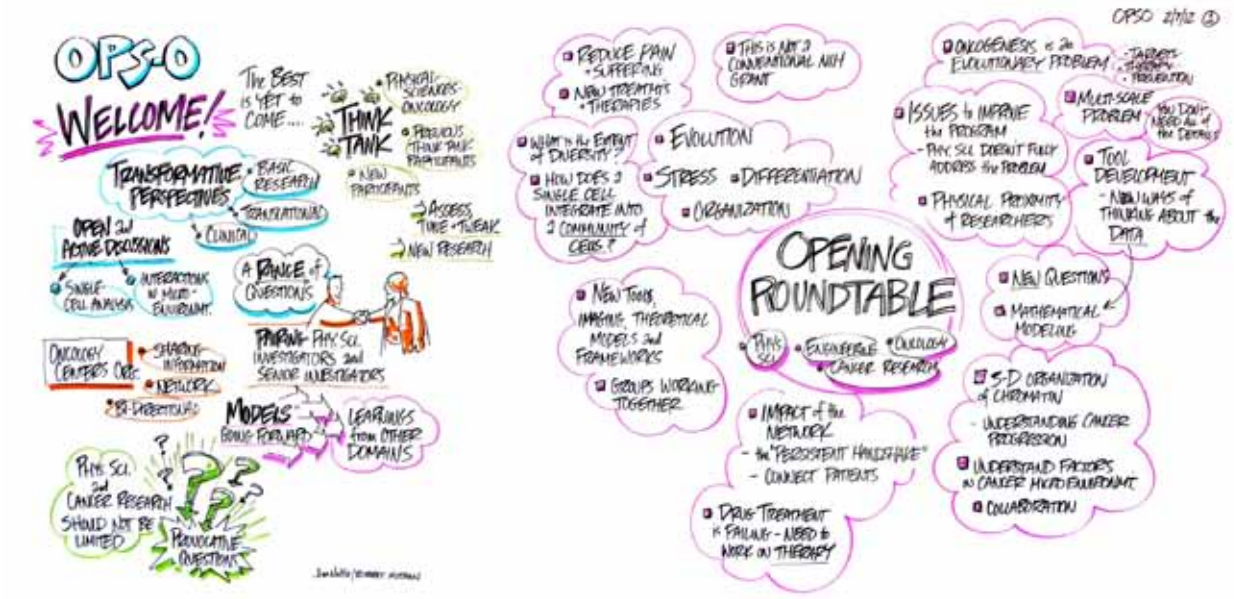

Figure 2: The welcome to the Think Tank and the summary of ideas generated from the Opening Roundtable exercise.

Keynote Address: Applying Physical Sciences Principles to Cancer Research
The Honorable Stephen Chu, Ph.D., Secretary, U.S. Department of Energy

In his introduction to the keynote address, NCI Director Harold Varmus, M.D., noted that Secretary Chu's work using optical tweezers to hold down the ends of actin and myosin was his introduction to the role that physics could play in biology. He also noted that Dr. Chu was slated to be a principal investigator of one of the PS-OCs before President Obama selected him to be Secretary of Energy.

To start his talk, Secretary Chu listed a number of detection and imaging methods, developed by physicists, that have allowed great advances in medicine and biomedical research. He then described the work that his group has done on developing sub-wavelength imaging of multiple probes. Through their efforts, he and his collaborators have reduced the limit of resolution from about 250 nanometers (nm) to 10 nm and have evidence suggesting that it will be possible to reduce the resolution limit even further. He described how the technique was developed and then described how his group is using its super-resolution imaging method to study RTK/Ras signaling at the cell membrane. Nanometer imaging showed that the molecule cRAF is distributed freely in the cytoplasm, exhibits low membrane binding, and does not tend to cluster in the cytoplasm. However, when activated by mutant Ras – a key event in triggering some cancers – cRAF binds strongly to the cell membrane and predominantly forms dimers and occasionally trimers.

Secretary Chu described a number of experiments that his colleagues conducted to tease out more of the details of the role that Ras-triggered dimerization plays in Ras/RAF/MEK/ERK signaling, and he also showed how these observations can be used in drug screening efforts. Two potential anticancer agents were added to cultured cells and imaged using super-resolution imaging. The resulting images clearly showed that the two drugs both triggered some cRAF dimerization, an unexpected – and undesired – effect. He remarked that a physical science-based tool designed to study basic cellular processes was capable of spotting an unintended consequence that bodes ill for the safety of either of these drugs.

He then briefly described biofilm imaging studies that aim to understand how these biofilms form. His group is using confocal microscopy, with multicolor imaging, to visualize single cells growing to mature biofilms and generate three-dimensional architectural images of the biofilms as they develop. These super-resolution images are capable of tracking the distribution of tagged proteins at the cell-surface interface and distinctly identify founder and daughter cells.

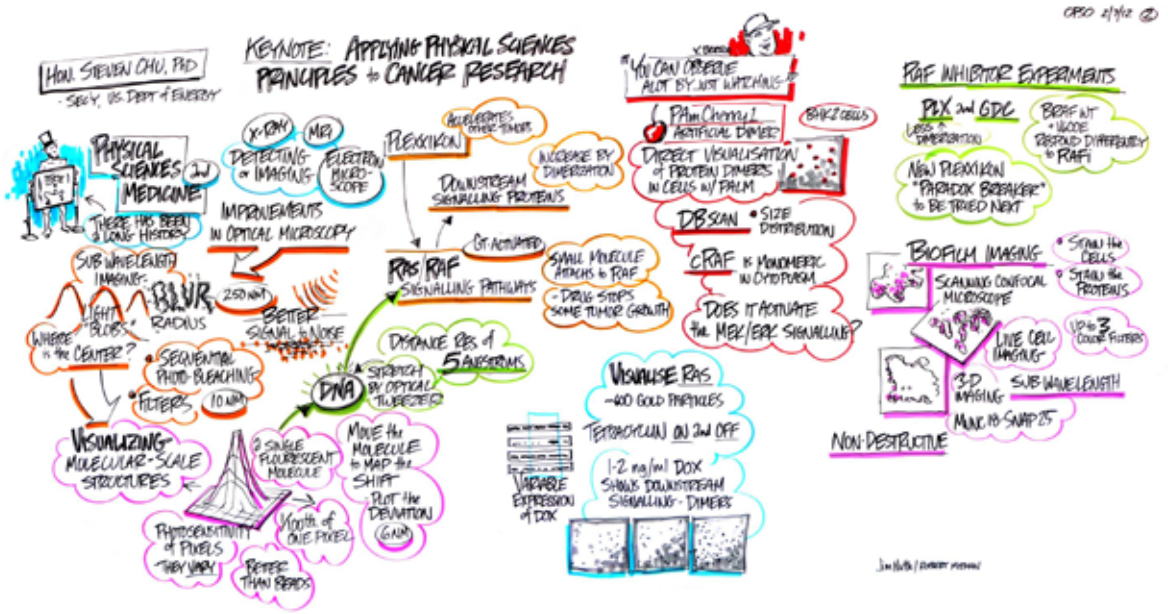

Figure 3: The graphic record of the Keynote Address "Applying Physical Sciences Principles to Cancer Research" by The Honorable Stephen Chu, Ph.D., Secretary, U.S. Department of Energy.

Panel Session: The Three-Dimensional Structure of the Genome and Cells Over Time

Panelists: ***Franziska Michor, Ph.D., Dana-Farber Cancer Institute***
Leonid Mirny, Ph.D., Massachusetts Institute of Technology
Lin Chen, Ph.D., University of Southern California
Tom Misteli, Ph.D., NCI
Alexander van Oudenaarden, Ph.D., Massachusetts Institute of Technology

Dr. Michor began the short presentations by noting that there are now many technologies available to look at the three-dimensional organization of the genome. This higher order organization of the genome is critical for many biological processes and may contribute to the generation of breakpoints seen so frequently in the genomes of malignant cells. Her group has used data from one of these technologies – the Hi-C technique, data which were generated by Dr. Mirny and his colleagues – to study the relationship between long-range interactions and breakpoint mutations. This comparison found that genomic regions with the same replication timing are likely to have long-range interactions between them that are predictive of the occurrence of breakpoint mutations. Her team then used an independent dataset – The Cancer Genome Atlas (TCGA) ovarian cancer data – to predict sites of amplifications and deletions, and were able to predict about half of these sites. She noted that those not predicted by this model must be occurring for other reasons and examining those sites should prove interesting.

What actually causes a break in those regions of the genome that come in close proximity to one another? To answer that question, Dr. Michor's group examined genomic data and found that the secondary feature most strongly associated with breakpoint mutations is a G-quadruplex (G4) structure. This secondary structure is only found in regions that are hypomethylated. She proposed a model that might explain how stochastic differential methylation in individual cells, common during aging and in some types of cancer, would create a local environment favorable to the formation of mutagenic G4 structures.

Dr. Mirny presented work from his laboratory that employed a computational physics approach to determining the three-dimensional architecture of the genome. Using mathematical techniques developed by polymer physicists, Dr. Mirny and colleagues modeled the genome as a fractal globule. This analysis posits that there is a non-equilibrium rapid collapse of a polymer chain that eventually equilibrates into an energetically favorable three-dimensional organization. Their work found that the global organization of the genome is consistent with the fractal globule model and that the distribution of loops and contact points in chromosome structure predicts copy-number alterations. Compared to models based on a uniform distribution or the Hi-C dataset, the fractal globule model most closely predicted the length distribution of copy number alterations. This was further enhanced by incorporating the idea of purifying selection. This is based on the negative correlation between the length of a region affected by a copy number alteration and cell fitness. Finally, Dr. Mirny said that this model, developed using a biophysical approach to genomic data, suggests that passenger alterations are not mere bystanders in cancer but appear to contribute to copy-number alterations through their effect on three-dimensional organization.

Dr. Chen then spoke of his group's interest in studying higher order transcription complexes. His team is exploring the finding that many transcription factors, especially those implicated in lineage control during cellular differentiation, can bind two DNA molecules in parallel and influence the three-dimensional structure of the chromosome in a way that controls epigenetic expression patterns. To test this hypothesis, his group developed a new technique, called tethered conformation capture, that measures the binary contacts between genomic loci throughout the genome in a way that improves the signal-to-noise ratio of information generated by techniques such as Hi-C. Data generated using tethered conformation capture suggest that the chromosome is organized in domains much like protein domains, and that these domains can be used to model the three-dimensional structure of the chromosome. Population-based modeling

and statistical analysis of the structural features of the human genome are revealing that certain of these domains account for the majority of interchromosomal interactions and that these are regions of high transcriptional activity.

In his comments, Dr. Misteli said that looking at higher order genome structure is a natural thing to do in the cancer area given that so little is known about various levels of organizational order. Three-dimensional organization, however, is a fundamental physical property of the molecule, DNA, that everyone is studying. It is clear that changing chromosomal organization affects all sorts of processes that alter protein landscapes, and that putting a gene in a different physical environment in the nucleus causes it to change behavior. One interesting observation, he noted, is that there are a number of diseases involving laminin mutations, suggesting that nuclear structure is important in genome function. He then remarked that only recently research has shown clearly that higher order genome organization is important, because previously most evidence was anecdotal. Today, however, with the technologies available to physically map higher order genome structure in three dimensions, it is important to think about which questions are important to answer. He nominated three:

- What physical property of the genome should the field examine?
- What do these properties mean in terms of genome function and expression?
- How can an understanding of the physical properties and function be applied in the clinic?

In the last of the panelist presentations, Dr. van Oudenaarden changed topics and spoke about the models that his group has been developing to explain how a single stem cell can produce a functional intestinal crypt. This is an attempt, he said, to determine whether general physical principles guide the development of a single stem cell to an organ. He explained that a stem cell can do three things: it can divide and create two stem cells, it can divide and create differentiated cells, and it can divide and produce a stem cell and a differentiated cell. From these three possibilities, it is possible to create an infinite number of lineage trees and determine which one or more would yield a strategy to develop into an organ.

At birth, the mouse intestine is lined with functional villi but lacks the crypts needed to absorb nutrients from mother's milk. To survive, the mouse needs to generate crypts quickly, and so the lineage tree must be optimized to do this as fast as possible. Finding the optimal tree is a mathematical problem that his group solved analytically. It turns out only two variables that describe this system – cell division rate and death rate. There are only two solutions, one in which all divisions are symmetric to a point followed by a switch to all asymmetric division, and vice versa. He calls these two options "bang-bang control," and they are based on optimal feedback used in control theory. Using technology his group developed that measures single-molecule expression in individual cells to track cell lineage, his group was able to confirm the model's prediction and confirm that the first of the two possibilities did in fact occur in the maturing intestine. Very small crypts show almost all symmetric division to produce more stem cells followed by a sudden switch to asymmetric division when the crypts reach a certain size. He noted in closing that this work was only possible because of collaborations that occurred though the PS-OC network.

Discussion

Secretary Chu opened the discussion by wondering if it would be possible, given the high viscosity of a live cell, to use the same techniques that his group has developed as a means of imaging single protein molecules interacting with these higher DNA structures. Both Dr. Misteli and Dr. Chen thought this to be a great idea that could provide very useful information that could be used to develop dynamic rather than static models of chromosome structure and explore how the dynamic three-dimensional structure of the chromosome affects biology. A member of the audience commented that approaches are now available for measuring chromosomal motion at 10 nm to 50 nm resolution.

A participant commented that it would be useful to see three-dimensional structural information

in a live cell while the genome is reorganizing. Secretary Chu remarked that his group can now label histones and may be able to image unpacking and repacking of chromatin in live cells. Dr. Mirny said that seeing chromatin is not a problem, but what is needed is the ability to watch what happens to specific genes, as well as large but limited numbers of genes, as the chromosome packs and unpacks. This is where tool development is needed because the models are now ready to be tested with this type of data.

Dr. van Oudenaarden was asked whether his methods could be applied to modeling and tracking cancer stem cell lineages, and if so, what was needed from the cancer community to make such studies possible. He replied that these methods are broadly applicable, and all that is required are specific cancer stem cell markers that could be fluorescently labeled. Dr. Michor wondered whether it would be possible to do this kind of study with brain tumors since there are some markers available. A participant added that clinical data show that there are both inappropriate expression of stem cell markers in malignant cells and suppression of markers for stem cells in normal cells.

An audience member then commented that the bang-bang control mechanism Dr. van Oudenaarden's group identified is also an optimal strategy for maintaining telomere length. That would be a testable hypothesis, replied Dr. van Oudenaarden, adding that his group has the tools to conduct the experiments that would confirm that idea.

Before concluding this session, the panelists were asked to comment on the most pressing need in the field. Dr. Chen nominated developing new techniques for determining three-dimensional structure of the genomes and computational methods to get information about the dynamics of chromosome organization. It would then be possible, he said, to combine these technologies with chemical probes to get information on the fine structure of the chromosome in three dimensions. Dr. Misteli seconded these suggestions, saying that tools are needed to probe and manipulate chromosomal structures in order to get temporal information and generate testable hypotheses.

Dr. van Oudenaarden said that the field needs technologies that can look at hundreds of genes in single cells. Population averages are interesting, he said, but it is clear now that getting information from single cells is more important. Along the same lines, Dr. Mirny remarked that the field needs a fusion of single cell level imaging techniques with techniques for imaging a large number of cells to get a better picture of the

Figure 4: The graphical record of the panel presentations and discussion on "The Three-Dimensional Structure of the Genome and Cells Over Time."

distribution of specific states across populations of cells, rather than just averages. He added that tools are also needed to understand higher level principles of organization with modeling. Dr. Michor noted that before going to single-cell high-resolution imaging, there is a great deal we could learn if the multiple laboratories would conduct a variety of measurements on the same tumor samples. The information gleaned from such a dataset could then be used to better inform single-cell studies. She noted that a PS-OC Trans-Network Project will begin such a study shortly.

In a final remark, Secretary Chu said that he sees this effort to combine data from multiple scales as very promising. He noted that the field has assembled many pieces of the puzzle and that there is now the opportunity to combine these pieces with new technologies to make very important insights that could have profound clinical implications.

Characterizing the Physical Sciences Perspective

A Facilitated Discussion

The Think Tank next moved into a discussion that aimed to characterize what a "physical sciences perspective" means and how that perspective integrates with the field of cancer biology. To start the discussion Jan Liphardt, Ph.D., principal investigator of the University of California, Berkeley PS-OC, was asked to explain what he meant when he once used the phrase "PS-OCness" in a talk. Dr. Liphardt replied that there are many things that feed into a physical sciences perspective, including an emphasis on measurement, on measuring multiple things, and on making multiple measurements simultaneously as a means of making correlations and drawing cause and effect relationships. A physical sciences perspective also includes the desire to discern fundamental principles. A participant added that the physical sciences perspective is a problem-driven approach that provides a means to an end, a way of solving an identified problem.

Following that remark, there were several comments about the state of modeling in regard to cancer. One participant noted that modeling and theory lag in the cancer area, particularly across scales that move away from a thermodynamic perspective to one that is not thermodynamic. The issue is not just one of modeling across time scales, but in accounting for the fact that the systems that interest the cancer community are often systems in higher energy states that are dynamic and lie far from equilibrium. Understanding and modeling such systems is the real challenge.

That comment prompted another participant to argue that the physics needed to address biological systems is a different physics. Traditionally, physicists take complexity and make it simple. In biology, models need to take complexity into account and incorporate that into the physics to create a new formalism for systems far from equilibrium. This community needs non-equilibrium models because at equilibrium a living system is dead, and classical thermodynamics describes dead things. Fortunately, as one participant pointed out, there are areas of physics that now look at complex adaptive systems and that develop theory for examining far-from equilibrium systems. Another participant added that the field should not underestimate the power of what 21st century physics can do to look at these systems across multilevel scales.

Albert Einstein, it was noted, said that the point of physics is to make things as simple as possible, but not any more simple. In biology, the situation is reversed: biology needs complexity, but just enough complexity. What a physical sciences perspective can bring to this problem is identifying the sufficient number of key factors that capture the complexity of the cancer system. A participant added that it is also important to understand diversity as well as complexity, particularly in the area of cancer. Again, there are techniques from physics to approach complexity and diversity, particularly in the area of information theory but also from the perspective of entropy, that the community could apply to cancer.

On the issue of complexity, a participant said that everyone agrees there is a great deal of complexity in these systems, but the real question to ask is how much detail is really needed to understand cancer.

Discussion on this point brought out the idea that multiscale approaches may be able to represent cancer in models that do not end up being as complex as the system being studied. In fact, there comes a place where there are too many parameters in a model and it becomes so complex that nobody can understand what the model is doing and what its output means. When a model becomes non-intuitive, it has probably exceeded the balance between simplicity and complexity. There is a sweet spot in the level of complexity to incorporate in a model that is understandable, perhaps in the 5 to 20 parameter range.

Models in the absence of data are not very useful, according to the tenor of the remarks that followed. One of the strengths of the PS-OC network, according to several participants, is that it uses tools from the physical sciences to generate the kind of data needed to initialize and define boundary conditions for models. One participant noted that while there is a wealth of data on molecular biology signaling pathways, there are very little data on physical parameters. Biologists typically have not been interested in studying parameters such as the viscoelastic properties of the interior of the cell or the diffusion rate of specific proteins and the number of molecules of those proteins in a variety of cell types. This is where the PS-OCs have been valuable because they are now generating this kind of data, but the modeling community needs more of it. Unfortunately, few researchers want to make these kinds of measurements and funding agencies are not enthusiastic about funding these studies. This is a strength of the PS-OC network but the field needs to excite more experimentalists, said one participant.

Continuing on the theme of modeling, it was noted that models are needed to explain intracellular biomolecular trafficking within a cell. Many processes depend on that very basic "hardware" of the cell, and models are needed to explore the role of diffusion versus active transport of proteins through the cell. Models are also needed that can apply to the bigger issues of the patient, but the cancer community still does a poor job of meeting patient needs. A better understanding of the patient, said one participant, would translate into clinical trials needing a smaller number of patients and a reduction in the apparent stochasticity that so confounds researchers and clinicians alike. Models are needed that can span multiple scales, from what is going on in a single cell or a tumor, up to the whole patient, and then provide new knowledge about the specific patient being treated.

A participant remarked that modeling must be done in context. Pathways are not isolated, but researchers rarely consider them in the larger complexity of the cell and the organism and that is why pathway-targeted drugs fail. These drugs are doing what they are supposed to do, but current models that biologists have created for specific signaling pathways do not account for cells that respond to perturbations in the targeted pathway. Models need to account for how the cells evolve and adapt when a given pathway is altered.

A participant who is a surgical oncologist and not a member of a PS-OC said that the PS-OC network provides the field with the opportunity to understand the physical characteristics of what is going on in the patient as well as the properties of the tumor itself and stroma. Another participant noted that clinical trials generate a wealth of data on patient response, genomics, and other patient characteristics. While far from complete, these data could be used to create models that might start connecting with models at smaller scales. However, aside from a few efforts such as the PS-OC program, there are few links between the clinical communities and the physical sciences community, so this opportunity is being lost.

The discussion then turned to the role of evolution in cancer and the failure to account for evolution in the design of treatments for cancer. Physics ignores evolution, said one participant, and the current approach of measuring everything and creating models that do not account for evolution will continue to fail to solve the problem just as current approaches to therapy fail. The question that is missing from the discussion is "why is cancer doing what it is doing?" That is an evolutionary question.

While not disagreeing with this comment completely, a participant said that there are investigators making progress in understanding how evolutionary principles and processes apply to cancer and how to apply that to treatment. Applying these principles could enable researchers to distinguish between chemotherapies that are successful and those that are not. However, said another participant, the bad news is that people don't understand how evolution works. The participant quoted Theodosius Dobzhansky, who wrote that nothing in biology makes sense except in the light of evolution, and yet biology is being viewed through evolutionary theory that has not itself evolved since the 1930s and does stand up in the face of evidence from modern molecular biology. In other words, not only must evolutionary theory be taken into account, we need to incorporate the latest developments in evolutionary theory, not just what was known 80 years ago. For example, she said, several research groups have discovered pathways whereby cells under stress turn up their ability to evolve, and this is not something that evolutionary biologists by and large consider as a possibility or account for. But what these new datasets show is that chemotherapy is destined to fail the way it is now used. Antiproliferative agents will fail – cancer therapy needs anti-evolution drugs. Another participant added that the variability of tumor cells and the link with evolution are what dooms the field to continued failure if it does not start adopting radically new approaches to therapy of the type that this PS-OC network could help develop by bringing new ideas to the field.

There is little doubt, said another participant, that anyone who studies cancer sees evolution play out when they examine populations of individual cells before, during, and after treatment. Clearly, therapies are removing certain populations and they are allowing others to emerge. The field lacks tools that would enable researchers and clinicians to follow these changes in patients in a way that allows for both the exploration of new ideas based on evolution and the development of new therapies or therapeutic regimens. This type of approach is how the field will get to the "so what" question of relating biology to therapy to outcome.

Participants commented on a few other subjects. One remarked that too much work in cancer biology is done in two dimensions, and so it is important that the PS-OC network continue its effort at developing three-dimensional systems and models that take into account the entire tumor and its environment. The PS-OCs should also work on developing approaches to studying cancers in vivo, rather than in vitro, over time in order to better understand the dynamics of cancer and to provide data that would feed into both computational and animal models.

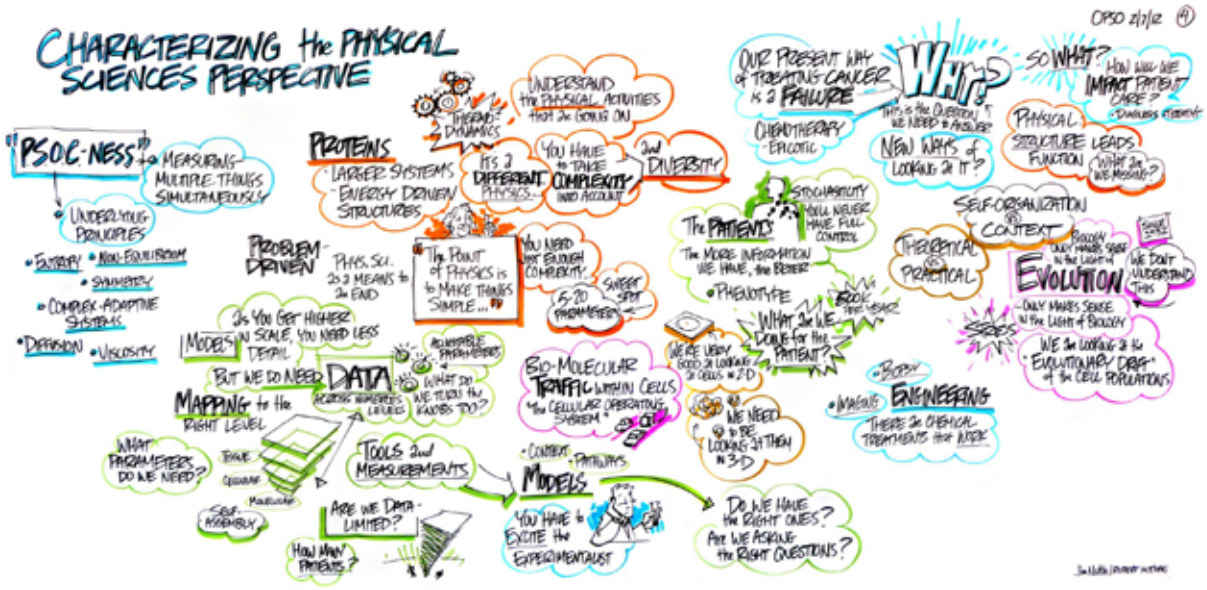

Figure 5: The graphical record of the facilitated discussion "Characterizing the Physical Sciences Perspective."

In wrapping up this discussion, Larry Nagahara, Ph.D., OPSO Director, remarked that while getting more data is certainly important, this program is not primarily about data, per se, but about thinking of new approaches to looking at cancer, and developing new perspectives that can ultimately improve the diagnosis, treatment, and prevention of cancer. The role of the PS-OCs is not to go deeper down the hole of more detail, but to think about cancer from a new perspective and the data needed to test the hypotheses that come from those new ways of looking at cancer. He acknowledged that there is the impulse to match the successes of physics in terms of bringing the techniques and tools for making better measurements to biology and oncology, but the focus still needs to be at the higher level contextual questions and the perspective of the patient.

Keynote Address: Physical Mechanisms of Tumor Metastasis

David Tarin, M.D., Ph.D., University of California, San Diego

In the day's second keynote address, Dr. Tarin talked about his perspective on the messy reality of tumors. To start with, tumors are messy things living in a messy, hostile environment, a different situation from tumor cells studied in isolation. When cells exit from the tumor they face an even more hostile environment. But before they exit, the interactions of tumor cells with each other and between tumor cells and the stroma change drastically. These changes allow pathologists to make predictions about the fate of a tumor and the patient. He added that tumor cells do not know what awaits them when they leave the tumor. They cannot anticipate those conditions, and those conditions kill the vast majority of those cells. But it is the cells that escape, survive, and then settle and grow that kill patients.

The vascular and lymphatic anatomies are critically important to the dissemination of cancer, explained Dr. Tarin. When a cell exits the breast, for example, it can travel via the blood system or lymphatic system. The flow conditions in these two systems are vastly different. Lymphatic flow is driven by muscular movement and is relatively gentle. Blood flow is driven by a pump and the flow is very jet-like. Tumor cells that enter the venous system cells eventually reach the right ventricle of the heart and are subjected to enormous turbulence. Some cells manage to survive these very hostile conditions, but then they go to the left ventricle, via the lungs, where there is even more turbulence. The very few cells that survive this beating are then disseminated through the entire body within 15 minutes.

Dr. Tarin then recounted the results of a study with which he was fortunate to be associated involving patients with ovarian cancer who were accumulating ascites fluid in their abdomens. These patients were treated by installing a shunt that drained fluid from the abdomen into the jugular vein, which gave Dr. Tarin and his collaborators a chance to study tumor cell circulation in about 30 patients for over 3 years. There was great variability in the results, he said, but patients fell into three categories: one group of patients had no metastases at death other than in the peritoneum, a second group that had metastases in specific organs, and a third that had metastatic disease at the time of diagnosis increased metastases after the shunt was installed.

In the next phase of their project, Dr. Tarin's team implanted fluorescently labeled, non-metastatic human breast cancer cells in mice and found that while the cells spread widely and settled in tissues other than breast, the cells did not grow in those tissues. Surprisingly, though, these cells remained viable – they could be removed, implanted in the primary site, and produce a tumor. When this experiment was repeated with metastatic human breast tumor cells, metastases were found only in lymph nodes and lungs, but individual cells were found adhering to the outside of the liver and spleen. When those cells were isolated and implanted back into the breast, they would produce tumors and metastasize to lymph nodes and lung again. These results strongly support what has been termed the "seed and soil" hypothesis.

Dr. Tarin concluded his remarks by noting that while angiogenesis is important, there are many other interactions between tumor cells and normal host cells. The interactions between metastatic cells and normal cells are key to the spread of cancer, and so there is a great need to develop drugs that target this interface. However, developing those drugs requires an understanding of the biophysics between the metastatic and normal cells, and this is where the PS-OC community can play an important role.

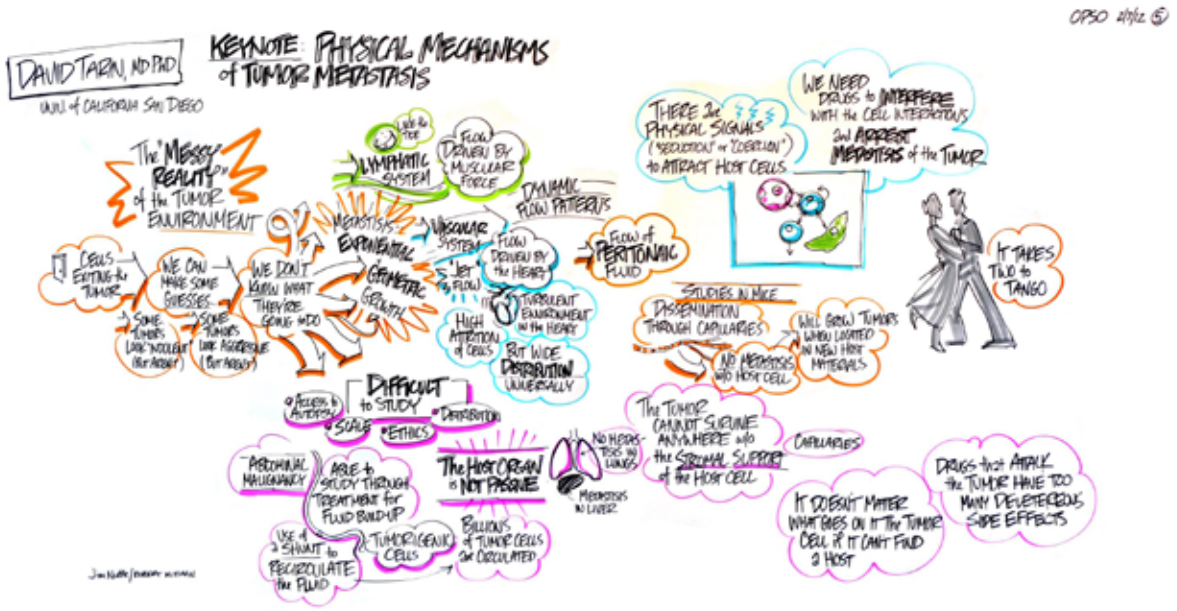

Figure 6: The graphical record of the Keynote Presentation by David Tarin, M.D., Ph.D. titled "Physical Mechanisms of Tumor Metastasis."

Panel Session: Movement of Cancer "Stuff" Through the Physiology

Panelists: ***Peter Kuhn, Ph.D., The Scripps Research Institute***
Rakesh Jain, Ph.D., Harvard University and Massachusetts General Hospital
Larry Norton, M.D., Memorial Sloan-Kettering Cancer Center
David Parkinson, M.D., Nodality, Inc.

Dr. Kuhn began this panel session by noting that hematogenous spread of cancer is the transition from curable to incurable disease. He also noted that 93% of early-stage breast cancer patients survive with surgery and adjuvant therapy, but that currently, it is not possible to identify the other 7% of patients until they develop metastatic disease at some unknown, unpredictable time. This is where physics should be able to help – by creating models that could predict this clinical outcome. It is important to remember, Dr. Kuhn said, that drug developers do a good job of creating drugs and that these drugs do what they are designed to do. The problem is that there is a deficit in understanding about which drug to give to which patient at what time, and also understanding what drugs really need to do in a particular patient at a particular time.

With this in mind, Dr. Kuhn introduced the topic of circulating tumor cells (CTCs), first discovered in 1868. He discussed some recent characterization of CTCs in which his group found that these cells clump and form what a pathologist said resembled primary tumors. He also explained that studies have shown that the number of CTCs in blood has prognostic value and can be an indicator of the emergence of drug resistance. Dr. Kuhn then discussed results from his PS-OC project aimed at mapping the dissemination of primary tumors in order to create a model that could account for the distinct patterns of secondary sites that are seen in metastatic disease. This network analysis of tumor dissemination classifies metastatic sites as sponges and spreaders, and that these are origin-dependent. In breast cancer, for example, the liver is a sponge, while the lung and bone are spreaders. For primary lung cancer, the liver is a sponge, while for primary colon cancer, the liver is a spreader. Dr. Kuhn concluded his remarks by noting that these metastatic network maps point to the importance of time as the missing dimension in how we use information to benefit patients. Oncologists, he said, have a large degree of intuition from clinical experience about the time development of disease in patients. The challenge is to use physics and mathematics to

quantify the dynamics of disease progression at the level of individual patients.

Dr. Jain focused his remarks on the tumor microenvironment and its influence on the development of cancer. The tumor is an organ, he said, and many of the components of this organ – not just the malignancy itself – are abnormal. His hypothesis is that alleviating the physical and biochemical abnormalities of the microenvironment of this organ will improve both the delivery and efficacy of many therapeutic agents.

As an engineer, Dr. Jain approached this problem by developing a model that could predict interstitial fluid pressure gradients in tumors, and this model proposed, long before experimental data existed, that the interstitial pressure would be higher in the center of the tumor than at the periphery. Experiments in mice using intravital microscopy demonstrated one of the consequences of this prediction: blood flow in the center of tumor was greatly restricted because the increased interstitial pressure was apparently clamping down on blood vessels there.

Support for Dr. Jain's overarching hypothesis has been obtained from clinical trials that found that patients with glioblastoma whose tumor blood flow increases after antiangiogenic therapy survive a year longer than those whose tumor blood flow decreases. In the patients who live longer, treatment is normalizing hypoxia and increasing pH in the interior of the tumor, and likely increasing the concentration of drugs reaching the interior of the tumor. Studies in animals found that there is a window of 5 to 6 days after antiangiogenic therapy during which time blood flow increases and chemotherapy or radiation therapy is more effective.

Rather than discuss experimental data, Dr. Norton said that he wanted to talk about philosophy. He recounted a story about a public presentation he gave in which he was asked "why is it not possible to detect all cancers early enough to prevent death? He replied that not only is it not possible, but that early detection does not guarantee successful outcomes. Although for some cancers, such as breast and colon cancer, early detection has great value, even then (as Dr. Kuhn pointed out) there are breast cancer patients whose disease is treated early but still die. What he wanted to argue for then, was that the field has to be careful about the things that everybody "knows." What are we missing because we see things through the lens of what everybody knows to be true but do not question? This, he said, is where bringing the unique perspectives of the physical sciences to the field of cancer is likely to produce real benefits. As an example, he showed a pixilated picture and noted how difficult it was to tell what the image showed until someone looked at the pixilated image in a different way. Once the new perspective was in place, everyone could make sense of the pixels and the underlying image became obvious.

We need to ask the question, he said, "What don't we know?" What are we not thinking of when we look at cancer? A good example of the consequences of neglecting to think about what we "know" is the work that Dr. Jain discussed on the failure of Avastin therapy. We can now see because of work from his group and others, that it is likely being used at the wrong time and with the wrong dosing schedule. The conventional wisdom was to give enough drug to shut down the blood supply to the tumor and starve it to death. Though that works for a while and patients do respond, ultimately Avastin and the other antiangiogenic drugs fail. The problem is that using too much of this drug triggers upregulation of other angiogenic mechanisms that may be more potent, and as Dr. Jain showed, there may be an optimal window in which to use this drug that is not part of clinical practice. The problem is not that this is a bad or ineffective drug, but rather that the conventional wisdom on how to use it is wrong.

Only through the use of engineering principles, mathematics, and physics, Dr. Norton said, will it be possible to develop the models needed to explain tumor growth and response to therapy that will enable the field to bring about meaningful advances in clinical outcomes. Without a mathematical, quantitative understanding of the processes involved in cancer, therapeutic development will still produce more misses than hits. The real challenge, then, is to develop a "Newtonian" theory of cancer, a simple mathematical understanding of tumor

growth so that it will be possible to design appropriate experiments and quantify the results in the same way that engineers quantify the results of their experiments.

In the last of the panel presentations, Dr. Parkinson explained that his perspective is that of a clinician who grew frustrated by the failures of clinical oncology and of a drug developer who grew frustrated by the fact that treating cancer using biologically targeted molecules was not leading to meaningful improvements in patient survival rates. The drug development industry is extraordinarily good at creating molecules that target specific pathways, but there is no good way to characterize signaling pathways at a single-cell level and use this approach to provide the tools that can say why a given drug does or does not work at the level of an individual patient.

Dr. Parkinson's company has developed a technology pioneered at Stanford University that provides a means to characterize signaling pathways at the single-cell level and is working to meet regulatory standards for clinical diagnostics. The result is a set of enabling tools based on flow and mass cytometry that can look at individual cells within complex cell populations to understand how and why a drug works. He said that if structure provides 1× of information, and function provides 10× of information, then looking at function in a well-annotated patient over a long enough time provides 100× to 1000× of information and essentially creates a clinical trial within a single patient.

From his perspective, cancer researchers and drug developers have no idea how drugs work and why drugs fail. The way to solve this problem, as Dr. Norton pointed out, is to identify what is not known and then create the tools to make the unknown known. One approach is to look at CTCs as liquid biopsies and ask whether CTCs can provide data relevant to therapy and patient outcome. He explained that his company is working with the Biomarkers Consortium to develop precompetitive information that may be able to explain why drugs that work in vitro do not work in vivo. The ultimate goal is to be able to follow what is going on in an individual patient over time. Without that information, the field will never make meaningful advances, and without the types of approaches that the PS-OC network is developing it will be difficult to get that kind of information.

Discussion

The initial comment from the participants was that it is the combination of new data and new ways of making sense of those data that is needed to advance this field, and this is an iterative process that goes from experiments and modeling to the clinic and then back again. This community must develop ways of integrating clinical data with biological research and modeling because that type of activity is not happening in the traditional oncology community. Another participant said that the cancer looks crazy and chaotic, but really it is predictable. The problem is that there is just no understanding of the connections and the rules, just as the motions of the planets remained a great mystery until Newton developed the very simple theory of gravitational attraction and suddenly the motion of the planets was explained completely.

The comment was made that a critical obstacle to making progress is the lack of support for intellectual thinking time, for getting together in meetings such as this and bandy about different ideas and concepts to come up with the new approaches that might lead to progress. The answers to cancer may already be out there, but because the field keeps taking the same approach, those answers are not being found, because the needed conversations are not occurring.

A participant made the observation that a critical time to look at a tumor is the time between the primary diagnosis and the beginning of metastasis, and wondered whether sequencing technologies could be used to map the natural history of a tumor. The problem is that the time window is not known. It was suggested, though, that functional imaging could follow tumor progression in patients and get at that time window. Functional nuclear magnetic resonance (NMR) imaging and positron emission tomography (PET) are just the start. Technologies are now being developed that can be used

in patients and provide a huge amount of information, even predictive information, which could help the field move forward.

When the panelists were asked for their closing thoughts, Dr. Tarin noted that it is important to find, study, and understand tumor cells in the blood. It is important to modulate intratumoral pressure, and it is important to address cancer through cells other than those in the tumor. Dr. Parkinson reiterated an idea heard several times that data are not in short supply, even fully annotated clinical data. Missing, though, are rigorous methodologies for handling and analyzing data, and then identifying what data are missing, as well as collaborations to make use of the data. Dr. Kuhn seconded these ideas and added that the major challenge is connecting the dots among all of the data in a way that is relevant to patients.

Dr. Norton restated his belief that the PS-OC community is on the right path in terms of thinking about a unified theory of cancer. He noted that two centuries ago, mathematics was at the core of science. Today, it is at the periphery, and the field suffers as a result. Cancer research needs more programs like the PS-OC, not fewer, to expand the number of mathematicians and physicists involved in cancer and to increase the level of communication between cancer biologists and clinicians and physical scientists. Dr. Jain added engineering to the list of disciplines that would benefit cancer research. The abnormal microenvironment of the tumor drives cancer and the field needs people who think about stress and pressure and other physical factors in the microenvironment that affect cancer therapy and the development of resistance to therapy.

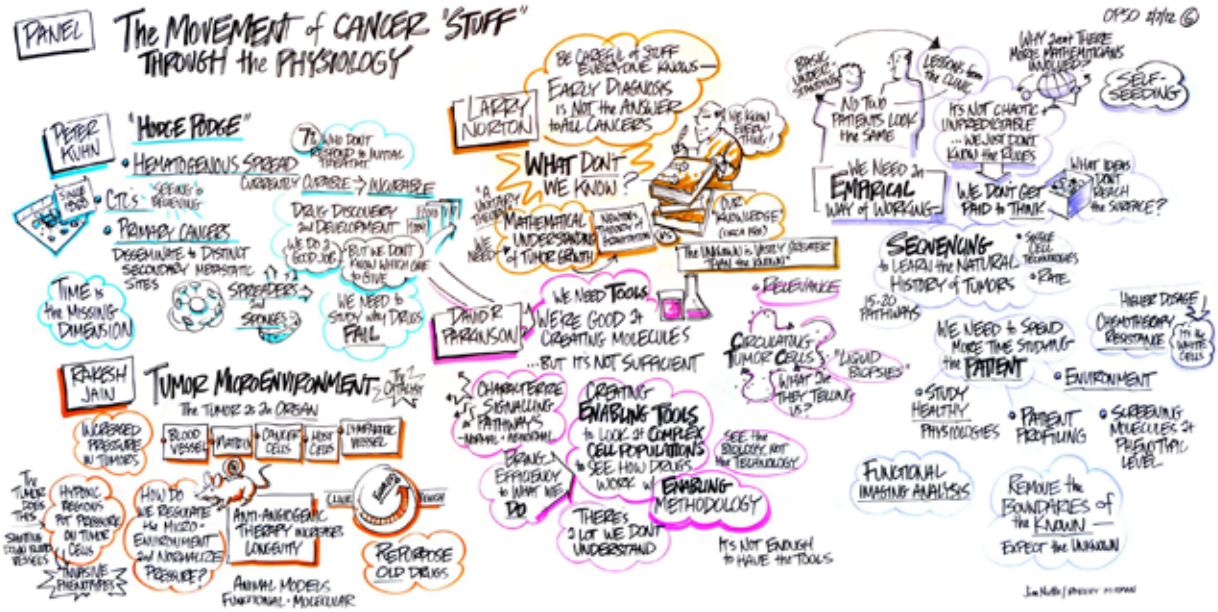

Figure 7: The graphical record of the panel presentations and discussion on "Movement of Cancer "Stuff" Through the Physiology."

Panel Session: Mechanical Forces/Properties in Tissue and the Cancer Microenvironment

Panelists: ***Jan Liphardt, Ph.D., University of California, Berkeley***
Chin-Lin Guo, Ph.D., California Institute of Technology
Mina Bissell, Ph.D., Lawrence Berkeley National Laboratory
Scott Manalis, Ph.D., Massachusetts Institute of Technology

Dr. Liphardt started the presentations by showing a picture of a cell interacting with its microenvironment, which illustrated in great detail how intimately and completely connected physically a cell is with its microenvironment, and how wrong it is to picture a cell as an isolated entity consisting of a plasma membrane filled with organized structures and molecules going about their business. The entire demarcation between inside and outside, as the picture showed, is academic, said Dr. Liphardt.

He then talked about the fact that solid tumors are solid, and solids have a variety of mechanical characteristics that differ from normal tissues that have largely been ignored by researchers. Yet that difference is what a woman detects during a breast self-exam. It should not be surprising, then, that changes in the mechanical properties of tumor tissue have an impact on cell signaling. Considering mechanosensing, not just chemosensing, and thinking about signaling as a mechanical process opens new avenues for thinking about developing therapies to disrupt abnormal signaling pathways in cancer.

Mechanical properties, said Dr. Liphardt, affect cell development as demonstrated by experiments with stem cells growing on materials of differing compliance. Put stem cells on a hard surface and they develop into bone progenitor cells, but put them on a material with the consistency of brain tissue and they develop into neural progenitors. This result shows that cells are exquisitely responsive to mechanical cues from the environment. He then listed a variety of signaling pathways involved in cancer that research has shown respond to mechanical as well as chemical signaling. Taking a mechanical perspective on cancer does not mean throwing out everything known. Rather, it means adding another dimension to the discussion and perhaps providing a way of integrating chemical signals into a simpler view that may provide approaches to revert the phenotype of malignant cells.

One challenge that comes from taking a mechanical view of cells interacting with their environment is that it necessarily spans many scales. To demonstrate this scale issue, Dr. Liphardt showed a movie of a single breast cancer cell dividing in a 3-D culture system and starting the process of growing into a mammary acinus. The cells did not simply divide, but performed a complex series of cell movements, involving rotation around one another. These coordinated movements were critical in weaving together the basement membrane required for normal acinus formation. He then showed a second movie of malignant breast acini reorganizing the extracellular matrix by exerting tension on collagen fibers. This led to the formation of collagen bundles that propagate over a distance of millimeters and this facilitated the migration of cells away from the acini. He concluded his remarks by noting that to this day, the field does not take into account the extracellular environment when targeted therapies are developed. This could account for the failure of these therapies and could also provide an opportunity to explicitly target the extracellular matrix as an approach to treating cancer.

Dr. Guo continued on the theme of the microenvironment with a short discussion of his work on how the effects of the microenvironment can propagate across many cells. He said that work in his laboratory has shown that it is possible to induce changes in cell shape through geometry-dependent stimulation involving either chemical or mechanical signaling. Moreover, changes in cell shape can then alter subsequent chemical signaling. He also reiterated Dr. Liphardt's comments that the mechanical interactions between cells are not restricted to cell-cell contact. His group has demonstrated that long range interactions, over 600 microns, can influence the self-organization of cells into long, unbranched epithelial tubules.

Dr. Guo noted that one way to look at the formation of metastases is as a competition

between malignant and normal cells to change the microenvironment. Tumor cells, when they leave the tumor and attempt to colonize a secondary site, may engage in this competition at every site at which they land, but they only form a metastatic lesion when they successfully outcompete normal cells, reorganize the extracellular matrix to their liking, and create an environment that favors their growth over that of the normal cells.

In her remarks, Dr. Bissell reminded everyone that there are more than 10 trillion cells, each with the same genetic information, that somehow coordinate their actions to become a person. The bottom line, she argued, is that architecture of the organ is absolutely crucial to sending cells the signal to remain what they are, be it a liver cell or a breast cell. Given that notion, Dr. Bissell asked the question "Does context determine what an oncogene can do?"

To study context, she and her colleagues developed a three-dimensional system for studying cell growth and seeded it with breast cancer cells. Cells in a matrix that mimicked the normal breast microenvironment generated normal acini, while cells in a stiffer matrix formed irregular acini that resembled malignancies. In this system, genetic changes and alteration of the microenvironment cooperated in producing a transformed phenotype. Interestingly, this could be reversed by modifying the interaction of cells with the extracellular matrix (using inhibitory antibodies) or by altering the microenvironment to normal tissue. Moreover, when they took the reverted cells and implanted them in mice, the cells did not form tumors as they normally would have.

Dr. Bissell said that these experiments show that phenotype can dominate genotype and that growth and malignant behavior are regulated at the level of tissue organization. In closing, she stated that research has revealed the language of the genome, but it has yet to reveal the language of form.

In the final presentation, Dr. Manalis described his work using a microchannel resonator to measure the physical properties of individual cells. While this is an artificial environment, it does provide the opportunity to make very high-precision measurements of basic cell properties. Moreover, measuring cell properties in isolation using a microchannel resonator can provide information about how tumor cells respond to drug therapy and be predictive of long-term patient outcome. In fact, the microchannel resonator device his group has developed is being used to monitor drug response in an ongoing clinical trial in patients with glioblastoma and to determine whether these measurements can be used to make patient-specific predictions. Already, Dr. Manalis and his collaborators have shown that patient samples can be analyzed within 2 hours of tumor resection and data from 20 patients recapitulates their tumors in terms of mutation and expression profiling.

The microchannel resonator used can measure the mass and deformability of single cells as it passes through a constriction in a microchannel. Plots of deformability, as measured by passage time through the device, versus cell mass distinguish normal mouse lymphoblasts from mouse tumor cells. These results suggest that it may be possible to detect CTCs using a physical property rather than a cell surface marker. He noted in closing that his group is in the process of building a device that will be capable of assaying 10,000 cells per second.

Discussion

To start the ensuing conversation, the panelists were asked to identify one thing they had heard over the course of the day's discussions, beyond measurements, that would benefit cancer research. Dr. Bissell said that models were important. The field needs models that can be tested and not models of cells but of organs and tissues and that include normal cells as well as tumor cells. Dr. Guo said that it is clear that cancer is a complex system, so the idea that temporal and spatial information across scales is important. The physical sciences community needs to contribute the methods and ideas to incorporate this kind of information into models of cancer. Dr. Liphardt added that coordinated action and collective phenomena are important in cancer and models must be able to reproduce and explain those characteristics of tumors. Dr. Manalis noted that his work is completely

dependent on collaborations with biologists and clinicians. The biggest question he wonders about is "How long does it take for cells removed from the microenvironment to lose what makes them what they are?" In other words, is there a time over which single cell measurements can still reflect the important and real characteristics of that cell that are clinically or biologically relevant?

Upon opening the discussion to the entire Think Tank, several participants noted the importance of the information contained in the spatial organization of a tumor and remarked how little attention is paid to that organization. It was suggested that high-resolution structural and functional imaging may provide important data that could be used to model tumors and perhaps lead to a unified theory of cancer. Given that the microenvironment is nonlinear, in vivo functional imaging may be one of the few ways to understand tumors in their native environment in a way that can truly inform modeling efforts.

Along the lines of modeling, one participant noted that there is at least one model based on a limited number of physical parameters and few equations that explain what a pathologist sees under the microscope. However, the clinical community has shown little interest in using this type of model.

Physicists, remarked one participant, have excellent models for the very small scale and the very large scale, but no models that span these two extremes. Nonetheless, the models are very successful in their respective regimes. The participant wondered if it might be asking too much to have a model of cancer that encompasses all scales and if instead the field should tackle models at discrete scales and then work to integrate these models across scales.

Given what the panelists had to say, one participant proposed that researchers should work on cataloging different types of extracellular matrix according to physical properties in order to test whether these parameters can explain the tissue tropism of metastases for different types of cancer. Another participant added that the extracellular matrix changes with age and wondered whether that was relevant to the development of cancer. It is known, for example, that age impacts drug resistance, and the reason for that might be linked to the changes in extracellular matrix that come with aging.

Tumors and their microenvironment also change over shorter time spans, added a participant. Over the very short term, tumors and normal tissue push on each other and experience changes in fluid pressure. Since it is clear that cells can

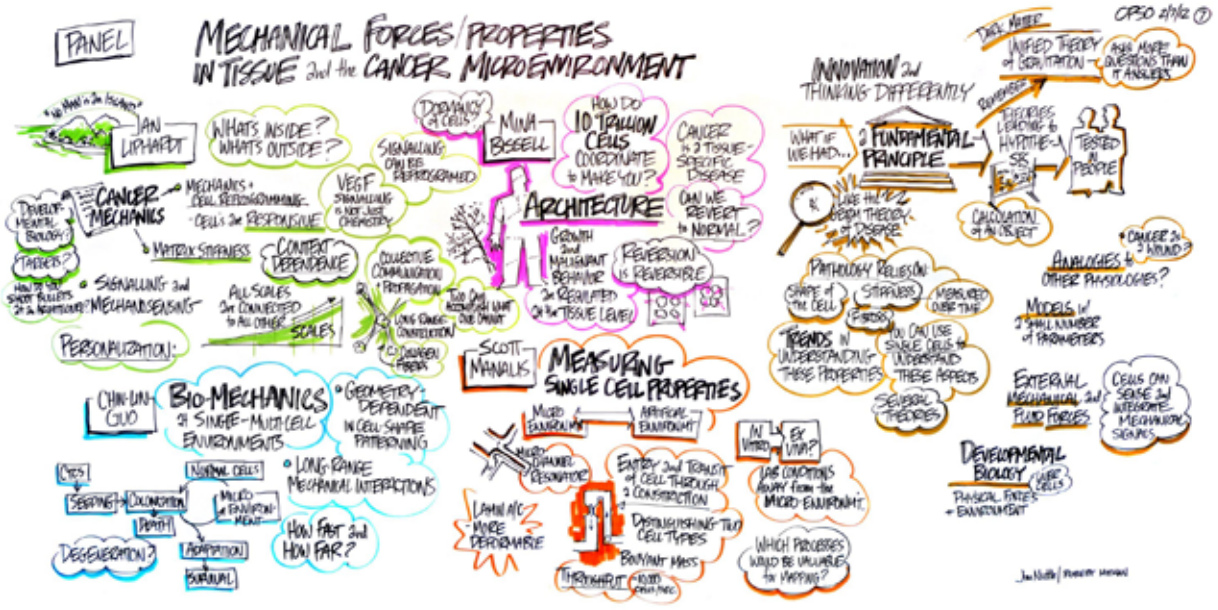

Figure 8: The graphical record of the panel presentations and discussion on the "Mechancal Forces/Properties in Tissue and the Cancer Microenvironment."

sense and integrate these forces, it is important to study the short-term dynamics of forces in the microenvironment and tumor.

To close this panel session, the panelists were asked to comment on the clinical relevance of the ideas that had been discussed. Dr. Manalis said it is still unknown which physical parameters are clinically important, and single cell technologies can help to identify those meaningful parameters. Dr. Guo commented that it should be possible to measure changes in the physical properties of the extracellular matrix as people age and that perhaps this could reveal risk factors for the development of cancer. Dr. Bissell said that the reversion model on which her group is working could potentially be used to determine what causes cells to wake up or remain dormant and whether the wakeup call is a mechanical trigger transmitted through the microenvironment. In the final comment, Dr. Liphardt raised two issues. The first was that the field needs to consider how to model from single cells to organs, to the organism, and then to cancer. The second was that from a clinical perspective, there are enormous opportunities for diagnostics and therapeutics if it becomes possible to target the microenvironment with drugs or other interventions.

Key Research Questions in Cancer

Facilitated Discussion

For the next exercise, each table was asked to hold a discussion to identify two needs or questions that, from a physical sciences perspective, have not been met or asked and that would lead to great progress in treating or understanding cancer.. The groups then reported back the following ideas:

- Create a realistic, standardized model of the microenvironment and its role in metastasis progression.
- Identify an objective set of quantifiable measures, both physical and genetic, that are prognostic for predisposition to cancer.
- Develop the data, theory, and models needed to build a unitary understanding of cancer.
- Can we characterize the thermodynamic states of cancer and establish free energy relationships that connect these states?
- How can we use the past history of a system to characterize its fitness?
- Given that cancer is a chaotic, dynamic system, is it possible to measure multiple dimensions and perturbations in a manner that will inform us about cancer?
- How does a tissue become deregulated and do senescent cells play a role in this deregulation?
- Are there markers of tissue deregulation that may predict susceptibility to cancer?
- Identify a minimum number of nodal points in signal transduction that can serve as intervention points.
- Are there physical parameters to distinguish in a clinically useful way between normal and tumor?
- Recapitulate the physical forces involved in developmental biology in such a way as to understand self-regulation.
- Identify the motifs that define the assembly of a small number of cells and a return to a starting state.
- Understand the contribution of physics to perturbation effects on cells.
- Is cancer one disease or many, and should each form of cancer be thought of separately?

- When and why do cells leave the primary tumor and are there signals that this event is about to occur?
- Develop evolution as an overarching theory of cancer and include the supporting/enabling role of the microenvironment and other nonmalignant cells.
- How is the microenvironment linked to the three-dimensional architecture of chromatin and mutational landscape?
- What is the extent of genetic heterogeneity within tumors?
- What noninvasive physical and mechanical properties of tumors can be used to predict the aggressiveness of cancer cells?

The day's activities were adjourned at this point, and OPSO staff convened to review this list. Four overarching topics were identified that would serve as a focus for the next day's discussions aimed at developing the next generation of OPSO programs. The four topics and key related questions for discussion were:

- Emergent Properties of Cancer
  - Key questions:
    1. How can we use the past history of the system to characterize fitness?
    2. What is the relevance of the extent of genetic heterogeneity of cancer cells?
    3. Can we use physics to understand the contribution that perturbations have on the fate of cells?
    4. What is the role of normal cells in the development of malignancy and metastasis?
- Universal Parameters of Cancer
  - Key questions:
    1. What is an objective set of parameters (including genetic, epigenetic, and physical paramaters) needed to characterize the predisposition of cells to malignancy?
    2. What is needed to characterize multiple dimensions of perturbation in a chaotic, dynamic system?
    3. How can measuring the physical and mechanical parameters of normal and malignant cells/tissues inform the development and validation of large-scale models of cancer?
    4. Which noninvasive physical and mechanical properties of tumors can be used to predict the aggressiveness of cancer cells?
- State Space of Cancer
  - Key questions:
    1. What are the energy relationships between the state spaces of cancer?
    2. Can we use the tools of the physical sciences to identify a minimal number of nodal points in signal transduction?
    3. What are the implications of identifying nodal points for the use of multiple interventions?
    4. Can we identify the key features of the microenvironment that shape the state space of cancer?

- Physical Dynamics of the Tumor System
  - Key questions:
    1. What are the physical forces involved in developmental biology that explain self-regulation and loss of self-regulation?
    2. When and why do cells leave the primary tumor, and are there signals that precede this?
    3. Are there links between physical changes in the microenvironment and the three-dimensional architecture of chromatin and the mutational landscape?
    4. Is there a realistic, standardized model of the microenvironment's role in the progression to metastasis?

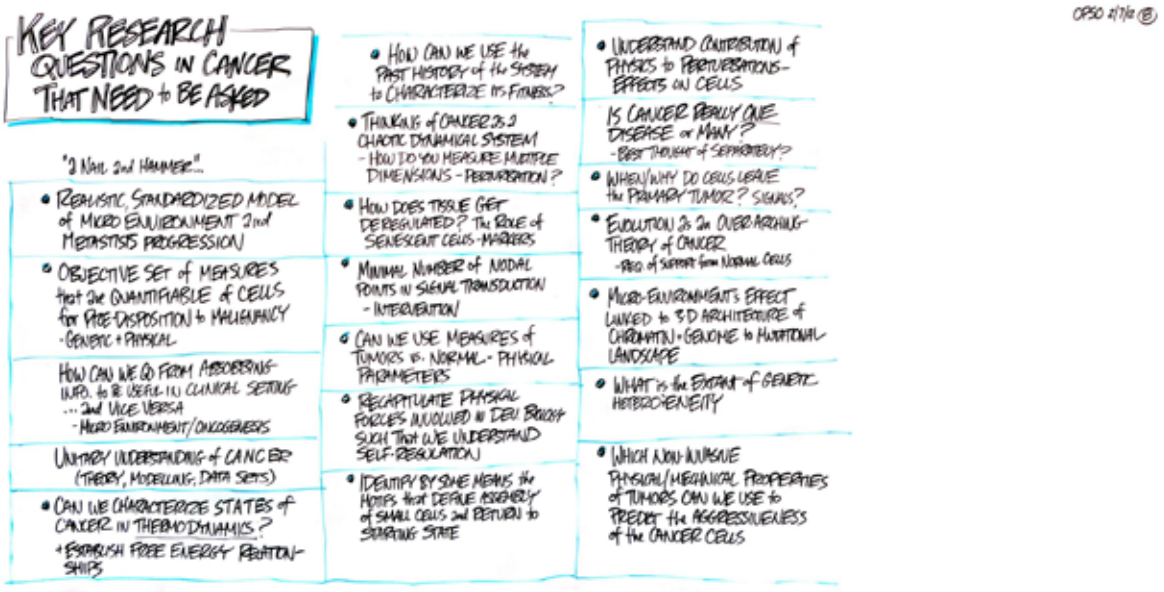

Figure 9: The list of the "Key Research Questions in Cancer" that need to be asked generated by Think Tank participants.

Day 2: February 8, 2012

Panel Session: Physical Markers and Universal Parameters in Cancer

Panelists: ***Denis Wirtz, Ph.D., Johns Hopkins University***
Vadim Backman, Ph.D., Northwestern University
Kelly Bethel, M.D., The Scripps Research Institute
James Heath, Ph.D., California Institute of Technology

Dr. Wirtz began this panel's comments by stating that isogenic cells exhibit a "zoo" of cellular properties. Typically, researchers make bulk measurements and get mean values, but this approach ignores variance, and variance may actually be an important parameter for characterizing metastatic disease. To get at variance, his group is using a custom scanning microscope to capture five-channel images of approximately 10,000 cells at very high throughput. Mean measurements of nuclear shape and size and cellular shape and size were not informative, but when a set of shape parameters were calculated for each cell individually, the results revealed that heterogeneity in these parameters correlated strongly with the stage of pancreatic cancer and glioblastoma.

Based on these results, his group is now developing approaches to measuring a wide range of physical parameters on individual cells within tissues. The methods his team is developing can be used to examine patient-derived cell lines, xenografts, and primary tissues for use in prospective studies and formalin-fixed, paraffin-embedded samples for retrospective studies. In a final comment, Dr. Wirtz wondered whether it would be possible to target a phenotype rather than specific molecules.

In his remarks, Dr. Backman said that laws of physics are derived by making physical measures that identify a system's common physical traits, and he wondered whether this community could take the same approach for carcinogenesis. Given the results that are coming from TCGA showing wide mutational variations in different types of cancer, common traits in cancer are not likely to be genetic. Perhaps the search for common traits should shift to physical characteristics such as changes in nuclear structure, elasticity, and chromatin architecture. His group has been examining cellular and nuclear architecture at the nanometer scale using partial wave spectroscopy (PWS) and has found that abnormal disorder strength, a measure of chromatin compaction, appears to be a common trait seen in every cancer examined so far. Moreover, the alterations in higher order chromatin structure that PWS is detecting appears early in the malignant transformation. Dr. Backman explained that chromatin compaction is caused in part by upregulation of histone deacetylase. Thus, a physical measurement, obtained using PWS, is connected to changes in gene transcription.

In a change of pace, Dr. Bethel gave a brief lesson about what a pathologist does to characterize a tissue sample as being malignant or benign. She showed slides of tumor, stroma, and normal tissue. She said that once she spots a malignancy, she then determines how big it is, whether the margins have been removed, and whether the blood supply has been engaged. Those simple measures lead to predictions of disease. For clinical oncology today, those are the universal parameters for cancer. She noted that a valuable piece of new information that pathologists cannot acquire now is whether the cells spotted in blood vessels will land and grow. She said that information on the stiffness of normal and malignant tissue would also likely be useful.

The last panelist, Dr. Heath, spoke about cancer as a thermodynamic system. This view has not been taken before and he believes it deserves a shot as a means of better understanding cancer. The second law of thermodynamics, he said, permits thermodynamic state descriptions to be extracted from quantitative measurements of fluctuations. He and his group measure the fluctuations of cancer cells by measuring the copy number per cell of 8-20 proteins using single cell assays. They use these data to extract the chemical potential of the proteins, describe the thermodynamic state of the cell by approximating that state as a constrained equilibrium, and use a chip-based assay to test that approximation using Le Chatelier's Principle. The data are used to create a free energy landscape that could represent states with various minima.

Using this approach, Dr. Heath and his colleagues studied glioblastoma under different conditions of hypoxia. It appears that there are two states, and there is a regime between these two states that could be a phase transition. According to the Gibbs phase rule, another principle derived from physics, a system loses one degree of freedom at a transition. When Dr. Heath's team looked at mTOR signaling, the researchers found that under various conditions of hypoxia and anoxia, the system lost a degree of freedom at an oxygen concentration of 1.5%-2.0% oxygen. What makes this finding relevant is that a drug that interacts with mTOR loses its effectiveness when delivered while the tumor microenvironment is between 1.5%-2.0% oxygen. The question, said Dr. Heath in closing, is whether a free energy landscape for cancer cells and even tumors can be developed that yields predictive capacity.

Discussion

To start the discussion, the panelists were asked to comment on the time domain of cancer. Dr. Bethel responded first by stating that much of what she and all other pathologists predict about the future of cancer is based on features defined at the moment they first encounter a tumor. It is rare to ever see the tumor again, so all she ever sees is a single snapshot of a tumor. She noted that so much patient-relevant information is being missed by not having technology to

conduct noninvasive biopsies over time. She recommended that it would be useful to re-biopsy every time there was an inflection in the course of the disease, such as when a tumor stops growing. Ethically, this cannot be done by traditional surgical methods, though, and so new imaging technologies are needed to provide this kind of temporal information.

There was substantial discussion about the relevancy of using fundamental physical laws such as those of thermodynamics to define cell states. Cells are not equilibrium states, said one participant, but another noted that the phase transition diagram developed using thermodynamics was able to explain why mTOR fails to respond to an inhibitor. Another participant thought that the idea of a thermodynamic model of cancer was a good one, and thought it merited further detailed discussions between biologists and modelers to further explore the idea. A theoretical physicist in the audience noted that phenomenological models can be very useful without having a detailed understanding. Thermodynamics, for example, is a phenomenological model that was very predictive long before it was finally explained by statistical mechanics.

It was noted by a participant that physical parameters are the universal parameters by which to assess tumors, and those are the very parameters that pathologists use. What is needed, said another participant is an integration of the way that pathologists look at the whole tumor with the detail at a cell level of the type that Dr. Wirtz and others in the PS-OC network are investigating.

Figure 10: The graphical record of the panel presentations and discussion on the "Physical Markers and Universal Parameters in Cancer."

Panel Session: Large-Scale Modeling of Cancer

Panelists: ***Kirk Jordan, Ph.D., IBM T.J. Watson Research Center***
Herbert Levine, Ph.D., University of California, San Diego
Efthimios Kaxiras, Ph.D., Harvard University

Dr. Jordan started the final panel session by noting that computers are changing in a big way and these changes present some tremendous opportunities for the physical sciences-oncology community. IBM is about to make a computer with 1 million processors and in the near future that number will increase to 100 million. This dramatic increase means that models can increase in complexity and will be able to handle rich datasets. Dr. Jordan showed a number of

examples of the success that computers with enormous numbers of processors have achieved, for example, complex models that forecast weather on a local scale.

He also described work that IBM is collaborating on to develop multiscale models of entire organs such as the heart and remarked that the kinds of multiscale models of tumors and their microenvironments that have been discussed at the Think Tank should be amenable to the same type of approach. In fact, colleagues of his at IBM are working on a multiscale model of cancer that uses clinical imaging data and regulatory pathway data to predict tumor cell phenotype distribution. He added that IBM would be a willing participant in collaborations with the PS-OC community. He also noted that IBM's goal is to make its computer modeling resources available to researchers in their laboratories and even mobile devices such as smart phones.

In the next presentation, Dr. Levine, who noted that he will be moving to Rice University soon to establish the Center for Theoretical Biological Physics, said models are what physicists use to test theoretical ideas. These models can be built at various scales – the motion of a molecule, the deformability of a cell – and using these models in isolation provides some useful information. But since it currently takes the most powerful computer to do fully resolved calculations of cells or even the interactions of multiple molecules, the best use of these limited scale models is to identify the features that are essential to include in calculations in order to simplify larger scale or more integrated models. As an example, he said that while methane gas is an important contributor to climate change, climate change models do not need to include information about the cow genome and metabolome to make an accurate global warming model.

In the third and final presentation, Dr. Kaxiras enumerated some of the key challenges for computational physical science. These included:

- Is it possible to predict from first principles the relevant structures and functions of complex systems?
- What are the key features at each scale?
- How are they coupled in a complex system?
- What are the variables, constants, and adjustable parameters that need to go into such models?

As an example of a multiscale model, he described a model that was used to show how sulfur impurities in a nickel alloy contribute to cracks forming in an airplane wing. He wondered if there might be approaches to use this type of model with the tumor microenvironment. In another example closer to the interests of cancer biologists, Dr. Kaxiras described a model of the structure of the chromosome that can model chromatin structure at the level of molecular details but then move to a more coarse-grained view to predict the double-stranded structure of DNA. As a last example, he described a model of acute myocardial infarction that can reproduce how blood flow reshapes vascular endothelium based on two parameters involving fluid-red blood cell interactions.

Discussion

To start the discussion, the panelists addressed the question of whether the types of multiscale models developed for climate change and particle physics are useful for thinking about cancer. The general consensus of the panel was no, because chemistry and physics are much simpler and involve well-described and discrete entities such as atoms and fundamental particles. Also, these systems, unlike cancer, do not evolve. That was not to say that multiscale modeling will not work in cancer or that the many efforts underway will not be productive, just that the problem is much more challenging. One piece that is missing today is data on the temporal course of cancer, and this is where imaging should be able to help. If models are to capture the evolution of cancer and its dynamic nature, then modelers need more time series data to begin conceptualizing those kinds of models.

Dr. Kaxiras noted that thanks to the dramatic increase in computational power that is now at hand, it will be possible to model very complex problems. He was confident, for example, that it will soon be possible to model the structure and dynamics of chromatin in great detail. A

participant noted that there is a company that has developed a model of the human body using 1,500 differential equations that is predictive of therapy response and that this is being used by at least one insurance company. Another participant said chemical engineers have developed models that are based on atomic scale information of chemical reactions, but that they then move across scales using modules to create a complete model of a chemical refinery. These are not continuous scale models, but chemical engineers have learned how to link models at different scales to accurately predict the behavior of the complex systems that make up a chemical refinery. A participant added that the FDA has approved a multiscale model of the heart for use in predicting response to drug therapy.

There were many comments from both the panelists and the audience that models do not need to be all-encompassing. A smaller scale model of the circulatory system could, for example, be used to predict where a metastatic cell might land in the body. A participant noted that coarse-graining may work with cancer because biology is coarse-grained at some level. The body is not a bag of enzymes and chemicals, but is organized into discrete units: organelles, cells, and organs, all with discrete barriers. The resemblance to a chemical refinery was again noted, triggering the comment that perhaps the PS-OC network needs to involve some chemical engineers in its efforts. Several participants suggested that modeling efforts might focus on the convergent points of cancer such as the hallmarks of the metastatic cell. Many participants noted that there is a tremendous unmet need for models that can help clinical decision-making.

In a final comment, Dr. Austin stated that he believes that all of these brute-force, high-end computational modeling efforts are doomed to failure without adding influences beyond the laws of physics. Comparing the problem to that of trying to model Germany invading Poland, he argued that this was an impossible challenge using the rules of physics because of the complexity of the problem. He opined that cancer probably falls into the same category of problems and may be impossible to model using only the laws of physics, no matter how powerful computers become. Other approaches that go beyond physics need to be explored to attack the complexity and emergent behavior of cancer. Dr. Michor added that building an all-encompassing model of cancer that stretches from nucleotide sequence to whole organism is not achievable today given that today's models are still rudimentary and not multiscale. However, she added, simple models, such as one of how blood flow affects where metastasis occurs and how long it takes, can have an immediate impact on research and clinical use.

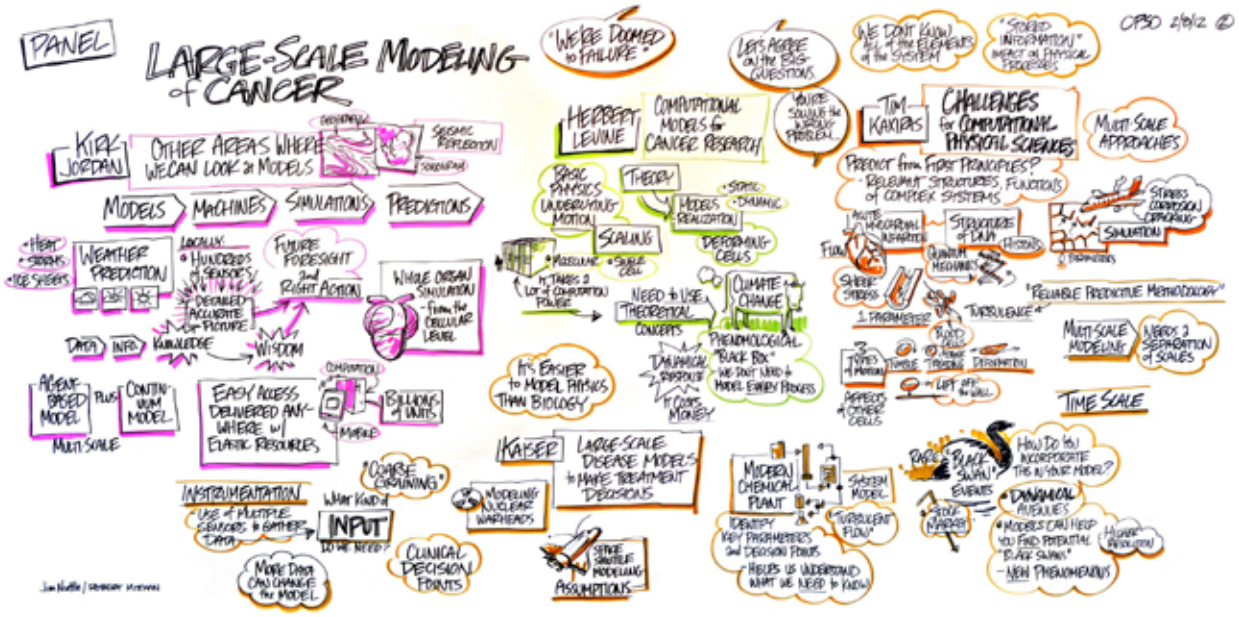

Figure 11: The graphical record of the panel presentations and discussion on "Large-Scale Modeling of Cancer."

The Next Generation of Physical Sciences-Oncology

Facilitated Discussion

In the final activity of the Think Tank, the participants were split into four groups that were asked to brainstorm on the four key topics that OPSO staff identified based on the Think Tank's earlier brainstorming session. These topics were:

- Emergent Properties of Cancer
- Universal Parameters of Cancer
- State Space of Cancer
- Physical Dynamics of the Tumor System

The brainstorming groups were asked to develop a relevant description of the topic; identify the clinical implications and why clinicians should be interested in this topic; enumerate a set of research questions and issues from both the cancer biology/oncology perspective and the physical sciences/engineering perspective; identify existing work relevant to the topic and who should be involved in addressing the topic; and finally to describe the pitch, the key story line. After their deliberations were complete, the four brainstorming groups reported on their work.

Emergent Properties of Cancer

This group described the topic as the search for properties that define cancer, its risk, and the potential solutions that arise from the action of relatively simple rules. Metastasis, angiogenesis, and resistance to intervention would fall into this category, as would all of the other well-known hallmarks of cancer. The clinical implications would be in two areas: therapeutic planning and prevention. Understanding the emergent properties of cancer could lead to the development of a metastatic potential index and to new strategies for avoiding the development of resistance to therapy or for overcoming resistance that does develop. Ideas to address this topic could lead to new strategies for developing vaccines and perhaps nutritional approaches to prevent the emergence of cancer. Clinicians and patients should be interested in this topic because it is important for personalizing therapy, developing risk/benefit profiles and screening approaches, and for monitoring patient response to therapy both while it is ongoing and for subsequent years.

Key research issues from the cancer biology/oncology perspective included:

- Identify the physical factors that affect nuclear organization and how are they tied to the development of oncogenic mutations.
- Define the angiogenic switch.
- Characterize the roles that factors such as interface roughness, stiffness, motility, and invasiveness play in the transition to metastasis.
- Turn cancer into a chronic disease by preventing the emergent properties of metastasis.

Key research issues from a physical sciences/engineering perspective included:

- Develop a qualitative and quantitative understanding of the three-dimensional heterogeneity of a tumor.
- Enumerate the physical properties that generate the emergent properties of cancer.

- Identify changes in the extracellular matrix that promote or inhibit the emergent properties of cancer.
- Identify the collective properties of CTCs that lead to metastasis.

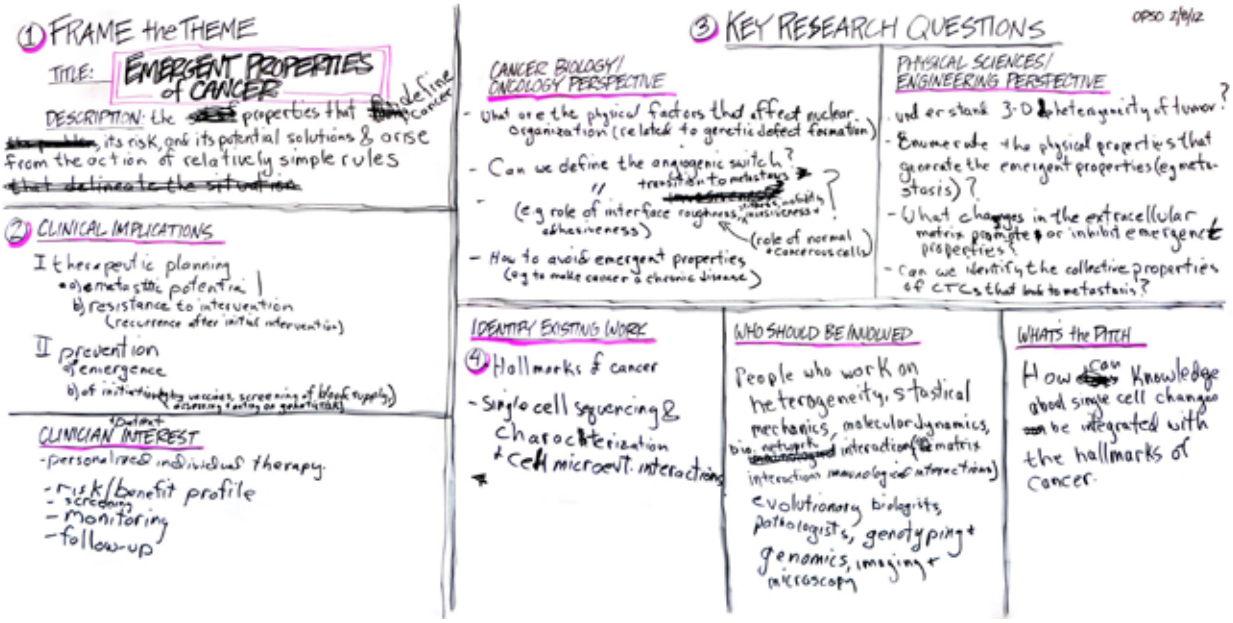

Figure 12: The notes of the Think Tank group focused on the theme of "Emergent Properties of Cancer."

The substantial body of data on the hallmarks of cancer lay a solid foundation for work on this topic. Single-cell sequencing data and work characterizing the interactions between cells and their microenvironment also provide valuable input. Efforts to tackle this topic require expertise in heterogeneity, statistical mechanics, molecular dynamics, biological networks, evolutionary biology, pathology, genotyping, genomics, imaging, and microscopy.

The single-sentence pitch: Integrating knowledge about single-cell changes and cell-microenvironment interactions with the hallmarks of cancer to improve our ability to treat and prevent cancer.

Universal Parameters of Cancer

This group described its topic as an effort to identify the core parameters at each clinical decision point for individual patients that define the cancer system and provide clinically actionable and mechanistically useful information. The clinical implications of success would be improvements in screening for and diagnosing disease, detecting recurrence, planning treatment, stratifying patients, predicting disease course, preventing disease progression and metastasis, and guiding research investments. Clinicians would be interested in this topic because it addresses the lack of clarity in making treatment decisions, and has implications for quantifying risk and empowering patients to make lifestyle changes that can prevent cancer, improve the outcome of treatment, and improve the quality of life during and after treatment.

Key research issues from the cancer biology/oncology perspective included:

- Utilize patient-derived biospecimens and medical records to identify parameters associated with the dynamics of cancer, including disease progression, metastasis, and treatment response.

- Validate and characterize parameters identified using patient-derived biospecimens and medical records.
- Obtain time-course, single-cell phenotype and genotype measurements on tumor and non-tumor cells.

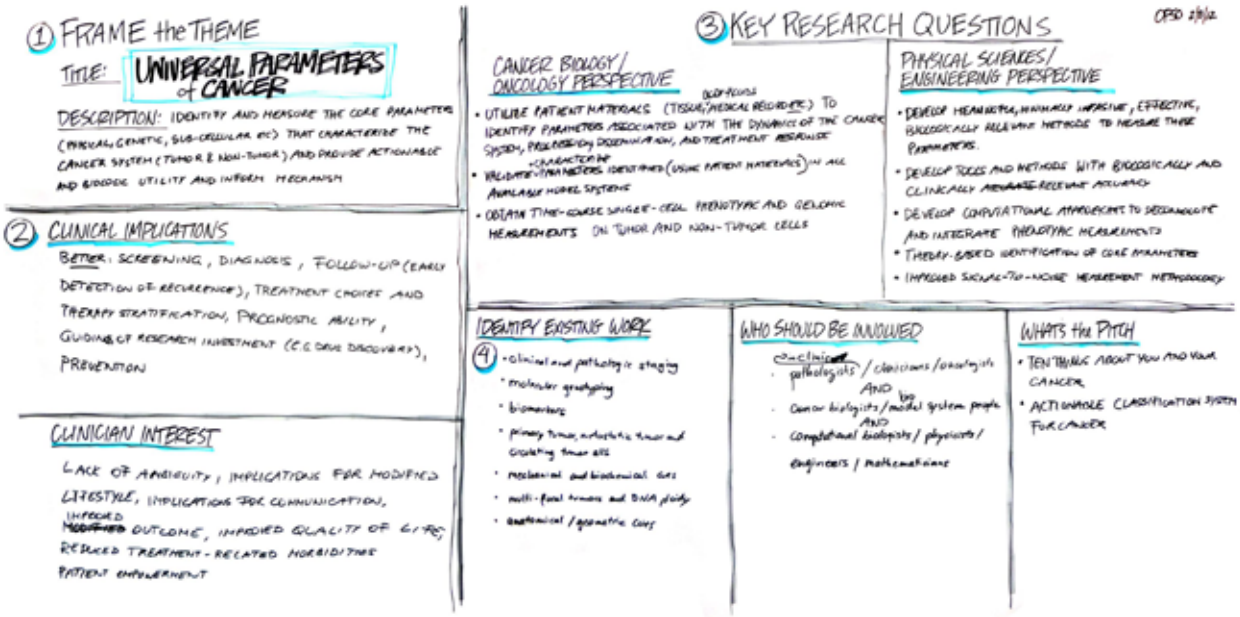

Figure 13: The notes of the Think Tank group focused on the theme of the "Universal Parameters of Cancer."

Key research issues from a physical science/engineering perspective included:

- Develop minimally invasive, effective, and biologically relevant methods to measure the desired parameters.
- Develop tools and methods with biologically and clinically relevant accuracy and sensitivity.
- Develop computational approaches to deconvolute and integrate phenotypic measurements.
- Use theory-based methods to identify core parameters.
- Improve the signal-to-noise ratio of measurement technologies relevant to the detection and quantification of core parameters.

Work on this topic will benefit from the use of current methods of clinical and pathologic staging, molecular genotyping, biomarker identification, and CTC characterization. Information on the mechanical, anatomical, geometric, and biochemical cues that impact cancer development, as well as on multifocal tumors and DNA ploidy will assist research on this topic. Clinical pathologists and oncologists, cancer biologists, biological modelers, systems biologists, computational biologists, physicists, mathematicians, and engineers need to be involved in this effort.

Two single-sentence pitches: (1) Ten things about you and your cancer. (2) An actionable classification system for cancer.

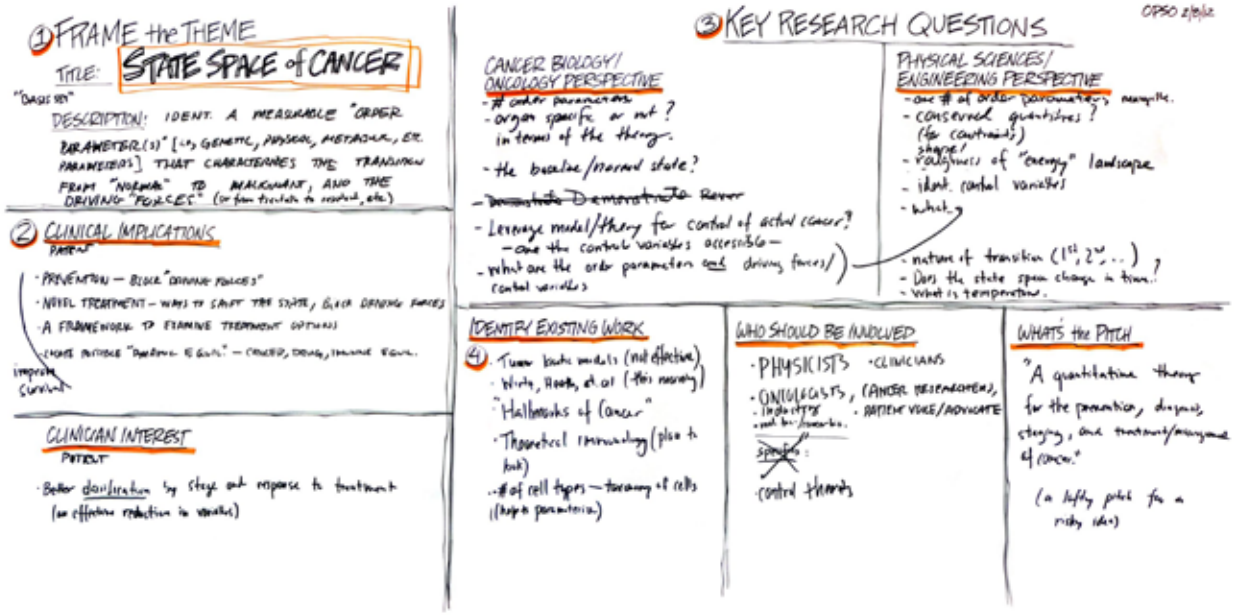

Figure 14: The notes of the Think Tank group focused on the "State Space of Cancer."

State Space of Cancer

This group defined its topic as the need to identify a small, measurable set of order parameters – genetic, physical, metabolic, and others – that characterize the transition from "normal" to malignant, or treatable to resistant, and also identify the driving forces involved in the transition. Such a landscape map could also be used to create novel treatments based on approaches to shifting the state space or blocking the driving forces, essentially holding cancer in a more stable and less harmful state. It could also provide a theoretical framework with which to examine treatment options. Clinicians should be interested because having such a landscape would provide a means to better classify tumors by stage and treatment response.

Key research questions from the cancer biology/oncology perspective included:

- Is the number of order parameters for cancer countable?
- What are the order parameters, driving forces, and control variables?
- Are order parameters organ-specific or potentially universal?
- What is the baseline/normal state?
- Will order parameters and a state space map provide clinically actionable information?

Key research questions from a physical sciences/engineering perspective, which were similar to those for the biology/oncology perspective, included:

- What is the number of order parameters?
- Are they conserved quantities?
- What is the shape and roughness of the energy landscape?
- Are control variables identifiable?

- What are the order parameters, driving forces, and control variables?
- Are the transitions zero order, first order, or second order?
- Does the state space change over time?

Efforts to address this topic can benefit from tumor kinetic models, the work of the PS-OC network on identifying and quantifying cancer characteristics, and theoretical immunology. Physicists, clinicians, patient advocates, industry scientists, and control theory specialists should be involved in this effort.

The single-sentence pitch: A quantitative theory for preventing, diagnosing, staging, treating, and managing cancer.

Physical Dynamics of the Tumor System

This group defined its topic as the effort to integrate a mechanical viewpoint of the tumor-host dynamics with the chemistry, physics, and genetics of the tumor system and to do so over multiple scales and in a way that reflects the history of the tumor. Success on this topic would have implications in the following clinical areas: diagnosis through the identification of physical parameters that can be used to spot cancer, and prevention and intervention by identifying therapies that change the mechanics and physical properties of the cancer system in a way that stops disease progression or prevents it from developing in the first place. Clinicians should be interested because success in this area could produce new classes of drugs or means to increase the efficacy of existing drugs. Success may also yield new imaging methods to measure these mechanical changes and relate those changes to disease prognosis.

This group thought there was no distinction between the two types of key questions and therefore developed two overarching questions: (1) How useful are these considerations if at all? (2) What happens first? The group then generated a single list of key questions and issues:

- What are the rates of tumor growth?
- Are there moments in the tumor's life when changes happen suddenly, and are these moments clinically relevant?
- Is it possible to parameterize a black-box model that will enable a physician to enter phenotypic data and receive treatment recommendations?
- Are certain patients predisposed to cancer because of genetically controlled or age-related alterations in the extracellular matrix that produce a better "soil" in which cancer can grow, and can comorbid conditions also produce such predisposing changes in the extracellular matrix?
- Is it possible to control the mechanical properties of the host in a clean way that discourages the development of cancer or the progression of disease?
- Develop tools and theory to better characterize and understand the role of three-dimensional structure in tumor development.
- Are there physical correlates to benign versus malignant tissue, and do they relate to the progression of disease?
- What roles do the mechanical properties of tumor systems play in the bidirectional communication between tumor and host?

- Do the mechanical properties of the tumor system mask diagnostic or prognostic signals or, conversely, to they provide a means of eavesdropping on the early stages of tumor development?

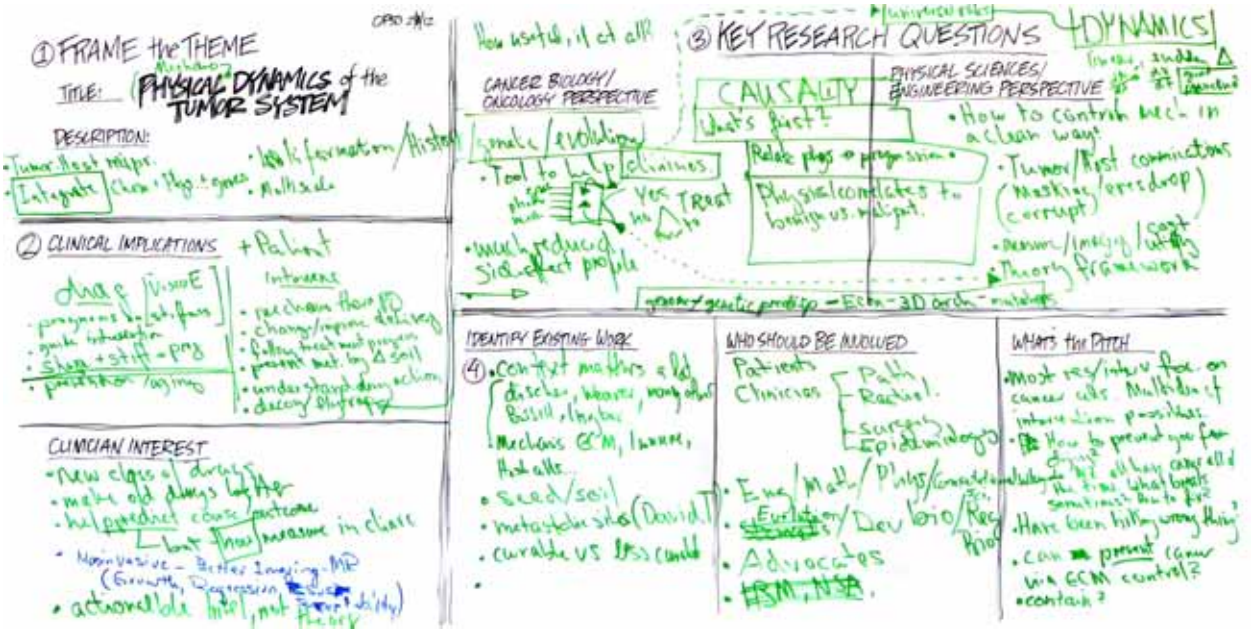

Figure 15: The notes of the Think Tank group focused on the "Physical Dynamics of the Tumor System."

Many of the PS-OCs are working on problems related to this topic, this group noted. In addition, research on seed and soil, metastatic sites, and curable versus less curable cancers inform research on this topic. Patients, oncologists, radiologists, pathologists, surgeons, epidemiologists, mathematicians, engineers, developmental biologists, physicists, computational scientists, and advocates should be involved in this research.

This group came up with two pitches to generate interest in this topic:

Single-sentence pitch 1: Have we been hitting the wrong thing? Most research focuses on cancer cells, but if cancer is thought of as a tissue disease, as a disease of context, a multitude of interventional possibilities arises, some of which may have a much reduced side-effects profile compared to the established therapies.

Single-sentence pitch 2: If we all have tumors growing in us all the time, why does this containment break sometimes and can we do something to prevent it from happening?

Adjournment

After the last group completed its report-out, Dr. Nagahara thanked the participants for two days of lively discussion and his gratitude for their thoughtful contributions. He remarked that the questions and ideas raised by the participants would continue to be deliberated within the PS-OC Network and that the Office of Physical Sciences-Oncology has plans to conduct workshops to develop some of these ideas further. He expressed his hope that in bringing together the diverse group of experts for this Think Tank, seeds for future scientific collaborations would be planted. Finally, he reminded the participants that the NCI would publish a meeting report of the Think Tank, and the meeting was then adjourned.

Appendix

Agenda

Outcomes

- Review key findings and leading-edge thinking from the work of the Office of Physical Sciences-Oncology
- Reflect on the progress of research to date at the interface of physical sciences/engineering and cancer biology/oncology
- Provide input to a research agenda for ongoing and future research in the Office of Physical Sciences-Oncology, including:
  - Assessing existing topic areas
  - Identifying scientific perspectives that could stimulate new topic areas and bring in new members to OPSO's network

Monday, February 6

6:00 p.m.	**Dinner and Welcoming Remarks** Larry A. Nagahara, Ph.D. National Cancer Institute, NIH	*Crystal Ballroom*

Tuesday, February 7

7:30 a.m. - 8:00 a.m.	**Registration**	
8:00 a.m. - 8:30 a.m.	**Welcome and Orientation** Douglas R. Lowy, M.D. National Cancer Institute, NIH Robert J. Mittman, M.S., M.P.P. Facilitation, Foresight, Strategy	*Crystal Ballroom*
8:30 a.m. - 9:00 a.m.	**Opening Roundtable**	
9:00 a.m. - 9:45 a.m.	**Introduction to Keynote Speaker** Harold E. Varmus, M.D. National Cancer Institute, NIH **Keynote: Applying Physical Sciences Principles to Cancer Research** The Honorable Steven Chu, Ph.D. Secretary U.S. Department of Energy	
9:45 a.m. - 10:00 a.m.	**Break**	

10:00 a.m. - 11:15 a.m.

Panel Session: The Three-Dimensional Structure of the Genome and Cells Over Time

Moderator: Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

Panelists: Franziska Michor, Ph.D.
Dana-Farber Cancer Institute

Lin Chen, Ph.D.
University of Southern California

Leonid Mirny, Ph.D.
Massachusetts Institute of Technology

Tom Misteli, Ph.D.
National Cancer Institute, NIH

Alexander van Oudenaarden, Ph.D.
Massachusetts Institute of Technology

11:15 a.m. - 12:15 p.m.

Characterizing the Physical Sciences Perspective
(Facilitated Discussion)
Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

12:15 p.m. - 1:15 p.m.

Lunch

1:15 p.m. - 1:45 p.m.

Keynote: Physical Mechanisms of Tumor Metastasis
David Tarin, M.D., Ph.D.
University of California, San Diego

1:45 p.m. - 3:00 p.m.

Panel Session: Movement of Cancer "Stuff" Through the Physiology

Moderator: Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

Panelists: Peter Kuhn, Ph.D.
The Scripps Research Institute

Rakesh K. Jain, Ph.D.
Harvard University/Massachusetts General Hospital

Larry Norton, M.D.
Memorial Sloan-Kettering Cancer Center

David R. Parkinson, M.D.
Nodality, Inc.

3:00 p.m. - 3:15 p.m.

Break

3:15 p.m. - 4:30 p.m.

Panel Session: Mechanical Forces/Properties in Tissue and the Cancer Microenvironment

Moderator: Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

Panelists: Jan T. Liphardt, Ph.D.
University of California, Berkeley

Chin-Lin Guo, Ph.D.
California Institute of Technology

Mina J. Bissell, Ph.D.
Lawrence Berkeley National Laboratory

Scott Manalis, Ph.D.
Massachusetts Institute of Technology

4:30 p.m. - 5:30 p.m.

Key Research Questions in Cancer
(Facilitated Discussion)
Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

6:00 p.m. - 7:30 p.m

Dinner

Wednesday, February 8

7:30 a.m. - 8:00 a.m.

Registration

8:00 a.m. - 8:30 a.m.

Recap and Reflections *Crystal Ballroom*
Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

8:30 a.m. - 9:45 a.m.

Panel Session: Physical Markers and Universal Parameters in Cancer

Moderator: Robert J. Mittman, M.S., M.P.P.
Facilitation, Foresight, Strategy

Panelists: Denis Wirtz, Ph.D.
Johns Hopkins University

Vadim Backman, Ph.D.
Northwestern University

Kelly Bethel, M.D.
The Scripps Research Institute

James R. Heath, Ph.D.
California Institute of Technology

9:45 a.m. - 10:00 a.m.

Break

10:00 a.m. - 11:15 a.m.	**Panel Session: Large-Scale Modeling of Cancer** Moderator: Robert J. Mittman, M.S., M.P.P. Facilitation, Foresight, Strategy Panelists: Kirk E. Jordan, Ph.D. IBM T.J. Watson Research Center Herbert Levine, Ph.D. University of California, San Diego Efthimios Kaxiras, Ph.D Harvard University Mauro Ferrari, Ph.D. The Methodist Hospital Research Institute	
11:15 a.m. - 12 noon	**The Next Generation of Physical Sciences-Oncology** (Facilitated Discussion) Robert J. Mittman, M.S., M.P.P. Facilitation, Foresight, Strategy	
12 noon - 1:50 p.m.	**Breakout Sessions and Lunch**	*Embassy-Patuxent* *Cartier-Tiffany* *Congressional*
1:50 p.m. - 3:30 p.m.	**Report-Outs and Closing Synthesis Session**	
3:30 p.m.	**Wrap-up**	
3:45 p.m.	**Adjournment**	

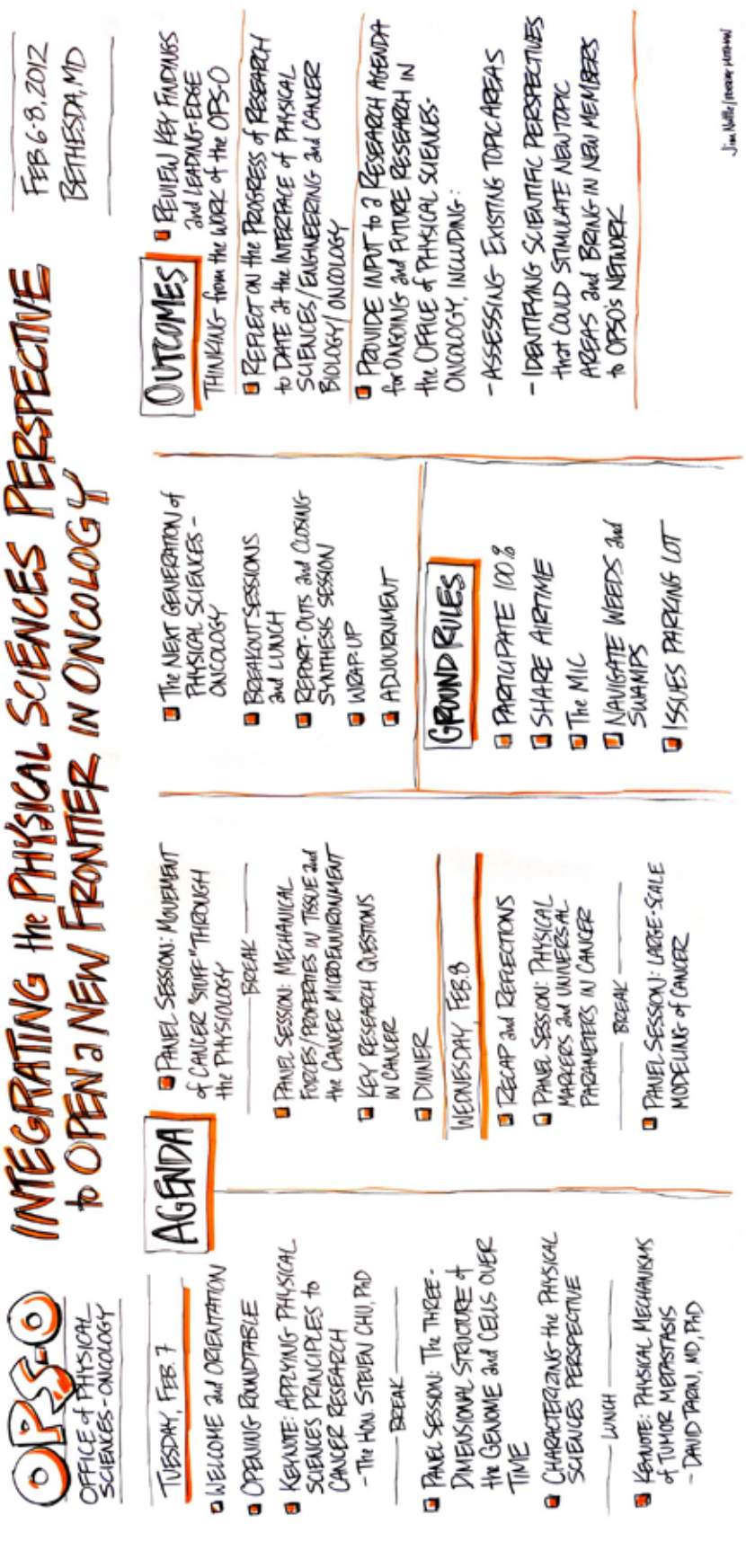

Figure 1: The agenda, ground rules, and expectations for the Office of Physical Sciences-Oncology Think Tank.

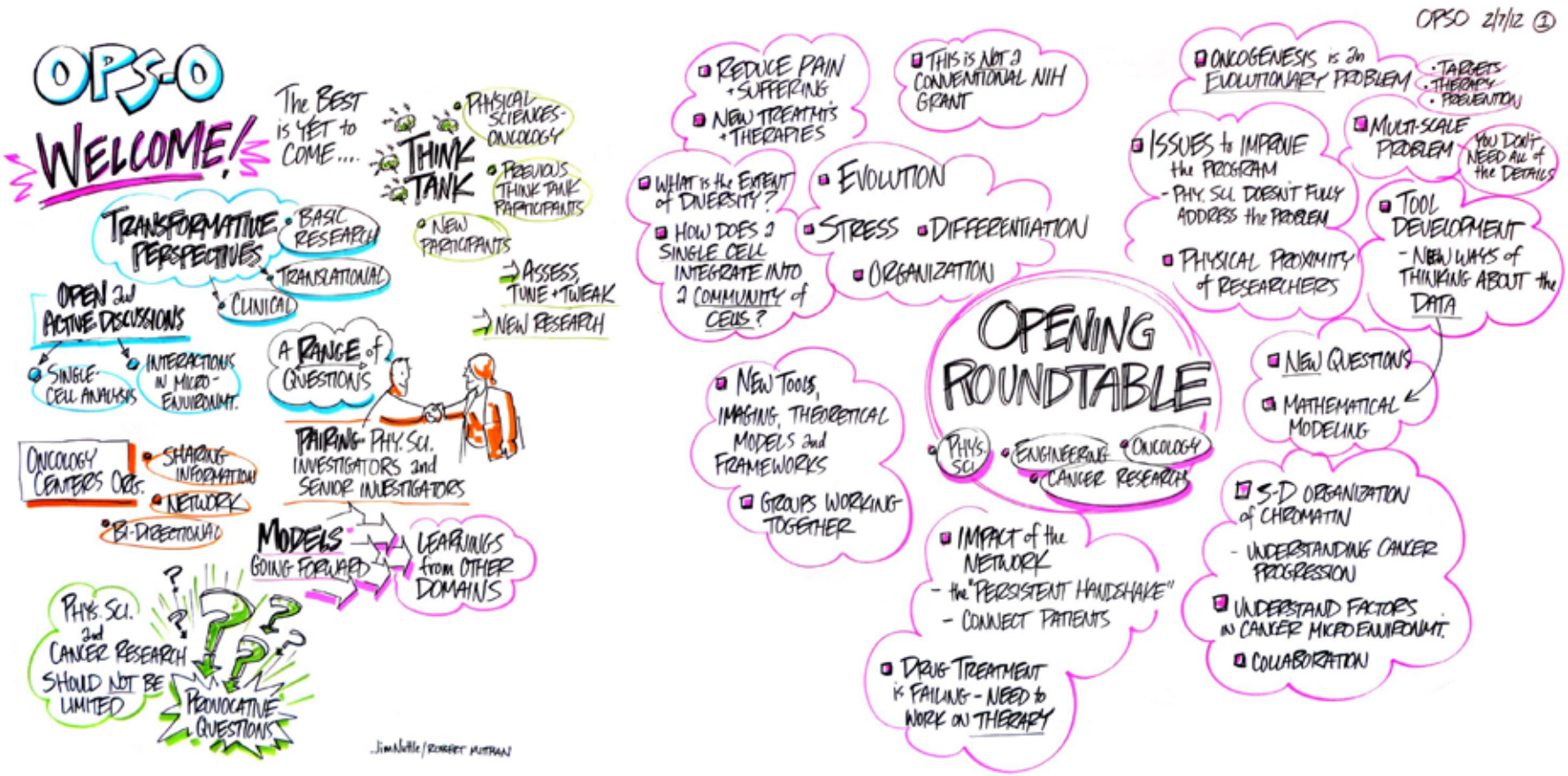

Figure 2: The welcome to the Think Tank and the summary of ideas generated from the Opening Roundtable exercise.

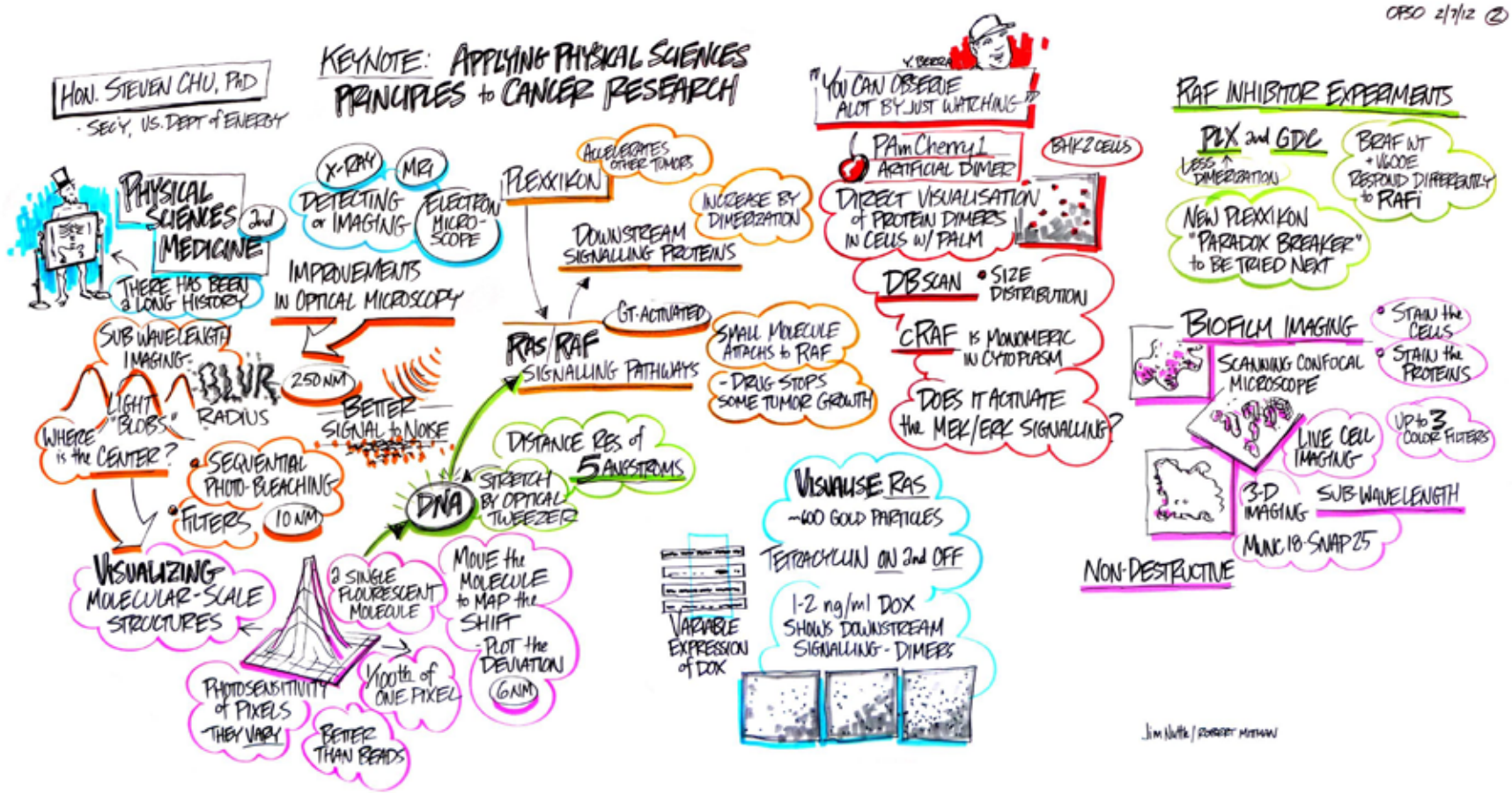

Figure 3: The graphic record of the Keynote Address "Applying Physical Sciences Principles to Cancer Research" by The Honorable Stephen Chu, Ph.D., Secretary, U.S. Department of Energy.

Figure 4: The graphical record of the panel presentations and discussion on "The Three-Dimensional Structure of the Genome and Cells Over Time."

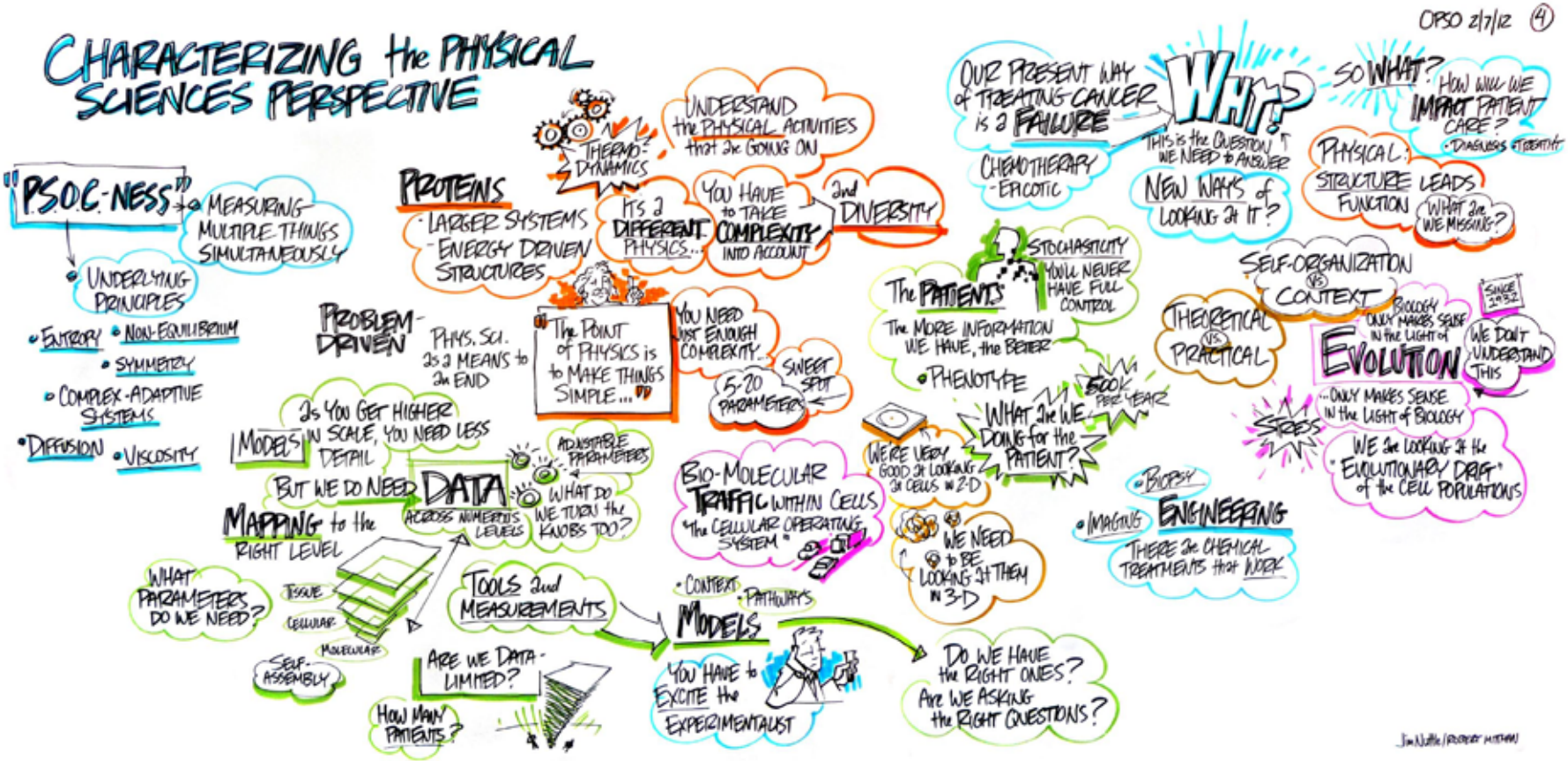

Figure 5: The graphical record of the facilitated discussion "Characterizing the Physical Sciences Perspective."

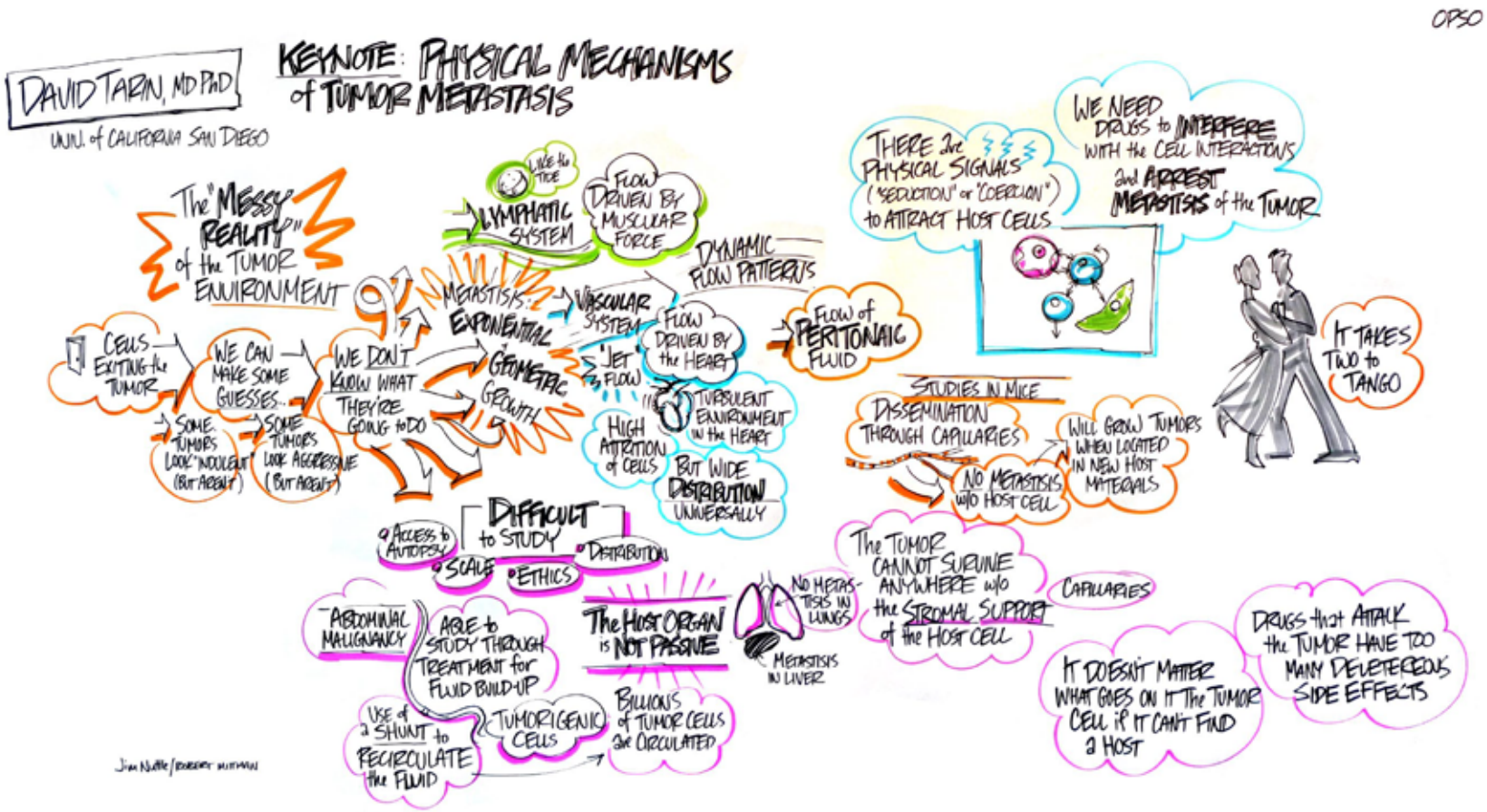

Figure 6: The graphical record of the Keynote Presentation by David Tarin, M.D., Ph.D. titled "Physical Mechanisms of Tumor Metastasis."

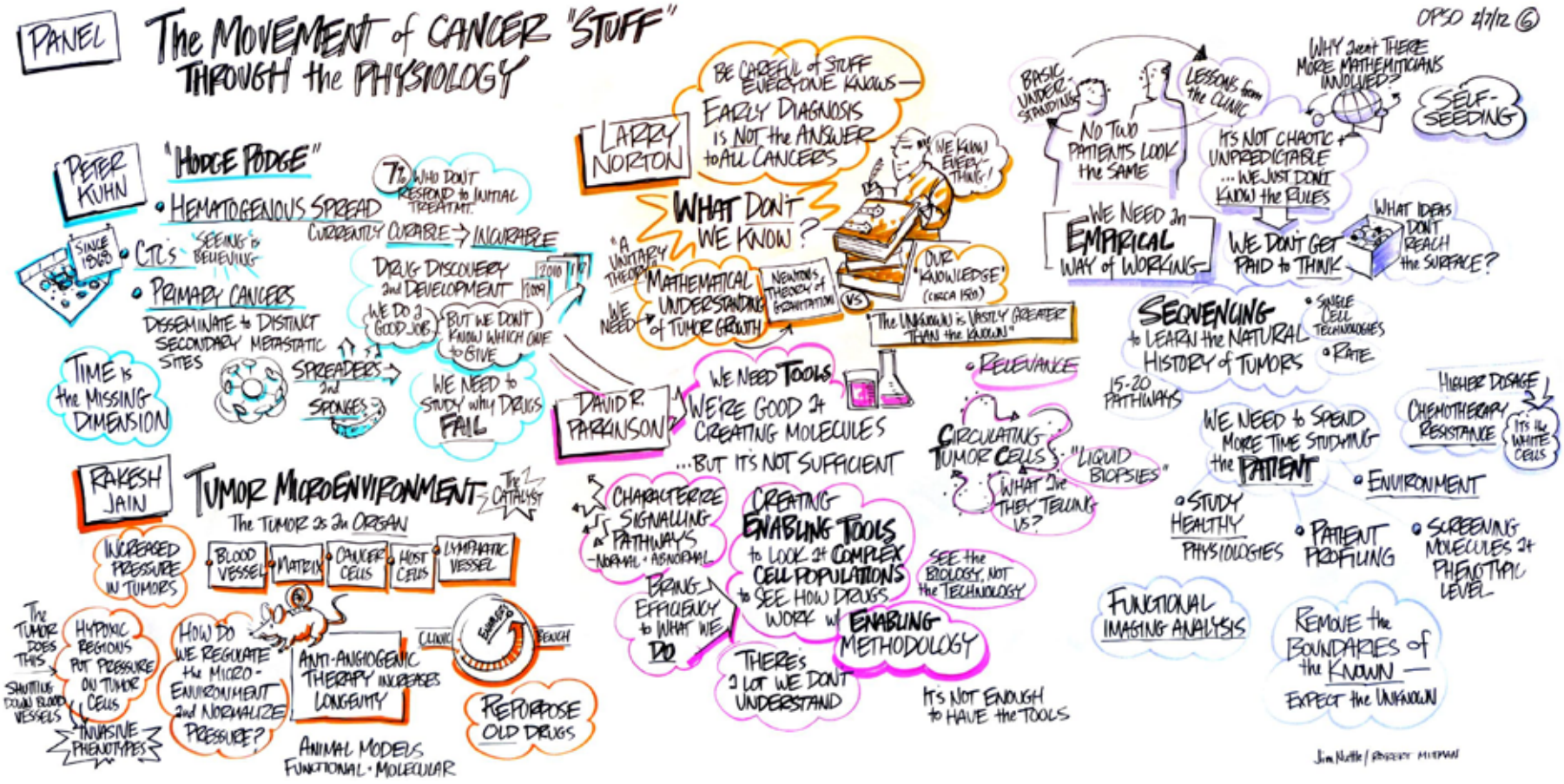

Figure 7: The graphical record of the panel presentations and discussion on "Movement of Cancer "Stuff" Through the Physiology."

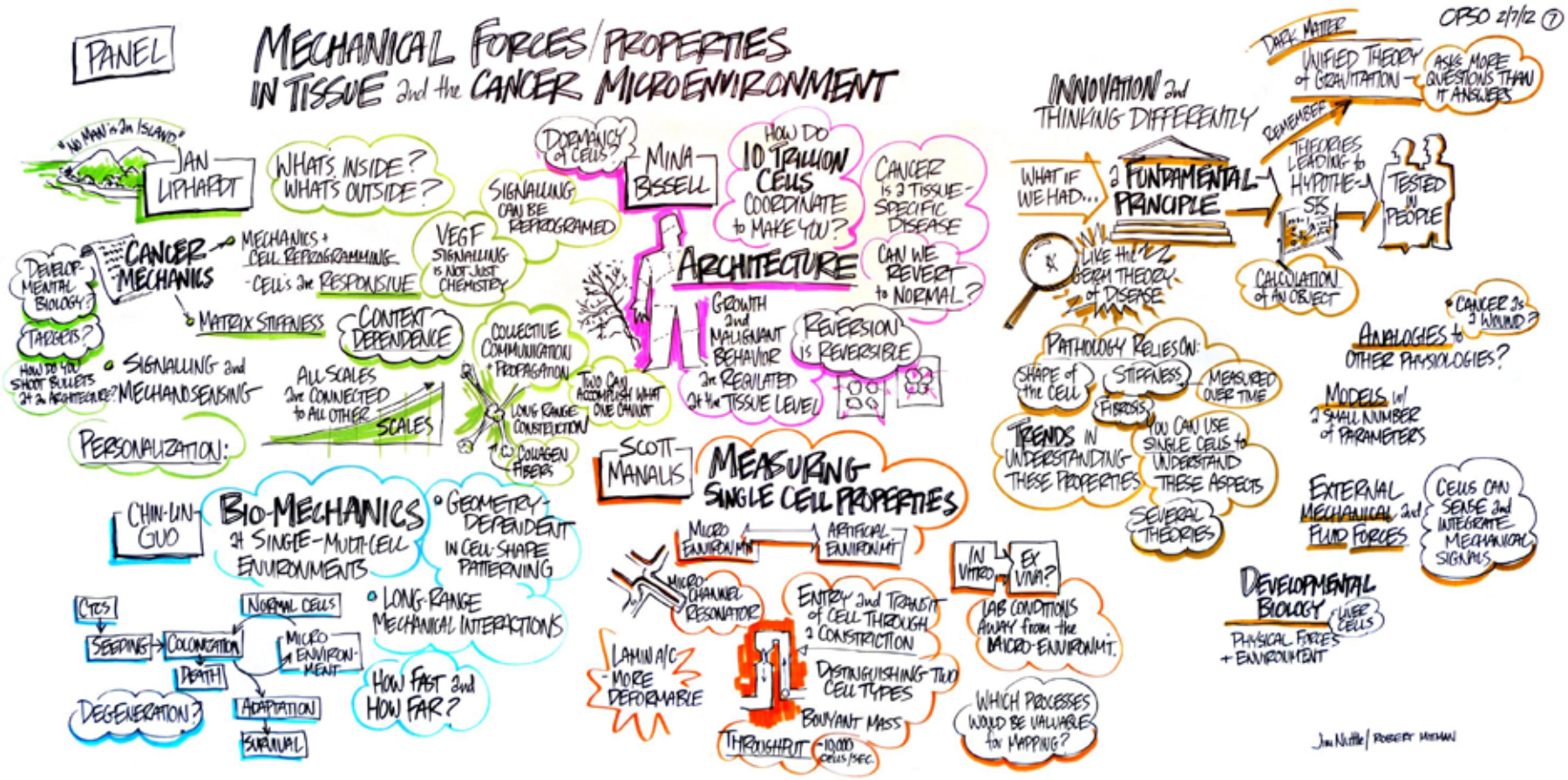

Figure 8: The graphical record of the panel presentations and discussion on the "Mechancal Forces/Properties in Tissue and the Cancer Microenvironment."

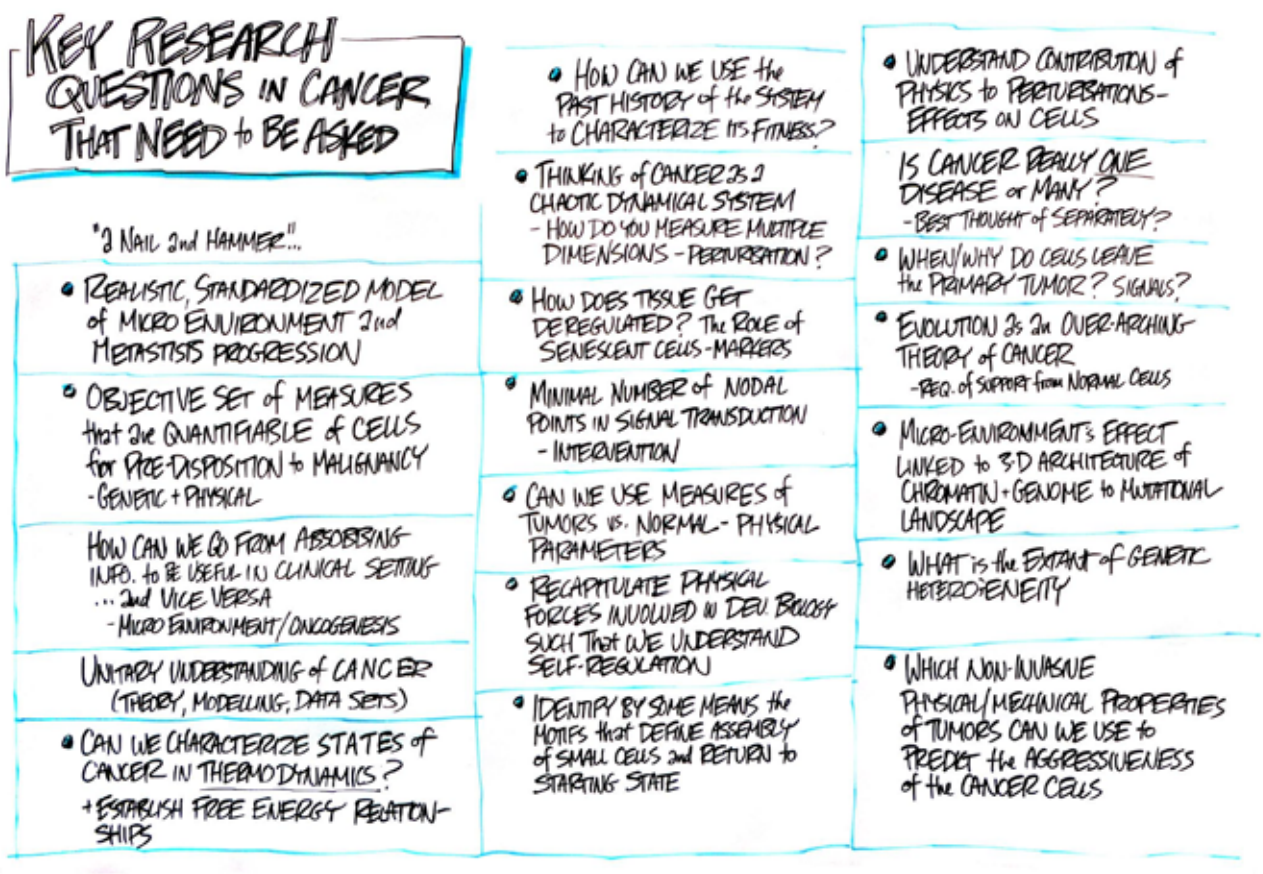

Figure 9: The list of the "Key Research Questions in Cancer" that need to be asked generated by Think Tank participants.

Figure 10: The graphical record of the panel presentations and discussion on the "Physical Markers and Universal Parameters in Cancer."

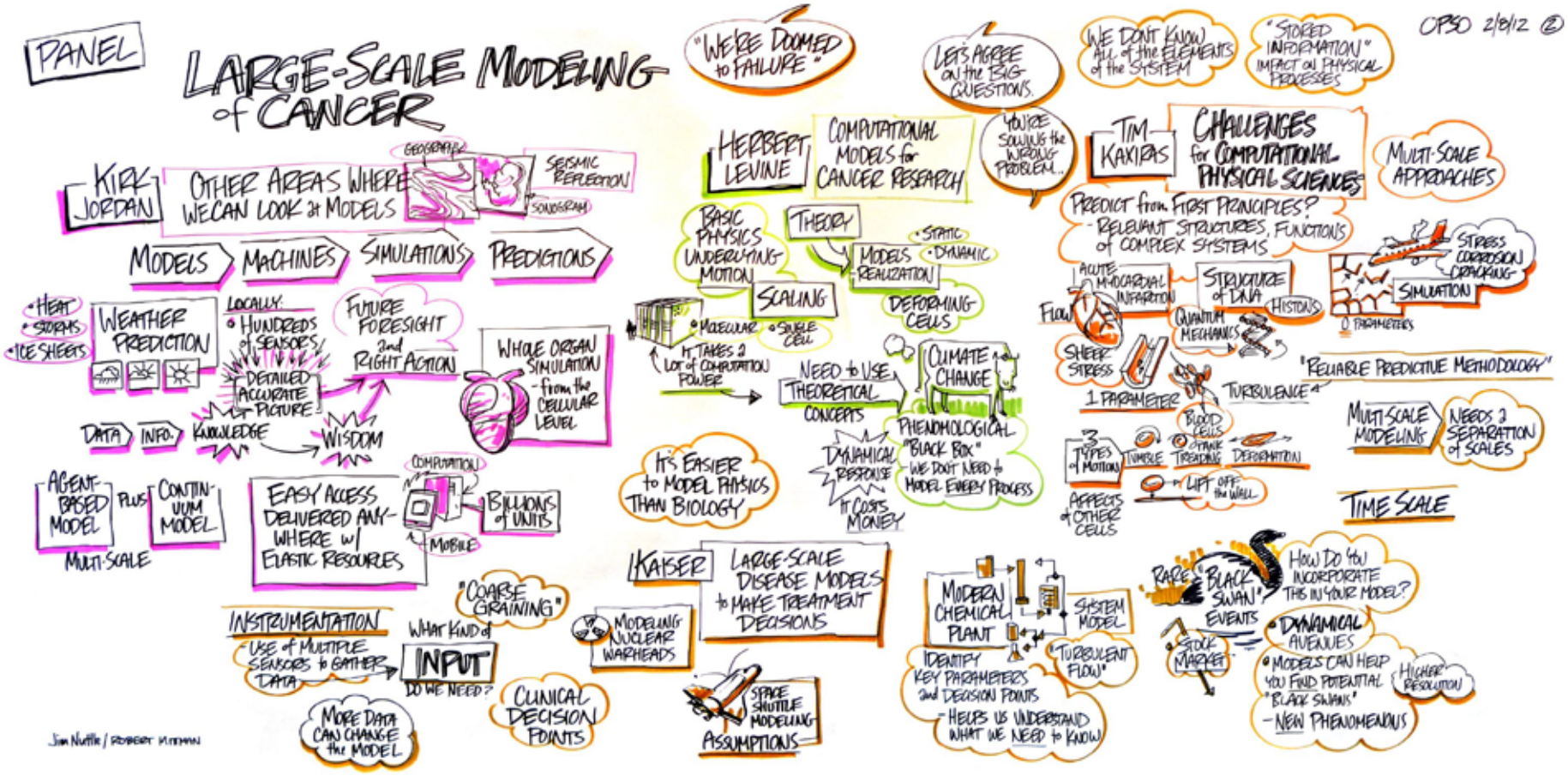

Figure 11: The graphical record of the panel presentations and discussion on "Large-Scale Modeling of Cancer."

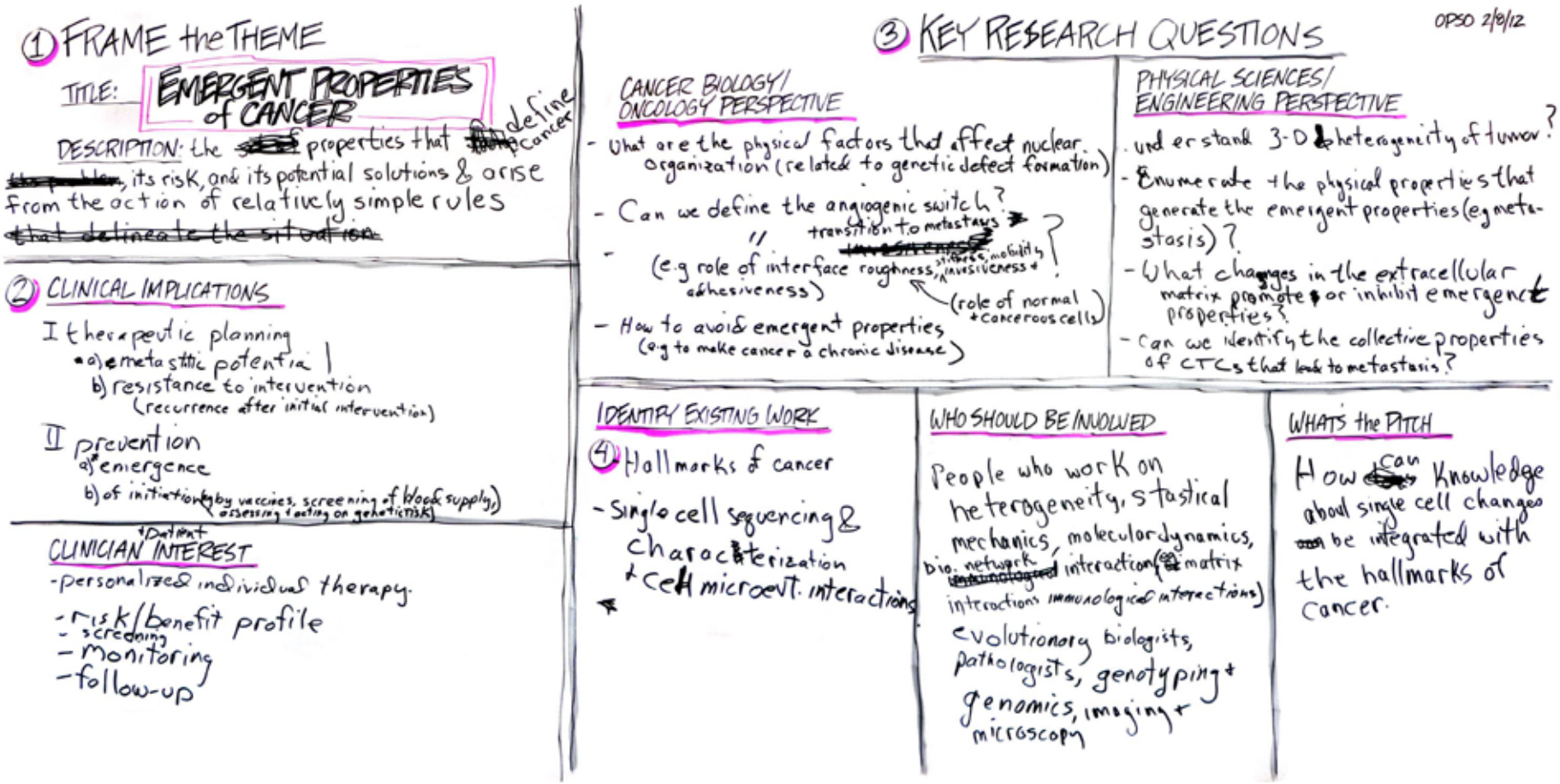

Figure 12: The notes of the Think Tank group focused on the theme of "Emergent Properties of Cancer."

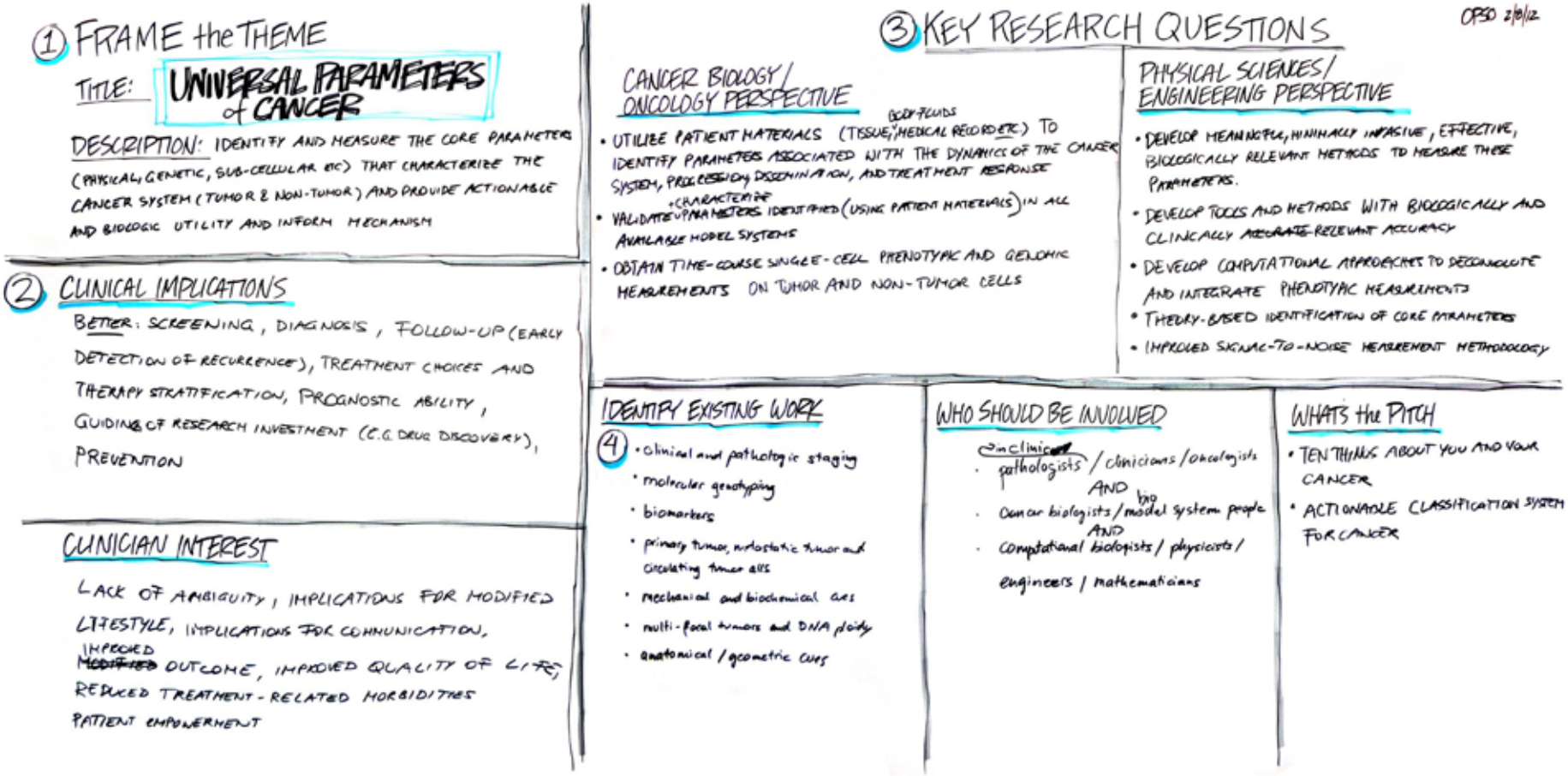

Figure 13: The notes of the Think Tank group focused on the theme of the "Universal Parameters of Cancer."

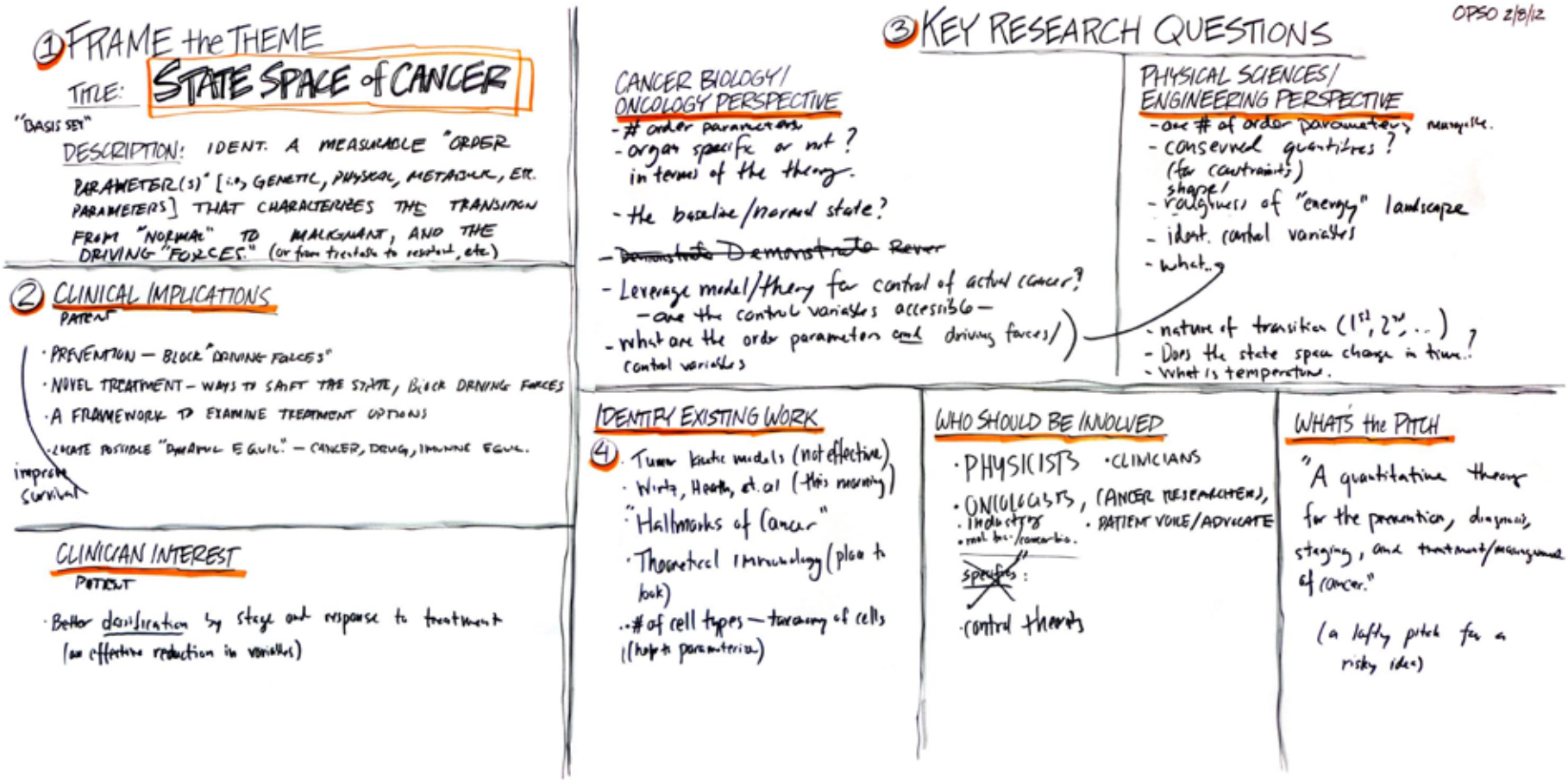

Figure 14: The notes of the Think Tank group focused on the "State Space of Cancer."

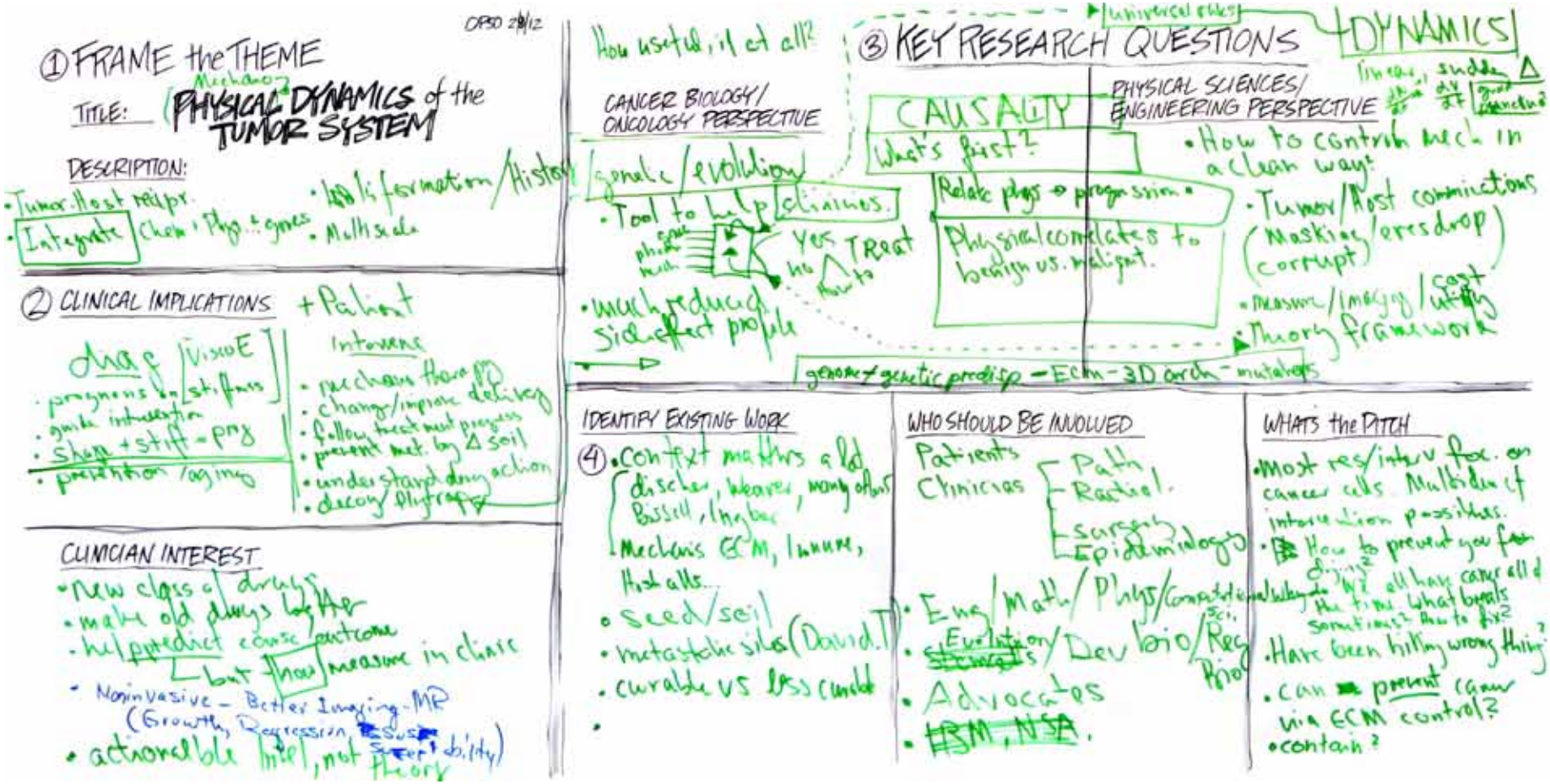

Figure 15: The notes of the Think Tank group focused on the "Physical Dynamics of the Tumor System."

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