Speaker Abstracts

(in alphabetical order)

Is Cancer A Disease or Does It Provide A Fitness Advantage?

Robert Austin
Princeton University

I would argue that treating cancer as another yet disease to be conquered possibly misses the point that cancer is qualitatively different from most other conditions that impact human health. Perhaps cancer fulfills an important fitness function to the collective community and it is qualitatively different then what is normally viewed as a disease. Perhaps it is a deliberately programmed event, and tolerated by the organism viewed collectively. The 4 related questions I will discuss are:

1) Why do we view cancer as a disease?
2) Why do we always try to destroy a tumor?
3) What is the role of game theory in cancer dynamics?
4) Is there a evolutionary function to the metastatic transition?

A Genomic Synthesis For Evolutionary Theory: Mutation Is Not Random

Lynn Caporale

The Theory of Evolution (TofE) states that selection acts upon heritable variation that affects fitness. In this talk, I will distinguish among the TofE itself, observations related to the theory, and interpretations (and misinterpretations) by scientists and by popular culture. The application of the TofE to biological evolution was incomplete in the 19th Century because, as Darwin himself recognized, the source of genetic variation was not understood. When the Modern Synthesis incorporated the concept of genes and mutation into evolutionary theory the term random mutation incorrectly became associated with Darwin himself and the TofE. However, simply due to biochemistry, the probability of distinct types of genetic change varies along a DNA sequence [non random in space]. Selection would act upon variations in mutation much as it acts on beaks and wings; thus the probability of distinct classes of genetic variation can become aligned with the potential consequence to survival of that type of mutation at that site. Further, since enzymes affect the generation and repair of variation, different classes of mutation can be regulated [i.e. mutation is not random in time]. The observation that mutation is not random deepens, rather than contradicts, our appreciation of the power of natural selection. A challenge in

interpreting the TofE is to avoid tautology when defining fitness. Because genomes survive through an unbroken chain of living beings across evolutionary timescales we should consider fitness as contributing to the survival of lineages. As illustrated by the rapid variation of certain pathogen surface antigens, the evolutionary success of a lineage may result from its being efficient at exploring variation that is aligned with the nature of challenges and opportunities the lineage has faced repeatedly during evolution in the context of an environment that is not random. Discussions of TofE in popular culture generally ignore the Theory itself, and focus on terms such as random mutation and descended from apes, and confuse victory in hand-to-hand battle with fitness. However, cooperation often contributes to fitness, through communication, sharing of DNA (particularly under stress), or exchanging metabolites. Since perfect but unchanging adaptation to a specific environment is risky (because the environment can change) diversity in a population, including human populations, also contributes to fitness. Because a lineage must balance the rate of variation with the need to maintain adaptation to its current environment, the ability to increase variation under stress (defined as a sensed maladaptation to the environment) can provide a selectable advantage. The TofE provides a valuable framework for medical science to understand the evolution of rapid growth and resistance to therapy in pathogens and tumors, and the presence in the population of traits that can be damaging, but are helpful in certain genetic contexts. In addition, TofE can contribute to fields outside of biology, expediting the availability of molecules and interacting systems with selected properties.

Spontaneous Emergence Of Modularity In An Evolving System: Nucleation Of Biology From Chemistry

Michael Deem
Rice University

We investigate the selective forces that promote the emergence of modularity in nature. We demonstrate the spontaneous emergence of modularity in a population of individuals that evolve in a changing environment. We show that the level of modularity correlates with the rapidity and severity of environmental change. The modularity arises as a synergistic response to the noise in the environment in the presence of horizontal gene transfer. We suggest that the hierarchical structure observed in the natural world may be a broken symmetry state, which generically results from evolution in a changing environment. To support our results, we analyze experimental protein interaction data and show that protein interaction networks became increasingly modular as evolution proceeded over the last four billion years. We also discuss a method to determine the divergence time of a protein.

Biophysics And Adaptation Of Bacteria In Nanofabricated Landscapes

Cees Dekker
Delft University of Technology

I will discuss various aspects of our research in Delft where--following pioneering work in the Princeton group--we use nanofabrication to construct landscapes for bacteria, which allows to study the interaction between bacteria and their habitat with an unprecedented control of the spatial structure and habitat parameters. We can use the technology to define food-rich and food-poor islands as well as channels that mutually couple the island populations with a controlled strength. Bacteria form a metapopulation, a set of local populations distributed across the islands. Single bacteria can hop from one island to the next through the channels, which we can track using fluorescence microscopy. The structure of the island habitats, the food-waste exchange and stress levels can all be nanofabricated. In this talk I will report two recent results:

1. Biophysics of bacteria in confined spaces. We study how Gram-negative E. coli and Gram-positive B. subtilis bacteria can grow, move, and penetrate very narrow constrictions with a size comparable to or even smaller than their diameter. We observe E. coli to penetrate channels with a width that is smaller than their diameter by a factor of 2. Within these channels, bacteria are considerably squeezed but they still grow and divide. After exiting the channels, these bacteria are found to display a variety of anomalous cell shapes. Tight confinement is found to exhibit a strong effect on the bacterial growth, division, and shape.
2. Cooperation and cheating among bacteria in space and time. The interests of an individual may be different from those of a community. To study this conflict in bacterial populations, we mix cultures of a wild type (cooperator) and a GASP-mutant (cheater) strain E. coli bacteria in an homogeneous environment (batch culture), but also in spatially structured environments (nanofabricated patches). We find that the bacteria play the Prisoners Dilemma in homogeneous environments and the Snowdrift Game in heterogeneous environments.

The Physical Aspects Of Stress In The Evolution Of Cancer

Robert Getzenberg
Johns Hopkins University

The specific spatial and temporal organization of DNA within the nucleus is central to its function. The DNA is functionally organized into domains of loops at the base of which are its association points with the nuclear structure and are the sites of DNA replication and transcription. Only 5% of the DNA encodes proteins and a majority of the DNA contains repetitive sequences, the elements behind the reorganization of the genomic sequences. The packing of DNA within the nucleus in an operationally functional fashion is an amazing feat of engineering. The structure of the nucleus has evolved significantly from the simplistic organization found in bacteria to the lamins that are an essential part of the nuclear matrix. One of the nuclear lamins, lamin B, is a prompt heat shock protein that is highly sensitive to temperature and can be found even in archaebacteria. A hallmark of cancer is alterations in nuclear shape and structure. This nuclear structure is tissue specific and responds to changes in the microenvironment including temperature. Despite our increased understanding of the molecular biology of cancer and new drugs that have been developed to attack the disease, we have made little impact on the mortality resulting from it. It is apparent that new approaches are needed to overcome the punctuated evolution associated with cancer cells and their resulting resistance to therapeutic approaches. The heterogeneous cancer cells are able to rapidly respond to challenges with therapies with the development of resistant cells. The price that cancer cells appear to pay for their ability to rapidly evolve is a sensitivity to microenvironmental stresses. Taking advantage of this Achilles heal of cancer, utilizing nanoparticles, we are utilizing thermal energy as a tool to increase the sensitivity of cancer cells to chemo-and radiation therapy. This approach is systemic in nature and the goal is to develop tools through which we can target these nanoparticles to metastatic cells throughout the body in a patient with cancer. Utilizing approaches such as our thermal enhanced metastatic therapy (TEMT), it is possible to go after cancer cells at their weakest points and take advantage of their evolutionary weakness to impact the disease.

Collective And Nonlinear Phenomena In Evolution

Nigel Goldenfeld
University of Illinois at Urbana-Champaign

During the last 50 years or so, molecular biology and genomics have revealed a picture of the microscopic mechanisms of evolution that considerably extends the assumptions built into the so-called Modern Synthesis. The Modern Synthesis is based upon the rediscovery of Mendelian genetics in the early 20th century, and is manifestly a theory of population genetics—but not of the evolutionary process itself. The discovery of mobile genetic elements in many forms, ranging from transposons to horizontal gene transfer, now known to be present in all of the three domains of life, requires a re-evaluation of the evolutionary process, whose goal would be a quantitative understanding of the rate of evolution, encompassing both rapid and geological time scales. A common feature of the recently uncovered microscopic genome dynamics is that they are collective in nature, in contrast to the random single nucleotide polymorphisms that are the foundation of the Modern Synthesis. Thus, it is essential that evolutionary theory be formulated in the spirit of statistical mechanics, where collective, many-body interactions constitute the foundation and are no longer regarded as a small perturbation to a nave mutation-drift-selection framework. Moreover, evolution needs to be properly understood as arising from a spatially-resolved ecological context, as was already emphasized by Wallace over 150 years ago. Thus, evolutionary theory will require proper integration with ecology. In this talk, I will describe several attempts to provide such a theoretical basis for evolution, in situations where the observed qualitative features seem only to be capable of explanation using a collective, nonlinear model of the genome dynamics. The examples presented include: (i) the evolution of the genetic code; (ii) the emergence of genome biases in microbial genomes; (iii) diversification fronts in both microbial and eukaryotic genomes. Lastly, I will briefly indicate some future directions that we and others are pursuing to integrate spatially-resolved ecology models with evolution.

Can Bacteria Be Programmed To Cure Cancer?

J. D. Huang
The University of Hong Kong

Cancer is a leading cause of death despite many years of research. Metastasis, relapse, and resistance to chemo-and radiotherapy are the main reason for lethality. This has prompted the development of many new approaches for the treatment of cancer, including the delivery of anti-cancer genes to tumors using viral and non-viral vectors. However, these approaches have inadequate specificity for tumors. Therefore, novel system is required to target both primary and metastatic tumors. One interesting method is to use bacteria as cancer therapeutic agent. The first reported treatment of tumor by bacteria was about 150 years ago. In 1868, the German physician W. Busch found that one of his sarcoma patient got the infection of erysipelas (Streptococcus pyrogenes), and surprisingly the primary tumor size was shrunk by a half within a week. Since bacteria can sense their environment, distinguish between cell types, and deliver proteins and RNAs to eukaryotic cells, current advances in synthetic biology technology have brought bacteria-tumor therapy back in focus. We attempted to program bacterial strains that can detect tumor microenvironment and launch attack specifically within the tumor. We tried to secure tumor-specificity by cumulatively combining three strategies: (1) preferential accumulation of bacteria in tumor mass; (2) preferential expression of therapeutic genes by bacteria only within the tumor microenvironment; (3) production of therapeutic molecules that specifically trigger the death of cancer cells but not normal cells. We have obtained encouraging data in vitro and in vivo using modified strains of E. coli and Salmonella according to our preliminary designs. In the discussion, we will present our data and discuss the existing problems.

Rapid Evolution of Drug Resistance Mediated By Global Feedback

Terence Hwa
University of California at San Diego

Rapid emergence of drug resistance is one of the biggest problem facing treatment of disease ranging from bacterial infection to cancer. Recently, we found that sublethal levels of translation-inhibiting antibiotics resulted in attenuation of constitutively expressed genes in bacteria, a generic effect which can be understood in terms of simple bacterial growth laws. This effect suggests a novel growth-mediated positive feedback mechanism by which weak expression of antibiotic resistance may be amplified without the need of any specific regulation. A distinct signature of such positive feedback is an abrupt change in bacterial growth over small changes in drug levels in the vicinity of a critical drug level. This abrupt response is validated using constitutive expression of antibiotic resistance in E. coli. The threshold drug level for growth is dependent on the degree of expression and activity of the protein(s) providing antibiotic resistance. This dependence gives rise to a mesa-shaped fitness landscape which provides a strong selective advantage for increasing the expression/activity of drug resistance across the fitness cliff at the edge of the mesa landscape. Synthetic evolution experiments using a range of drug levels allowed us to breed successively stronger expression of antibiotic resistance de novo within a few rounds of evolution. Detailed theoretical studies of evolution on mesa-shaped fitness landscape in environments with varying drug levels indicate a drastic speed up of evolution along the fitness cliff, at a rate even exceeding that of evolution on smooth Fuji-shaped fitness landscape. The results of these studies establish a dynamic mechanism of evolution driven by fitness cliff and environmental variability, and are conceptually distinct from the classical Darwinian notion of climbing fitness gradient. The existence of global feedback by translation-inhibiting drugs in bacteria also raises the question of whether similar feedback effects (along with the rapid evolution of drug resistance) may occur in proliferating cancer cells treated by mTOR-inhibiting drugs which target translation.

Evolutionary Biophysics Of Bacteria In Adaptive Landscapes On-chip: From E.coli To Cancer?

Juan Keymer
Delft University of Technology

After learning from landscape ecology that ecosystems are made of (renewable) nodes (Micro Habitat Patches) and ecological corridors (Confined interconnecting channels) of spatially distributed habitat, we can follow Keymer and collaborators work at Princeton in order to drive evolutionary change in bacteria adapting on-chip by using biophysics and nanotechnology. Keeping in mind that the context of the workshop is on evolution, and disease (cancer), I will put into context how this novel technology can be applied to cancer research from the perspective of (bio) physical science. I will also report on the role of cooperation, selfishness, and self-control play in the organization of multi-cellular systems (highly condensed meta-populations). For this, I will discuss how spatial structure, confinement, and ecosystem function affect cooperative behavior in a simple bacterial model system for cooperation which I developed first at Princeton and which is based on the social contract required when cells entry into stationary phase. I will focus on demographics and inter-generational justice in cellular assemblages on-chip and I will report new findings we have seen here since my arrival in Delft. I will draw examples from Patches and Corridors on-chip environments where observations seem to hint towards how demographic self-regulation in multi-cellular systems can be studied using bacterial systems. Of course I will end up with speculations on what are the theoretical considerations missing and what are the following experiments to be done to develop our insight in the proposed direction.

Synthesis Of Organic Matter By Stars And Its Effect On The Origin Of Life On Earth

Sun Kwok
The University of Hong Kong

The last 50,000 years of stellar evolution represents the most active period of synthesis of organic com-pounds in a stars life. Over 60 gas-phase molecules, including rings, radicals, and molecular ions have been identified by millimeter-wave and infrared spectroscopic observations through their rotational and vibrational transitions. Space infrared spectroscopic observations of emissions from the stretching and bending modes of aliphatic and aromatic compounds have revealed a continuous synthesis of organic material over a period of only a few thousand years under vacuum conditions. These organic gases and solids are ejected into the interstellar medium through stellar winds and spread all over the Galaxy. Isotopic analysis of meteorites and interplanetary dust collected in the upper atmospheres have revealed the presence of pre-solar grains similar to those formed in evolved stars. This provides a direct link between star dust and the solar system and raises the possibility that the early solar system was chemically enriched by stellar ejecta. In this talk, we discuss the chemical structure of stellar organic matter and compare them to the organics found in meteorites, comets, asteroids, planetary satellites, and interplanetary particles. The possibility that external delivery of stellar organic matter has contributed to the origin of life of Earth is discussed.

RNA-mediated Epigenetic Inheritance In Oxytricha

Laura Landweber
Princeton University

RNA, normally thought of as a conduit in gene expression, displays a novel mode of action inciliates, where RNA molecules provide both an organizing role in DNA rearrangements and a template that can transmit somatic substitutions to the next generation (Nowacki et al. 2008. Nature 451, 153-158). The opportunity for RNA-guided DNA repair is profound in Oxytricha, which destroys 95% of its germline genome through a process that severely fragments its chromosomes and then sorts and reorders the hundreds of thousands of tiny pieces remaining. Information for reordering comes from transiently-expressed maternal non-coding RNAs. A complete RNA cache of the maternal somatic genome may be available at a specific stage during development to provide a template for DNA rearrangement and to transmit heritable information. Furthermore, the occasional transfer of point mutations from these RNA templates to the rearranged molecules supplies a viable mechanism for stable inheritance of acquired characters (in either DNA sequence or alternative splicing pattern) without altering the germline. This mechanism for inheritance beyond the conventional DNA genome can pass information across multiple generations, hinting at the power of RNA molecules to reshape genome information.

Darwinian Evolution As Front Propagation In Fitness Space

Herbert Levine
University of California at San Diego

Motivated by experiments on laboratory-scale evolution in both microorganisms and biomolecules, we introduce and study a class of multi-locus evolution models, These models assume that the fitness landscape is smooth (not glassy). This can actually be justified for the case of evolving protein binding sites for DNA, but is otherwise an assumption that can be compared with the experimental data. For these models, the population advances via being dragged forward by its most fit members and can be quantitatively studied using ideas from the theory of non-equilibrium spatially-extended processes. A key finding is the anomalously large dependence on population size and the related anomalously large usefulness of genetic recombination.

Microfluidic Continuous Cancer Cell Culture And Passage With Hydrodynamic Forces

Liyu Liu
Princeton University

We demonstrate a novel and robust microfluidic chip with combined functions of continuously culturing and outputting PC-3 prostate cancer cells. With digital controls, polydimethylsiloxane (PDMS) flexible diaphragms are able to apply hydrodynamic compression and shearing forces on cultures, detaching a fraction of attached cancer cells from the surface for output while leaving others for reuse in subsequent cultures. The fractions of detached cells and remaining cells can be precisely controlled. The system has the advantages of small size with high cancer cell culture efficiency, digital control, simple fabrication at low cost, easy operation and robust performance. The chip also performs 9 passages during 30 day of continuous culture and shows promise for a broad range of applications for other kinds of cells

Evolution In Cancer

Carlo Maley
The Wistar Institute

Our current theory of carcinogenesis is that mutant clones arise through genetic or epigenetic instability, and if they have a reproductive or survival advantage over other cells in the tumor, within their microenvironment, they will expand in the tumor in a selective sweep. Thus, we believe carcinogenesis is characterized by a series of selective sweeps. However, virtually all data on that process to date is cross-sectional, with observations of genetic diversity and large clonal expansions within neoplasms at a single time point. Furthermore, it is unclear if clones complete their selective sweeps, driving all other clones extinct, or if many clones may co-exist over long periods of time. Both clinical experience and genetic data suggest that most cancer therapies fail because they select for resistant clones. Thus evolution explains both how we get cancer and why it has been so hard to cure. This evolutionary theory of cancer has withstood over 30 years of testing, though we still know relatively little about the dynamics of evolution in tumors. I will present data that shows that there is genetic and epigenetic diversity within tumors, that clones do expand within tumors, that phenotypes evolve that are associated with increases in the reproduction and survival of those clones, and that therapies select for genetic mutations in tumors that make the clones resistant to the therapies.

What Is Evolution? Towards A New Synthesis

Masatoshi Murase
Kyoto University

The year 2009 is the bicentennial of Charles Darwins birth. In addition, it is the bicentennial since Jean-Baptiste Lamarck published the book Zoological Philosophy. It is, therefore, timely to hold the international workshop on Evolution. Although Darwins natural selection theory has been well acknowledged in contrast to Lamarcks inheritance of acquired character in biology, the discovery of horizontal transfer of genes among various bacteria proved that Lamarcks theory is basically true, as well. Indeed, we are very familiar with the dichotomy of yes or no with regard to any given statement but not the complementary relationship of yes and no. An understanding of this complementary relationship enables us to understand that seemingly irreconcilable views in general need not be contradictory. This provides a good guiding principle for addressing complex problems for which dichotomous answers of yes or no do not generally apply. Likewise, we have to consider evolution as multiphase dynamical processes involving Darwinian natural selection and Lamarckian inheritance of acquired character. In addition to the origin of species, there is another interesting feature of evolution: the origin of extinctions. Several different explanations have been proposed to account for the causes of extinctions on the assumption that the magnitude of responses of the ecosystem is simply proportional to the magnitude of stimuli. However, the theory of self-organized criticality given by Per Bak provided quite a different interpretation: slowly driven non-equilibrium systems show self-organized critical state sudden to break down. Along this line, the opposition of evolution and extinction may be plausible within the same paradigm. Furthermore, disease such as cancer and Alzheimers Diseases can be viewed as microevolution at the cellular and intracellular level, respectively. This implies the double-edged sword of evolution itself. In other words, quite different phenomena often opposed to one another can be understood within a simple framework. The advancement of our understanding about life phenomena in this way must be considered as real evolution of our knowledge. There must be some parallel between the evolution of species and that of our knowledge at the phenomenological basis. To achieve a synthesis on the theories of evolution, a new paradigm of endo-exo circulation is introduced from interdisciplinary perspectives.

NCI's Physical Sciences In Oncology Initiative: An Evolutionary Perspective Future

Larry Nagahara
The National Cancer Institute

Cancer is one of the main public health problems facing the world today. The statistics for cancer in the United States alone are daunting with the number of Americans who will die of cancer in 2009 being projected to be over 550,000 (over 7.5 million/year worldwide). The number that will be diagnosed with the disease will exceed 1.4 million. On the positive side, there are over 12 million cancer survivors today in the United States mainly due to progress in early detection and treatment. With regards to cancer diagnostic and prognostic indicators, clinicians currently depend on the morphological and histological characteristics of a tumor or by some other biomarkers, such as prostate-specific antigen (PSA). Recently, the National Cancer Institute (NCI) has awarded multiple institutional grants to establish twelve Physical Sciences-Oncology Centers (PS-OC) as part of its Physical Sciences in Oncology initiative to better understand the physical laws and principles that shape and govern the emergence and behavior of cancer. The goal of the five-year initiative is to engage trans-disciplinary scientific teams from fields of physics, mathematics, chemistry and engineering to examine new, non-traditional approaches to cancer research. Researchers will explore the physical laws and principles of cancer; evolution and evolutionary theory of cancer; information coding, decoding, transfer and translation in cancer; and deconvoluting cancers complexity. These ongoing efforts will enable experts to explore new and innovative approaches to better understand, diagnose, treat, and control cancer. The NCI anticipates that this initiative will foster the development of innovative ideas and new fields of study based on knowledge of the biological and physical laws and principles that define both normal and tumor systems.

Other People's Money: A Lawyer's Perspective

Philip Papier, Esq.

No abstract submitted.

Mutation As A Stress Response And The Regulation Of Evolvability

Susan Rosenberg
Baylor College of Medicine

Our concept of a stable genome is evolving from one in which the DNA sequence is passed faithfully from generation to generation to another in which genomes are plastic and responsive to environmental changes. Growing evidence shows that environmental stresses induce genomic instability in bacteria, yeast, and human cancer cells, generating occasional fitter mutants and potentially accelerating adaptive evolution. The emerging molecular mechanisms of stress-induced mutagenesis vary but share telling common components that underscore two common themes. The first is the regulation of mutagenesis in time by cellular stress responses, which promote random mutations (i.e., those with neutral, deleterious, or adaptive consequences) specifically when cells are poorly adapted to their environments, i.e., when they are stressed. A second theme is the restriction of random mutagenesis in genomic space, achieved via coupling of mutation-generating machinery to local events such as DNA repair or transcription. We have hypothesized that such localization may minimize accumulation of deleterious mutations in the genomes of rare fitter mutants, and promote local concerted evolution (adaptive evolution requiring multiple mutations). These themes will be illustrated by the example of the E. coli Lac system for starvation-inducible mutagenesis. These themes are widespread in mutagenesis in many different bacterial experimental systems and natural isolates, yeast and human cells. Such mechanisms probably fuel many instances of biological evolution, including evolution of microbial pathogenesis and antibiotic-resistance, and human tumor-progression and resistance mechanisms much of which occurs under stress, driven by mutations. The multiple, similar-but-not-identical molecular mechanisms of stress-inducible mutagenesis observed in different environmental conditions, assays, strains and organisms, suggest multiple independent evolutions of stress-inducible mutagenesis, with regulation by stress responses emerging as an overarching common theme.

Leader Cells In Collective Migration

Pascal Silberzan
Institut Curie

We generate model wounds by using an original microfabrication-based technique based on a microstencil that masks portions of the surface during the growth of a monolayer. Removing the stencil at the confluence of epithelial MDCK cells does not damage the border cells but triggers the collective motility of the epithelium, while cells maintain strong adhesions between them. By using hydrodynamics derived techniques such as Particle Image Velocimetry (PIV), based on the correlations between successive images, we observe that this collective motility involves long-range coordinated displacements of large groups of cells well within the monolayer. This observation contradicts the commonly accepted view in which only the border cells are affected. A simple model describing these behaviors will be presented. In a second stage, the edges of these wounds roughen drastically and exhibit a strong directional fingering where a leader cell, that exhibits a clearly non-epithelial phenotype, leads the others. Interestingly, before they become leaders, these cells are identical to the others. Similarly looking leader cells are found in a large number of different situations in morphogenesis or local invasion from epithelial tumors. We fully map the velocity field (intensity and orientation) in the fingers and we quantify the orientation of the cells themselves, their division axis and their polarity through the position of their centrosome relatively to their nucleus. We find that all these directions align with the fingers but are described by different order parameters and kinetics. To elucidate the exact role of the leader, we also map the traction forces exerted by the cells in the fingers using a microfabricated array of force sensors and correlate it to the velocity distribution as well as with the activity of Rac proteins involved in migration that we simultaneously measure using FRET bioprobes. Complementary laser photo-ablation experiments help to clarify the contribution of the leader vs. the other cells of the fingers in these structures.

Who Will Fund The High-Risk Projects In The Life Sciences?

Nancy Sung
Burroughs Wellcome Fund

Support for science in the United States is dominated by federal funding agencies and industry. The small proportion of support for biomedical research that comes from private foundations is meant to be catalytic; providing risk capital to prove principles that can then be taken to scale by other funders. In the mid-1990s the Burroughs Wellcome Fund (BWF), a private foundation, identified the interface between physics and biology as an area ripe for scientific advance, however hospitable habitats, in which young scientists could be cross-trained, did not exist. BWF invested in ten training programs aimed at introducing students and fellows with backgrounds in non-biological areas (primarily physics and mathematics) to address biological questions. At the time, institutional, departmental, and disciplinary structures were not aligned to enable this sort of education, and there was a perception that graduates of such programs would have difficulty building careers. An analysis of the early career outcomes of program graduates indicates that many of them have gone on to productive tenure-track positions in academia. BWF learned that the more successful programs were those that paid careful attention to the language and cultural barriers that exist between disciplines, and those that intentionally built interdisciplinary communities. This presentation will lead into a discussion of the institutional and funding structures that are needed now to exploit the emerging scientific opportunities at the interface of physics and biology.

Evolution And Cancer

Thea Tlsty
University of California at San Francisco

Previous studies of gene expression changes within pre-malignant and benign lesions have not explored the potential significance of intralesional heterogeneity of marker expression. In our studies of DCIS, we find a broad range of expression of a given marker; heterogeneity is the rule rather than the exception. Heterogeneity may represent regional differences in cellular stress or perhaps different snapshots in time of stress responsiveness. Alternatively, heterogeneity may represent mixed molecular subtypes or perhaps the active process of clonal evolution. Given that differences in gene expression signaling distinguish intrinsic molecular subtypes and predict clinical outcome, further exploration of the molecular basis for heterogeneity may provide insights into the evolutionary processes that underlie cancer formation and progression. Tracing this emerging molecular process backwards to pre-malignant lesions may identify subpopulations representing the origin of molecular diversity.

The Dynamics Of The Immune Repertoire Of An Organism

Josh Weinstein
Stanford University

The adaptive immune system enables an individual to defend against previously unencountered pathogens by trial and error: randomly recombining and mutating sequences coding for pathogen-binding proteins, known as antibodies. This talk will focus on the burgeoning use of the adaptive immune system in zebrafish as a case study in the dynamics of evolving populations of antibody-producing B-cells. Specifically, highthroughput sequencing technology will be shown capable of measuring the diversities and distributions of antibodies. The surprising result of universality in the distributions of antibody abundances of individual zebrafish will lead into a discussion of simple but powerful models of immune dynamics.

Round-table Discussion On Understanding Evolution Without Darwin

Carl Woese
University of Illinois at Urbana-Champaign

We will only begin to understand evolution as a scientific problem if we start afresh ––by which I mean going back to the original phenomenology, “descent” with modification, that was the coin of the intellectual realm circa 1800, when one could count Erasmus Darwin, Goethe, Kant, and Lamarck, among those who pondered it. And this is what we are doing now here at Illinois-–starting from the ground up, grounding our thinking in a non-Darwinian (sometimes anti-Darwinian when necessary to overcome obstructions) foundation in modern physics, not biology.