RNA Structure and Function:

a new frontier in biomedical research

24th Annual International Symposium

SYMPOSIUM PROGRAM

http://rnasymposium.hunter.cuny.edu

January 21, 2011 8:30 AM - 5:30 PM | Hunter College, East 68th, Room 714 Hunter West Building | NYC

24th Annual International Symposium

Sponsors:
Hunter College of the City University of New York,
Center for Study of Gene Structure & Function.

Weill Cornell Medical College,
Clinical & Translational Science Center.

Additional CTSC member institutions:
Memorial Sloan-Kettering Cancer Center, Hospital for Special Surgery,
Hunter College School of Nursing, Cornell University Cooperative Extension.

The 24th Annual International Symposium of the Center for Study of Gene Structure & Function at Hunter College, with Weill Cornell Medical College Clinical and Translational Science Center, is supported by the National Institutes of Health, National Center for Research Resources, Research Centers in Minority Institutions - G12-RR-003037 and Clinical Translational Science Award - UL1RR024996

The Research Centers in Minority Institutions (RCMI) Program of the National Institutes of Health enhances the research capacity and infrastructure at minority colleges and universities that offer doctorates in health sciences. http://www.ncrr.nih.gov/resinfra/ri_rcmi.asp

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The NCRR provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level, move to animal-based studies, and then are translated to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. NCRR connects researchers with one another, as well as with patients and communities across the Nation, to harness the power of shared resources and research. http://www.ncrr.nih.gov

The NIH, a part of the U.S. Department of Health and Human Services, is the primary Federal agency for conducting and supporting medical research. Composed of 27 Institutes and Centers, the NIH provides leadership and financial support to researchers in every state and throughout the world. Its mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. http://www.nih.gov

RTRN is strategically positioned to facilitate interdisciplinary clinical and translational research.RTRN has established a solid technological foundation to support intellectual exchange, generate innovative inter- and multi-disciplinary research and facilitate the movement of scientific advances throughout the translational research spectrum.

Center for Study of Gene Structure and Function

The Center for Study of Gene Structure and Function (Gene Center) is a consortium of researchers within Hunter College of The City University of New York - one of the largest public universities in the nation. At the heart of the Gene Center's mission is an imperative to build unique collaborations among biologists, biochemists, bio-psychologists, bio-physicists, bio-anthropologists and researchers from the Hunter School of Social Work and Urban Public Health; to recruit and equip outstanding faculty; to facilitate translational research; to develop and share core research facilities; and to implement strategies for scientific networking.

Since the Gene Center's inception, the growing number of papers published in peer-reviewed journals and the number and amount of grants obtained by the faculty have been the most visible hallmarks of its success. The Gene Center provides a vibrant research environment marked by: workshops on cutting-edge research techniques; frequent research colloquia and seminars by guest scientists; an annual international symposium, which is a major event on the New York scientific calendar; and a strong emphasis on collaborative translational research.

In addition, the Gene Center encourages bright undergraduates, including minorities, to make a career in biomedical research by hosting a Summer Program for Undergraduate Research (SPUR) and supports the professional development of minority scientists through the JustGarciaHill science web site.

The Gene Center is a key partner in the Clinical and Translational Science Center (CTSC), an enterprise that also includes the Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center, Hospital for Special Surgery and the Hunter College School of Nursing. The CTSC was established in 2007 with the aim of accelerating translational research. The overall goal is to facilitate the transition of laboratory work into state of the art clinical research (T1 research), and to provide research (T2) that improves patient care and health outcomes in the general community (T3). The Gene Center encourages collaborations among its members and with scientists at these and other institutions. In conjunction with CTSC and Weill Cornell Medical College, the Gene Center offers qualified pre-doctoral research associates the opportunity to pursue a certificate in Clinical Translational Research from Weill Cornell Medical College (WCMC). This track culminates in a PhD from Hunter/CUNY with a certificate or Masters in Clinical Investigation from Weill Cornell Medical College (WCMC). The Gene Center also participates in a national consortium, the RCMI Translational Research Network (RTRN), that facilitates collaboration, large-scale projects and sharing of facilities among RCMI institutions.

Visit the Gene Center website: http://genecenter.hunter.cuny.edu

Clinical and Translational Science Center

The Clinical and Translational Science Center (CTSC) is a unique collaboration between renowned biomedical and community organizations centered on Manhattan's east side. Weill Cornell Medical College and Graduate School of Medical Sciences is home to the administrative core of the CTSC, led by CTSC Program Director Julianne Imperato-McGinley, MD, Associate Dean of Translational Research and Education at Weill Cornell Medical College (WCMC).

In addition to WCMC, the CTSC partner institutions include:

- Hunter College, Center for Study of Gene Structure and Function
- Hunter College, School of Nursing
- Hospital for Special Surgery
- Memorial Sloan-Kettering Cancer Center
- Cornell University Co-operative Extension in New York City

Affiliated hospitals include New York-Presbyterian Hospital, Lincoln Medical Center, Methodist Hospital, New York Downtown Hospital, New York Queens Hospital, Wyckoff Heights Medical Center, and Brooklyn Hospital.

The CTSC is designed to bring together the resources of all partner and affiliate institutions to facilitate novel translational research. Separately, these institutions include superb academic centers of excellence, a diverse patient base, and a unique community-engagement program designed to foster collaboration between community groups and translational research scientists. Each partner and affiliate has an unmistakable character that enhances multi-disciplinary interaction. Integration of these unique resources and intellectual assets will facilitate translation of research findings in the laboratory to clinical research at the bedside and ultimately to best practices within underserved communities.

A Translational Research Support Team and a wide range of services, including core laboratories and professionally staffed patient care inpatient and outpatient units, are available to support clinical and basic science investigators who are interested in translational research. Contact a CTSC Research Facilitator to find out more: hks2001@med.cornell.edu.

The CTSC is funded through the Clinical and Translational Science Awards, a national consortium that is transforming how clinical and translational research is conducted.

For more information about the CTSC, please visit http://www.med.cornell.edu/ctsc.

MORNING SESSION

8:30 Breakfast

9:00 Introduction and welcome:
Robert P. Dottin, Director of the Center for Study of Gene Structure & Function and Professor of Biology at Hunter College, CUNY
Jennifer J. Raab, President, Hunter College, CUNY
Julianne Imperato-McGinley, Associate Dean of Translational Research, Weill Cornell Medical College

9:30 **Joan A. Steitz**
Howard Hughes Medical Institute, Yale University
Noncoding RNAs: With a Viral Twist

10:20 **Mariano Garcia-Blanco**
Duke University Medical Center
Discovery and Characterization of Flaviviral Host Factors

11:00 **Juli Feigon**
University of California, Los Angeles
Structure and Dynamics of Telomerase and Riboswitch RNAs

11:40 **Robert Schneider**
NYU Langone Medical Center
AUF1, a Protein Regulator of mRNA Decay,
Links Chronic Inflammation to Chromosome Maintenance,
Accelerated Aging and Tumorigenesis

12:00-1:20 Lunch provided for pre-registered participants.
Poster Session

AFTERNOON SESSION

1:20 **Robert P. Dottin**, Director of the Center for Study of Gene Structure & Function and Professor of Biology at Hunter College, CUNY

Remarks by Sponsoring Agency

2:00 **Phillip A. Sharp**
Koch Institute for Integrative Cancer Research, MIT
Gene Regulation by RNA as a New Frontier in Biomedical Research

2:50 **Luca Cartegni**
Memorial Sloan-Kettering Cancer Center
Therapeutic Modulation of RNA Processing

3:20 **Dixie Goss**
Hunter College, CUNY
Regulation of Iron Homeostasis Through
Metal Ion Sensing by mRNA: a Mammalian Riboswitch

3:45 Coffee and Posters Session

4:20 **Nahum Sonenberg**
Rosalind and Morris Goodman Cancer Centre, McGill University
Mechanism of Action of microRNAs

5:00 Poster Awards Ceremony

5:05 Closing Remarks

Joan A. Steitz

Howard Hughes Institute, Yale University

NONCODING RNAs: WITH A VIRAL TWIST

Abstract: Noncoding RNAs come in many sizes and flavors. Most – like snRNAs, snoRNAs, scaRNAs, and microRNAs – contribute to the regulation of gene expression. Gamma herpesviruses, an oncogenic class of viruses that infects and establishes latency in primate lymphoid cells, also make noncoding RNAs. We have been studying three instances where such viral RNAs appear to mimic their host counterparts but display unanticipated activities or modes of biogenesis, revealing how components borrowed from host cells can be manipulated to the advantage of the virus.

Two examples are from the monkey virus Herpesvirus saimiri (HVS). HVS makes 7 HSURs during latency that resemble host snRNAs in both their structures and bound proteins. Instead of acting in splicing, two HSURs selectively bind host microRNAs, leading to enhanced decay and thus significantly lower levels of one of these microRNAs. MicroRNAs synthesized by HVS during latency are also unusual in that they arise from chimeric transcripts including other noncoding RNAs and do not follow the canonical microRNA processing pathway.

Kaposi's sarcoma associated virus (KSHV) makes a noncoding RNA called PAN (for polyadenylated nuclear) RNA that accumulates to extraordinarily high levels late in lytic infection. It binds the normally cytoplasmic PAB (polyA binding) protein. Its stability is dependent on the presence of an element called the ENE located close to its polyA tail. We have solved a high resolution Xray structure of the ENE, revealing that it engages polyA by triple helix formation and suggesting the existence of cellular homologs that likewise counteract nuclear RNA decay.

Bio: Dr. Steitz earned her BS in chemistry from Antioch College in 1963. Significant findings from her work emerged as early as 1967, when her Harvard PhD thesis with Jim Watson examined the test-tube assembly of a ribonucleic acid (RNA) bacteriophage (antibacterial virus) known as R17.

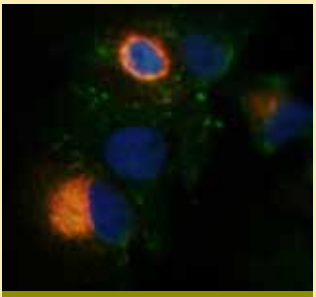
Dr. Steitz spent the next three years in postdoctoral studies at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, where she used early methods for determining the biochemical sequence of RNA to study how ribosomes know where to initiate protein synthesis on bacterial mRNAs. In 1970, she was appointed assistant professor of molecular biophysics and biochemistry at Yale, becoming full professor in 1978. At Yale, she established a laboratory dedicated to the study of RNA structure and function. In 1979, Dr.Steitz and her colleagues described a group of cellular particles called small nuclear ribonucleoproteins (snRNPs), a breakthrough in understanding how RNA is spliced. Subsequently, her laboratory has defined the structures and functions of other snRNPs, such as those that guide the modification of ribosomal RNAs and several produced by transforming herpesviruses.

Dr. Steitz is an investigator of the Howard Hughes Medical Institute, a member of the American Academy of Arts and Sciences, the American Philosophical Society, the National Academy of Sciences, and the Institute of Medicine. Her many honors include the U.S. Steel Foundation Award in Molecular Biology (1982), the National Medal of Science (1986), the Lewis S. Rosenstiel Award (2002), the FASEB Excellence in Science Award (2003), the RNA Society Lifetime Achievement Award (2004), E.B. Wilson Medal (2005), Gairdner Foundation International Award (2006). Albany Medical Center Prize in Medicine and Biomedical Research, Connecticut Women's Hall of Fame Award, and the New York Academy of Medicine Medal for Distinguished Contributions in Biomedical Science (2008). Honorary Fellow of The New York Academy of Medicine, (2009). She is the recipient of 13 honorary degrees.

Mariano Garcia-Blanco

Duke University Medical Center

DISCOVERY AND CHARACTERIZATION OF FLAVIVIRAL HOST FACTORS



Colocalization of host RBPs and viral RNAs

Abstract: Dengue fever (DF) and yellow fever (YF) are arthropod-borne flaviviral disease of humans and almost half of the world's population at risk of contracting one or both of these illnesses. The infectious agents that cause these are dengue viruses (DENV 1-4) and yellow fever virus (YFV). These RNA viruses require an extensive number of factors in the human host and the insect vector, yet only a limited number of human and an even smaller number of dipteran factors have been identified. To discover factors that impact on DENV and YFV propagation we have employed two complementary strategies: identification and characterization of proteins that interact with the viral genome, and RNA interference (RNAi)-based functional genomic screens that identify host proteins required for efficient viral propagation. I will summarize findings obtained with both strategies.

Bio: Dr. Mariano A. Garcia-Blanco MD, PhD is Professor of Molecular Genetics and Microbiology, and Medicine, and Director of the Center for RNA Biology at Duke University in the USA. He is also Professor of Emerging Infectious Diseases at the Duke-NUS Graduate Medical School in Singapore. Dr. Garcia-Blanco obtained his AB in Biochemical Sciences at Harvard College, and his MD and PhD (in Molecular Biophysics and Biochemistry) at Yale University. He obtained postdoctoral training in RNA biology with Nobel laureate Phillip A. Sharp at MIT. He is an internationally recognized expert in RNA biology and is an author in approximately 120 scientific publications. Dr. Garcia-Blanco is a co-founder of Intronn Inc. (now part of VIRxSYS, Rockville MD USA), Veri-Q Inc. (a Proteomics Company subsidiary, Surrey UK), and more recently SABio pte ltd (Singapore). He serves on several important national and international board. He is a member of the NIGMS Advisory Council, a trustee of the Puerto Rico Science Technology & Research Trust, and a member of the scientific advisory board of the European Alternative Splicing Network.

Website: http://mgm.duke.edu/faculty/garcia/index.htm

Singapore Website: http://www.duke-nus.edu.sg/web/research_faculty_mariano.htm

Juli Feigon

University of California, Los Angeles

STRUCTURE AND DYNAMICS OF TELOMERASE AND RIBOSWITCH RNAs

Abstract: RNA pseudoknots are commonly occurring secondary structural elements, found in many non-coding and regulatory RNAs, that provide long-range tertiary interactions, and they can have essential roles in both structure and function. We have been investigating the structure and dynamics of the core domain of human telomerase RNA, which contains a template enclosing large pseudoknot that is essential for catalysis.

Telomerase is a large RNP that replicates the 3' ends of linear chromosomes using an integral RNA template and a unique reverse transcriptase. We report progress on determining the structure and role of dynamics in function of the core domain of human telomerase RNA. We recently determined the solution structure of the aptamer domain of the preQ1 riboswitch from Bacillus subtilis. Riboswitches are a class of regulatory mRNA elements that bind specific metabolites, and are most often found in bacterial operons coding for protein products that produce or transport the related metabolite. The preQ1 riboswitch forms an unusual pseudoknot on binding preQ1. We report NMR studies of the dynamics of the riboswitch binding pocket and effect of cations on structure that provide new insights into 'catch and capture' of the preQ1 ligand. This work highlights the applications and importance of NMR for the study of biologically important RNAs.

Bio: Dr. Feigon received her BA from Occidental College and her MS and PhD from the University of California, San Diego where she studied with Dr. David Kearns. Her postdoctoral work was completed at the Massachusetts Institute of Technology, where she was a Damon Runyon-Walter Winchell Cancer Fund Postdoctoral Fellow with Dr. Alex Rich. Dr. Feigon joined the UCLA faculty in 1985.

Robert Schneider

NYU Langone Medical Center

AUF1, A PROTEIN REGULATOR OF mRNA DECAY, LINKS CHRONIC INFLAMMATION TO CHROMOSOME MAINTENANCE, ACCELERATED AGING AND TUMORIGENESIS

Abstract: Regulation of telomere length by telomerase plays an essential role in maintaining genetic stability. In mice, lack of adequate telomerase expression results in progressive telomere shortening over several generations. We show that the protein AUF1, a major attenuator of the inflammatory response through accelerated decay of inflammatory cytokine mRNAs, is also an essential regulator of telomere length and telomerase activity in mice, and also regulates cellular senescence. Late generation AUF1-deficient mice exhibit greatly accelerated aging and reduced life-span, increased cellular senescence due to increased stabilization of AUF1 target mRNAs p16ink4a and p21CIP, as well as shorter telomeres, abnormal chromosomes and a significant increase in DNA damage and a sharp increase in a variety of cancers. Backcross of late-generation mice to wild-type mice rescues the decrease in the number and survival of AUF1-/- progeny. Mechanistically, there is a reduction in the expression of the two core telomerase components, the catalytic subunit, TERT, and the RNA subunit, TERC, in AUF1-deficient cells. We demonstrate that AUF1 acts in part by regulating the transcription of TERC and TERT and can be foot-printed to the TERT promoter. Collectively, these and other data demonstrate that AUF1, which acts as an essential regulator of the inflammatory response via its ability to target specific inflammatory mRNAs for rapid decay, is also an essential regulator cellular senescence and telomere maintenance and impacts on the process of aging and cancer.

Navid Sadri, Adam Pont, Susan Smith, Susan Hao and Robert J. Schneider, Department of Microbiology, Skirball Institute and Department of Pathology, NYU School of Medicine, New York, NY 10016

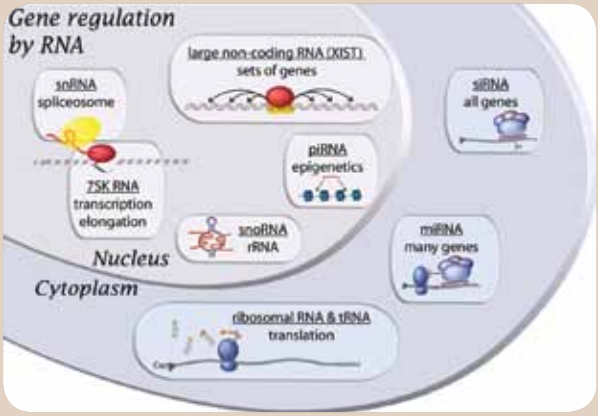
Bio: Dr. Schneider holds the Albert B. Sabin endowed chair for molecular pathogenesis at NYU School of Medicine. He conducts research in two areas. One research program is directed to the development, progression and metastasis of breast cancer and the interplay of the inflammatory response. He has published more than 120 research papers in these and related areas. His research effort is directed to the molecular and genetic understanding of advanced breast cancers and the development of new treatment strategies and therapeutics for advanced breast cancer. Dr. Schneider performs research on the molecular basis locally advanced breast cancer and the development of new therapeutics from these findings. His research played a significant role in the development of the small molecule inhibitor of VEGF mRNA translation known as PTC299 by PTC Therapeutics, that targets a molecular switch he identified in breast cancer cells that is required to promotes the formation of the tumor vasculature. His breast cancer research also includes a program to understand the molecular and genetic alterations that underlie inflammatory breast cancer. His second research program is focused on a molecular understanding of gene regulation by targeted accelerated mRNA decay, particularly in inflammatory cytokine expression, and use of this knowledge for development of new treatment strategies. This research involves the numerous intersections of control of rapid mRNA decay with human disease, including cancer, inflammatory disorders and aging. Dr. Schneider has trained over 50 graduate students and postdoctoral research fellows and has awarded 27 Ph.D. degrees from his laboratory. Dr. Schneider is an Associate Director of the NYU Cancer Institute, Director of Translational Cancer Research for the NYU Cancer Institute, co-Director of Translational Research for NYU School of Medicine, and Co-director of the Breast Cancer Research Program at NYU School of Medicine.

Phillip A. Sharp

Koch Institute for Integrative Cancer Research, MIT

GENE REGULATION BY RNA AS A NEW FRONTIER IN BIOMEDICAL RESEARCH

Abstract: Small RNAs regulate the expression of genes at the levels of transcription, mRNA stability and the efficacy of translation. In somatic tissue, microRNAs are engaged in an extensive network of regulation of thousands of mRNAs controlling processes extending from cell division, to differentiation to cell death. Loss of regulation by some microRNAs promotes cancer while occasional increase in a specific microRNA promotes tumor development. Surprisingly, many cell lines such as embryonic stem cells and some tumor cells can grow with mutations that cause loss of all microRNAs. This raises the paradox of extensive microRNA regulation and modest effects of loss of microRNAs. The evidence of roles of small RNAs in the regulation of transcription in somatic cells is incomplete. In the germline of vertebrates small RNAs clearly control expression of transposable elements although at the mechanistic level this is not well understood. Elucidation of the mechanisms by which RNAs control gene expression has generated new insights into disease processes and offered new approaches to therapy. With the advent of inexpensive high throughput sequencing with the new ability to analyze all of the RNAs expressed in a cell, this revolution in RNA biology will continue over the coming decades.



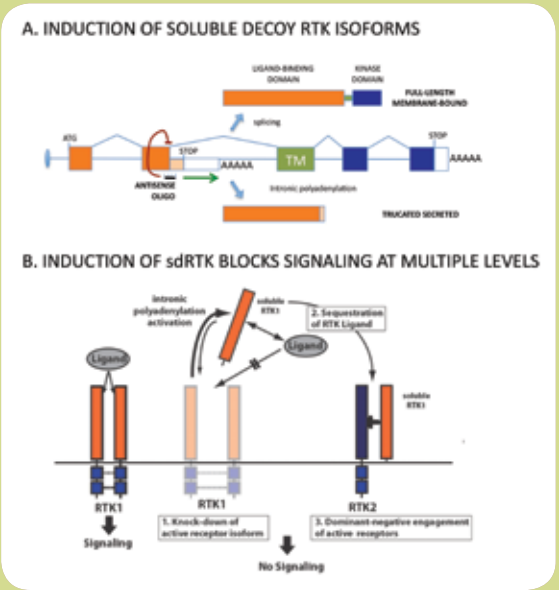
Bio: Dr. Phillip A. Sharp is Institute Professor and member of the Koch Institute at MIT. He joined the MIT faculty in 1974 after completing his postdoctoral training at Caltech and Cold Spring Harbor. Dr. Sharp's research on the molecular biology of gene expression relevant to cancer and the mechanisms of RNA splicing provided one of the first indications of the startling phenomenon of "discontinuous genes" in mammalian cells. For this work, Dr. Sharp was awarded the 1993 Nobel Prize in Physiology or Medicine. His work has earned him numerous cancer research awards and presidential and national scientific board appointments. He is elected member of the National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences, and is also the recipient of the National Medal of Science. He served as director of the Center for Cancer Research, now the Koch Institute, was Head of the Department of Biology and more recently was Founding Director of the McGovern Institute. A native of Kentucky, Dr. Sharp obtained his PhD in Chemistry from the University of Illinois. He is Co-founder of Biogen (now Biogen Idec) and Alnylam Pharmaceuticals.

Luca Cartegni

Memorial Sloan-Kettering Cancer Center

THERAPEUTIC MODULATION OF RNA PROCESSING

Abstract: Alternative RNA splicing and polyadenylation constitutes an essential step in gene expression regulation, which allows cells to generate multiple functionalities from a single gene. Often this alternative processing generates antagonistic products by including or excluding important functional domains from the mature expressed polypeptide.Many genetic disease are caused by the aberrant processing of pre-mRNAs and dysregulation of such processes is an evident characteristic of cancer cells.We have been investigating antisense approaches to directly and specifically modulate such aberrant events with the goal of re-directing expression from a pathological variant to dominant-negative one with therapeutic potential. In particular we have shown that re-direction of a specific splicing event of transcription factor Stat3 can lead to full tumor regression in vivo and that similar approaches directed at the induction of natural secreted 'decoy' variant of several Receptor Tyrosine Kinases (RTKs) show a broad potential for the reversal of pathological signaling in cancer.



Bio: Luca Cartegni earned his Doctorate degree in Genetics in Pavia, Italy, working on the biochemical properties of RNA-binding protein hnRNP A1 and its function in pre-mRNA processing, and has been working on RNA metabolism ever since.

His interest in the regulation of pre-mRNA alternative splicing brought him in Cold Spring Harbor, NY where he joined Adrian Krainer's lab to work on alternative splicing determinants and on the role of deregulated splicing in genetic diseases, in particular spinal muscular atrophy (SMA). At CSHL he developed a novel antisense approach to modulate splicing events and applied it to the SMN2 gene with the goal of re-directing its splicing to production of a functional protein with therapeutic properties.

To pursue his interest in the role of alternative RNA processing in disease, he then moved to Memorial Sloan-Kettering, NY where he is an Assistant Member and studies the contribution of deregulation of alternative splicing in glioblastoma multiforme and other cancers. Here he expanded the application of antisense-based technologies to the induction of dominant negative isoform of oncogenes by manipulating splicing and polyadenylation patterns, in vitro and in vivo.

He has a dual appointment at the MSK Molecular Pharmacology and Chemistry Program and at the Pharmacologhy Department of Cornell-Weill Medical School. He is also a member of MSK Experimental Therapeutic Center and of MSK Brain Tumor Center.

Dixie Goss

Hunter College, City University of New York

REGULATION OF IRON HOMEOSTASIS THROUGH METAL ION SENSING BY mRNA: A MAMMALIAN RIBOSWITCH

Abstract: Iron deficiency and iron overload are both major health problems throughout the world. Hematologists and other physicians treat ~ 31.4 million people in the US for iron related disorders. Proper iron balance in cells is essential because the element is needed to biosynthesize heme, iron-sulfur clusters in enzymes, and other structures, but the metal is toxic in excess. Iron response proteins (IRPs) control iron levels through binding to specific mRNA. These mRNA contain three-dimensional noncoding structures (iron response elements, IREs) in their 5′ untranslated region. It is known that binding of the IRPs to IRE-mRNA represses translation by inhibiting ribosome binding. When iron levels in the cell are high, IRE-containing mRNA are derepressed, the fraction of RNA bound by IRP proteins is decreased, leading to increased synthesis of the iron storage protein, ferritin and decreased transport of iron into the cell. However the mechanism to explain dissociation of IRP/IRE complexes, and allow assembly of the ribosome-mRNA is largely unknown. Here we show that Fe2+ interacts directly with the IRE-mRNA and destabilizes the IRP/IRE complex, acting as a riboswitch. The effects of metal ions on the kinetics of these interactions and the binding of initiation factors involved in assembly of the initiation complex have been elucidated. These data provide a more detailed description of the molecular mechanism of IRP/IRE-mRNA regulation.

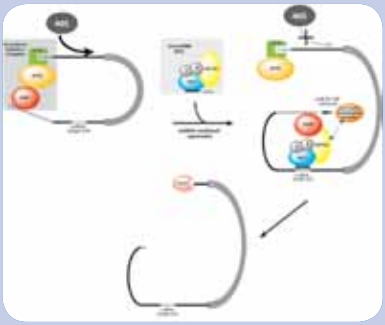
Bio: After early education in a one-room schoolhouse in rural Nebraska, Dixie J. Goss obtained her BS degree from Nebraska Wesleyan University and her PhD degree from the University of Nebraska. She did postdoctoral research in the Biophysics Department at the University of Georgia. She is currently Professor and Gertrude Elion Endowed Scholar, Chemistry Department, Hunter College. She has served as Chair of the Research Committee of the American Heart Association Heritage Affiliate, on NSF and NIH Review Panels and is currently a member of the editorial board of the Journal of Biological Chemistry. Her research interests include macromolecular assembly, regulation of mRNA translation, and kinetics of protein-RNA interactions.

Nahum Sonenberg

Rosalind and Morris Goodman Cancer Centre, McGill University

MECHANISM OF ACTION OF microRNAs

Abstract: MicroRNAs (miRNAs) inhibit mRNA expression in general by base pairing to the 3'UTR of target mRNAs and consequently inhibiting translation and/or initiating poly(A) tail deadenylation and mRNA destabilization. We established a mouse Krebs-2 ascites extract that faithfully recapitulates the miRNA action in cells (Mathonnet et al., 2007). We demonstrated that the let-7 miRNA inhibits translation of reporter mRNA at the initiation step. Translation inhibition is subsequently consolidated by let-7-mediated deadenylation, which requires both the poly(A) binding protein (PABP) and the CAF1 deadenylase, which interact with the let-7 miRNA-loaded RNA-induced silencing complex (miRISC) (Fabian et al., 2009). Importantly, we demonstrated that GW182, a core component of the miRISC, directly interacts with PABP via its C-terminus and that this interaction enhances miRNA-mediated deadenylation (Fabian et al., 2009; Jinek et al., 2010). The miRISC binds the deadenylation machinery independently of PABP. We will discuss how miRISC recruits the deadenylation machinery in a PABP-independent manner.



Bio: Dr. Nahum Sonenberg received his PhD (Biochemistry) at the Weizmann Institute of Science (Rehovot, Israel). He then joined the Roche Institute of Molecular Biology in Nutley, New Jersey with a Chaim Weizmann postdoctoral fellowship. He moved to McGill University, Montreal, Canada, in 1979, and is today a James McGill Professor in the Department of Biochemistry and the Rosalind and Morris Goodman Cancer Research Centre.

Dr. Sonenberg's primary research interests have been in the field of translational control. With Aaron Shatkin he identified the mRNA 5' cap-binding protein, eIF4E, in 1978. He and his colleagues have studied the factors that recruit ribosomes to the mRNA. He discovered the IRES mechanism of translation initiation in eukaryotes, and the regulation of cap-dependent translation by eIF4E binding proteins. He also discovered that eIF4E is a proto-oncogene, whose protein levels are elevated in tumors. Consequently, he showed that rapamycin (an anti-cancer drug) inhibits eIF4E activity. While generating eIF4E binding protein 'knock-out' mice, he found that the protein plays important roles in metabolism, in learning and memory and in innate immunity.

In 2002, Dr. Sonenberg was awarded the Robert L. Noble Prize from the National Cancer Institute of Canada. He is an International Research Scholar of the Howard Hughes Medical Institute and has been a fellow of the Royal Society of Canada since 1992. Dr. Sonenberg was awarded the 2005 Killam Prize for Health Sciences. In 2006, he was elected to the American Academy of Arts and Sciences and The Royal Society, UK. Dr. Sonenberg was awarded the 2007 Katharine Berkan Judd Award from Memorial Sloan-Kettering Cancer Center, the 2007 Roche Diagnostics Award and he was the recipient of the 2008 Gairdner International Award. In 2009, Dr. Sonenberg was awarded the CIHR Health Researcher of the Year Award in Biomedical and Clinical Research. Recently, Dr. Sonenberg was made an Officer of the Order of Canada (2010).

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Fabian MR, Mathonnet G, Sundermeier T, Mathys H, Zipprich JT, Svitkin YV, Rivas F, Jinek M, Wohlschlegel J, Doudna JA, Chen CY, Shyu AB, Yates JR 3rd, Hannon GJ, Filipowicz W, Duchaine TF, Sonenberg N. (2009). Mammalian miRNA RISC recruits CAF1 and PABP to affect PABP-dependent deadenylation. Molecular Cell 35(6): 868-80.

Jinek M, Fabian MR, Coyle SM, Sonenberg N, Doudna JA. (2010). Structural insights into the human GW182-PABPC interaction in microRNA-mediated deadenylation. Nature Structural and Molecular Biology 17(2): 238-40.

Symposium Planning Committee

SYMPOSIUM PLANNING COMMITTEE

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Center for Study of Gene
Structure and Function

Thank you for attending the
24th Annual International Symposium
of the
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