THE GOVERNOR'S CONFERENCE
ON EFFECTIVE PARTNERING IN CANCER RESEARCH

Systems Biology & Cancer

APRIL 22, 2010

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This is the seventh in a series of conferences made possible by an annual appropriation to The Cancer Institute of New Jersey through the generous support of the recent Governors past and present and The New Jersey Legislature. The Governor's Conference series seeks to bring together international experts in the field of cancer research from academia, the private sector – including the New Jersey pharmaceutical industry – and state and national government agencies to share their respective expertise on important aspects of the prevention, diagnosis, and treatment of cancer. These conferences are designed to promote New Jersey's leadership in cancer care and research and to develop strategies through which New Jersey scientists can work together more effectively to achieve these goals.

The first conferences took the form of interactive workshops with the goals of facilitating the translational research process and identifying and implementing strategies for cancer prevention.

Beginning in 2007, the focus of the series evolved to highlight research breakthroughs and new technologies and the resulting advances that they facilitate. The 2007 conference focused on the field of genomics, with an emphasis on cancer prevention. The 2008 conference explored stem cells and cancer. In 2009, the conference examined human viruses and their interrelationship with cancer. Each conference has succeeded in bringing together experts throughout the continuum from basic laboratory research through clinical studies, which has been a hallmark of the series.

This year's conference brings together the fields of systems biology and cancer biology. Speakers will focus on studies that characterize normal and cancer cells and discuss how the new technologies might be used to enhance our understanding of cancer biology and lead to advances in the diagnosis and treatment of cancer.

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Wolfensohn Hall
Institute *for* Advanced Study
PRINCETON, NEW JERSEY

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NJCCR NEW JERSEY COMMISSION ON CANCER RESEARCH

Conference Schedule

Thursday, April 22, 2010

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Welcoming Remarks
8:45 a.m. – 9:00 a.m.

Robert S. DiPaola
The Cancer Institute of New Jersey, UMDNJ-Robert Wood Johnson Medical School

Arnold J. Levine
The Simons Center for Systems Biology, Institute for Advanced Study

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"Genome-Wide Allele-Specific Analyses"
Andrew Chess
Massachusetts General Hospital and Harvard Medical School
9:00 a.m. – 9:45 a.m.

"The Universe of Normal & Cancer Cell Line Responses to Small Molecules: Lessons for Anticancer Therapy"
Alexei Vazquez
The Cancer Institute of New Jersey
9:45 a.m. – 10:30 a.m.

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Break
10:30 a.m. – 11:00 a.m.

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"Proteomic & Genetic Analysis of the Ubiquitin System"
J. Wade Harper
Harvard Medical School
11:00 a.m. – 11:45 a.m.

"Next Generation Quantitative Proteomic Tools for Understanding Epigenetic Mechanisms"
Benjamin A. Garcia
Princeton University
11:45 a.m. – 12:30 p.m.

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Conference Schedule

Thursday, April 22, 2010

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Lunch
Available in the Institute Dining Hall
12:30 p.m. – 2:00 p.m.

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"Exploring the Systems Pathology/Biology of Breast Cancer"
Anne-Lise Børresen-Dale
Norwegian Radium Hospital, Oslo University Hospital
2:00 p.m. – 2:45 p.m.

"Network Polymorphisms & Cancer"
Gurinder S. Atwal
Cold Spring Harbor Laboratory
2:45 p.m. – 3:30 p.m.

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Afternoon Tea Break
Fuld Hall Common Room
3:30 p.m. – 4:00 p.m.

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"The Evolution of the p53 Family of Genes: Somatic Cell & Germ Cell Fidelity"
Arnold J. Levine
The Simons Center for Systems Biology, Institute for Advanced Study
4:00 p.m. – 4:45 p.m.

"Surprisingly Small Effective Size of the Human TCR Repertoire Creates Large Overlap Between Individuals"
Harlan Robins
Fred Hutchinson Cancer Research Center
4:45 p.m. – 5:30 p.m.

(End of Program)

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Biographical Sketches

(in alphabetical order)

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GURINDER S. ATWAL

Gurinder S. (Mickey) Atwal is currently an Assistant Professor at Cold Spring Harbor Laboratory, holding appointments in the departments of Quantitative Biology and Cancer Biology. His work currently focuses on developing mathematical and computational approaches to population genetics, with a view to understanding the evolutionary forces at play on the human genome and to underpin the genetics of cancer.

After abandoning medical studies at the University of Cambridge in 1996, he continued to break his family's heart by pursuing a Bachelor's and a Master's degree in theoretical physics. Following his Ph.D. in theoretical condensed matter physics at Cornell University he made the steady transition into systems biology during his postdoctoral appointments at Princeton University and The Institute for Advanced Study. Recently, he was named in Genome Technology magazine as one of the top 25 young investigators in genomics. Nevertheless, his mother still thinks he should have been a medical doctor.

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ANNE-LISE BØRRESEN-DALE

Anne-Lise Børresen-Dale, Ph.D., M.D. (h.c.) earned her M.Sc. in Biochemistry in 1970 from the Technical University of Norway, Trondheim, and her Ph.D. in 1978 in Medical Biochemical Genetics from University of Oslo, Norway. In 1992 she became a full Professor at the University of Oslo, Faculty of Medicine and since 1999, has headed the Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet. She is among the leading geneticists in research on the molecular biology of breast cancer, and was among the pioneers in expression profiling of breast carcinomas in collaboration with groups at Stanford, demonstrating that breast cancer can be divided into distinct sub-groups by molecular profile, and by overall and relapse-free survival. She has received several prizes and awards, including the Swiss Bridge Award for outstanding Cancer Research in 2004 and the Möbius prize for outstanding Research from the Research Council of Norway in 2008. Børresen-Dale is a Member of the Board of Directors of ECCO, current president of the EACR, and an Elected Member of The Royal Academy of Science, Norway and The Norwegian Academy of Science and Letters. Her current research projects focus on the systems biology of breast cancer using high dimensional data in integrated approaches to identify genotypes and gene expression profiles contributing to elevated cancer risk, radiation sensitivity, tumor aggressiveness and therapy

resistance, in order to follow the linear time course of predisposition, initiation, early stages and advanced disease; to dissect the molecular mechanisms triggered at each stage; and to follow the multidimensional interactions at various levels to improve risk estimation, prognostication and prediction.

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ANDREW CHESS

Andrew Chess completed his undergraduate work at the Massachusetts Institute of Technology (MIT), and obtained his M.D. at Columbia University College of Physicians and Surgeons. He then did post-doctoral training with Dr. Richard Axel at Columbia. From 1996 – 2004 Dr. Chess was a faculty member in the MIT Department of Biology at the Whitehead Institute for Biomedical Research. He joined the faculty of Harvard Medical School and the Massachusetts General Hospital (MGH) in 2004, and his lab has since then been part of the Center for Human Genetic Research at MGH.

Chess has a longstanding interest in studying gene regulatory mechanisms underlying the specification of individual cell type in general and in the nervous and immune systems. His work has uncovered aspects of odorant receptor gene expression, neutral-specific extensive alternative splicing and also uncovered a structural role for large non-coding RNA. The Chess lab played a central role in defining a class of autosomal genes with properties similar to X-inactivation. Much recent work has focused on genome-scale approaches to studying DNA methylation, and genome-scale analyses of allele-specific transcription. These studies have taken advantage of genome-wide arrays allowing the analyses of single nucleotide polymorphisms (SNPs) and also emerging high capacity DNA sequencing technologies.

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BENJAMIN A. GARCIA

Benjamin A. Garcia received his B.S. in Chemistry from the University of California, Davis where he conducted undergraduate research studying the interactions of protein and peptides with oligosaccharides in the gas phase in the laboratory of Prof. Carlito B. Lebrilla. He then enrolled in graduate school at the University of Virginia and obtained his Ph.D. under Prof. Donald F. Hunt. During his graduate studies, Dr. Garcia developed mass spectrometry methodology to investigate: phosphoproteins involved in the Wnt Signaling pathway, biomarker discovery in human fluids and tissues and histone post-translational modifications on many proteins including histones (working in collaboration with Prof. Davis Allis). In postdoctoral work with Prof. Neil Kelleher at the University of Illinois, Urbana-Champaign, Dr. Garcia continued his studies of histones, using Top Down mass spectrometry. Dr. Garcia is now an Assistant Professor of Molecular Biology and Chemistry at Princeton University. His current interests include continued development of proteomic methodolo-

gy for interrogating post-translationally modified proteins, especially those involved in transcriptional regulation, such as histone and other chromatin-associated proteins. His group also is successfully merging cell and molecular biology approaches with proteomics and genomics analyses for a systems-wide look at epigenetic signaling mechanisms. Dr. Garcia was recently awarded a National Science Foundation Early Faculty CAREER award, the American Society for Mass Spectrometry research award and was named an Emerging Investigator by the Molecular BioSystems journal.

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J. WADE HARPER

J. Wade Harper received both his B.S. and Ph.D. in chemistry from the Georgia Institute of Technology in 1980, and 1984. He was a post-doctoral fellow at Harvard Medical School from 1984 to 1988, when he joined the faculty of Baylor College of Medicine. He has been the B. and N. Vallee Professor of Molecular Pathology at Harvard Medical School since 2003, where he directs a laboratory in the analysis of biochemical pathways and networks controlling aspects of cell division, the DNA damage response, and ubiquitin-mediated protein turnover.

Dr. Harper's awards and honors include an NIH Heart, Lung, and Blood Institute Postdoctoral Fellowship, an American Cancer Society Junior Faculty Award, the Michael E. DeBakey Award for Excellence in Research, 1994, for discovery of the p21 CDK inhibitor, the Michael E. DeBakey Award for Excellence in Research, 2000 for discovery of the SCF ubiquitin ligase, and the Vallee Visiting Professorship, Oxford University, United Kingdom, June/July 2000.

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ARNOLD J. LEVINE

Arnold J. Levine's research centers on the causes of cancer. In 1979, Levine and others discovered the p53 tumor suppressor protein, a molecule that inhibits tumor development. The p53 protein was originally thought to be an oncogene, or tumor accelerator. Levine received a B.A. from Harpur College, SUNY, in 1961 and a Ph.D. from the University of Pennsylvania in 1966. He was elected to the National Academy of Sciences in 1991 and to its Institute of Medicine in 1995. Dr. Levine has received numerous awards and prizes including the American Association of Cancer Research Kirk A. Landon – AACR Prize for basic cancer research in 2008 and the American Cancer Society Medal of Honor in 2009. He now heads The Simons Center for Systems Biology at the Institute for Advanced Study, and is a Professor at The Cancer Institute of New Jersey, UMDNJ-Robert Wood Johnson Medical School.

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HARLAN ROBINS

Harlan Robins received his undergraduate degree from Harvard. In 2001, he earned a Ph.D. in theoretical particle physics from the University of California, Berkeley. The following

year he went to the Weizmann Institute in Israel as a Koshland Scholar. From 2002-2006, he joined the Institute for Advanced Study's Simons Center for Systems Biology as a postdoctoral member. At the IAS, Dr. Robins was given the Ambrose Monell Foundation Member Award. In 2006, Dr. Robins joined the faculty at the Fred Hutchinson Cancer Research Center in the Computational Biology Program. He has spent the last few years developing a new technology to sequence T cell receptors, a vital part of the adaptive immune system. In 2009, he was awarded an Ellison Medical Research Foundation New Scholarship in Aging for the application of this technology to the study of immunosenescence.

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ALEXEI VAZQUEZ

Alexei Vazquez began his studies in Physics at the University of Havana, Cuba, where he obtained his B.Sc. (1995) and M.Sc. (1997). He then moved to the International School of Advanced Studies in Trieste, Italy, where he obtained a Ph.D. (2002) in Statistical and Biological Physics.

Subsequently, he held a postdoctoral research position at the University of Notre Dame, Indiana, USA. During this time, he worked on modeling cell metabolism and strategies to fully map the human protein – protein interaction network, the latter during a one year visit to the Dana-Farber Cancer Institute, Massachusetts. From 2006 to 2009, Dr. Vazquez was a member of The Simons Center for Systems Biology at the Institute for Advanced Study (IAS) in Princeton, New Jersey. At the IAS, he worked on cancer systems biology, with an emphasis on the contribution of genetic variations to cancer. Since 2009, Dr. Vazquez has been an Assistant Professor in the Department of Radiation Oncology, at The Cancer Institute of New Jersey, UMDNJ-Robert Wood Johnson Medical School in New Brunswick, New Jersey. His research focuses on the broad area of cancer systems biology, including research on cancer genetics and pharmacology and cancer cell metabolism.

Scientific Presentations *(in order of Program)*

✧

Andrew Chess

Genome-Wide Allele-Specific Analyses

Epigenetic marks along the genome play important roles in the regulation of gene expression and therefore, on development and disease. These marks, sometimes called the epigenome, are perhaps best studied by approaches that examine the two alleles at each position across the genome. Studies of allele-specific DNA methylation and allele-specific transcriptional regulation will be presented.

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Alexei Vazquez

The Universe of Normal & Cancer Cell Line Responses to Small Molecules: Lessons for Anticancer Therapy

According to the most recent Surveillance Epidemiology and End Results (SEER) report, it is estimated that 1,479,350 men and women will be diagnosed with and 562,340 men and women will have died of cancer of all types in 2009. These statistics indicate that about 40% of the cancer patients do not respond well to current anticancer therapies. Using data characterizing the response of normal and cancer cell lines to anticancer treatments, we show that this high mortality rate is rooted in inherent features of anticancer treatments that are based on chemotherapy and radiation.

Specifically, whereas on average anticancer treatments exhibit a twofold higher efficacy when applied to cancer cell lines, the response distributions of cancer and normal cell lines have a significant overlap. Focusing on specific treatments, we provide evidence indicating that the therapeutic index is proportional to the fraction of cancer cell lines manifesting significantly good responses, and propose the latter as a quantity to identify compounds with best potential for anticancer therapy.

Based on this evidence we conclude that there is no single treatment targeting all cancer cell lines at a non-toxic dose. However, there are effective treatments for specific cancer cell lines, which, when used in a personalized manner or applied in combination, can target all cancer cell lines.

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J. Wade Harper

Proteomic & Genetic Analysis of the Ubiquitin System

Protein homeostasis in eukaryotes is controlled by proteasomal turnover of unstable proteins via the ubiquitin system and lysosomal turnover of the majority of stable proteins through a pathway called autophagy. In the ubiquitin pathway, proteins are tagged with a chain of ubiquitin molecules through an E1-E2-E3 cascade, which is represented by several hundred genes in humans, and is reversed by the action of deubiquitinating enzymes. E3 proteins provide specificity to the system and dictate substrate choice in regulated protein turnover pathways, although a global understanding of these systems are limited. In contrast, autophagy is controlled by a distinct UBL conjugation system which functions in the bulk degradation of stable and sometimes toxic proteins, and has recently been linked to degradation of selective organelles (e.g. mitochondria). In this process, cellular proteins are encapsulated into a membrane structure called the autophagosome and delivered to the lysosome via vesicle fusion events. Autophagy is under control of nutrient, energy, and growth factor signaling systems and is activated by diverse mechanisms including starvation, but precisely how protein kinase, lipid kinase and UBL conjugations systems function together remains largely unknown in mammals. Our work has focused on the use of systematic genetic and proteomic methods to address the architecture of pathways in the ubiquitin and autophagy protein degradation systems. We have developed a proteomics platform, referred to as CompPASS (Comparative Proteomics Analysis Software Suite), that greatly facilitates the identification of high-confidence candidate interacting proteins in semi-high throughput proteomic data and have used this platform to systematically examine the interaction landscape of a family of human deubiquitinating enzymes and a large class of E3 ubiquitin ligases, thereby revealing biological pathways in which these proteins function. We have also applied this approach to the autophagy interaction network (AIN) in human cells, revealing a network of 763 interactions among 439 candidate interacting proteins with extensive connectivity among functional sub-networks that control autophagosome formation and fusion with the lysosome. Many new AIN components have roles in vesicle trafficking, protein or lipid phosphorylation, and protein ubiquitination, and affect autophagosome number when depleted by RNAi. The six ATG8 orthologs in humans (MAP1LC3/GABARAP proteins) interact with a cohort of 67 proteins, with extensive binding partner overlap between family members, and frequent involvement of a conserved surface on ATG8 proteins for direct interaction with LC3-interacting regions (LIR) in partner proteins. These studies provide a global

view of the mammalian autophagy interaction landscape and will serve as a resource for mechanistic analysis of this pathway critical for protein homeostasis.

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Benjamin A. Garcia

Next Generation Quantitative Proteomic Tools for Understanding Epigenetic Mechanisms

Several single histone modifications are associated with both gene activation and silencing. However, what type of effect distinct combinations of simultaneously occurring histone modifications (Histone Codes or patterns) have upon cellular events is poorly understood. The main reason for this lack of knowledge is that techniques for quantitative characterization or even qualitative identification of combinatorial Histone Codes by any method do not readily exist. We plan to specifically address this deficiency by developing novel mass spectrometry based methods for (i) rapid comparison of histone modifications from multiple cellular states (ii) quantitative tracking of hundreds of combinatorial Histone Codes in a single experiment (iii) monitoring in vivo Histone Code dynamics, and (iv) investigating the role of Histone Code interpreting proteins in reading Histone Code patterns. These studies in combination with biological experiments will help provide a systems-wide outlook that will lay down the basic scientific foundation to understand several key biological areas where epigenetic alterations are believed to exist, such as during cancer progression.

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Anne-Lise Børresen-Dale

Exploring the Systems Pathology/Biology of Breast Cancer

Microarray technologies, applied to the study of DNA/mRNA/miRNA, can be used to portray a tumor's detailed phenotype in its unique context, and to generate molecular signatures that will improve our understanding of the causes and progression of the disease, for the discovery of new molecular markers, for therapeutic intervention and for developing new prevention strategies. We have performed such analyses of more than 1000 breast carcinomas of different stages and histological types aiming at novel tumor classification that can predict survival and treatment response.

Two platform independent algorithms were developed to explore genomic architectural distortion using aCGH data to measure whole arm gains and losses (WAAI) and complex rearrangements (CAAI). By applying this to our datasets the

relationship between structural genomic alterations, expression subtypes and clinical behavior can be found.

Using SNP arrays and a novel bioinformatic approach, ASCAT (Allele-Specific Copy number Analysis of Tumors) we are able to accurately dissect the allele-specific copy number in each tumor, simultaneously estimating and adjusting for both tumor ploidy and non-aberrant cell admixture, allowing calculation of "Tumor Profiles" (genome-wide allele-specific copy-number profiles) from which gains, losses, copy-number-neutral events and LOH can be determined. From these Tumor Profiles we are able to construct a genome-wide map of allelic skewedness, indicating loci where one allele is preferentially lost while the other allele is preferentially gained. We hypothesize that these alternative alleles have different influences on breast carcinoma development.

By integrating data from the patient's own genotype with data from the tumor at the DNA level, (copy number mutations, methylation), mRNA and miRNA level, as well as metabolic profiles revealed from HR-MAS MR analyses of the tumor, we seek to reach a more fundamental understanding of the biological dynamics of breast cancer. This will facilitate the identification of risk factors, the search for novel cancer diagnostics, and the prediction of therapeutic effects, prognosis and identification of new targets for therapy.

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Gurinder S. Atwal

Network Polymorphisms & Cancer

Mathematical models of population genetics provide a quantitative basis for understanding human genetic variation and the resulting population heterogeneity in cancer risk. Recent computational investigations of the population genetics of the p53 pathway have hinted at signatures of recent positive selection, providing a novel and expeditious route to uncovering functional genetic polymorphisms with relevance to both cancer risk/survival and female infertility. Hitherto, most association studies have ignored higher-order interactions between genetic variants in the network of oncogenes and tumor suppressor genes. Our work has revealed statistical correlations between selected haplotypes, not only in the p53 network but also genome-wide, due to the confounding combined effects of sampling, synergistic interactions and population structure.

We present and utilize a quantitative framework to describe the functional network of polymorphisms in the p53 pathway.

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Arnold J. Levine

The Evolution of the p53 Family of Genes: Somatic Cell & Germ Cell Fidelity

The human genome contains three transcription factors termed p53, p63 and p73 which are related orthologues. The function of the p53 protein is to respond to a wide variety of stresses which can disrupt the fidelity of DNA replication and cell division in somatic cells of the body. These stress signals, such as DNA damage, increase the mutation rate during DNA duplication and so an active p53 protein responds by eliminating clones of cells with mutations employing apoptosis, senescence or cell cycle arrest. In this way the p53 protein acts as a tumor suppressor preventing the mutations that can lead to cancers. The p63 and p73 proteins act in a similar fashion to protect the germ line cells in females (eggs). In addition the p63 protein plays a central role in the formation of epithelial cell layers and p73 plays a critical role in the formation of several structures in the central nervous system and the immune system.

Based upon amino acid identities and structural considerations, some invertebrates have a p53-like gene while others appear to contain a p63/p73 ancestoral hybrid gene. The present day representatives of these animals that contain a p63/p73 like ancestor gene (flies and worms) have a protein that functions in the germ cells of animals to enforce the fidelity of DNA replication after exposure to stresses. The withdrawal of a food source from a worm results in the p63/p73 mediated apoptosis of the eggs so that new organisms will not be hatched into a poor environment. Thus this ancestor gene ensures the fidelity of the next generation of organisms.

In vertebrates a clearly distinct new p53 gene arises in the cartilaginous fish. In the bony fish a separation of the p63 and p73 gene occurs. After that there are very limited evolutionary changes that are found in the p63 gene and only a few changes in the p73 gene core. By contrast the p53 gene evolves rapidly and extensively obtaining the new functions of surveillance of DNA replication and cell division after stress in the somatic tissues of the body. This appears to coincide with the enhanced use of the strategy of stem cells to regenerate tissues throughout the life of the organism.

As Caucasians and Asians evolve from their African ancestors polymorphic changes in the p53 gene occur and are rapidly selected for in these populations. This results in the further selection of alleles in genes whose products interact with and regulate the p53 protein. These polymorphisms have dramatic impacts upon the age of onset of cancers, and even the reproductive fecundity of a population. The p53 protein is

required for efficient implantation of a fertilized egg into the uterus of a female and this helps to explain the strong selection pressures upon these genes. The p53/p63 and p73 genes are not only selected by evolutionary forces but help to set the rate at which evolutionary changes can occur. For those reasons these genes have preserved a one billion year history.

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Harlan Robins

Surprisingly Small Effective Size of the Human TCR Repertoire Creates Large Overlap Between Individuals

Diversity in T-lymphocyte antigen receptors is generated by somatic rearrangement of T-cell receptor (TCR) genes and is concentrated within the third complementarity-determining region (CDR3) of each chain of the TCR heterodimer. We sequenced the CDR3 regions from millions of rearranged TCR beta chain genes in naïve and memory CD8 T-cells of seven adults. The CDR3 sequence repertoire realized in each individual is strongly biased toward specific V beta – J beta pair utilization, dominated by sequences containing few inserted nucleotides, and drawn from an effective sequence space 250-fold smaller than predicted. Surprisingly, the overlap in the naïve CD8 CDR3 sequence repertoires of any two of the individuals is ~ 1000-fold larger than predicted and essentially independent of the degree of HLA matching.

(End of Program)

The Cancer Institute of New Jersey

The Cancer Institute of New Jersey (CINJ) is the state's first and only National Cancer Institute-designated Comprehensive Cancer Center. As one of only 40 such centers nationwide, CINJ is dedicated to improving the prevention, detection, treatment, and care of patients with cancer, through the translation of laboratory discoveries into clinical practice. The war against cancer is particularly important for New Jersey, a state that ranks in the top ten nationally for cancer incidence. Although survival rates are increasing due to improvements in prevention and early detection, much remains to be done. As a Center of Excellence of the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School, CINJ is committed to learning more about cancer and making its discoveries available to the public to aid in disease prevention.

At CINJ, laboratory research is being conducted in areas that include: oncogenes, epidemiology, chemical carcinogenesis, tumor virology and immunology, drug development and resistance, the relationship between cellular and genetic mechanisms and tumor development, and cancer genomics. CINJ researchers hold faculty positions at UMDNJ-Robert Wood Johnson Medical School, UMDNJ-School of Public Health, and Rutgers, the State University of New Jersey.

Basic scientists and clinical researchers meet regularly to exchange information and ensure that laboratory discoveries are refined and applied to clinical care as quickly as possible, and that clinical observations reach laboratory researchers on a continuing basis. Understanding the molecular and biological nature of cancer influences how oncologists at CINJ think about prognosis and treatment. In addition to enabling more accurate prognosis, information about molecular and biological characteristics of a tumor can be used to design more rigorous treatment strategies for patients who cannot be cured by current standard methods.

CINJ is a resource for physicians and patients throughout the state and region, via outreach and educational programs, as well as through collaborative efforts in clinical and basic research. The CINJ Network is composed of partner and affiliate hospitals and practicing oncologists. It provides a mechanism to rapidly disseminate important, valid discoveries into the community. Through the CINJ network, member hospitals and physicians make clinical trials and new investigational treatments available in the communities they serve.

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The Simons Center for Systems Biology

The Simons Center for Systems Biology at the Institute for Advanced Study conducts research at the interface of molecular biology and the physical sciences. Led by Professors Arnold J. Levine, a leading figure in cancer research, and by Professor Stanislas Leibler, who has made important contributions to theoretical and experimental biology, the Center hosts a range of distinguished Members and Visitors annually, and fosters original research in the field of systems biology.

Recent high-throughput technologies have generated enormous amounts of hitherto unseen biological data such as DNA sequences and genome-wide epigenetic changes. Modern computational and analytical tools enable integration of such data, allowing scientists to draw conclusions that will result in leaps of fundamental understanding of biological design principles and basic molecular biology, and will reduce – perhaps by years – the time leading to significant breakthroughs in developing personalized approaches to diagnosis and treatment of cancer, viruses, and other diseases.

Researchers at the Center comprise a diverse group trained in theoretical physics, mathematics, computer science, medicine and computational biology. They are engaged in detailed analyses of the large-scale genomic, structural, and clinical databases, as well as in developing theoretical and experimental methods for conducting studies in the collective behavior of biomolecules, cells and organisms. The Center seeks to explore and understand how the gene networks are regulated in time (from the development of the embryo to adult deterioration), space (specificity arising from intra-cellular localization and tissue type), and in different human conditions (disease, aging, stress), and to understand how individual components can give rise to complex, collective phenomena.

The post-doctoral training model at the Center includes conferences, symposia and seminars and encourages collaborations with other academic, clinical and industrial groups, both locally (Lewis-Sigler Institute for Integrative Genomics at Princeton University, BioMaPS Institute at Rutgers, The Cancer Institute of New Jersey, The Rockefeller University, Johnson & Johnson, Bristol-Myers Squibb, and Merck & Co.) and around the world, to pool biological data and to confirm hypotheses. As a leading center for theoretical research, the Institute is a natural locus for research biologists to visit and work, as research in the life sciences increasingly requires extensive skills in the quantitative sciences. These interactions help to promote the exchange of ideas and formulation of questions for future discoveries.

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The Institute for Advanced Study

The Institute for Advanced Study is one of the world's leading centers for theoretical research and intellectual inquiry. The Institute exists to encourage and support fundamental research in the sciences and humanities – the original, often speculative, thinking that produces advances in knowledge that change the way we understand the world. It provides for the mentoring of scholars by Faculty, and it offers all who work there the freedom to undertake research that will make significant contributions in any of the broad range of fields in the sciences and humanities studied at the Institute.

The Institute is a private, independent academic institution located in Princeton, New Jersey. It was founded in 1930 by philanthropists Louis Bamberger and his sister Caroline Bamberger Fuld, and established through the vision of founding Director Abraham Flexner. Past Faculty have included Albert Einstein, who remained at the Institute until his death in 1955, and distinguished scientists and scholars such as Kurt Gödel, J. Robert Oppenheimer, Erwin Panofsky, Homer A. Thompson, John von Neumann, George Kennan and Hermann Weyl.

Work at the Institute takes place in four Schools: Historical Studies, Mathematics, Natural Sciences, and Social Science. Currently, a permanent Faculty of twenty-nine eminent academics guides the work of the Schools and each year awards fellowships to some 190 visiting Members, from about one hundred universities and research institutions throughout the world. Dr. Peter Goddard is the current Director of the Institute.

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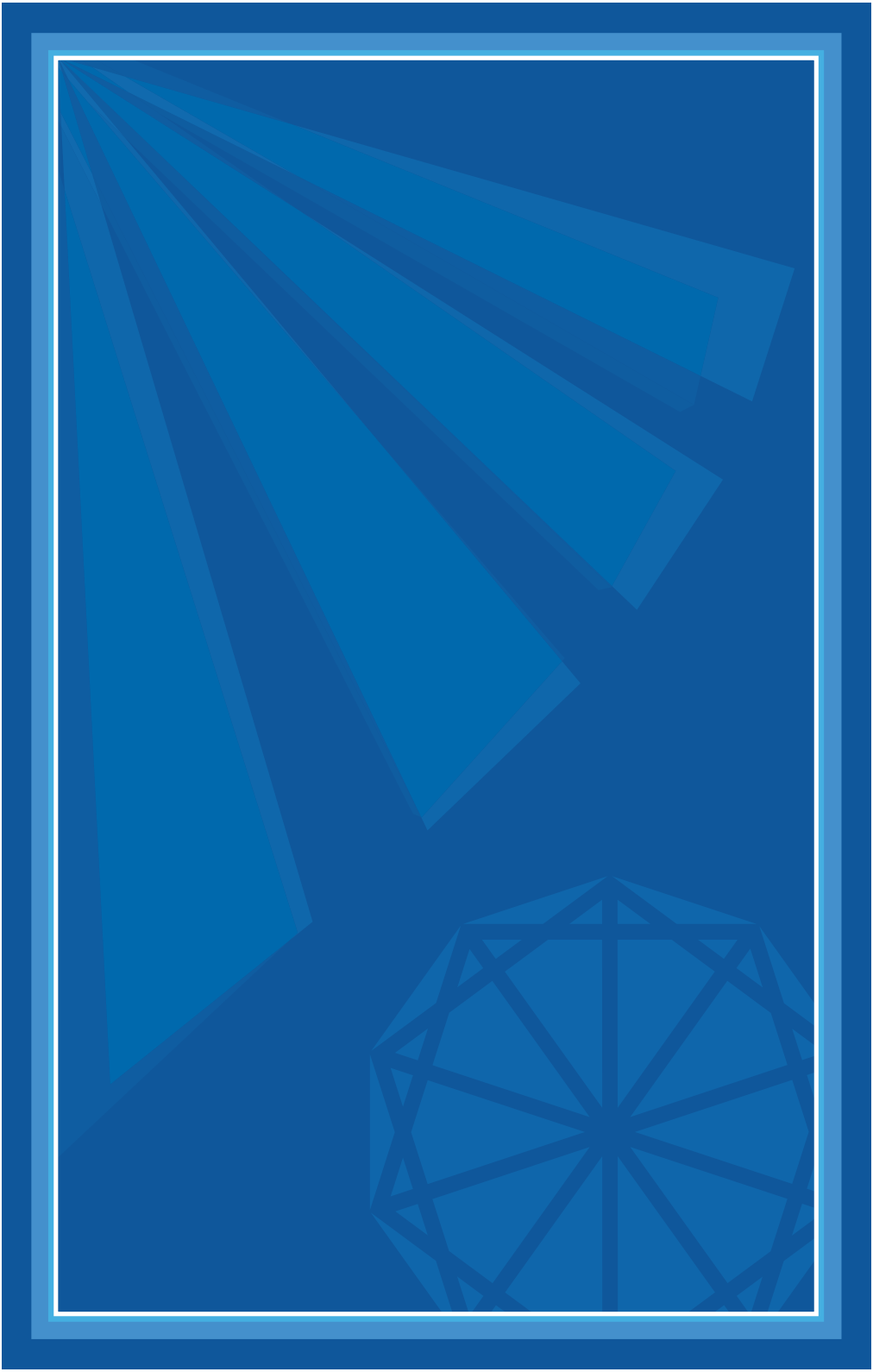

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