National Cancer Institute

PHYSICAL SCIENCES in ONCOLOGY

Perspectives

News from the collaborative Network of Physical Sciences-Oncology Centers Spring 2013

Arizona State University, 2

Cornell University, 4

Dana-Farber Cancer Institute, 6

H. Lee Moffitt Cancer Center & Research Institute, 8

Johns Hopkins University, 10

The Methodist Hospital Research Institute,12

Massachusetts Institute of Technology, 13

Northwestern University, 15

Princeton University, 17

The Scripps Research Institute, 19

University of California - Berkeley, 21

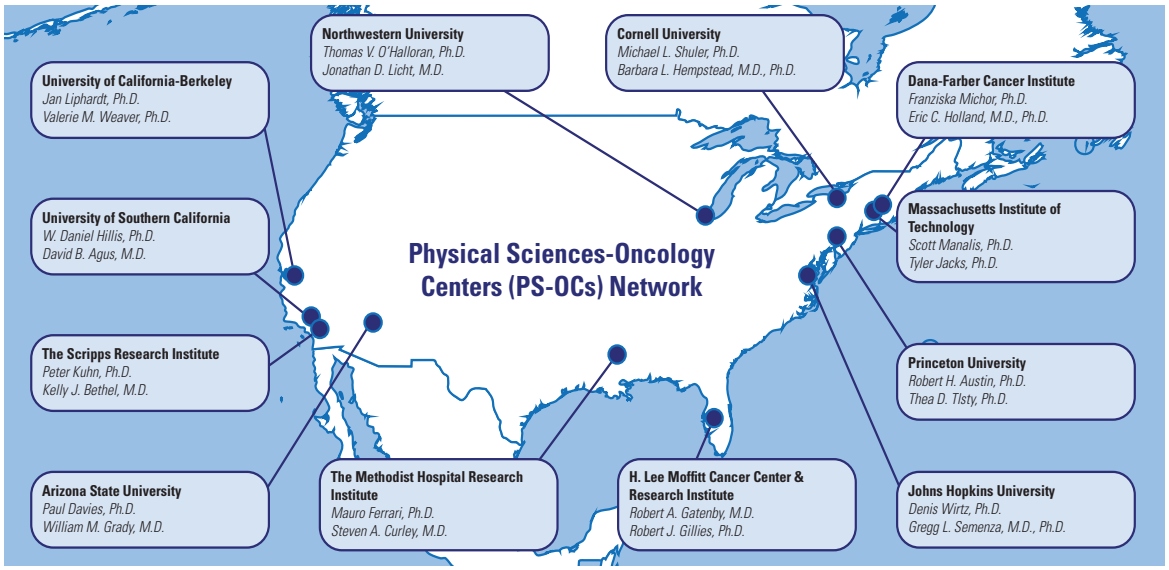
University of Southern California, 23

Pilot Project, 25

Young Investigator Highlights 26

Advocate Perspectives, 27

The Physical Sciences-Oncology Center (PS-OC) program launched by the National Cancer Institute in 2009 is a virtual network of 12 research centers.

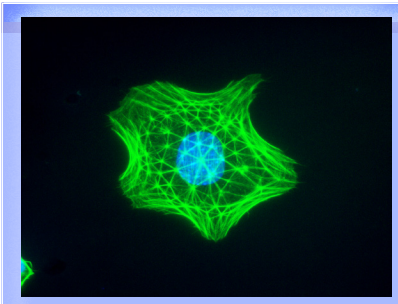


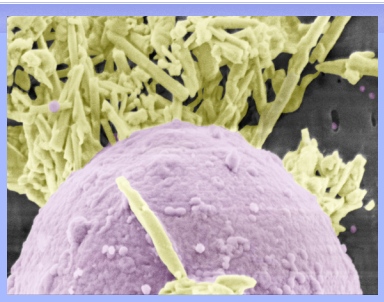
Its goal is to foster the development and testing of innovative approches to understand cancer processes and new fields of study based on knowledge of both biological and physical laws and principles that define normal and tumor systems.

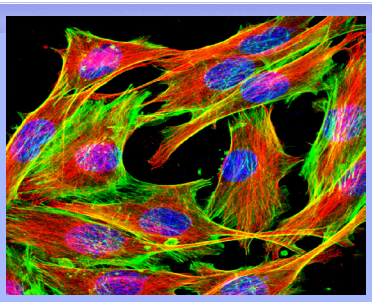
This program aims to bring new perspectives and knowledge to cancer research by encouraging transdisciplinary collaborations of mathematicians, physicists, engineers, and chemists with cancer biologists and clinical oncologists to tackle some of the big questions in cancer research.

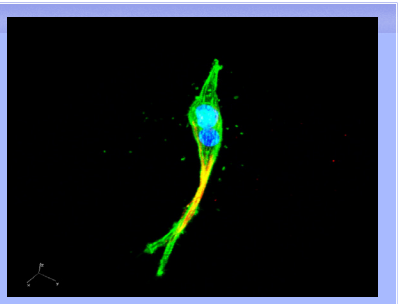
Each PS-OC's framework and research projects are organized around one or more themes such as evolutionary theory of cancer, the physical laws and principles of cancer, and information transfer in cancer.

This issue of the PS-OC Perspective highlights some of the research projects taking place at the different PS-OC centers. In addition it emphasizes team science that is abundant within each center and across the PS-OC network, training of a new generation of transdisciplinary scientists, and the involvement and impact of patient advocates in this field.









The Origin of Cancer *By Pauline Davies, Director, Education and Outreach*

Why does cancer exist? Why do most normal somatic cells come pre-loaded with a 'cancer subroutine' that can be triggered by a wide range of insults? And why does cancer, once initiated, progress in such a deterministic and predictable manner?

These basic questions, often overlooked in the headlong rush for a cancer 'cure,' form the core investigation of ASU's cancer theory group.

Cancer is not just a human malfunction, but is widespread among mammals, fish, birds, reptiles and even plants.

Something so deeply embedded in the workings of biology suggests deep evolutionary roots, possibly dating back to the dawn of multicellularity. Sure enough, oncogenes and tumor suppressor genes have been found even in "primitive" organisms such as sponges.

Work by theoretical physicist and astrobiologist Paul Davies and his Australian-based collaborator Charles Lineweaver postulates that cancer is a type of atavism or evolutionary throwback.

It is well known that complex organisms often retain ancient developmental pathways that are normally silenced. For example, early human embryos possess gills, reminiscent of our fishy ancestry. Davies and Lineweaver claim that:

"Cancer is retained by evolution because those same cancer genes play an indispensable role in embryo development."

"As cancer cells get progressively deregulated by the host organism, they default back to earlier and earlier ancestral phenotypes."

They predict that cancer progression runs the arrow of evolution backward at high speeds, so the most malignant cancer cells recapitulate ancestral forms dating back a billon years.

Support comes from the fact that cancer cells prefer a hypoxic (low-oxygen) environment, which could reflect conditions on Earth before the second great oxygenation event hundreds of millions of years ago. Thus cancer is a window onto the past.

Davies and Lineweaver plan to test their theory by examining the various well-known hallmarks of cancer and mapping their gene expression profiles onto phylogenetic trees. Their goal is to answer the over-arching question:

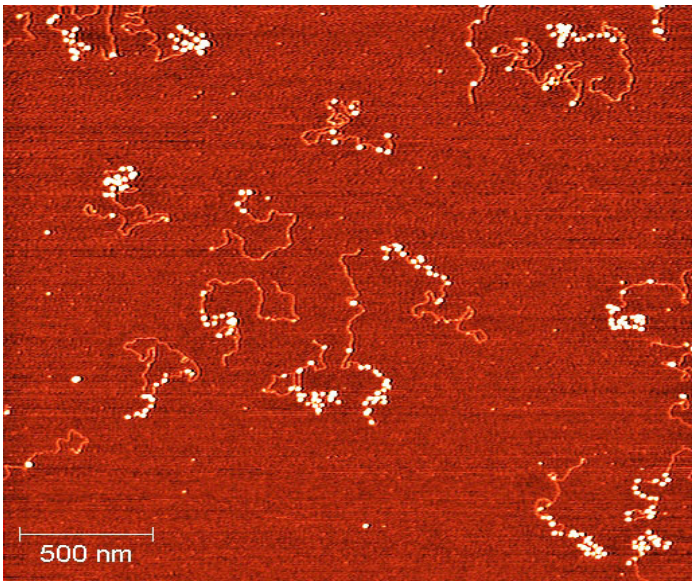
What is the place of cancer in the great story of life on Earth?

Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors; P C W Davies and C H Lineweaver 2011 Phys. Biol. 8 015001 http://iopscience.iop.org/1478-3975/8/1/015001

Why Does Methylation Silence a Gene?

Scientists have long known that when a gene is methylated (i.e. have methyl groups attached to GC pairs) the gene gets switched off. But why?

Parminder Kaur PhD



Nucleosome array reconstituted with designed 601 histone favorable sequence and imaging with AFM. In the image, each small white particle is formed by DNA wrapping around the histone octamer with almost two left-handed turns. A lot of these white particles formed along the DNA and present a 'bead-on-string' structure and this structure is the fundamental unit of chromatin. Image captured by Qiang Fu, Arizona State University.

ASU's epigenetics research group discovered the answer a few months ago, and it is an elegantly simple physical mechanism.

Stuart Lindsay and his graduate student Parminder Kaur had been studying the mechanical properties of Methylated DNA. They were intrigued by a result discovered in Steve Chu's lab (Berkeley) that methylated DNA sticks more fiercely to nucleosomes, thus making the chromatin stiffer. But the explanation was obscure.

The flexibility of a DNA molecule is known to be limited by the repulsive effect of electric charges strung out at intervals along the strand. But methylation doesn't affect this pattern. Furthermore, strands of DNA in solution are measured to have very similar flexibility whether they are methylated or not.

But the solution to the puzzle came when the Lindsay and Kaur scrutinized methylated DNA under water lying close to a mica surface. Using an atomic force microscope, they found that, in this location, the strands were dramatically stiffer than when floating freely in water. The explanation then dawned on the researchers; the methyl group has a hydrophobic tail. Methylated DNA therefore resembles a furry caterpillar that repels water. In turn, water pushes back.

So although methylated DNA is not intrinsically stiffer, it becomes effectively stiffer when "pushed" by water against a hard surface or object and that includes a nucleosome. This resulting rigidity when methylated DNA is wrapped around a nucleosome and surrounded by water compromises the molecular read-out machinery and silences the gene.

1 - Choy, J. S. et al. DNA Methylation Increases Nucleosome Compaction and Rigidity. J. Am Chem Soc 132, 1782–1783 (2010).
2 - Kaur, P. et al. Hydrophobicity of Methylated DNA as a Possible Mechanism for Gene Silencing. Physical Biology 9, 0605001-0605009 (2012).

http://cancer-insights.asu.edu/

By Teresa Porri, PhD, Outreach & Dissemination Leader

Engineering Analysis of Surgical Technique Reveals Interactions Between Stem Cells and Tumors

Biomedical engineers studying an increasingly common reconstructive surgery technique have discovered that this technique may have unforeseen risks.

Using adipose-derived stem cells from the patient's own body to reconstruct breast tissue holds great promise for patients that have gone through surgical treatment for breast cancer. The advantages of this technique lie in its ability to regenerate fully functional tissue.

Cornell's Center on the Microenvironment and Metastasis (CMM) researcher Claudia Fischbach-Techl has been using tools from clinical, biological, and physical sciences to look at the way these adipose-derived cells interact with cancer cells, to determine whether they create an environment which promotes tumor growth.

Claudia Fischbach-Techl

In the presence of even a small number of cancer cells, such as might remain in a symptom-free postsurgical breast cancer patient, adipose-derived stem cells undergo a variety of chemical, mechanical, and contractile changes.

Not only do these changes promote the growth of cancer cells, they also encourage these changes in neighboring adipose-derived stem cells, creating a positive feedback loop of tumorigenicity.

To determine whether the in vitro results were relevant in vivo, animal tests were performed in which tumor cells were injected on their own or together with adipose-derived stem cells. The tumors composed of a mixture of the two cells were on average 50% larger, and had a considerably enhanced access to blood flow.

Reference: Proc Natl Acad Sci U S A. 2012 June 19; 109(25): 9786-9791. doi: 10.1073/pnas.1121160109. Fischbach C. et. al.

Microvasculature Plays a Big Role in Metastasis

Cornell's Center on the Microenviroment and Metastasis has developed a cross-center focus on microvasculature, because of the way that potentially metastatic cells can use the blood vessels as a highway to distant sites to form tumors. Once implanted, the new tumor has the ability to divert nutrient flow to itself via the process of angiogenesis.

Cornell PS-OC researchers Abe Stroock and Mike King have engineered different systems, both of which are designed to answer different questions about the microvasculature's role in metastasis and metastatic tumor formation. A variety of approaches to modeling the same tissue structure lead to a richness in how we understand the tissue's role in metastasis and tumor growth.

Continued from previous page.

Abe Stroock's lab specializes in applying microfluidic techniques to biological questions. As part of the PS-OC, his group has engineered living microvascular networks composed of vascular endothelial cells, which line microfluidic tissue scaffolds.

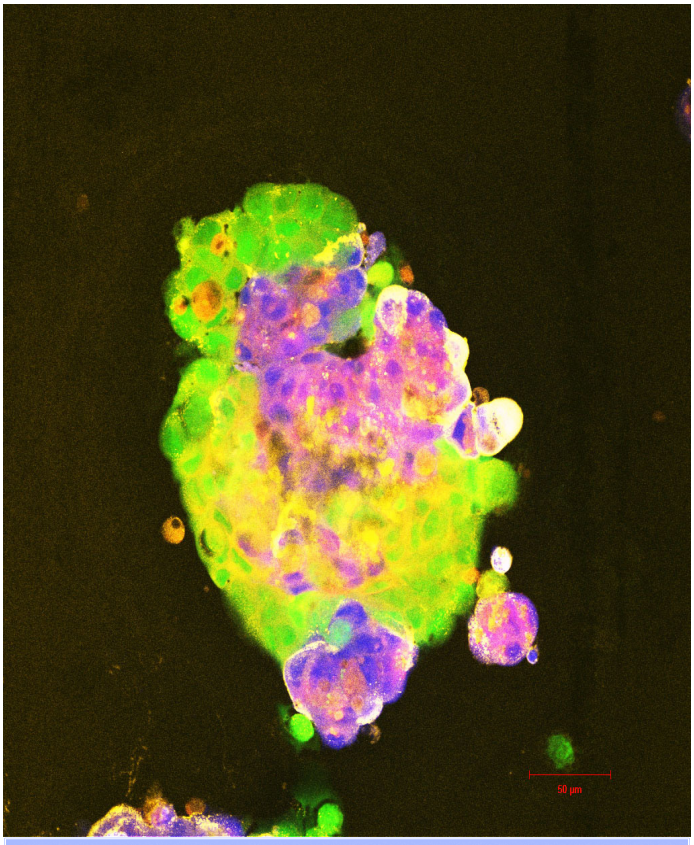
These networks are surrounded by collagen matrix as would exist in vivo, and can also be seeded with cells of interest.

This technique combines the advantage of in vitro microvascular studies—recreating the physiology of cells confined within a 3D geometry—while also having the ease of imaging and control that comes from traditional 2D in vitro studies.

This engineered microvasculature mimics various properties of the native microvasculature, such as undergoing inflammation when exposed to inflammatory stimuli.

The scaffolds also underwent angiogenesis when supplied with pro-angiogenic factors, a process which was affected by normal cells seeded into the collagen and supporting the artificial vessels.

This synthetic microvasculature can be used to study the angiogenesis that occurs during tumor growth, and may provide a method of testing anti-angiogenic therapies.



BT20, MCF7 & MCF10A cells labeled with CellTracker blue, green, and red respectively were cocultured in a tumor spheriod and uncubated with flourescent soluble E-selectin (orange) and imaged using Zeiss 710 Confocal Microscope in sequential (multitrack) acquistion mode.

While Stroock's group develops tools for preventing tumor growth, Mike King's lab seeks factors, which would prevent cancer cells from adhering in the first place. They have developed a microfluidic assay for looking at the rolling and sticking behavior of circulating tumor cells.

Circulating tumor cells originate from a primary tumor and are released into the bloodstream, where they can travel to distant sites and form secondary tumor sites—but only if they can find purchase.

King's lab has found that a variety of factors play into the ability of circulating tumor cells to stick to the endothelial-lined microvasculature.

These factors include expression of the MUC-1 protein on the surface of the circulating cells (present in greater concentrations in highly metastatic cells), and presence of pro-inflammatory molecules IL-6 and TNF-α.

These techniques are being used to determine possible sites for targeting anti-metastatic therapies.

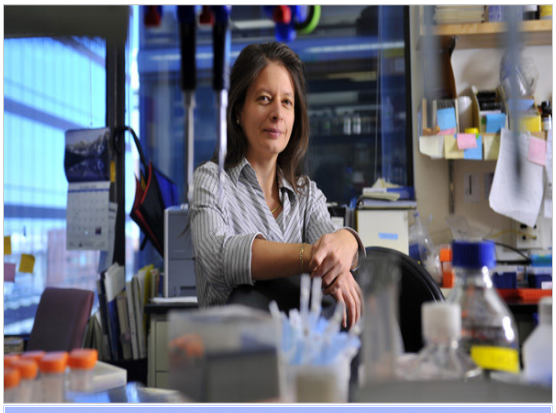
Reference: Proc Natl Acad Sci U S A. 2012 June 12; 109(24): 9342-9347. doi: 10.1073/pnas.1201240109. Stroock A. et. al.

http://www.psoc.cornell.edu/

By Dr. Franziska Michor & Dr. Ingo Mellinghoff

Recent advances from the Dana-Farber Cancer Institute Physical Sciences-Oncology Center (DFCI PS-OC) have investigated the temporal sequence in which genetic alterations arise during breast tumorigenesis.

In a collaboration between the laboratories of Dr. Kornelia Polyak and Dr. Franziska Michor, both at the Dana-Farber Cancer Institute, researchers addressed the order in which mutations arise in three key genes important for breast cancer development (BRCA1, PTEN, p53).



Dr. Kornelia Polyak

Defining the temporal order in which these mutations arise is critical for early detection, risk stratification, and the design of chemopreventive therapies.

The team focused on BRCA1-associated breast tumors. This subtype of tumors displays loss of the tumor suppressor BRCA1, which is often passed on from one parent and leads to a large chance of developing this type of breast cancer.

In addition to BRCA1 mutations, such tumors also frequently display mutations of PTEN and p53. The researchers analyzed the mutational status of BRCA1, PTEN, and p53 at the single cell level in 55 BRCA1-associated breast tumors.

Dr. Franziska Michor

They developed computational methods to predict the relative temporal order of mutations, on the basis of the frequency of cells with single or combined alterations.

These methods, designed by DFCI PS-OC Principal Investigator Dr.Michor, investigator Dr. Subhajyoti De from the University of Denver Medical School, and biostatistician Dr. Mithat Gonen from the Memorial Sloan-Kettering Cancer Center (MSKCC), utilized the single-cell based data to identify the most likely order of events.

Interestingly, the team found that, although there was no obligatory order of events, loss of PTEN was the most common first event. This ordering was associated with the basal-like subtype of breast cancer.

In contrast, in the majority of luminal breast tumors, mutation of p53 occurred first. The researchers also found that within the same tumor some cells carry BRCA1 mutation while others do not.

Furthermore, they found evidence for increased cell proliferation in normal breast tissue of BRCA1 mutation carriers.

These results have important implications for the design of chemopreventive and therapeutic interventions in this high-risk patient population.

Reference: Martins FC, De S, Almendro V, Gonen M, Park S-Y, Schnitt SJ, Tung N, Garber JE, Fetten K, Michor F, Polyak K (2012) Evolutionary pathways in BRCA1-associated breast tumors. Cancer Discovery 2, 503-511.

In other news from the DFCI PS-OC, researchers led by investigator Dr. Ingo Mellinghoff from the MSKCC have elucidated the patterns of treatment response in lung and brain cancer.

The team was interested in finding the cause of the poor responses to targeted therapy in glioblastomas, the most aggressive form of brain cancer in adults. Approximately 40% of these tumors harbor specific mutations in the Epidermal Growth Factor Receptor (EGFR). These mutations were predicted to sensitize the tumors to EGFR inhibitors. Such drugs have led to impressive results in lung tumors harboring similar mutations.

However, attempts to therapeutically target EGFR with first-generation EGFR inhibitors in glioblastoma have failed. The investigators first observed that activation of EGFR in glioblastoma occurs through mutations or deletions in the extracellular part of the receptor. This stands in contrast to lung cancers, in which an intracellular part of the EGFR is mutated.

Knocking down the expression of EGFR induced cell death in brain cancer cells with extracellular EGFR mutation, proving that these cells require the EGFR for survival.

The Mellinghoff group then tried several drugs that can block the EGFR and found that EGFR inhibitors that bind to a particular shape of the receptor (the so-called “inactive” conformation of the kinase domain) were much more active than commonly used EGFR inhibitors.

These results provide first evidence that glioblastoma cells with EGFR mutation rely on signals from this receptor for their survival.

Furthermore, they suggest that the disappointing clinical activity of first-generation EGFR inhibitors in glioblastoma may be attributed to the type of EGFR mutations in this cancer.

Dr. Ingo Mellinghoff

Ongoing work within the DFCI PS-OC now aims at utilizing mathematical modeling to identify the best treatment dosing schedule to induce maximum responses in glioblastoma patients.

Cancer Discov. 2012 May;2(5):458-71. doi: 10.1158/2159-8290.CD-11-0284. Epub 2012 Mar 31. Mellinghoff et. al.

http://psoc.dfci.harvard.edu/

By Robert Gillies PhD & Kristin Swanson PhD

Integrating Experiments, Imaging and Mathematics to Predict the Behavior of Cancers in Human Patients

Tumors are complex and composed of many different interacting components, which make them difficult to understand and even more difficult to treat.

Mathematical modeling helps simplify the complexity by focusing on the key actors in a patient's tumor and then explores their likely interactions using mathematical equations.

This integrated mathematical-experimental-clinical-theoretical system is central to the Moffitt approach and has been used to investigate prognostic factors in a number of cancers, for instance, in the agressive skin cancer, melanoma.

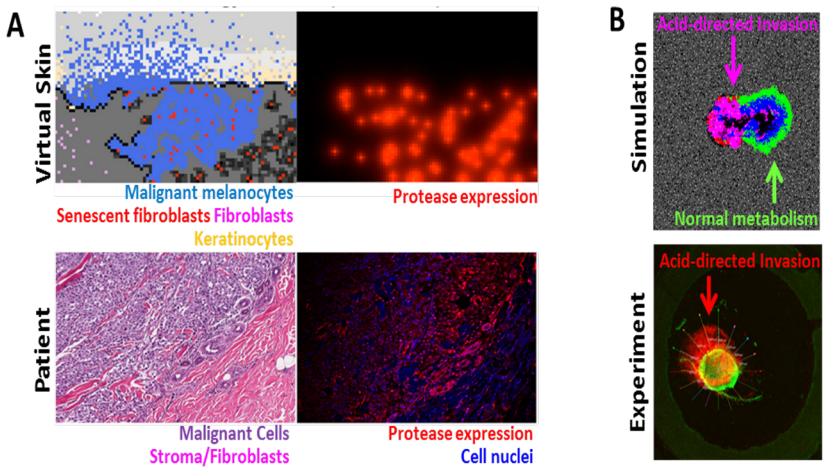
The scientists examine the role of fibroblasts, cells responsible for the structural framework of the tissue, in driving melanoma initiation and progression. They are particularly interested in the role of senescent fibroblasts, those that are old and no longer dividing.

They have developed a mathematical model of normal skin (virtual skin) that has demonstrated that specific factors produced by fibroblasts play a key role in maintaining the stability and the health of the skin.

Furthermore, senescence in fibroblasts can drive melanoma progression by producing two key factors: enzymes which break down the proteins holding the cells together (proteases), and growth factor hormones, which induce cellular division. Surprisingly the culprit for this increased protease production was not the cancer but the senescent fibroblasts.

These model predictions prompted experimentalists to look for this possible phenomenon in both 3D cell culture and human samples and found the expression pattern to match (Figure 1A).

This finding identified potential new targets for therapy - the proteases secreted by senescent fibroblasts.



Combining biological data with mathematical modeling at the tissue scale. (A. Melanoma). Top panel, left, shows a virtual skin model simulation and, right, expression of proteases (enzymes that degrade proteins).

Bottom panel - a human melanoma specimen stained, left, for malignant melanocytes (purple) and normal connective tissue (pink); and, right, for proteases, which agrees with the model prediction.

(B. Colon Cancer).
Top- a snapshot of math model capturing invasion of cancer cells into the surrounding connective tissue, acid-producing/acid-resistant cells are red-purple, and cells with normal metabolism are blue-green.

Bottom - invasion towards acid regions of colon cancer cells into normal tissue at 4 days (green) and 14 days (red) post-implantation into dorsal window chamber.

Moffitt Researchers Study Breast and Colon Cancers

Tumor cells often produce more acid than normal cells so Moffitt PS-OC scientists want to understand the implications of this. One hypothesis they are investigating is that the acid may help the tumor cells invade the surrounding tissue, a critical step in the formation of metastases.

The scientists created a math model incorporating the acid produced by the tumor cells and allowing the cancer cells to evolve complex metabolic behaviors based on their microenvironment. They found that if tumor cells are able to produce acid and survive in an extremely acidic environment, they will inevitably invade.

The result of this model simulation is shown in Figure 1B (top), where the acid-producing/acid-resistant cells are red-purple, and cancer cells with more normal metabolisms are blue and green.

This prediction was then tested in a mouse model wherein breast and colon cancer cells were imaged as they invaded into normal tissue (Figure 1B, bottom). This invasion was totally dependent on the local generation of acid at the leading edge, and was inhibited when the acidity was neutralized.

Experiments have shown that neutralization of tumor-derived acid with oral buffers prevents metastasis in mice, and clinical trials in humans are underway.

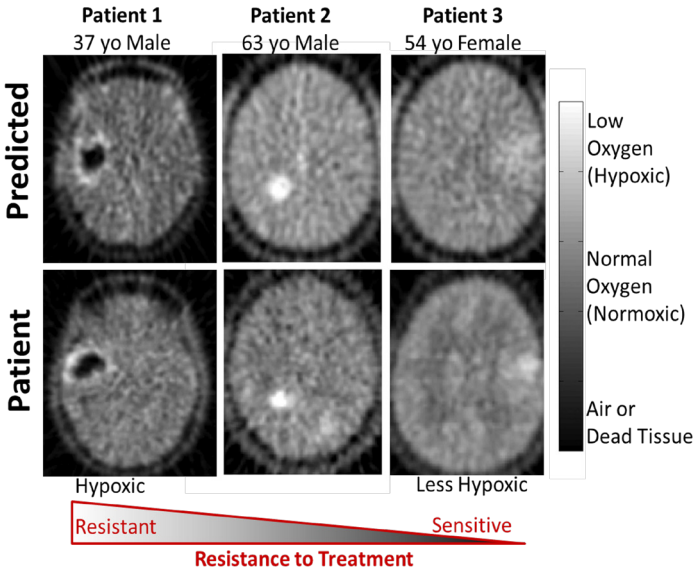
Moffitt and Northwestern PS-OCs use an integrated mathematical-experimental approach to study gliomas, highly invasive forms of primary brain cancer.

Magnetic resonance images (MRIs) are routinely used to inform the physician's understanding of tumor growth and response to treatment, yet MRIs are only able to show the tip-of-the-iceberg of the actual disease and do not highlight the entire region containing tumor cells.

Other forms of clinical imaging are used, such as positron emission tomography (PET) to highlight tumor regions low on oxygen (hypoxic), which is an important predictor of treatment resistance, but these are expensive and time consuming. Building on the work of the Moffitt PS-OC, Northwestern University researchers have developed mathematical models for gliomas that predict not only growth of overall tumor (analogous to that visible on MRI) but also the progression of hypoxia and the tumor's microenvironment (visible on PET).

By tuning these models to each patient (using MRI), they have been able to accurately predict the amount of tumor that is hypoxic and to reproduce the individual patient's PET image (Figure 2). The positive comparison of the model predictions of areas of low oxygen (Figure 2, top row) to the actual human data (Figure 2, bottom row) provides confidence that the model may be useful in predicting the likely treatment resistance of individual patients.

http://www.moffitt.org/psoc



The Moffitt PSOC approach of combining patient data with mathematical modeling at the clinical imaging scale.

Three glioblastoma patient PET images of hypoxia are shown on the bottom row and the corresponding patient-specific model simulation prediction is shown on the top row. Bright areas correspond to regions low in oxygen (hypoxic), while gray areas indicate regions, which have sufficient amounts of oxygen. Black regions correspond to air (outside the skull) or to dead tissue. The agreement of the prediction and the actual PET image provides validation of the mathematical model.

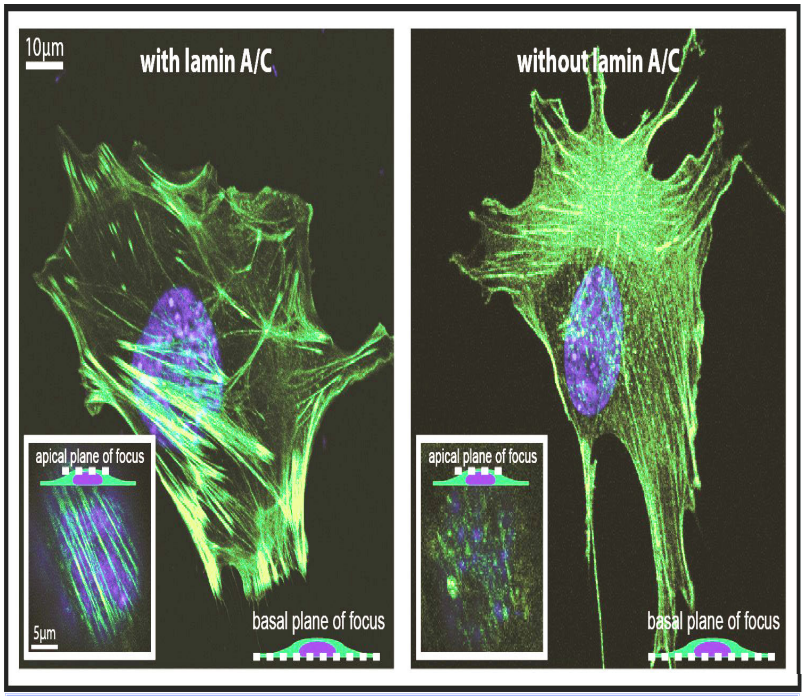
Actin "Cap" Triggers Action In the Nucleus *By Mary Spiro, Science Writer*

Researchers in the Denis Wirtz's lab have shown for the first time that there is a direct physical linkage of proteins from the cellular membrane to the inside of the nucleus that communicate information to the DNA.

The linkage stems from a "cap" of actin fibers from the extracellular milieu into the nucleus and allows for ultrafast mechanotransduction.

The Wirtz group exposed cells to shear flow, similar to what they might experience with fluid rushing through a blood vessel or between tissues.

The nuclear protein lamin, which helps connect actin to the nuclear envelope was key to mechanotransduction.



Healthy cells form an actin (green) cap over the nucleus (blue) in response to a shear flow stimulus (left). Cells lacking the protein lamin A/C are unable to form the actin cap (right).

Study lead Allison Chambliss, a doctoral student in Wirtz's lab, said that lamin is mutated in progeria (the rapid aging disease) and muscular dystrophy. Cell response to shear flow is very important in cardiovascular disease and cancer, so that's where the future work would be with the endothelial cells (cells that line blood vessels).

Chambliss said the next steps would be to measure the extent of DNA rearrangement on different types of cells using high throughput cell phenotyping.

Chambliss collaborated with Didier Hodzic and Gregory D. Longmore, both PS-OC faculty at Washington University in St. Louis. Additional authors include Shyam B. Khatau, PhD (a postdoc in Wirtz lab), Nicholas Erdenberger, an undergraduate in Wirtz lab and D. Kyle Robinson, an undergraduate intern from Oregon Health and Science University.

The paper, "The LINC-anchored actin cap connects the extracellular milieu to the nucleus for ultrafast mechanotransduction," published in NATURE: Scientific Reports, January 18, 2013 can be found here: http://www.ncbi.nlm.nih.gov/pubmed/23336069.

Engineers Coax Stem Cells to Diversify

Researchers in the Sharon Gerecht lab are prodding stem cells to become two different types of tissue needed to build veins and arteries. Synthetic smooth muscle cells migrate through the surrounding tissue, continue to divide and help support the newly formed blood vessels.

Contractile smooth muscles cells remain in place, stabilize the growth of new blood vessels and help them maintain proper blood pressure. In cancer, small blood vessels are formed to nourish the growing tumor.

Principal Investigator Gerecht says: *"Finding out how to steer these stem cells into becoming critical*

Continued from previous page.

building blocks to make blood vessel networks is an important step in understanding how blood vessels are stabilized in tumors," which could be useful in the treatment of cancer.

Lead author Maureen Wanjare used growth factors to control the stem cell response. When more of the growth factor and serum were used, the stem cells turned into synthetic smooth muscle cells. When less was provided, they became contractile smooth muscle cells.

Additional authors include Frederick Kuo, an undergraduate majoring in chemical and biomolecular engineering and Linzhao Cheng, a hematology professor in the Johns Hopkins School of Medicine, who provided the human induced pluripotent stem cells used in the above experiments.

The study was published in the January 2013 journal Cardiovascular Research.
http://www.ncbi.nlm.nih.gov/pubmed/23060134.

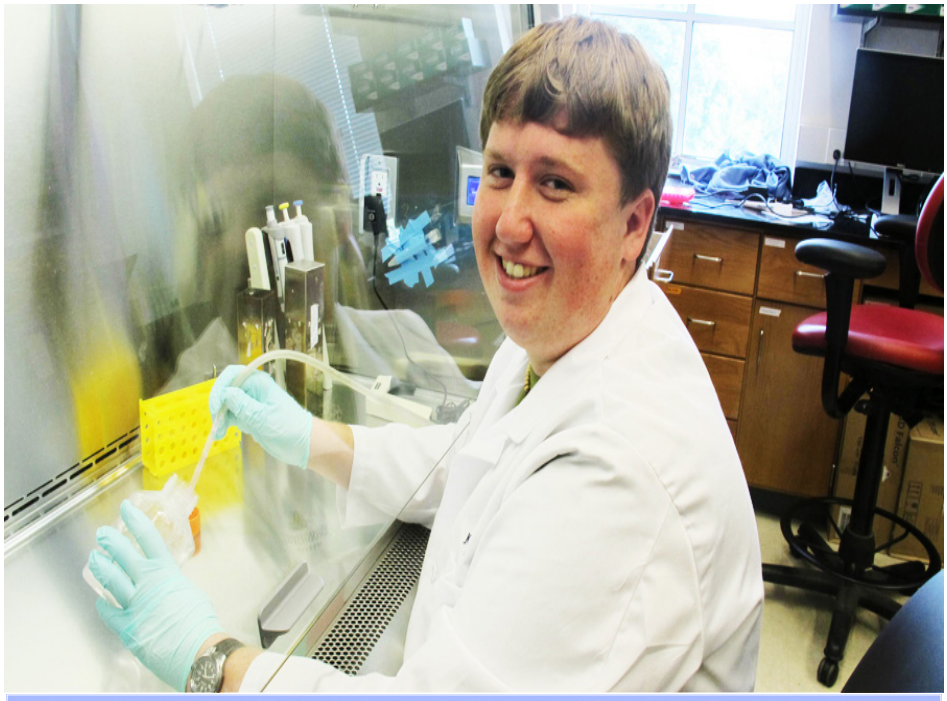
Interns Advance Johns Hopkins PS-OC Projects Over Summer

Four research interns who worked at Johns Hopkins over the summer were hosted in PS-OC laboratories.

Interns conducted 10 weeks of research and at the end of that time; students presented theirwork in a university wide poster session.

Jacqueline Carozza of Cornell University used high throughput cell phenotyping (HTCP) to investigate the physical differences in a variety of cancer cell lines in response to varying concentrations of the cancer drug doxorubicin.

Cassandra Loren of Oregon State University used HTCP to examine the physical characteristics of cells growing through various life cycle stages, particularly quiescence or cell inactivity. Both worked in the Wirtz lab.



Josh Porterfield (Cornell) in the Gerecht lab at Johns Hopkins.

Josh Porterfield of Cornell interned in the Gerecht lab at Johns Hopkins. He studied the influence of a transcription factor associated with the formation of blood vessels in breast cancer tumors called HEYL on the patterns of vascularization in the extracellular matrix.

Carolyn Zhang of University of California, San Diego worked on optimizing a template containing a growth factor gradient upon which endothelial colony-forming cells could establish a tubular structure of viable cells.

http://psoc.inbt.jhu.edu/

By Jason Sakamoto, PhD, PS-OC Center Manager

Highlights of Center Activities: Education & Outreach

Caught on Camera

Like other Physical Sciences-Oncology Centers, the Center for Transport Oncophysics (CTO) develops sophisticated technologies and services that represent the core of innovation for this Houston-based PS-OC. Under the CTO Education & Outreach activities, we are developing a video library as a mechanism to disseminate knowledge in the most exciting and efficient manner. Each video will portray the details of specific CTO technologies and protocols that feature PS-OC post-doctoral fellows and students "in the act" of demonstrating their areas of expertise.

Thus far we have taped two projects: 1) a behind-the-scenes look into silicon particle fabrication, which is one of the flagship platform technologies that the CTO employs to understand and manipulate particle transport for the treatment of cancer; and 2) a 2-photon intravital microscope used to observe real time transport phenomena of nanovectors and drug distribution within a live animal.

The CTO hopes to utilize the videos as a training vehicle for current and future investigators, and as a platform for collaborative expansion.

Seminar Series

Although most CTO Investigators are centrally located within the Texas Medical Center, long hours in the lab often make it difficult to "mingle" and engage nearby colleagues in scientific conversations. To break down the institutional silos, the center has introduced the Bi-weekly Seminar Series for hardworking, time-strapped post-docs and students to gather at one location.

"Getting an overview of the achievements between researchers from MD Anderson and the Methodist groups was very important. We realized how the projects can enrich each other and how the current goals can be expanded. Our collaborations led to new research opportunities."

Nadya Koshkina, PhD, Young Investigator

Senior researchers, post-docs, gather for presentations and discussion at the Bi-Weekly Seminar Series

1st Annual Collaborative CTO Workshop for Young Investigators

This one day event was held in January 2013 and began with Drs. Mauro Ferrari and Steven Curley **(bottom picture)**, the scientific and clinical leaders of the center, answering a barrage of questions from young researchers about the topic, "Connecting the Dots: Barriers, Treatment and Cancer." The Workshop continued with presentations from both Young Investigators and Faculty and ended with a round table discussion where participants exchanged new ideas that they had developed during the day.

One of the workshop objectives was to prepare the Young Investigators to compete for funding opportunities between different PS-OC centers.
www.methodisthealth.com/tmhri.cfm?id=39932

1st Annual Collaborative Workshop for Young Investigators

Recent advances from MIT PS-OC have revealed surprising answers to two important questions:

What is the role of the numerous mutations seen in cancer cells, and how do growing cells know when to divide? *By Anne Trafton, MIT News Office*

Some Mutations Slow Tumor Growth

A typical cancer cell has thousands of mutations scattered throughout its genome. However, only a handful of those mutations, known as drivers, are responsible for cancerous traits such as uncontrolled growth. Cancer biologists have largely ignored the other mutations, believing they had little or no impact on cancer progression.

But a new study from Prof. Leonid Mirny at MIT reveals for the first time that these so-called passenger mutations are not just along for the ride. When enough of them accumulate, they can slow or even halt tumor growth.

"The findings suggest that cancer should be viewed as an evolutionary process whose course is determined by a delicate balance between driver-propelled growth and the gradual buildup of passenger mutations that are damaging to cancer," says Mirny.

"Furthermore, drugs that tip the balance in favor of the passenger mutations could offer a new way to treat cancer; beating it with its own weapon — mutations."

"Cancer may not be a sequence of inevitable accumulation of driver events, but may be actually a delicate balance between drivers and passengers."

Passenger mutations that arise randomly alongside drivers (such as Ras and p53) were believed to be fairly benign: In natural populations, selection weeds out deleterious mutations. However, Mirny and his colleagues suspected that the evolutionary process in cancer could proceed differently, allowing mutations with only a slightly harmful effect to accumulate.

To test this theory, the researchers created a computer model that simulates cancer growth as an evolutionary process during which a cell acquires random mutations. They found that during the long periods between acquisitions of driver mutations, many passenger mutations arose. When one of the cancerous cells gains a new driver mutation, that cell and its progeny take over the entire population, bringing along all of the original cell's baggage of passenger mutations.

This process repeats five to 10 times during cancer development. If enough deleterious passengers can

Continued from previous page.

accumulate, their combined effects can slow tumor growth, the simulations found. Tumors may become dormant, or even regress, but growth can start up again if new driver mutations are acquired.

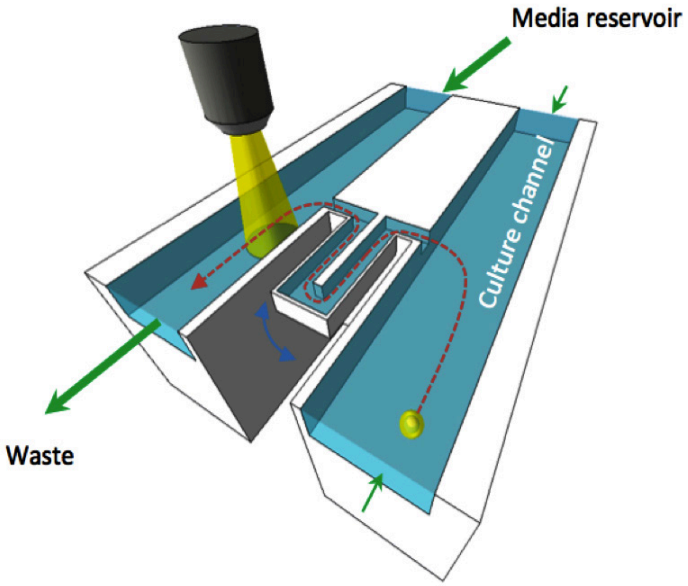
In computer simulations, the researchers tested the possibility of treating tumors by boosting the impact of deleterious mutations. In their original simulation, each deleterious passenger mutation reduced the cell's fitness by about 0.1 percent. When that was increased to 0.3 percent, tumors shrank under the load of their own mutations.

The Link Between Cell Division and Growth Rate

Recent research in the lab of Prof. Scott Manalis (MIT) helps to answer the longstanding question of how cells know when to progress through the cell cycle. In simple organisms such as yeast, cells divide once they reach a specific size. However, determining if this holds true for mammalian cells has been difficult, in part because there has been no good way to measure mammalian cell growth over time.

Manalis' team precisely measured the growth rates of single cells, allowing them to answer that fundamental question. They found that mammalian cells divide not when they reach a critical size, but when their growth rate hits a specific threshold.

This first-ever observation of this threshold was made possible by a technique that Manalis and his students developed in 2007 to measure the mass of single cells. In the new study, Manalis and his colleagues were able to track cell growth and relate it to the timing of cell division by measuring cells' mass every 60 seconds throughout their lifespans.



The finding offers a possible explanation for how cells determine when to start dividing, the researchers believe. It's easier for cells to measure their growth rate, because they can do that by measuring how fast something in the cell is produced or degraded, whereas measuring size precisely is very difficult for cells.

The researchers' measurement system flows cells through micro channels that run across a tiny silicon cantilever vibrating within a vacuum. When a cell flows through the channel, the frequency of the vibration changes, and the cell's mass can be calculated from that change in frequency.

The system also measures fluorescent signals from a cell in addition to its mass. Cells are programmed to express fluorescent proteins at various points in the cell cycle, allowing the researchers to link cell cycle nformation to growth. The researchers tracked cell growth throughout mitosis and found that growth rate increases rapidly during the G1 phase.

This rate varies a great deal from cell to cell during G1, but converges as cells approach the S phase, during which DNA is replicated in preparation for division. Once cells complete the transition into S phase, growth rates diverge again. Building on the feature of the new system that precisely controls the environmental conditions inside the channel, researchers can also change the conditions very rapidly, allowing them to monitor how cells respond to changes in nutrient conditions or exposure to a drug.

http://ki.mit.edu/approach/partnerships/psoc

Coding, Decoding, Transfer, and Translation of Information in Cancer

By Benette Phillips, PhD, Co-Director, Education & Training

An important goal of the research at Northwestern PS-OC is to identify links between the chemical and physical properties of chromatin and its biological functions.

A further goal is to characterize the differences in these properties between normal and tumorigenic cells and to examine whether these differences contribute to the tumorigenic phenotype.

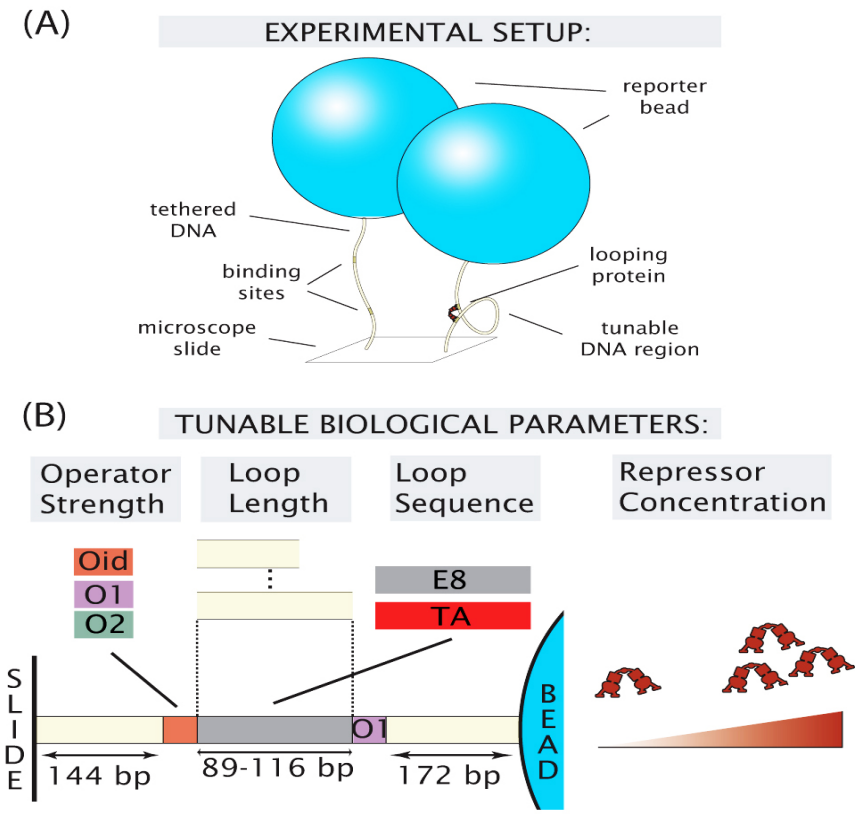
DNA Flexibility and Regulation of Gene Expression

DNA is not a rigid structure. It can wrap around histone octamers to form nucleosomes, and it can form loops, often bringing into proximity transcription factors bound at sites distant from one another on the DNA.

In so far as nucleosome formation is concerned, the degree to which DNA is flexible is determined largely by its sequence.

Certain DNA sequences are incompatible with the ability of DNA to wrap itself around histone octamers while other sequences favor nucleosome formation.

Rob Phillips, PhD a PS-OC investigator and biological physicist based at Cal Tech, predicted that loop formation by DNA would show this same sequence dependence, i.e., that specific sequences of DNA that favored nucleosome formation would also show a propensity to form loops.



Phillips and colleagues tested this prediction in a sophisticated assay whereby loop formation could be measured in a single DNA molecule which contained two separated binding sites for a bacterial regulatory protein. Data from this experiment was analyzed by plugging it into a model that incorporated ideas from statistical mechanics.

Surprisingly, the results of these studies, published in 2012 in the journal Nucleic Acids Research, did not support their prediction.

These findings suggest that the flexibility conferred by DNA sequence is context dependent and that different rules, yet to be determined, govern the ability of DNA to wrap around nucleosomes and to form loops when bound to transcription factors.

Reference: Johnson, S.; Linden, M.; Phillips, R. Nucleic Acids Res. 2012 Sept; 40(16): 7728–7738

Epigenetics and Cancer

Epigenetics is the study of how heritable changes to the genome that do not involve changes in the DNA sequence itself can influence gene expression.

The discovery of this phenomenon quickly led to the realization that epigenetic changes are very prevalent in most tumors and, importantly, they often occur in genes that are implicated in tumorigenesis. Moreover, epigenetic modifications are, in principle, reversible, raising the possibility of treating cancers with drugs that could reverse the modifications.

One class of epigenetic changes involves modifications of the histone proteins around which DNA wraps to form nucleosomes.

Extensive studies of histone modifications revealed a high degree of complexity, with multiple types of modifications possible on a single histone protein. This complexity makes it very difficult to decipher what came to be known as the "histone code."

The laboratory of Senior Investigator Jonathan Licht, MD, studies a methyltransferase, MMSET that modifies histones by adding methyl groups to lysine 36 on histone H3.

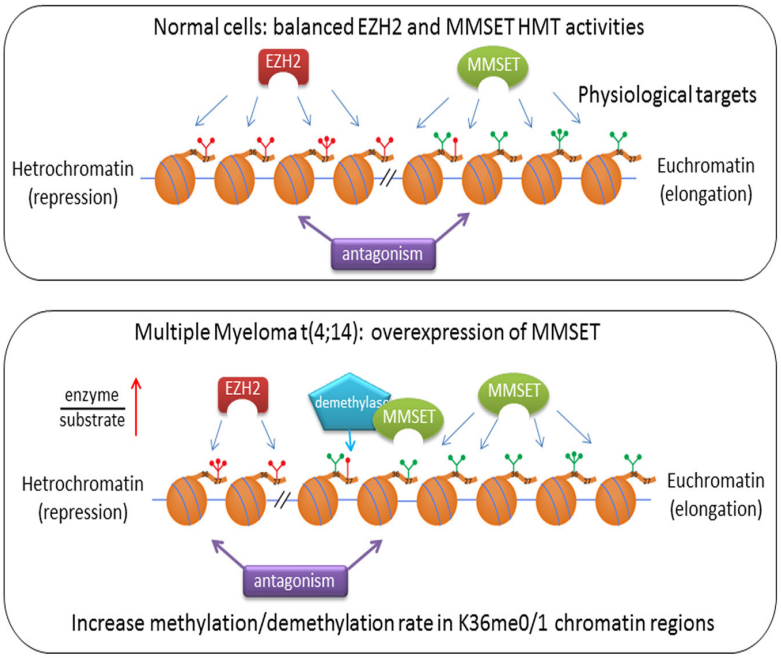
In 15-20% of multiple myeloma patients, the levels of MMSET are much higher than normal, and this epigenetic change is accompanied by an increase in lysine 36 methylation on many histones in the genome and in alterations in the expression of many genes that impact cellular behaviors associated with tumorigenesis.

Over-expression of MMSET is thus thought to be one of the changes that drives the development and progression of multiple myeloma.

An unexpected finding was that the increase in lysine 36 methylation was accompanied by a decrease in the methylation of another lysine in the histone protein, lysine 27, even though MMSET does not act on lysine 27.

To figure out how these two events are connected, Dr. Licht teamed up with Neil Kelleher, PhD, and an expert in proteomics.

From Kinetics to Mechanism



The results from the Licht and Kelleher labs, which were published in a 2012 issue of the Proceedings of the National Academy of Science, demonstrated that in fact, MMSET-induced methylation at lysine 36 antagonizes methylation at lysine 27. Results of this analysis should be widely applicable to other attempts to decipher the histone code.

Reference: Zheng, Y.; Sweet, SM.; Popovic, R.; Martinez-Garcia, E.; Tipton, JD.; Thomas, PM.; Licht, JD.; Kelleher, NL. Proc Natl Acad Sci U S A. 2012 Aug 21;109(34):13549-54

http://www.psoc.northwestern.edu/

Designing a Death Galaxy To Demystify Cancer Cell Resistance *By Melissa R. Aranzamendez*

The Princeton Physical Sciences-Oncology Center is using tiny 'time machines,' to study the evolution of bacteria in response to antibiotics as a model for the more complicated evolution of cancer cells due to stresses such as chemotherapy and radiation.

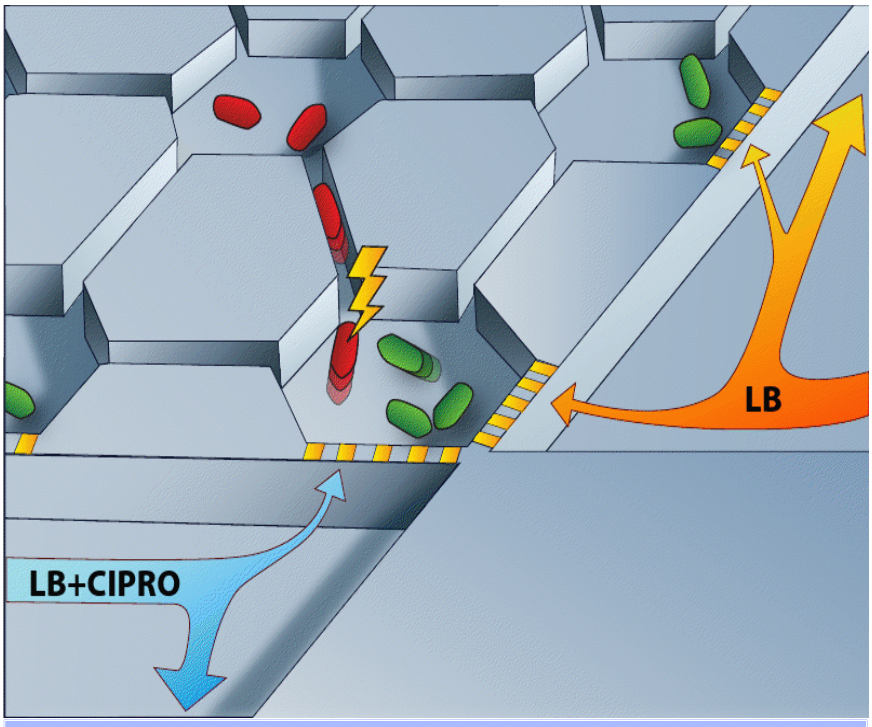
Principal investigator Robert Austin's team created a labyrinth of microbial habitats they nickname the Death Galaxy, to observe how bacteria cope with various toxins and mechanical challenges, to serve as an analog for cancer evolution under treatments stress.

The microhabitat patches, or MPHs, were designed in co-investigator Jim Sturm's Princeton lab using a system of pumps and valves which allow locally-specific and precisely-controlled administration of chemical stressors.

These devices accelerate the emergence of evolution in bacteria and identify potential mechanisms of evolutionary strategy.

Work on the microhabitat cell culture technology was transferred to senior investigator Thea Tlsty's lab at the University of California, San Francisco (UCSF) and to co-investigator Beverly Emerson's lab at Salk Institute for Biological Studies.

The chips are being used to culture cancer cells in a drug gradient.



The evolution of bacterial resistance to antibiotics serves as a model for how cancer cells become resistant to treatment. In this experiment, a silicon-based microenvironment where nutrients (LB) are scarce serves to enable the study of how bacterial cells become resistant to an antibiotic (CIPRO). (Image courtesy of Robert Austin)

The hardware installed at UCSF is designed to also be capable of metronomic or time-varying dosing of drugs on the on-chip cell culture.

The in-depth description of principles describing stochastic fluctuations at the cell population and the single cell level has enabled us to design a tool, called a "metronomogram," to optimize drug treatment to minimize drug resistance and optimize killing of tumor cells.

It is our ultimate goal to use the metronomogram in the clinic to decrease cancer relapse due to drug resistance.

Additionally, the MPH technology will be used to study the cooperation and parasitism of cancer and host cells within a 3-D microenvironment at co-investigator Ken Pienta's lab at Johns Hopkins University.

Continued from previous page.

In our nanoanalysis core facility, co-investigator Nader Pourmand at the University of California, Santa Cruz, subjects cells that were found to be both resistant and sensitive to chemotherapy drugs to synthesis and sequencing, with the goal of enabling expression and mutational analysis of drug resistant cell lines.

Our 'Death Galaxy' technology has also transitioned into a successful trans-network project with the Moffitt PS-OC looking at the onset of resistance in multiple myeloma and interactions with other projects in the PS-OC working on breast cancer.

Preliminary evidence suggests that the fundamental heterogeneity of differential expression at the single cell level drives the expansion of resistance.

Future efforts are focused on single cell genotyping, single cell tracking of cells in the devices, more emphasis on understanding the interactions and mutational changes of the stroma during the development of resistance, and advancing therapeutic tools.

Microfluidics Technology Drives Our Key Educational Offering

Each summer, we hold a Microfluidics Boot Camp, held at our core laboratory facility, which allows microfluidic and microfabrication technology to be broadly accessible to researchers and students. The facility consists of three parts - a clean room for photo-lithography and microfabrication, a microscopy room for experiments, and a design room for Computer Aided Design. During the Boot Camp, attendees learn to create microfluidic devices by soft lithography and perform several experiments using them. The course consists of lectures and hands-on laboratory experience.

Students at the 2013 Microfluidics Boot Camp

Our workshops have been focused on understanding tumor heterogeneity and failures in the clinical treatment of cancer.

"Cancer remains a persistent and fundamental problem to human health for basically 3 reasons," says Prof. Austin.

"(1) We certainly know ways to cut in half the cancer rate tomorrow (remove smoking and obesity) but the prospects for that happening given our political will power are basically zero, which is tragic.
(2) We do not have a deep understanding of the origins of cancer: why has it not been selected out by evolution, how does it begin, how does it progress?
(3) Our present main treatment of cancer, chemotherapy, is probably doomed to failure because we do not understand the origins of resistance.

The Princeton PS-OC can do nothing about (1), but is trying to make fundmental inroads on (2) and (3)."

References:
1) Zhang, Q.; Robin K.; Lambert G.; Liao, D.; Kim H.; Pourmand, N.; Austin, R.H. Acceleration of Emergence of Bacterial Antibioti Resistance in a Microenvironment. Science. 2011 Sep 23;333(6050):1764-7.
2) Zhang, Q.; Austin, R. Applications of Microfluidics in Stem Cell Biology. Bionanoscience 2012, 2(4), 277-286.

www.princeton.edu/psoc

By Peter Kuhn, PhD, PS-OC Principal Investigator

A center focused on the understanding of the fluid phase of solid tumors

Cancer cells leaving the primary site travel through the blood to eventually colonize a distant site causing metastatic disease. Our primary goal is to understand this process and utilize that understanding to manipulate the process through therapeutic intervention.

We are approaching the problem from three perspectives of identifying these cells, characterizing them and then integrating the data into a large-scale mathematical model to describe the overall metastatic process. The fundamental scientific approaches encompass single-cell measurements at different resolutions and different population sizes.

Exquisite quantitative measurements allow us to understand the mass distribution in cancer cells vs. normal cells; whole-genome analyses are being performed to evaluate the genetic changes during treatment; large scale single cell quantitative imaging is being used to monitor patients over the course of treatment.

One of the core technologies is a very sensitive method to find, count and characterize circulating tumor cells (CTCs) in patient blood samples. CTCs are cancer cells that have escaped from the primary tumor site and are traveling through the blood to other locations in the body, which may lead to metastatic disease. We call this the High Definition-CTC (HD-CTC) assay. These HD-CTCs could provide crucial information about how a patient is responding to the current treatment.

This information could help oncologists monitor patient status more frequently and less invasively, enabling better detection, prognosis, and individualized therapy management for cancer patients.

HD-CTCs are present in over 70% of Stage IV patients and have been detected in many patients who are stage I-III. Enumeration and characterization of these HD-CTCs can provide the data needed to predict efficacy of a treatment and may help physicians better treat their patients through knowledge of both the volume of cells and their specific phenotype and genotype.

Our fluid biopsy is a minimally invasive approach to monitoring cancer and could allow physicians to understand a person's cancer at all times during treatment. A minimally invasive approach could result in less scans, less radiation exposure, shorter times spent at the clinic, and reduced healthcare costs.

While our research is still investigational and does not directly benefit the individual patient yet, the blood sample donations help advance our research, leading to future benefits for the cancer community.

With the support of the NCI, the technology has been licensed to Epic Sciences for the purpose of creating products that are directly clinically useful.

Our results demonstrate that scientists, clinicians, and patients working together will make a difference in cancer research and ultimately make cancer a managed disease.

References: Kuhn P and Bethel K. A fluid biopsy as investigating technology for the fluid phase of solid tumors. Phys Biol 2012;9:010301.

Nieva JJ, Kuhn P. Fluid biopsy for solid tumors: a patient's companion for lifelong characterization of their disease.

Community Involvement

We are regularly opening our doors to the community of patients, families and all interested parties during a “Night at the Lab”.

During the last event, visitors were greeted with a small reception followed by presentations by our scientists and clinicians on our most recent research as well as taking the opportunity to express our gratitude for the contributions made by the cancer patients and their families.

After the presentations, smaller groups were invited to take a behind-the-scenes tour of the laboratory, which included the blood processing room, the high performance scanning systems where plated glass slides are imaged, the single-cell picking room and finally the data analysis and images station.

In a similar outreach effort in January 2013, we had the opportunity to reach a philanthropic audience, which was made possible by a generous supporter from the San Diego community.

By means of a dinner party cruise, ‘Navigating Cancer Research’, hosted by the anonymous donor and The Scripps Research Institute, participants learned more about the progress in personalized cancer care.

The particular excitement in the audience was evident when learning about advances made possible by the revolutionary collaborations between doctors, scientists and patients which are leading us towards meaningful innovation in cancer care.

The presentations focused on what tomorrow will look like and how it is up to us individually to invest in this future for it to happen NOW.

Toward the end of the presentations, the lasting impression was summed up by Dr. Kuhn:

“What we are seeing in this new approach to cancer care is an example of unwillingness to sit on the sidelines, but instead grabbing the opportunity to really make a difference for ourselves, our loved ones, and future generations to come.”

This event led to many meaningful follow-up conversations and meetings.

The Scripps Physics Oncology PS-OC is a consortium between The Scripps Research Institute, Oregon Health Sciences University (OHSU), University of Southern California, Scripps Clinic, University of California-San Diego Moor’s Cancer Center and Billings Clinic. It has substantial clinical translation collaborations with the USC PS-OC and basic science collaborations with many of the other PS-OC centers.

http://physicsoncology.org/default.aspx

Biologists' conceptual landscape of still, cartoonish images is being upgraded to increasingly detailed and insightful visions of how cells push, pull, crawl, spread, shrink, expand, connect, and interact with their environment - in both healthy and cancerous tissue.

By Saheli Datta, UC-Berkeley PS-OC Education & Outreach Manager

UC-Berkeley PS-OC scientists are assembling exquisite movies of cells' surface machinery rising and falling, of cells spreading and contracting in response to the severing of internal tensile fibers, and of them crawling through tiny channels of materials simulating the pliability of real tissue.

This imaging allows researchers to test and improve their understanding of mechanotransduction and its role in tumors. Mechanotransduction is the transmission of information and signals - the on/off switches and high/low dials inside living organisms - through mechanical means like pressure and tension.

The new technique allows biologists and physicists to create precise moving maps of cells' nanoscale machinery as they undulate and exert forces around them. These maps can show a moving structure every second with the precision of five billionths of a meter. Scientists are applying these methods to understanding cell-cell signal transduction in realistic contexts: closer to the kind of environment in which a tumor grows.

In a paper that was published in 2012, a team led by PS-OC Senior Investigator Valerie Weaver, PhD **(right)**, unveiled an innovative method of constructing maps of fluorescently labeled proteins near the surfaces of cells by rapidly scanning rotating laser beams across the cells and analyzing the resulting interference. This builds a detailed picture of cells reacting to forces in their immediate environment.

This technique has already been used to explore the impact of altered cellular force generation, a hallmark of cancer cells.

It's a big step for basic biology research because it allows scientists to measure the relative heights of several important proteins in living cultures over time.

After fluorescently labeling the proteins with different color dyes, the scientists scan the sample with a laser, the angle of which is constantly and rapidly changing. The team has been able to visualize the proteins' movement as the cells move around, tug on the material supporting them, and bump into each other.

"A major improvement is how this technique can visualize and quantify mechanotransduction in real time at resolution as high as 5 nanometers," says Weaver.

"This now permits investigators to actually understand the dynamics of how cells read their microenvironments and respond to mechanical inputs. It also gives us information about responses to chemical inputs, because it can be used to study receptor tyrosine kinase signaling," says Dr. Weaver.

In addition to her position of Senior Investigator, Dr. Valerie Weaver is also a Professor of Surgery and Bioengineering at UCSF.

Continued from previous page.

A postdoc in Weaver's lab, Matthew Paszek, led the technique's development. He studied patches of the cell's surface that attach to the external layer of proteins and sugars known as the extra cellular matrix (ECM), called focal adhesion complexes. These patches transmit forces from the ECM to the skeleton of protein scaffolding that makes up the cell's internal skeleton.

Paszek used his scanning lasers to watch the parts of the complex, the intermediary signal transducers which react to forces by moving and changing orientation and conformation, setting off a signaling process inside the cell. Watching the proteins move up and down like the pistons on a crankshaft is helping the scientists figure out how the inner gears of this signaling process work.

"The better we understand the mechanics of this signaling processes, the better we can eventually figure out how to disrupt them when they've been hijacked by a tumor."
UC-Berkeley PS-OC Director, Professor Jan Liphardt, PhD

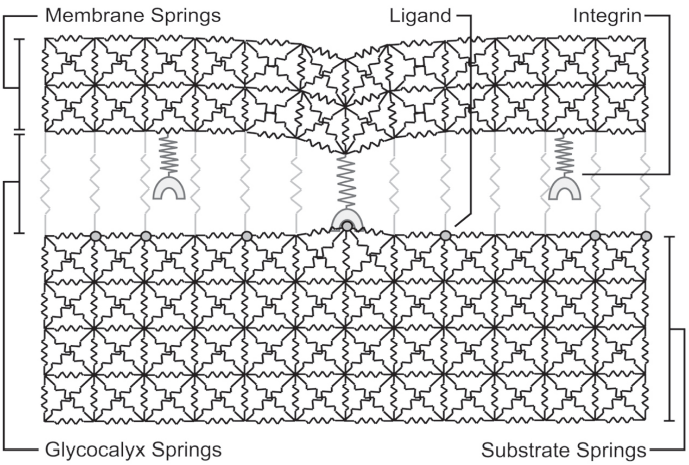
Crawling Glioblastoma Cells

Glioblastoma is a lethal and aggressive kind of brain cancer that is characterized by its rapid spread through the narrow pores and along the white matter tracks of the brain's soft tissue.

In a paper published in 2012, PS-OC Investigator and Professor of Bioengineering, Sanjay Kumar and his post-doc Amit Pathak studied the crawling and stretching behavior of glioblastoma cells in spaces of varying softness and constriction.

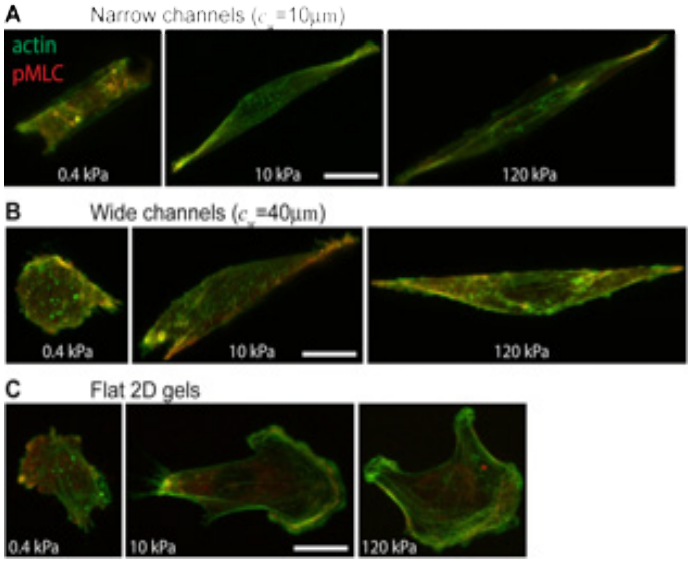
The Kumar lab specializes in using lasers to suddenly and selectively sever the fibers inside cells that form their cytoskeleton and power their motion, and also in chemically engineering special chambers that better simulate the physical environment of tissue. The lab can film what happens.

By combining movies of their projects, the UC-Berkeley PS-OC can better understand how tumor cells spread - one of the hallmarks of aggressive cancer.



Above - *Paszek's model of cells surface machinery. Paszek et al, PLoS Computational Biology 2009*

Below - *Kumar's lab studies stress fibers and spreading confined cells. Pathak & Kumar, PNAS June 2012*



http://www.bayareapsoc.org

Painting Biology with a Physicist's Brush *By Dan Ruderman PhD*

As a physicist venturing into cancer research as part of the USC PS-OC, I initially felt daunted by all the biological details that come so naturally to cancer biologists.

After all, we physicists like to paint the world with the broad strokes of theories that capture essential phenomena, and often leave the details to other disciplines.

I saw it as my particular challenge to actively contribute to our PS-OC's investigation and modeling of lymphoma, while at the same time assimilating biological details by naïvely questioning my collaborators. Fortunately, the PS-OC program structure is stacked in my favor.

With the program's belief in the importance of physical scientists' viewpoints to advancing cancer research, my biologist colleagues have been generous with their data and the time to explain them. I soon familiarized myself with the many platforms our investigators employ, including NAPPA (Dr. LaBaer), magneto-nanosensors (Dr. Wang), and mass spectrometry (Dr. Mallick, Dr. Nolan). My research aims include interpreting these combined data using functional pathway techniques, which build on those I co-developed when in the biopharmaceutical industry.

While reviewing preliminary data and discussing future experiments, it became clear that I could contribute to experimental design and quality control as well. I had gained expertise in these fields at Applied Proteomics, where I used them to ensure accuracy and eliminate experimental bias in discovering biomarkers.

While these branches of statistics might seem very dry to some, I find the process of learning experimental details and constructing optimal experiments to be very enjoyable. It's the same kind of puzzle solving that initially sparked my interest in math and physics. Our PS-OC's goal is to build a predictive multi-scale model of drug response in lymphoma.

This process is iterative, starting from simple models where the mouse is essentially a petri dish with a tail, and moving up to models, which include realistic biological details such as non-uniform drug distribution, angiogenesis, and host immune response.

As my biologist colleagues continue to teach me about these concepts, my questions are perhaps becoming a bit less naïve.

I am most pleased that the PS-OC has enabled me to pursue the goal of contributing to cancer research in a manner sensitive to biological detail while still allowing me to think like a physical scientist.

USC and The Scripps Research Institute Create Consortium for Integrative Computational Oncology

In 2012, Paul Macklin (USC PS-OC) and Paul Newton (Scripps PS-OC) founded the Consortium for Integrative Computational Oncology (CICO) at the University of Southern California.

CICO is working to promote the ideas of physics-based computational oncology to the USC community, facilitate clinically-focused integrative computational oncology projects, increase collaboration among existing cancer modeling groups, and help train the next generation of interdisciplinary cancer scientists.

Though CICO is currently in its formative stages, it is already mentoring undergraduate and graduate mathematics and engineering students in computational oncology projects, developing user-friendly software tools in order to make computational cancer modeling accessible to biology and medical students and increasing cross-mentoring of graduate students between the medical and engineering campuses.

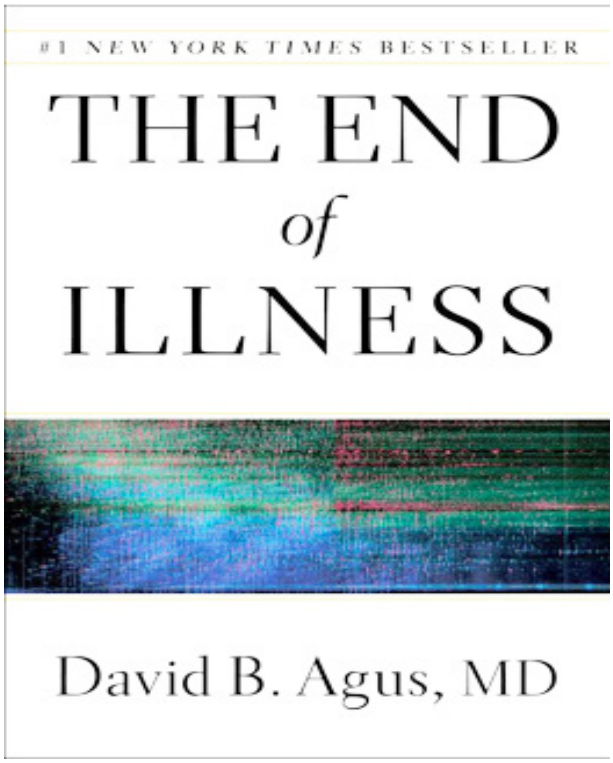
To learn more about CICO visit http://CICO.MathCancer.org.

USC PS-OC Education Outreach

In *The End of Illness,* David B. Agus, MD, one of the world's leading cancer doctors, researchers and technology innovators, dispells long-held erroneous wisdom and tackles misconceptions about the meaning of health.

With a blend of storytelling, landmark research and provocative ideas, Dr. Agus presents an eye-opening picture of the complex and endlessly enigmatic human body, and all of the ways it works—and fails.

Ultimately, Agus shows us how a new perspective on our individual health will allow each of us to achieve that often elusive but now reachable goal of a long, healthy life.



Dr. Agus also offers insights and access to breathtaking and powerful new technologies that promise to transform medicine in our generation. In the course of offering recommendations, he emphasizes his belief that there is no "right" answer, no master guide that's "one size fits all."

Each one of us must get to know our bodies in uniquely personal ways, and he shows us exactly how to do that so that we can individually create a plan to live longer. This groundbreaking approach will change not only how we care for ourselves but also how we develop the next generation of treatments and cures.

http://physics.cancer.gov/centers/adv_usc.asp

By Luis Cisneros PhD Sara Walker PhD and, Arizona State University

Cancer and the Origin of Multicellularity

Cancer is a breakdown in the normal cooperative relationship between somatic cells and the organism.

The widespread nature of cancer among animals suggests it has deep evolutionary roots, and that the cancer phenotype is an unavoidable part of the basic logic of multicellularity.

To test this theory, two postdoctoral researchers at ASU, Luis Cisneros and Sara Walker, are studying a mathematical model of the transition to multicellularity developed in the Rainey Laboratory at Massey University in New Zealand.

The central idea is that the transition from a single-celled world to cooperating assemblages is facilitated by cancer-like "cheater cells" that defect from the cooperative and flourish at the expense of the collective, implying that cancer is a hangover from this momentous evolutionary step.

Sara Walker and Luis Cisneros state, "Cancer hovers on the borderline between selfish and cooperative behavior. The project will explore the underlying mathematics of this flexible state."

Cisneros and Walker are appealing to "agent-based" models – computer simulations of interacting cells that can switch between two states: a reproductive phase, and a non-reproductive cooperative phase.

The evolutionary strategy the system adopts will be explored by running large statistical samplings of the model system for different parameters such as abundance of resources, critical phenotypic switching, metabolism, cell differentiation and adhesive properties.

A key facet of their model is to track information flow within the system as it self-organizes into cooperative collectives, hopefully showing which dynamical features tip the balance between aggregate dynamics and "selfish" behavior.

A pilot project is a small, initial investigation of a speculative but potentially significant new direction of research.

http://cancer-insights.asu.edu/

By Hannah Kim

When Dr. Eugene Koay joined Dr. Mauro Ferrari and The Methodist Hospital Research Institute in July 2011 as a postdoctoral associate, one of the first things that struck him was the multi-disciplinary nature of the group.

He felt right at home but did not anticipate that his prior experience as a physician, scientist, engineer and inventor would lead to potentially ground-breaking research. The idea that physics is an important consideration in cancer has not gained full traction for the rest of oncology, however.

Dr. Koay realized that part of the reason for this disconnect is that the communication between scientists and physicians was lacking. He knew that proper studies had to be conducted to convince the medical community that physics could be applied in many ways to improve patient care, including diagnosis, therapeutic planning, and monitoring treatment response.

"I was inspired by the work that was being done by others at the Methodist Hospital Research Institute including Dr. Ferrari's theory of Oncophysics and work by Dr. Anne van de Ven," says Dr. Koay.

"For example, the studies with intravital microscopy set off a light bulb in my head to study similar phenomena in human patients."

Dr. Eugene Koay, MD, PhD

Dr. Koay developed his postdoctoral thesis around Dr. Ferrari's concept of Transport Oncophysics, which describes how altered physical transport is characteristic of cancer. To extend the concept to humans, Dr. Koay reached out to several physicians at M.D. Anderson such as Dr. Jason Fleming and to Dr. Vittorio Cristini at the University of New Mexico to develop and apply a mathematical model of mass transport using readily avaiable patient data.

Dr. Koay adds, *"Clinical studies are not much different from basic science studies when you get down to the fundamentals of needing controls and experimental groups.The language that clinician scientists and basic scientists use is very different though. I was fortunate to have the training to be able to communicate with both."*

The results support the Oncophysics idea that transport mechanisms in human tumors dictate response to cancer treatments. These findings may have important implications for patient diagnosis and therapeutic management.

Dr. Koay continues to be an integral part of a multi-disciplinary and multi-institutional team on the frontier of pre-clinical and clinical trials. He completes his residency training in 2014 and plans a career in academics.

http://www.methodisthealth.com/tmhri.cfm?id=39932

By Deborah Collyar, Patient Advocates In Research (PAIR)

Deborah Collyar

I am an advocate impatient for change!

I joined the Princeton PS-OC in 2012, and have participated in their meetings and webinars. The exchanges are stimulating, and the challenges that surface when bringing disciplines together are receding.

These kinds of challenges have faced all multidisciplinary efforts, such as the NIH funded Specialized Programs of Research Excellence (SPOREs). Even when people want to work together, disparate cultures, concepts, and approaches can stymie true progress until they are acknowledged and altered.

After 20 years of working with cancer scientists and researchers, I had become wary of "new" areas in science, including the Physical Sciences-Oncology Centers program. Too often, new programs lead to more grants for those involved without creating better results for cancer patients and survivors.

Have to admit… I'm pleasantly surprised to learn that melding physics and cancer biology might actually move us forward!

Even though cancer research has helped more people live longer, we cannot call efforts to date truly successful. Today's emphasis on genomics offers potential progress, but we must also learn how cancers operate and interact with their environment if we hope to eradicate latent cells that current therapies leave behind. Evolution and ecology principles make sense when applied to learning how cancer cells evade most defenses we currently use.

These concerns were emphasized when the Princeton PS-OC asked me to present the clinical (and patient) perspective at their site visit (see http://www.slideshare.net/Collyar/collyar-final-6page-2012-nih-site-v-isit). My points included: respecting differences, questioning hidden assumptions, sharing data and ideas from each field, understanding how cancers differ, and creating ACTIONABLE goals. I also showed how common terms used in each field mean very different things. For instance, while physics "models" reflect mathematics, biology studies animal "models." Both models have distinct limitations when applied to a whole human being. We have to build common understanding and tools for physicists, biologists, clinicians, and patient advocates to solve perpetual cancer problems together.

When all is said and done, this work is about people, not theories, "cool" science, or careers. I appreciate the support and enthusiasm of Princeton PS-OC members to answer important questions together.

Challenges between physics and biology can be quickly overcome with dedicated commitment and communication. Please keep this in mind as we all work together to solve problems that can achieve better cancer prevention, treatment, and care for people.

www.princeton.edu/psoc

On the Cover

Images: left to right

Figure 1: A mouse embryonic fibroblast placed on type-I collagen coated glass slide. Nucleus (blue) and geodesic actin structure (green) on top of the nucleus were imaged by Nikon TE2000 fluorescence microscope. Horizontal cross-sectional images of actin filaments were projected onto the same plane. Awarded an honorable mention in the 2011 Nikon Small World imaging contest. Image by Dong-Hwee Kim, PhD. Denis Wirtz Lab, Johns Hopkins PS-OC.

Figure 2: Cells+Halloysite Nanotubes. Credit: Andrew Hughes and Michael King, Cornell University.

Figure 3: Mouse embryonic fibroblasts placed on type-I collagen coated glass slide. Nucleus blue), actin filaments (green), and microtubules (red) were imaged by nikon A1 confocal laser microscope with 60x magnification. Image by Dong-Hwee Kim, Denis Wirtz Lab, Johns Hopkins PS-OC.

Figure 4: A mouse embryonic fibroblast embedded in 4mg/ml of type-I collagen matrix. Nucleus (blue), actin filaments (green), and microtubules (red) were imaged by nikon A1 confocal laser microscope with 60x magnification. Horizontal cross-sectional images were 3D-reconstructed. Image by Dong-Hwee Kim, Denis Wirtz Lab, Johns Hopkins PS-OC.

PS-OC Perspectives Spring 2013 is produced by Pauline Davies and Chevas Samuels, Hugh Downs School of Human Communication at Arizona State University. We thank the PS-OC Network Centers for their contributions to this newsletter. This publication and the works herein were supported primarily by the NCI Physical Sciences in Oncology initiative. Any opinions, findings, conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Cancer Institute.

Back to menu