



NYSTEM

NEW YORK STATE STEM CELL SCIENCE

# 1st NYSTEM MEETING

## Stem Cell Science in New York State: Emerging Opportunities

June 12, 2009

7:30 am - 5:00 pm

The Desmond Hotel and Conference Center  
660 Albany-Shaker Road  
Albany, New York

# **Stem Cell Science in New York State: Emerging Opportunities**

*The Desmond Hotel and Conference Center*

## **PROGRAM COMMITTEE**

**Elaine Fuchs, Ph.D.**, *The Rockefeller University*

**Steven Goldman, M.D., Ph.D.**, *University of Rochester*

**Ruth Lehmann, Ph.D.**, *New York University School of Medicine*

**Ihor Lemischka, Ph.D.**, *Mount Sinai School of Medicine*

**Lorenz Studer, M.D.**, *Sloan-Kettering Institute*

**Gordana Vunjak-Novakovic, Ph.D.**, *Columbia University*

## **CONFERENCE COORDINATORS**

**David Anders, Ph.D.**, *Chair*  
*Chief Scientific Officer, NYSTEM*

**Linda Tripoli, R.N.**, *Coordinator, NYSTEM*

**Matthew Kohn, Ph.D.**, *Scientific Officer, NYSTEM*

**Kathy Chou, Ph.D.**, *Scientific Officer, NYSTEM*

**Marti McHugh.**, *Director, Clinical Program Development*

**Virginia Reyes**

**Sophia Pallone**

**The Wadsworth Center Photography and Illustrations Unit**

**Tracy Godfrey**

**Carmen Mannella, Ph.D.**, *Associate Director*  
*Science and Technology, NYSTEM*

## PROGRAM AT-A-GLANCE

- 7:30 AM Registration and Poster Setup
- 8:30 AM Welcome, Introductions and Overview  
**Richard F. Daines, M.D.**, Chair, Empire State Stem Cell Board and Commissioner of Health  
**Lawrence S. Sturman, M.D., Ph.D.**, Executive Director, NYSTEM and Director, Wadsworth Center
- 8:50 AM **KEYNOTE ADDRESS: Susan Solomon, CEO, The New York Stem Cell Foundation**  
“Opportunity for Excellence: The Critical Role of State Programs in the New Federal Landscape”
- 9:15 AM **PLENARY SESSION: “Models and Tissues”**  
Chair: Marja Timmermans, Ph.D., *Cold Spring Harbor Laboratory*
- 9:20 AM **Ruth Lehmann, Ph.D.**, *New York University School of Medicine*  
“Germ Line Stem Cell Development in *Drosophila*”
- 9:50 AM **Gordana Vunjak-Novakovic, Ph.D.**, *Columbia University*  
“Tissue Engineering for Regenerative Medicine and Stem Cell Research”
- 10:20 AM **Tudorita Tumber, Ph.D.**, *Cornell University*  
“Control of Hair Follicle Stem Cell Dynamics in the Hair Follicle Native Niche”
- 10:50 AM **Fiona Doetsch, Ph.D.**, *Columbia University Medical Center*  
“Stem Cells and their Niche in the Adult Mammalian Brain”
- 11:20 AM Break
- 11:25 AM **PLENARY SESSION: “Programs and Reprogramming”**  
Chair: John Schimenti, Ph.D., *Cornell University*
- 11:30 AM **Ihor Lemischka, Ph.D.**, *Mount Sinai School of Medicine*  
“Exploring Pluripotency”
- 12:00 PM **Ali Brivanlou, Ph.D.**, *The Rockefeller University*  
“Genetic Dissection of Pluripotency in Human Embryonic Stem Cells and Induced Pluripotent Cells”
- 12:30 PM Lunch; Poster Session; Institutional Development Awardees
- 1:55 PM **PLENARY SESSION: “Neurons and Disease/Toward the Clinic”**  
Chair: James Goldman, M.D., Ph.D., *Columbia University Medical Center*
- 2:00 PM **Sally Temple, Ph.D.**, *New York Neural Stem Cell Institute*  
“Neural Stem Cell Potential Is Stage-Specific: Hidden Embryonic Cells in the Adult”
- 2:30 PM **Shahin Rafii, M.D.**, *Weill Cornell Medical College*  
“Contribution of the Vascular Niche to Organ Regeneration”
- 3:00 PM **Steven Goldman, M.D., Ph.D.**, *University of Rochester*  
“Cell-based Treatment of Myelin Diseases”
- 3:30 PM **Lorenz Studer, M.D.**, *Sloan-Kettering Institute*  
“Human Pluripotent Stem Cells: Applications in Neural Development and Disease”
- 4:00 PM **PANEL DISCUSSION:**  
**“Translational Stem Cell Research: Opportunities and Challenges”**  
Moderator: Allen Spiegel, M.D., Dean, *Albert Einstein College of Medicine*  
Panelists: Stelios Andreadis, Ph.D., *SUNY Buffalo*  
Ira Cohen, M.D., Ph.D., *SUNY Stony Brook*  
Sanjeev Gupta, M.D., *Albert Einstein College of Medicine*
- 5:00 PM Adjourn



# Stem Cell Science in New York State: Emerging Opportunities

## PROGRAM SCHEDULE

Friday, June 12, 2009

- 7:30 AM Registration and Poster Setup
- 8:30 AM Welcome, Introductions and Overview  
**Richard F. Daines, M.D.**, Chair, Empire State Stem Cell Board and  
 Commissioner of Health  
**Lawrence S. Sturman, M.D., Ph.D.**, Executive Director, NYSTEM and  
 Director, Wadsworth Center
- 8:50 AM **KEYNOTE ADDRESS:**  
**Susan Solomon, CEO**  
*The New York Stem Cell Foundation*  
**“Opportunity for Excellence: The Critical Role of State Programs  
 in the New Federal Landscape”**
- 9:15 AM **PLENARY SESSION:**  
**“Models and Tissues”**  
 Chair: Marja Timmermans, Ph.D.  
*Cold Spring Harbor Laboratory*
- 9:20 AM **Ruth Lehmann, Ph.D.**  
*New York University School of Medicine*  
**“Germ Line Stem Cell Development in *Drosophila*”**  
 The *Drosophila* germ line provides an excellent system to understand the genetic and cellular basis of a well-defined stem cell system. In males and females, germ line stem cells produce gametes throughout adulthood by asymmetric stem cell division. We will discuss recent findings suggesting that RNA regulatory pathways control cell-autonomous as well as niche-germ line interactions required for maintenance of the stem cell population and gamete differentiation.
- 9:50 AM **Gordana Vunjak-Novakovic, Ph.D.**  
*Columbia University*  
**“Tissue Engineering for Regenerative Medicine  
 and Stem Cell Research”**  
 Tissue development and regeneration are orchestrated by spatial and temporal gradients of multiple regulatory factors. Tissue engineering provides controllable tissue models of high biologic fidelity - through an integrated use of stem cells, scaffolds and bioreactors - that have great potential for regenerative medicine and stem cell research. We discuss here tissue engineering of functional human grafts, and the utilization of engineered tissues as models of development and disease.

10:20 AM

**Tudorita Tumar, Ph.D.***Cornell University***“Control of Hair Follicle Stem Cell Dynamics in the Hair Follicle Native Niche”**

We employed novel *in vivo* mouse transgenic tools to test two assumptions in the stem cell field: that tissue stem cells are infrequently dividing and that they maintain tissue homeostasis by asymmetric cell fate decisions. We provide evidence that all the surviving cells in the hair follicle divide on average only ~20-50 times during a lifetime, and they behave as a population in determining their fate, mainly if not entirely guided by unidirectional fate decisions. We found Runx1, a cancer gene also important in hematopoietic stem cell emergence, regulates the concerted processes required for adult stem cell activation.

10:50 AM

**Fiona Doetsch, Ph.D.***Columbia University Medical Center***“Stem Cells and their Niche in the Adult Mammalian Brain”**

Neural stem cells continuously generate new neurons throughout life in the adult mammalian brain. I will present our recent findings on a specialized vascular niche for adult neural stem cells, and on micro-RNA regulation of adult neurogenesis.

11:20 AM

Break

11:25 AM

**PLENARY SESSION:****“Programs and Reprogramming”**

Chair: John Schimenti, Ph.D.

*Cornell University*

11:30 AM

**Ihor Lemischka, Ph.D.***Mount Sinai School of Medicine***“Exploring Pluripotency”**

Dr. Lemischka's laboratory has been focusing on deriving in-depth molecular and biochemical "portraits" of the pluripotent "state" in mouse and human embryonic stem cells (ESC). The approach initiates with down-regulation of individual gene-products that are required to maintain the pluripotent state. The epigenetic, transcriptional, mRNA and proteomic changes are measured as a function of time. In this way a dynamic view of a cell fate transition is obtained. These studies inform strategies to reprogram adult cells to a pluripotent state in order to create novel models of human diseases.

12:00 PM

**Ali Brivanlou, Ph.D.***The Rockefeller University***“Genetic Dissection of Pluripotency in Human Embryonic Stem Cells and Induced Pluripotent Cells”**

12:30 PM

Lunch; Poster Session  
Institutional Development Awardees

1:55 PM

**PLENARY SESSION:****“Neurons and Disease/Toward the Clinic”**

Chair: James Goldman, M.D., Ph.D.

*Columbia University Medical Center*

2:00 PM

**Sally Temple, Ph.D.***New York Neural Stem Cell Institute***“Neural Stem Cell Potential is Stage-Specific: Hidden Embryonic Cells in the Adult”**

Temporal regulation of stem cell behavior is critical to produce the correct types of central nervous system cells in order, and ultimately to achieve the normal cytoarchitecture. Our work demonstrates how neural stem cells change over time during this process as they proliferate and differentiate. This predicts that cells that lie dormant for long periods could possess properties of earlier stage cells. We have discovered that the single layer of retinal pigment epithelium in the adult eye, which is held in a non-proliferative state throughout normal life, retains some properties of neuroepithelial cells found in the early embryo.

2:30 PM

**Shahin Rafii, M.D.***Weill Cornell Medical College***“Contribution of the Vascular Niche to Organ Regeneration”**

Vascular endothelial cells not only provide a conduit for delivery of oxygen and nutrients but also support organogenesis. However, the mechanism by which endothelial cells support stem and progenitor cell maintenance and expansion is not known. We have developed unbiased *in vitro* and *in vivo* models to identify factors elaborated by the endothelial cells that balance stem cell proliferation and differentiation. We show in serum-free and cytokine-free conditions endothelial cells maintain the homeostasis of organ-specific progenitor cells. These studies may lay the foundation to employ primed endothelial cells to induce and sustain organogenesis.

3:00 PM

**Steven Goldman, M.D., Ph.D.***University of Rochester***“Stem and Progenitor-cell Based Treatment of Myelin Disorders”**

Diseases of glial cells – which include both astroglia and myelin-producing oligodendroglia – may provide readily accessible targets for cell-based therapies, given the relative uniformity of CNS glial populations. The myelin diseases, which involve the loss of dysfunction of oligodendroglia in the brain and spinal cord, are among the most prevalent and disabling conditions in neurology. This talk will focus on the potential utility of glial progenitor cell transplantation as a therapeutic strategy for both congenital and acquired diseases of myelin. It will also emphasize the utility of human glial chimeric mice as models by which to study the physiology of human glia and their progenitors in the live adult brain.

3:30 PM

**Lorenz Studer, M.D.***Sloan-Kettering Institute***“Human Pluripotent Stem Cells: Applications in Neural Development and Disease”**

4:00 PM

**PANEL DISCUSSION:****“Translational Stem Cell Research: Opportunities and Challenges”**

Moderator: Allen Spiegel, M.D., Dean

*Albert Einstein College of Medicine*Panelists: Stelios Andreadis, Ph.D., *SUNY Buffalo*Ira Cohen, M.D., Ph.D., *SUNY Stony Brook*Sanjeev Gupta, M.D., *Albert Einstein College of Medicine*

5:00 PM

Adjourn

## SPEAKER BIOGRAPHIES

**STELIOS T. ANDREADIS, Ph.D.** – *Professor, Chemical and Biological Engineering and Co-Director, Center for Biomedical Engineering, University at Buffalo*

Stelios T. Andreadis received his B.S. degree in Chemical Engineering from the Aristotle University of Thessaloniki, Greece and his M.S and Ph.D. degrees from the University of Michigan, Ann Arbor. Following his graduate studies, he joined the Center for Engineering in Medicine at Harvard Medical School for two years as a post-doctoral fellow. He is currently Professor of Chemical and Biological Engineering and co-director of the Center for Biomedical Engineering at the State University of New York at Buffalo. He also holds adjunct appointment in the Department of Biological Sciences and he is member of the newly founded New York State Center of Excellence in Bioinformatics and Life Sciences. His research interests include lentiviral vectors for gene therapy, adult stem cells for cell therapies, tissue engineering of skin and wound healing and cardiovascular tissue engineering.

**ALI BRIVANLOU, Ph.D.** – *Professor and Head at the Molecular Embryology Laboratory at The Rockefeller University*

The Brivanlou Laboratory aims to identify the molecular factors that regulate germ layer specification in human embryonic stem cells (hESCs) by testing candidate pathways previously described in model organisms, and by developing screens to identify novel molecules implicated in early human differentiation. In addition, they aim to identify genes implicated in the self-renewal pluripotency of hESCs in culture by analyzing the transcriptional profiles of hESCs in various experimental paradigms, and conducting screens to isolate factors that promote self-renewal. The overall aim is to use hESCs as windows to study early human embryonic development.

**IRA S. COHEN, M.D., Ph.D.** – *Leading Professor, Physiology & Biophysics and Director of the Institute for Molecular Cardiology, State University of New York at Stony Brook*

Dr. Cohen is investigating electrical and mechanical regeneration of cardiac function. Dr. Cohen's lab generated a biological pacemaker in the canine ventricle using human mesenchymal stem cells (hMSCs) transfected with a pacemaker gene. Now, they are investigating hMSC based therapies for other arrhythmias. For mechanical regeneration, they developed a novel approach to enhance cardiac differentiation of hMSCs as well as a means to track them *in vivo* using quantum dot nanotechnology. The lab is also studying cardiac stem cells and has entered into a collaboration to study human embryonic stem cells to determine which stem cell type can optimally regenerate electrical and mechanical function in the heart.

**RICHARD F. DAINES, M.D.** – *Chair of the Empire State Stem Cell Board, is the fourteenth New York State Health Commissioner*

Prior to becoming Commissioner, Dr. Daines was the President and CEO of St. Luke's-Roosevelt Hospital Center from January 1, 2002 until January 2007. Previous to joining the Hospital Center as Medical Director in 2000, he served as Senior Vice President for Professional Affairs of St. Barnabas Hospital in the Bronx, New York since 1994 and the Medical Director from 1987 to 1999. Dr. Daines received a Bachelor of History degree from Utah State University in 1974 and served as a missionary for the Church of Jesus Christ of Latter-day Saints in Bolivia, 1970-1972. He received his medical degree from Cornell University Medical College in 1978. He served a residency in internal medicine at New York Hospital and is Board Certified in Internal Medicine and Critical Care Medicine (1987-1997).

**FIONA DOETSCH, Ph.D.** – *Assistant Professor of Pathology, Neurology and Neuroscience at Columbia University, College of Physicians and Surgeons*

Stem cells persist in specialized niches in the adult mammalian brain where they continuously generate large numbers of neurons that become functionally integrated into neural circuits. Dr. Doetsch's team has shown that the stem cells for *in vivo* adult neurogenesis are a subset of astrocytes, glial cells classically associated with support functions in the brain. They are using a variety of molecular, cellular and genetic approaches to discover the regulation, lineage relationships, diversity and function of stem cells and neuronal production in the adult mammalian brain. Uncovering the biology of neural stem cells and their *in vivo* niche is key to understanding brain repair and neural pathologies.

**STEVEN GOLDMAN, M.D., Ph.D.** – *Dean Zutes Chair and Professor of Neurology at the University of Rochester Medical Center*

Dr. Goldman is engaged in a broad spectrum of research relative to gene and cell-based strategies for repairing the damaged or diseased nervous system. The Goldman lab is focused on targeting and mobilizing endogenous stem and progenitor cells of the adult brain and spinal cord. The lab is studying the biology of adult progenitor cells in systems as diverse as the songbird neostriatum and the adult human temporal lobe, and their potential therapeutic roles in a correspondingly varied range of disease models. Goldman's group is working on isolation and molecular characterization of different progenitor cell types of both the fetal and adult human central nervous system (CNS), isolation and telomerase immortalization of developmentally-restricted neuronal progenitor cells from fetal CNS, and generating experimental models of cell type-selective neurodegenerative diseases, such as Parkinson's, ALS, Huntington's and dementia.

**SANJEEV GUPTA, M.D.** – *Professor, Department of Medicine (Hepatology) and Pathology, Albert Einstein College of Medicine*

Dr. Gupta is interested in understanding the biology of stem cells for cell and gene therapy applications. A major focus concerns the liver, as numerous acquired and genetic disorders are particularly amenable to liver-directed therapies. Studies of hESC and fetal cells are being pursued to define how suitable lineage-specific cells can be obtained, expanded and genetically manipulated for cell transplantation studies in animal models of human diseases. These studies are identifying genetic characteristics of stem cells, such that hESC-derived cells can advance along fetal-like, endodermal lineages. Parallel work with fetal stem/progenitor cells addresses further lineage differentiation and cell therapy mechanisms.

**RUTH LEHMANN, Ph.D.** – *Professor of Cell Biology and Director of the Skirball Institute at the New York University School of Medicine*

Germ cells are the stem cells for the next generation. Set aside during embryogenesis, they have the potential to generate a new organism through the fusion of sperm and egg. Professor Lehmann is interested in understanding how germ cells are specified in the early embryo, how they migrate through the embryo to reach the somatic part of the gonad, and how they become stem cells that continue to produce egg and sperm throughout adulthood. Dr. Lehmann's team is studying germ cell development in *Drosophila*, where they combine large-scale genetic analysis with sophisticated imaging techniques to identify and characterize factors that regulate germline development.

**IHOR LEMISCHKA, Ph.D.** – *Professor, Gene and Cell Medicine and Director of the Black Family Stem Cell Institute, Mount Sinai School of Medicine*

Dr. Ihor R. Lemischka's laboratory focuses on defining the cellular and molecular mechanisms that control cell fate decisions in both adult and embryonic stem (ES) cells. A variety of genomic and functional genomic approaches have been utilized, and have led to important insights into how ES cells can maintain their undifferentiated state *in vitro*, and how these cells choose to commit to specific programs of differentiation. Currently, the insights gathered in the mouse ES cell system are being investigated in human ES cells. Efforts in the human ES cell system will become a major research focus.

**SHAHIN RAFII, M.D.** – *Professor of Medicine and Genetic Medicine and Director of the Ansary Stem Cell Center for Regenerative Medicine, Weill Cornell Medical College*

Shahin Rafii graduated from Cornell University and received his MD degree from Albert Einstein College. He completed his internship and residency in internal medicine followed by a fellowship in Hematology-Oncology at Weill-Cornell. He completed his post-doctoral training in vascular and hematopoietic stem cell biology and became Professor in Genetic Medicine at Weill Cornell Medical College. Since then, he has been studying the role of vasculature in orchestrating homeostasis of normal and malignant organ-specific stem and progenitor cells. He is currently the co-director of Ansary Stem Cell Institute, serves in the advisory board of New York Stem Cell Foundation (NYSCF) and is a Howard Hughes Medical Institute investigator at Weill Cornell.

**SUSAN SOLOMON, Esq.** - *Chief Executive Officer and Co-Founder of The New York Stem Cell Foundation (NYSCF)*

NYSCF is a non-profit organization established in 2005 to accelerate stem cell research to cure the major diseases of our time. NYSCF supports the pursuit of advanced stem cell research by leading scientists through its state-of-the-art, collaborative stem cell research laboratory, fosters the next generation of stem cell researchers through the NYSCF Fellowship Program, and convenes educational stem cell research conferences and meetings for scientists and the general public. A longtime health-care advocate, Ms. Solomon is a founding member of NYAMR (New Yorkers for the Advancement of Medical Research) and the New York Council for the Joslin Diabetes Center, and has served on the Board of Directors of the Juvenile Diabetes Research Foundation, New York Chapter, since 1994. Additionally, Ms. Solomon serves on the Government Affairs Committee for the International Society for Stem Cell Research. Ms. Solomon was integral to the establishment of the Empire State Stem Cell Trust and is a member of the Strategic Planning Committee of the Empire State Stem Cell Board. In March 2008, Ms. Solomon received a New York State Women of Excellence Award from State Governor David A. Paterson. In September 2008, she received the Triumph Award from the Brooke Ellison Foundation.

Ms. Solomon is currently on the Board of Directors and Executive Committee of the Regional Plan Association of New York. Prior to founding NYSCF, Ms. Solomon established and ran Solomon Partners LLC to provide strategic management consulting to corporations, cultural institutions, foundations and non-profit organizations. She was the founding Chief Executive Officer of Sothebys.com, has served as Chairman and Chief Executive Officer of Lancit Media Productions and was President of Sony Worldwide Networks. Ms. Solomon has also held executive positions at MacAndrews and Forbes Holdings and at MMG Patricof and Co. An attorney, Ms. Solomon practiced law with Debevoise & Plimpton before beginning her career in business. Ms. Solomon received her BA from New York University and her JD from Rutgers University School of Law.

**ALLEN SPIEGEL, M.D.** – *Dean of the Albert Einstein College of Medicine of Yeshiva University*

Prior to joining Einstein, Dr. Spiegel was director of the National Institute of Diabetes & Digestive Diseases & Kidney Diseases (NIDDK) at the National Institutes of Health, the culmination of a distinguished 33-year-career at the NIH. A member of the Institute of Medicine of the National Academy of Sciences, Dr. Spiegel began his career at the NIH in 1973 as a clinical associate in its Endocrinology Training program. He then served as a senior investigator in the Metabolic Disease Branch from 1977 to 1984. In 1985 he was appointed chief of Molecular Pathophysiology, and then chief of the Metabolic Diseases Branch. In 1990, he was appointed Director of the NIDDK's Division of Intramural Research. He served in these various capacities until his appointment as Director of the NIDDK in 1999. In this role, Dr. Spiegel had responsibility for a staff of 625 full-time employees and a \$1.7 billion budget.

Dr. Spiegel is a widely renowned physician-scientist and endocrinologist with extensive experience in translational research programs. His research has centered on G-protein-regulated signaling dysfunction in human disease, and his work on signal transduction helped to clarify the genetic basis of several endocrine diseases. He has published extensively, with more than 250 peer-reviewed papers and 100 reviews and book chapters to his name, as well as two books on G proteins.

**LORENZ STUDER, M.D.** – *Associate Member of Developmental Biology and Neurosurgery at Sloan-Kettering Institute*

The Studer laboratory has become one of the leading groups in mouse embryonic stem cell differentiation and hESC biology. Among the team's early key achievements were the first report on establishing and differentiating mouse ESCs via somatic cell nuclear transfer (ntESC lines), followed by a similar collaborative study describing the derivation and *in vitro* directed differentiation of primate pathenogenic stem cells. Studer's group published the first evidence on the successful preclinical use of ntESC derived neurons in an animal model of Parkinson's disease. This effort was followed by work on human ES cell derived neural stem cells shown to fully integrate in the adult neural stem cell niches generating a human/rat chimeric SVZ region. Studer has extended into various other CNS and non-CNS lineages pioneering strategies for the isolation of multipotent mesenchymal precursors and skeletal muscle cells from hESC cells.

**LAWRENCE S. STURMAN, M.D., Ph.D.** – *Executive Director of NYSTEM and Director of the New York State Department of Health's Wadsworth Center*

He received his medical training at Northwestern University Medical School and the Hospital of the University of Pennsylvania, and earned a doctorate in virology from The Rockefeller University. Prior to joining the Department of Health, Dr. Sturman was affiliated with the Laboratory of Viral Diseases at the National Institutes of Health. In 1989 he became Director of Wadsworth Center's Division of Clinical Sciences, and three years later was appointed Director. During the past two decades, Dr. Sturman has participated in several state and privately funded efforts to advance New York research programs in AIDS, drug abuse, immunology, breast cancer, spinal cord injury research and structural biology. As Executive Director of the New York State Health Research Council since 1987, he has worked to enhance biomedical research in New York State. Dr. Sturman serves on the Boards of Directors of the New York Structural Biology Center and Health Research, Inc., an independent not-for-profit agency closely affiliated with the Department of Health, which manages the Department's externally funded research programs.

**SALLY TEMPLE, Ph.D.** – *Professor and Scientific Director of the New York Neural Stem Cell Institute*

Dr. Temple is studying how embryonic neural progenitor cells generate the numerous, diverse, cell types of the adult CNS. These studies may lead to therapies for neurodegenerative disorders or for neural tumors. The Temple laboratory has designed a culture system in which single CNS progenitor cells can divide and differentiate into clones of neurons and glial cells. This led to the identification of different classes of progenitor cells in embryonic forebrain, including one that may play a key role in brain development. Molecular mechanisms regulating division and differentiation of brain progenitor cells will be the focus of future studies in the Temple lab.

**TUDORITA TUMBAR, Ph.D.** - *Assistant Professor in the Department of Molecular Biology and Genetics at Cornell University*

Dr. Tumar received a BS/MS (Diploma) in Biochemistry from University of Bucharest, Romania in 1993. She then moved to University of Illinois at Urbana-Champaign in 1994 and received her Ph.D. in cell biology in January 2000. She received a Life Science Research Foundation Post-doctoral Fellowship in 2001 while at University of Chicago, and completed her post-doctoral studies at The Rockefeller University in New York City. She joined the Cornell faculty in 2004. Her laboratory is interested in elucidating the basic cellular and molecular mechanisms implicated in cell fate choice and stem cell activity within tissues. An important focus is on the control of nuclear function and structure including transcriptional networks, chromatin structure and dynamics, and DNA replication. Understanding how progenitor and differentiated cells function in normal tissue morphogenesis and homeostasis will reveal how deregulation of their precise control of growth and differentiation can lead to diseased tissues and cancer.

**GORDANA VUNJAK-NOVAKOVIC, Ph.D.** - *Professor of Biomedical Engineering at Columbia University, where she directs the Laboratory for Stem Cells and Tissue Engineering*

The Vunjak-Novakovic laboratory is focused on engineering functional human tissues by an integrated use of human stem cells in conjunction with cell-instructive scaffolds and bioreactors. The goals are to create functional tissue grafts for regenerative medicine, and to develop tissue models of development and disease for controllable studies of stem cells. Dr. Vunjak-Novakovic has published two books, over 200 peer-reviewed articles and holds 30 patents. She is a frequent advisor to governmental organizations on tissue engineering and regenerative medicine, and the chair of her National Institutes of Health study section. In 2002, she was elected a Fellow of the American Institute for Medical and Biological Engineering. In 2007, she gave the Director's lecture at the NIH, as the first woman engineer to receive this distinction. In 2008, she was inducted into the Women in Technology International Hall of Fame "for developing biological substitutes to restore, maintain or improve tissue function".



## EINSTEIN COMPREHENSIVE HUMAN PLURIPOTENT STEM CELL CENTER

**Bouhassira, Eric E.**, Etzion, Zipora, Grealley, John, Gupta, Sanjeev, Shamoon, Harry, and Steidl, Uli

*Albert Einstein College of Medicine of Yeshiva University, Bronx, NY*

A Human Embryonic Stem Cell Center in Einstein was created five years ago when several investigators at Einstein pooled their resources and expertise to enhance their ability to work with multiple hESC cell lines. The objectives of the Center were to improve quality-control and permit more rapid testing and adoption of novel methods than would be possible in individual labs. We also expected that the Center would be effective by streamlining training of staff in hESC work for multiple Einstein investigators and achieve economic efficiencies through bulk purchases of materials at discounted prices. Finally, we hoped that a community of investigators studying hESC would form around the Core facility, not only by fostering interactions among the PIs but also among all users and staff, and that this would create a unique intellectual environment that would help spread good scientific ideas rapidly throughout the College and create new opportunities for collaboration.

The Center was supported for three years by a P20 Exploratory Center Grant from NIH. NYSTEM funding has allowed this original Center to evolve into the Einstein Comprehensive Human Pluripotent Stem Cell Center that consists of three major components: a Pluripotent Stem Cell Unit, a Stem Cell Genomic Unit, and a Xenotransplant Unit. Each unit is run by a Technical Director and is supervised by Dr. Bouhassira, by Zipora Etzion the general manager of the facilities and by scientific directors. When all recruitments will have been accomplished, the Center will have a staff of 10.

**The Human Pluripotent Stem Cell Unit** (Technical Director: Vladik Sandler, Scientific Advisor: Eric Bouhassira) provides undifferentiated hESC plates and hESC reagents, produces iPS, and offers a variety of cell differentiation (EB formation, Hematopoietic differentiation) and phenotyping services.

The facility is in the process of acquiring an automated cell culture system that will greatly increase its capacity to produce plates of hES and iPS cells.

**The Human Stem Cell Genomic Unit** (Technical Director: Nathalie Lallier, Scientific Advisor: John Grealley) works in close collaboration with the Epigenomic Center and provides bioinformatic support for the stem cell community. A Solexa sequencer has been purchased with funds from NYSTEM and is operated by staff from the Epigenomic Center. The unit is currently staffed by two bioinformaticians and has funding for a third one.

**The Flow Cytometry and Xenotransplant Unit** (Technical Director: Guillermo Simkin. Scientific Advisors: Sanjeev Gupta and Uli Steidl) is equipped with a FACSAria II and is staffed with a FACS operator and an animal technologist (recruitment in process). This unit provides dedicated flow cytometry services for primary human stem cells and transplantation of human stem cells in mice. Several colonies of immuno-deficient mice are kept in stock.

Number of users: In 2008 the Center served 22 users. During the first half of 2009, the three units have been recruiting staff and purchasing equipment. Three labs are in the process of being constructed or renovated to accommodate the three units. When the three units will be fully operational, the number of users is expected to reach 25 to 40.

## **DIVISION-COUPLED ASTROCYTIC DIFFERENTIATION OF NEURAL STEM CELLS IN THE ADULT HIPPOCAMPUS**

**Enikolopov, Grigori<sup>1</sup>**, Encinas, Juan M.<sup>1</sup>, Michurinaa, Tatyana V.<sup>1</sup>, Peunova, Natalia<sup>1</sup>, Tordo, Julie<sup>1</sup>, Peterson, Daniel A.<sup>2</sup>, Fishell, Gord<sup>3</sup>, and Koulakov, Alex<sup>1</sup>

<sup>1</sup>*Cold Spring Harbor Laboratory, Cold Spring Harbor, NY*; <sup>2</sup>*Rosalind Franklin University of Medicine and Science, North Chicago, IL*; <sup>3</sup>*Smilow Neuroscience Program, New York University School of Medicine, New York, NY*

NYSTEM Institutional Development funding of our group was used to study the regulation of quiescence and division of neural stem and progenitor cells in the adult brain. The ability of the adult brain to generate neurons from stem cells may be important for learning, memory, and mood regulation. Generation of new neurons in the hippocampus decreases with age, and this decline may underlie age-related impairment in learning and memory. We found that the age-related decrease in hippocampal neurogenesis is driven by the continuous depletion of the adult neural stem cell pool and that the disappearance of the stem cells is directly coupled to their division.

In contrast to the conventional model of continuously self-renewing stem cells with repeated cycles of division and quiescence, our results suggest that upon exiting their quiescent state adult hippocampal stem cells do not return to it. Instead, they rapidly undergo a series of consecutive asymmetric divisions, generating symmetrically dividing precursors that proceed to differentiate into neurons. Once the neural stem cells exit the last cell cycle, they convert into mature astrocytes and lose their stem cell capabilities. Thus, the decrease in the number of neural stem cells in the hippocampus, and therefore the decrease in neurogenesis, is a division-coupled process directly related to their production of new neurons. We developed a new scheme of the neurogenesis cascade in the adult hippocampus and propose a “disposable stem cell” model that explains the disappearance of neural stem cells, the appearance of new astrocytes, the remodeling of the neurogenic niche, and the age-related decline in the production of new neurons in the hippocampus.

## **A FLUORESCENCE-ACTIVATED CELL SORTER, DEEP GENOMIC SEQUENCERS, AND ULTRASOUND-GUIDED MICROINJECTION EQUIPMENT AS STEM CELL CORE INSTRUMENTATION**

**Goldman, James E.**

*Columbia University, New York, NY*

The money obtained from the Award, “NYSTEM INSTITUTIONAL DEVELOPMENT of STEM CELL RESEARCH CAPACITIES” was used to establish three much-needed resources for stem cell researchers at Columbia University Medical Center. 1. A new Fluorescent-Activated Cell Sorter, FACS Aria II that can sort 4 populations simultaneously into either tubes or 96 well plates. The instrument is up and running and investigators reserve time on the machine via a Columbia web site. 2. Two Deep Genomic Sequencers. We were able to purchase two Applied Biosystems SOLID 3 sequencers through NIH and HHMI funds and used NYSTEM funds to purchase hardware and software for the sequencers and startup salaries for technicians. One sequencer is in place and operational. A bioinformatics analyst has been hired. 3. Ultrasound-Guided Microinjection system, Visualsonic Vevo 770 High Resolution *In Vivo* Imaging System, which is equipped with ultrasound probes for rat and mouse, heated table for anesthetized animals, integrated Rail System III (promotes set-up, alignment and adjustment of the ultrasound probe) and a micro-injection system (for image-guided injections).

## HIPPOCAMPAL STEM CELLS AND DEPRESSION

**Hen, René<sup>1</sup>**

*Departments of Neuroscience, Psychiatry & Pharmacology, Columbia University & New York State Psychiatric Institute, New York, NY*

Various chronic antidepressant treatments increase adult hippocampal neurogenesis, but the functional importance of this phenomenon remains unclear. Using radiological and genetic methods, we show that disrupting neurogenesis blocks behavioral responses to antidepressants. X-irradiation of a restricted region of mouse brain containing the hippocampus prevented the neurogenic and behavioral effects of two classes of antidepressants. Similarly, a genetic strategy that ablates adult progenitor cells, resulted in a lack of effect of antidepressants. In addition, we have identified a form of long-term potentiation in the dentate gyrus which is dependent on the presence of young neurons and which is stimulated by antidepressants. These findings suggest that the behavioral effects of chronic antidepressants require hippocampal neurogenesis and are mediated by an increased synaptic plasticity in the dentate gyrus.

## INSTITUTIONAL DEVELOPMENT OF STEM CELL RESEARCH CAPABILITIES AT CORNELL UNIVERSITY

**Nikitin, Alexander Yu**<sup>1</sup>, Fischbach-Teschl, Claudia<sup>2</sup>, Fortier, Lisa<sup>3</sup>, Kotlikoff, Michael I.<sup>1</sup>, Lis, John T.<sup>4</sup>, Schimenti, John C.<sup>1</sup>, Travis, Alexander<sup>1</sup>, Tumber, Tudorita<sup>4</sup>, and Yen, Andrew<sup>1</sup>

*Cornell Stem Cell Program and Departments of <sup>1</sup>Biomedical Sciences; <sup>2</sup>Biomedical Engineering; <sup>3</sup>Clinical Sciences; and <sup>4</sup>Molecular Biology & Genetics, Cornell University, Ithaca, NY*

NYSTEM funding has provided an essential support to three main areas of stem cell related interests at Cornell: (1) Deriving, maintaining and selectively differentiating embryonic and adult stem cells and reprogrammed pluripotent cells, (2) Recreating the temporal and spatial environment encountered in developing and adult tissues, and (3) Understanding the relevance of fundamental processes governing the control of stem cells to diseases such as cancer. These areas were supported by four mechanisms: (1) Bridge Funding, (2) Supplemental Funding, (3) Stem Cell Research Training and (4) Shared Equipment/Core Facility. Investigators supported by bridge funding have been successful in collection of preliminary results essential for further grant applications in areas of stem cell and retinoic acid and new mouse infertility genes on the X chromosome.

Investigators funded by supplemental funding have made a progress in developing tissue-engineered neural stem cell niches, defining the subpopulations of mesenchymal progenitor cells in adult bone marrow aspirates, elucidating of microRNA functions in regulation of normal adult stem cells, pursuing spermatogonial stem cell transplantation and identifying a new cell surface marker of stem cells of the skin. Training in stem cell research facilitated research projects aimed at directed differentiation of human ES cell in rats and preparation of stem cells for a genome-wide analysis of nascent transcription complexes. Acquisition of the additional equipment enhanced the existing the Fluorescence Activated Cell Sorting (FACS) Core facility, which is the key facility for stem cell research-related activities on campus.

Additionally, the NYSTEM funding has provided a crucial support for formation of a Cornell Stem Cell Program (CSCP). CSCP goals are to provide the necessary opportunities and structure for coordinating activities of investigators involved in stem cell research, promoting cross-campus interactions and enhancing the existing platform for teaching and training in stem cell biology at Cornell. The program launched a Web site (<http://stemcell.cornell.edu>), instituted seminar series featuring distinguished guest speakers, initiated Annual Stem Cell Research Symposia, and funded requests by stem cell researchers to travel to stem cell-related scientific conferences. The success of the program is reflected by securing NYSTEM awards for development of a consortium on stem cells, microenvironment and cancer and for establishment of the Cornell mammalian cell reprogramming core. Taken together, NYSTEM grant for Institutional Development of Stem Cell Research Capabilities significantly invigorated stem cell research at Cornell University. It also provided the most fertile background for further growth of Cornell stem cell research community and solidification of Cornell University position as a unique cross-disciplinary center of stem cell research in New York State.

## **INSTITUTIONAL DEVELOPMENT OF STEM CELL RESEARCH CAPABILITIES AT THE CITY COLLEGE OF NEW YORK / CUNY**

**Wang, Sihong, Gilchrist, Lane, Fu, Bingmei, and Tarbell, John**

*Biomedical Engineering Department, The City College of the City University of New York, New York, NY*

A group of faculty members at the City College of New York (CCNY) is actively working in several areas of stem cell research. Projects are under way using either mouse embryonic stem cells or adult human mesenchymal stem cells from bone marrow. However, overall stem cell research at CCNY is in its infancy.

Comprehensive training in core methods for individuals who conduct stem cell research provides the foundation for development of long term research capabilities using human stem cells at CCNY. The isolation and characterization of stem cells are the first critical steps in most stem cell research projects. A fluorescence-activated cell sorting (FACS) system is essential equipment for stem cell characterization and isolation with high purity.

The funds from this development grant provided this critical FACS instrument to the Biomedical Engineering (BME) Department, home of four faculty members participating in this grant, to enhance the future of stem cell research at City College. The specific aims of the grant were: 1) to set up the core facility of flow cytometry in the BME department for stem cell research and 2) to provide stem cell training funds for the participating faculty and their graduate students. BD FACSCalibur, a four color flow cytometer, was purchased and installed in October 2008. Two participating PIs ( Drs. Sihong Wang and Lane Gilchrist) have been using it intensively in their stem cell-related experiments. We expect that it will be continuously used by all BME faculty and other City College faculty working on stem cell research. Besides setting up the core stem cell facility, four participating PIs and their Ph.D. students have attended several stem cell training courses/conferences, including Methods in Human Embryonic Stem Cell Research in Jackson Laboratory, Cell-Based Therapies & Tissue Engineering in Case Western University, Frontiers in Human Embryonic Stem Cells in Marine Biological Lab by Pittsburgh Development Center, and Stem Cell Therapy for Cardiovascular Disease in New York City. In summary, this development grant provides critical funds for training and core equipment that has been moving stem cell research at CCNY to the next level.

## **INTRODUCING STEM CELL RESEARCH AT HUNTER COLLEGE: *IN VITRO* DIFFERENTIATION OF LYMPHOCYTES FROM MOUSE EMBRYONIC STEM CELLS**

**Ortiz, Benjamin**<sup>1</sup>, Armin, Lahiji<sup>1</sup>, Kucerová-Levisohn, Martina<sup>1</sup>, Holmes, Roxanne<sup>2</sup>, and Zúñiga-Pflücker, Juan-Carlos<sup>2</sup>

<sup>1</sup>*Department of Biological Sciences, City University of New York, Hunter College, New York, NY;* <sup>2</sup>*Sunnybrook Research Institute, University of Toronto, Toronto, ON*

This one-year project has enabled Hunter College to incorporate embryonic stem (ES) cell research into its science research program. The effort involves two sub-projects. In the first project, carried out in the laboratory of Ben Ortiz, rare and challenging technology has now been established to direct embryonic stem cell differentiation towards lymphocyte lineages. This will enable his lab to more rapidly and less expensively assess the activity of gene regulatory elements during T cell development and participate in translational research projects with clinical implications. This technology will be shared with other labs in CUNY that may benefit from it. In the second project, carried out in the laboratory of Paul Feinstein, equally challenging technology is being developed where neuronal cells can be re-programmed to adopt an embryonic cell like state.

With the help of NYSTEM funding, each project has shown significant progress in mastering these technical challenges. The analysis of how ES cells are able to reprogram somatic cells into ES cells will eventually lead to the generation of designer ES cells for each individual. The combined efforts of both laboratories are aimed at stem cell engineering and customizing the ES cells for gene transfer, tissue transplantation and therapeutic intervention. The project of the Ortiz lab represents Hunter College's stem cell program at this meeting and is described here.

*We gratefully acknowledge the funding of this project by the NYS DOH via NYSTEM Grant C023048 and the support of Associate Dean Ann Henderson and the Hunter College School of Arts and Sciences. We also acknowledge NIH/NCRR/RCMI grant RR03037 to the Hunter College Center for the Study of Gene Structure and Function.*

## **ENHANCING STEM CELL RESEARCH AT MONTEFIORE MEDICAL CENTER**

**Hatcher, Victor, Currie, Brian, Vasovic, Ljiljana, and Gupta, Sanjeev**  
*Montefiore Medical Center, Bronx, NY*

### **Montefiore Medical Center (MMC) Hematopoietic Progenitor Cell (HPC)**

**Processing Laboratory:** As indicated in the original grant application and interim report, this component supports a longstanding Bone Marrow Transplant Program at MMC. During the funding period, HPC Processing Laboratory maintained licensing from New York State and served institutional needs through Standard Operating Procedures (SOPs) and a Quality Assurance Program, in accordance with guidelines of AABB, FDA and NY State.

The HPC Processing Laboratory was augmented with additional equipment during the grant period. Moreover, original research was performed in the laboratory through a project entitled, "Bioengineering of a stem cell coated vascular graft derived from placental vessels", PI, Ljiljana V. Vasovic, MD.

### **MMC-Albert Einstein College of Medicine (MMC-Einstein) Stem Cell Consortium:**

According to our proposed plans, we successfully invigorated stem cell activity at MMC-Einstein, including through configuration of the MMC-Einstein Stem Cell Consortium. The major immediate component of this consortium concerns liver-based stem cell therapies. Several major milestones were reached in the institutions, including establishment of a new Unified Division of Hepatology housed in the Department of Medicine, formation of a clinical MMC-Einstein Liver Center, recruitment of four transplant surgeons, and three transplant hepatologists, along with support staff to activate a Liver Transplantation program. This liver transplant program is on target and several patients have already been treated with donor livers at MMC. This constitutes a critical component for further development of stem cell therapies in the MMC-Einstein Consortium. A stem cell consortium planning group has been assembled and has identified liver stem cell therapy for liver failure, hemophilia A and genetic deficiency disorders as initial stem cell targets. Appropriate pre-clinical animal models have been developed to identify and evaluate the fate of transplanted liver stem cells, using PCR probes and III Indium labeling and to examine the impact of whether the introduction of therapeutic genes in stem cells can block hepatitis virus replication.

## RECOVERY OF ISCHEMIC LV FUNCTION USING HUMAN VASCULAR PROGENITOR CELLS

Hintze, Thomas<sup>1</sup> and Anversa, Piero<sup>2</sup>

<sup>1</sup>New York Medical College, Valhalla, NY; <sup>2</sup>Brigham and Women's Hospital, Boston, MA

The human heart possesses a coronary vascular progenitor cell (VPC) which regulates the growth of endothelial cells (ECs), smooth muscle cells (SMCs), and vasculogenesis. They are contained in vascular niches and are composed of c-kit-positive KDR-positive VPCs within the coronary circulation. Isolated VPCs are self-renewing and clonogenic and differentiate into ECs and SMCs. We tested whether human VPCs possess the ability to create conductive coronary arteries in immunosuppressed dogs with critical coronary stenosis. The presence of a critical stenosis was documented by the absence of reactive hyperemia after the release of a 15 sec occlusion of the LAD. VPCs expressing EGFP were then injected directly into the myocardium above, laterally and below the site of constriction. At 10 days, the lack of reactive hyperemia persisted. Myocardial perfusion was determined at 30 days; gold-labeled microspheres were injected with the LAD open to establish baseline CBF and lutetium-labeled microspheres were administered during LAD occlusion. Multiple sections from the region proximal and distal to the occlusion were processed to evaluate CBF distribution. Every other section was collected for histology. CBF at baseline was similar in all sections but after LAD occlusion there was an unexpected doubling in CBF in the fully dilated coronary circulation distal to the stenotic vessel. Histologically, new coronary arteries, 0.8–1.5 mm in diameter containing red cells, were detected in proximity of the stenotic vessel together with resistance arterioles and capillaries, pointing to vessel regeneration as the mechanism of enhanced CBF in the ischemic myocardium. ECs and SMCs within the vessel wall were all EGFP-positive; the human origin of these cells was confirmed by the detection of human DNA sequences with an *Alu* probe. In conclusion, the human heart possesses a coronary VPC that can be isolated and expanded *in vitro* for subsequent transplantation as a treatment for patients with coronary artery disease.

NYSTEM funding (C023052) was used in two ways at New York Medical College, one to supplement ongoing research and the other to provide training in stem cell research through our Stem Cell center, headed by Drs. Leonard and Carol Eisenberg. The supplemental funding allowed us to finish the scientific project written above. That project has shown that we can use human vascular progenitor cells to grow blood vessels in the ischemic area of the dog heart. The research training section has allowed us to recruit two postdoctoral fellows into our developing Stem Cell Center and three graduate students. One of the fellows has traveled to Dr. Piero Anversa's laboratory at Brigham and Women's hospital in Boston to acquire new techniques. These techniques include use of the confocal microscope, which we have purchased, and learning animal surgery on mice for future studies of stem cell development and potential therapeutic use. Funding for training is still being used and we are acquiring techniques for microinjection of stem cells and also to make uniform our histology across laboratories, especially with Dr. Anversa.

## IN-DEPTH ANALYSIS OF PLURIPOTENT CELLS USING HIGH-THROUGHPUT SEQUENCING

**Birnbaum, Kenneth D. and Piano, Fabio**

*The Center for Genomics and Systems Biology, New York University*

The PIs at NYU's Center for Genomics and Systems Biology study pluripotent cells in plants and animals, largely using *Arabidopsis* *Caenorhabditis elegans* model systems. Investigators at NYU's Dental School school, which is part of the NYSTEM grant to NYU, also study the use of pluripotent cells for tissue replacement therapies. Together these groups used NYSTEM instrument funding to purchase sequencing technology that will enable them to explore the molecular characteristics of pluripotent cells in depth, purchasing a SOLiD v. 3 high throughput sequencer (Applied Biosystems). This system brings down the cost of sequencing by orders of magnitude permitting researchers to generate in-depth profiles of single cell types by sequencing virtually the entire transcriptome, including coding and non-coding RNAs and targeted UTR sequencing in an unbiased fashion. In addition, the instrument will permit an investigation of structural changes in chromatin and DNA associated with pluripotent cells using CHiP-seq, for example. The current output of the SOLiD is 20 to 40 gigabytes per run at 50 bp read lengths. With a cost of about \$6,000 per run, each run can be divided into at least 8 samples or more with bar coding. This brings the cost of such in-depth interrogation down to a point where sequencing can reveal aspects of molecular nature of stem cells at a reasonable cost. For example, the Birnbaum lab will isolate stem cells of the plant root and compare their transcriptome to other cells using high throughput sequencing. The Piano lab, which studies embryogenesis, is developing techniques to investigate variation in 3' UTRs on a transcriptome-wide basis. These techniques will be combined with high throughput sequencing.

## DIRECT AND INDIRECT INVOLVEMENT OF BONE MARROW STEM CELLS IN DEVELOPMENT OF CANCERS AFTER TRANSPLANTATION OF MALE MMTV-PyMT BONE MARROW INTO WILD-TYPE FEMALE FVB/N MICE

Sell, Stewart<sup>1,2</sup>, Guest, Ian<sup>1</sup>, Ilic, Zoran<sup>2</sup>, Ma, Jun<sup>2</sup>, Glinsky, Gennadi<sup>2</sup>

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The hypothesis that the bone marrow (BM) contains cells that could give rise to breast cancer was tested by transplantation of BM from male mice bearing a strong oncogene (polyoma middle T antigen gene, PyMT) under the control of a promoter activated in the mammary gland (mouse mammary tumor virus promoter, MMTV), into irradiated syngeneic non-transgenic female recipients. Eight female FVB/N mice were irradiated with 900 to 1050 rads at two months of age and rescued by transplantation of  $2 \times 10^6$  male BM cells from transgenic MMTV-PyMT FVB/N donors. By the age of 14 to 21 months, 8 of the 8 transplanted female mice developed a number of tumors of various tissue types, with a significantly higher incidence and variation in types than 24 month old un-irradiated female FVB/N controls or controls transplanted with non-transgenic male bone marrow. In addition, one of the 8 recipient mice developed a breast cancer histologically indistinguishable from the primary breast cancers in MMTV-PyMT mice. By fluorescent *in situ* hybridization over 80% of the breast cancer cells contained a Y-chromosome. The breast cancer was essentially diploid, suggesting that cell fusion was not involved. None of the other mice developed a breast cancer, but they did exhibit a number of other cancer types including squamous cell carcinoma, fibrosarcoma, lung and adrenal adenomas, an Harderian gland adenocarcinoma. None of these cancers contained Y-chromosomes, including a mixed cell cleaved lymphoma and an adrenal adenoma and found in the same mouse that had the breast adenocarcinoma. Tests for production of the PyMT antigen by the tumor stromal cells have been negative. Our results suggest that donor derived BM mesenchymal stromal cells may indirectly induce development of cancer in both the epithelial and mesenchymal tissues of a recipient, as well as directly produce breast cancers by mesenchymal-epithelial transition. The transdifferentiation of hematopoietic stem cells to breast cancer cells cannot be ruled out at this time.

## DEVELOPMENT OF FUNCTIONAL SURFACES AND THREE-DIMENSIONAL NANOFIBER SCAFFOLDS FOR TISSUE ENGINEERING

Tuckett, Andrea and **Levon, Kalle**

*Polymer Research Institute, Polytechnic Institute of NYU, Brooklyn, NY*

Polytechnic University has gratefully proceeded with the NYSTEM grant support and experienced a wonderful and exciting transition from Polytechnic University to Polytechnic Institute of New York University, bringing our research to a broader environment with an enormous expansion of opportunities. The doctoral students were excited by the NYSTEM grant with the hopes for improved research infrastructure. Our MSc students in Biomedical Engineering, Biotechnology and Bioinformatics MSc programs have become an active part in our research in tissue engineering and we have eagerly given the students novel educational opportunities in order for them to become better prepared when employed by our NY State industry. Similarly, we have presently a large group of undergraduate students taking their first steps in preparing scaffolds and surfaces for tissue engineering. The participation in scientific meetings like ISSCR in Philadelphia has ensured that the information from recent developments reaches our students. Overall, the NYSTEM grant has had a very deep impact on the education and research activity in a small institute like ours.

The cell culture facilities at Polytechnic Institute of NYU are still limited and the PI, with the help of the NYSTEM grant, has prepared proposals for infrastructure improvement. The development of multifunctional surfaces and scaffolds has been done in Brooklyn but most of the *in vitro* and all of the *in vivo* work has been done elsewhere.

The NSF-funded collaboration with Professor Rafailovich at Stony Brook University offered the opportunity for our biomedical engineering graduate students to work in the cell culture laboratory during 08-09 fiscal year. Similarly, Dr. Marcel van den Brink at Memorial Sloan Kettering Cancer Center has kindly assisted us to evaluate the use of three-dimensional nanofibrous scaffolds (NFS) as an experimental approach for regenerating the native structural and functional properties of living tissue. We have transformed a two-dimensional culture system for T cell development into a three-dimensional culture system using synthetic polymer nanofiber scaffolds. The biodegradable electrospun NFS were seeded with OP9-DL1 cells, a murine bone marrow stromal cell line expressing the Notch 1 ligand Delta-like 1 (DL1).

## **RENSSELAER POLYTECHNIC INSTITUTE STEM CELL RESEARCH: NEW TECHNOLOGIES TOWARDS DIRECTED DIFFERENTIATION AND THERAPEUTIC APPLICATIONS**

**Paluh, Janet**, Kane, Ravi, Thompson, Deanna, Linhardt, Robert et al.  
*Rensselaer Polytechnic Institute, Center for Biotechnology & Interdisciplinary Studies,  
Troy, NY*

Rensselaer's strengths in development and application of new technologies is being directed towards expanding knowledge of adult and embryonic stem cells to broaden basic concepts and accelerate therapeutic applications. Two recent NYSTEM awards to Dr. Robert Linhardt and Dr. Russell Ferland address the glycobiology of hESCs and the role of cilia in neural stem cells, respectively. RPI researchers take advantage of a multi-disciplinary environment supported by a state-of-the-art Center for Biotechnology, including a new animal BioResource Center, and Centers for Supercomputing and Nanotechnology. Additional expertise is present in materials science, multi-dimensional imaging and high-throughput analysis. Stem cell specific research guidelines are monitored by the RPI ISCRO: Institutional Stem Cell Research Oversight Committee. RPI is also an active member of UPSTEM, an Upstate NY stem cell consortium of 10 Institutions and over 100 stem cell Researchers including NYNSCI, Wadsworth, Ordway, AMC, Trudeau Institute, U. Albany SUNY, U. Buffalo SUNY, SUNY Upstate, and Syracuse. UPSTEM promotes collaborative science, clinical efforts and education at both multi-Institute & multi-disciplinary levels.

## DEVELOPMENT OF STEM CELL RESEARCH CAPABILITIES AT ROSWELL PARK CANCER INSTITUTE

Gudkov, A.V., **Smith, G.J.**, Baumann, H., Gross, K.W., Matta, K., Morgan, J., Nagase, H., Oseroff, A., Repasky, E.A., Rustum, Y.M., and Wallace, P.K.  
*Roswell Park Cancer Institute, Buffalo, NY*

The NYSTEM grant for Development of Stem Cell Research Capabilities awarded to Roswell Park Cancer Institute was allocated to both improvement of infrastructure critical for stem cell research, and to support pilot projects focused on the clinical significance of stem cells in cancer biology, both for targeting cancer stem cells and for protecting benign stem cells in chemotherapy/radiotherapy sensitive organs/tissues. Availability of cell sorting capability was a major limitation of the stem cell research community, a need addressed in the NYSTEM program by acquisition of a FACSAria II SORP with four lasers and 12 fluorescent detectors, plus forward and side scatter, with the capability of two way, and four way, aseptic sorting, and the capacity to regulate the temperature in both the sample intake and sort chambers. Pilot research projects enabled by the access of the new FACSAria SORP dedicated to NYSTEM supported investigators have focused on isolation/enrichment of cancer stem cell populations from prostate cancer (GJS,KM), lung cancer (HB), human tumor cell lines (JM,AO,HN,YMR), and human tumor xenografts (EAR), as well as isolation of pericyte precursors (KWG). These studies utilize FACS-based selection dependent on expression of a variety of putative stem cell markers, including antibodies for CD24, CD34, CD44, CD90, CD117 and CD133, or fluorescent substrates exported by multi-drug resistance transporters, such as DyeCycle Violet, Hoechst 33342 or ALDEFLUOR.

The pilot studies have resulted in significant new findings, including: 1) characterization of the gene expression profile of human prostate cancer stem cells as a source for identification of putative biomarkers; 2) validation of a co-culture model allowing analysis of stem cell-mesenchymal interactions and capitalizing on the co-culture model to propagate lung cancer stem cells for transplantation; 3) demonstration that Ren-GFP+ positive transgenic cells are representative of activated pericytes in developing renal vasculature, and as suggested by gene expression profiling, also representative of mesenchymal stem cells and renal cancer cells; 4) determination that the presence of ABCG2 in cancer stem cells is a significant modulator of Photodynamic Therapy, and that the PDT substrate HPPH-Gal is more effective at targeting SP cells than the ABCG2 substrate HPPH, and co-incubation with Gleevec, an ABCG2 substrate, enhanced the PDT response of HPPH-PDT, suggesting the enhanced response was due to increased retention of HPPH; 5) demonstration that CSCs are sensitive to targeting of death receptors (DR4 and DR5), and that CSCs from human tumors are differentially susceptible to induction of apoptosis via the external apoptotic pathway, suggesting a novel approach for therapy tailored to individual tumors; 6) intracellular distribution of beta-catenin in cancer stem cells expressing ABCG2/CD133 serves as a surrogate marker of activation of Wnt signaling, and an indicator of potential response to irinotecan and selenium. Lastly, studies focused on protection of benign stem cells demonstrated that pharmacological activation of the pro-survival NF- $\kappa$ B pathway by bacterial factors, agonists of Toll-like receptors (TLRs) 5 (flagellin) and 2/6 (Mycoplasma lipopeptide), results in powerful, long-lasting protection from lethal irradiation. However, the radio-protective effects do not extend to cancer cells.

## INSTITUTIONAL DEVELOPMENT OF STEM CELL RESEARCH CAPABILITIES AT THE UNIVERSITY AT BUFFALO

Laychock, Suzanne<sup>1</sup>, Stachowiak, Michal<sup>1</sup>, Lee, Techung<sup>1</sup>, Andreadis, Stelios<sup>2</sup>, Canty, John<sup>1</sup> and **Tramposch, Kenneth M.**<sup>1</sup>

<sup>1</sup>*School of Medicine and Biomedical Sciences and* <sup>2</sup>*School of Engineering and Applied Sciences, University at Buffalo, Buffalo, NY*

A key objective of the project was to enhance the ability to perform stem cell research at the University of Buffalo. One aim was to equip a state-of-the-art Stem Cell Research Core Facility. The goal was to expand the current capabilities of the current Zeiss LSM510 confocal microscope system to a multiphoton confocal system for use in stem cell research. To this end we have acquired the Coherent Chameleon Ultra 2 laser system to convert the confocal microscope to a multiphoton confocal system. The multiphoton confocal microscope is currently being used by a large cadre of stem cell researchers.

We have also made significant advances on four research projects using the NYSTEM funding:

- 1) Neurogenesis, the process of differentiation of neuronal stem/progenitor cells (NS/PC) into mature neurons, holds the key to the treatment of various neurodegenerative disorders. We report that targeting the novel Integrative Nuclear FGF Receptor-1 Signaling (INFS) pathway enhances the latent potential of NS/PCs to undergo neuronal differentiation. Employing organically modified silica (ORMOSIL)-DNA nanoplexes to efficiently transfect recombinant nuclear forms of FGFR1 and its FGF-2 ligand into the brain subventricular zone, we find that INFS stimulates the NS/PC to withdraw from the cell cycle, differentiate into doublecortin expressing migratory neuroblasts and neurons.
- 2) The dynamics of gene expression is fundamental for the understanding of the complex regulatory machinery of stem cells. The ability to measure the transcriptional changes during physiological or pathological responses in real-time would facilitate our understanding of cellular regulation and control. We now report development of a novel technology that allows monitoring of gene expression in a non-destructive manner by utilizing fluorescent reporter proteins under the control of a regulatory sequence. Thus, the change in transcription activity of stem cells could be simply monitored by quantifying the fluorescent intensity change.
- 3) We have made considerable progress to understand the underlying mechanisms that control pravastatin-mediated myocardial regeneration to begin to understand why statins facilitate myocardial regeneration in a large animal model of chronic myocardial ischemia but not in humans with ischemic cardiomyopathy. To determine the mechanism underlying these statin-based changes, we made use of a transcriptional profiling approach to identify changes that are specific to pravastatin-induced myocardial regeneration in comparison to untreated animals with hibernating myocardium, and with normal animals. This approach will provide experimental targets to determine the specific effects of statins on the growth versus survival of cardiac stem cells.
- 4) One of our long-term objectives is to develop novel and effective stem cell-based strategies to reduce death and disability from heart failure and sudden death. Both human and porcine MSCs constitutively expressing cdk1 have been successfully generated and found to be stably maintained in culture. Notably, although cdk1-MSCs do not undergo cellular senescence, we do not observe tumor formation upon transplantation of these cells in mice, hamsters, and pigs. The cdk1-MSCs upon intramuscular injection in the cardiomyopathic hamsters improve cardiac function similar to that observed with their parental MSCs. We further show that improved cardiac function can be achieved using a culture medium conditioned by cdk1-MSCs, indicating that the therapeutic effects of MSCs is mediated by their trophic activities.

## REGULATION OF INTESTINAL L CELL PROGENITOR PROLIFERATION BY THE GLUCAGON FAMILY OF PEPTIDES

Grigoryan, Marine, Kelaid, Mamdouh, Guz, Yelena, and Teitelman, Gladys  
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Enteroendocrine L cells are the main source of Glucagon like peptide 1 (GLP-1), an incretin hormone that stimulates insulin secretion and improves glycemia in type 2 diabetes. Although GLP-1 based treatments are clinically available, alternative strategies to increase endogenous GLP-1 release from L cells are limited. In this study we sought to determine whether glucagon signaling regulates the number of L cells. We examined mice: a) with a global deletion of the glucagon receptor (Gcgr<sup>-/-</sup>) and b) lacking mature glucagon due to a mutation in PC2, a proglucagon processing enzyme (PC2<sup>-/-</sup> mice). Gcgr<sup>-/-</sup> mice (but not PC2<sup>-/-</sup>) displayed a 3-10 fold increase in circulating levels of GLP-1. We found that this increase in GLP-1 levels in Gcgr<sup>-/-</sup> mice was due to an augmentation in L cell number per villus in Gcgr<sup>-/-</sup> mice (Gcgr<sup>-/-</sup> : 2.56±0.32 vs Grgr<sup>+/+</sup> : 1.17±0.24; PC2<sup>-/-</sup> : 1.78±0.22. N=6/line, P<0.005). This increase was not due to an autocrine loop since L cells did not express the GLP-1 receptor.

The augmentation in L cell number was not due to proliferation of terminally differentiated cells since mature L cells of Gcgr<sup>-/-</sup> and Gcgr<sup>+/+</sup> mice did not replicate. To ascertain whether the deletion of Gcgr increased the mitotic activity of L cell progenitors, Gcgr<sup>-/-</sup> and Gcgr<sup>+/+</sup> mice were given Bromo-2'deoxyuridine (BrdU) in the drinking water for six days. This time sufficed for intestinal stem cells to migrate along the crypt-villus axis, become quiescent and differentiate into GLP-1+ cells. We found that the ratio of GLP-1(+) BrdU(+) L cells/ total number of GLP-1(+) L cells was 75 % higher in Gcgr<sup>-/-</sup> than in Gcgr<sup>+/+</sup> mice. In contrast, the number of other intestinal epithelial cells from enteroendocrine (CCK, serotonin cells) and nonenteroendocrine (goblet cells) lineages was similar in Gcgr<sup>-/-</sup> and Gcgr<sup>+/+</sup> mice. We conclude that the lack of the Glucagon receptor specifically contributes to an increase in the rate of proliferation of L cell progenitors.

We then asked whether the high levels of circulating GLP-1 in Gcgr<sup>-/-</sup> mice activate L cell precursor proliferation. Gcgr<sup>-/-</sup> mice were injected with Exendin (9–39), a specific GLP-1 receptor (GLP-1 R) antagonist, for two weeks. These mice were also administered BrdU during the last six days of the Exendin (9-39) treatment. Analysis of the rate of L cell precursor proliferation indicated that the ratio of GLP-1(+) BrdU(+) L cells /total number of GLP-1(+) L cells was 55 % lower in Gcgr<sup>-/-</sup> mice that received Exendin (9-39) compared with control Gcgr<sup>-/-</sup> mice injected with vehicle. In contrast to L cells, chronic treatment with Exendin (9-39) did not affect the number of CCK cells.

This finding suggests that inhibition of GLP-1 R signaling in Gcgr<sup>-/-</sup> mice blocks the increase of L cell progenitor's proliferation. Since inhibition of GLP-1 R decreases insulin secretion from pancreatic beta cells, we hypothesize that the rate of proliferation of L cell progenitors is regulated by insulin.

## **BUILDING A STEM CELL COMMUNITY AT STONY BROOK UNIVERSITY**

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The overall goal of this project is to increase awareness within the scientific community here at Stony Brook with regard to stem cell research, while generating new knowledge on the use of stem cells for human therapies. The facilities and supplement grant, with funding from April of 2008 to April of 2009 has allowed the purchase of an Olympus FluoView laser scanning confocal microscope that has been installed in a common use space within the Health Science Center at Stony Brook to provide a core facility for stem cell research. Moreover, it created a university-wide stem cell seminar series that has brought the current population of investigators together on a regular basis while providing an interesting stimulus for additional investigators to consider entering the field. It has also allowed expansion of the already existing stem cell journal club in the Institute for Molecular Cardiology to attract those with an interest in initiating stem cell research. In addition, it has allowed the seven participating laboratories to augment their research on stem cell biology and therapeutics. These projects include: 1) Characterization of gap junction mediated communication in human adult mesenchymal stem cells by optimizing cell to cell coupling to facilitate the delivery of small solutes in order to improve mechanical function in the heart, 2) Mechanical regeneration of the heart and the basis of stem cell homing and their differentiation to cardiac myocytes with a mature sarcomere structure, 3) Proteomic characterization of mouse embryonic neurospheres in culture with terminally differentiated neuronal cells and identifying proteins involved in shaping the characteristic properties of neural stem cells, 4) Expression profiling of Wnt and Frizzled isoforms in stem cells to investigating the role of Wnt family in embryonic stem cell renewal, growth and differentiation. It was shown that pluripotent human H7 and mouse F9 embryonal cells express the genes for most of the Wnts and Frizzleds. In contrast, multipotent human mesenchymal cells are deficient in expression of Frizzled-8 and of 6 Wnt genes, 5) Investigating the potential of post-mitotic differentiated keratinocytes to revert to epidermal stem cells and participate in skin regeneration by using Cre-Lox lineage tracing of differentiated keratinocytes, 6) The use of allogeneic stem cells for the treatment of extensive full-thickness chemical and thermal burns can provide therapeutic advantage for mass casualties under conditions of limited hospital access including; industrial accident, war, terrorist attack, and 7) Investigation of the function of two proteins in TGF $\beta$  and wnt signaling pathways including; npw38 and GTPBP2 which appear to be required for normal pluripotent embryonic and cultured cell responses to wnt and BMP4 ligands.

## PROCUREMENT OF A XENOGEN IVIS<sup>®</sup> 200 *IN VIVO* IMAGING SYSTEM FOR THE HUMANIZED SCID (HU-SCID) MOUSE CENTER AT SUNY UPSTATE MEDICAL UNIVERSITY

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The humanized severe combined immunodeficient (HU-SCID) mouse is a novel *in vivo* model which has the potential to become a broad platform for investigations of stem cell biology, human viral infections, initiation of oncogenesis and in translational development of anti-virals and chemotherapeutics. In the Center for Humanized SCID Mouse Models, we have developed a number of model systems to utilize the HU-SCID mouse. One of the challenges in developing preclinical models is the need for assays that are specific and sensitive, do not rely on single-end point measurements, and reduce the numbers of animals employed. Bioluminescent imaging is a recently developed whole-animal imaging system that can achieve this goal. In this technology, cells or pathogens are either generated to stably express luciferase, or tagged with fluorescent markers such as red fluorescent protein or near infrared dyes. Imaging of the living whole mouse is done with the *in vivo* imaging system (IVIS)<sup>®</sup> 200 (Caliper Life Sciences Corp.) that detects photons or fluorescence emitted even in deep body tissues; LivingImage<sup>®</sup> software translates the data so it can be visualized and quantified. It is also possible to localize the luminescent cells or pathogens within mouse organs using 3-D tomography. The IVIS<sup>®</sup> 200 can detect both luminescence as well as bio-fluorescence in a single animal. The use of the *in vivo* imaging will eliminate the need for invasive procedures to verify that stem cells engraft and proliferate in the mice. An IVIS<sup>®</sup> 200 has been procured with funding from NYSTEM and has resulted in a reproducible evaluation of the efficacy of viral oncolytic vectors on tumor cells *in vivo*, in the engraftment of human red blood cells, infection of mice with a luciferase tagged Plasmodium falciparum and in the evaluation of the expression of gene therapy (i.e., lentiviral) vectors in HU-SCID mice.

## CAN NAÏVE CD4 T CELLS NEWLY DERIVED FROM STEM CELLS OVERCOME AGING AGE-ASSOCIATED DEFECTS IN IMMUNE FUNCTION?

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Our studies show that immunological memory generated during youth functions well into old age, while that generated later in life from aged naïve cells is impaired as a result of declines in the function of naive CD4 T cells from aged individuals and contributes to reduced efficacy of vaccines in the elderly.

Haynes and Swain have used NYSTEM Institutional Development funds to advance studies that ask if newly generated naïve cells that develop either *in situ* in aged hosts or after transfer of bone marrow to young hosts, function like young naïve cells, overcoming aging defects. We find that the newly generated naïve CD4 T cells, in either case, give robust primary responses, generation of primary effectors and also give rise to memory T cells that do not express age-associated impairments (1, and Haynes et. al., unpublished). Importantly, memory CD4 T cells generated from aged BMPC exhibit potent cognate helper function for humoral responses, which are critical for effective immunization. These results indicate that there are no apparent age-related intrinsic defects in BMPC with regards to generation of functional memory T cells.

We have found that in addition to functional defects in response to antigen, aged naïve CD4 T cells are longer-lived *in situ* and after adoptive transfer to intact hosts and they express reduced levels of the pro-apoptotic protein, Bim (Tsukamoto, Haynes and Swain, unpublished). We suggest that the longevity of the cells is responsible for their development of functional defects and that defects develop post-thymically. We transferred young and aged BM as a source of BMSC to young, lethally irradiated hosts and assessed new naïve CD4 T cells that developed. The newly generated naïve CD4 T cells from aged BMSC expressed high levels of Bim, comparable to cells from young mice and were not longer-lived than young naïve CD4 T cells. Together these results indicate that both functional defects and increased cellular longevity develop as naïve CD4 T cells persist in the periphery and that BMSC give rise to newly generated CD4 T cells with normal function and longevity.

Cooper has used NYSTEM funds to initiate studies to determine whether the stromal cells in inducible broncho-associated lymphoid tissue (iBALT) are generated by mesenchymal stem cells (MSC) that are mobilized from the bone marrow or by local MSC that reside in the lung. Given that RORgt is one identifying feature of lymphoid tissue inducer (LTi) cells, we used the RORgt-GFP reporter mice to follow the accumulation of RORgt expressing cells in the lung and draining lymph node following *Mycobacterium tuberculosis* (MTb) infection. We find that the RORgt expressing cells that accumulate in the draining lymph node of the lung in response to infection are T cells by surface phenotype. However among RORgt-expressing cells that accumulate in the lung, there is a substantial portion of cells that do not express the lineage specific markers (TCR, B220 CD11c etc.). These cells have a phenotype similar to the LTi. This supports the hypothesis that Mtb infection serves to promote the accumulation of progenitor cells within the lung that can generate new lymphoid tissue. We also observed that areas of lymphoid tissue formed around the site of granuloma formation, suggesting that local LTi cells were promoting the differentiation of MSC into stromal cells.

## **ECHOCARDIOGRAPHY & STEM CELL PHYSIOLOGY CORE FACILITIES, SPECIALIZED TRAINING PROGRAMS & SUPPLEMENTAL FUNDING FOR STEM CELL RESEARCH**

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An unlimited supply of vascular endothelial cells (VEC) is among the most promising dividends of human embryonic stem cell (hESC) application in regenerative medicine, yet the routine generation of large volumes of hESC-derived VECs for therapeutic application remains elusive. We have generated a vascular specific fluorescent reporter construct in a lentiviral vector for the purpose of analysis and purification of hESC-derived endothelial cell populations. Specifically, we have created a construct containing the green fluorescent protein under control of the VE-Cadherin promoter, which is expressed exclusively in the endothelial lineage. In stably transduced hESCs, this reporter exhibited an expression pattern that was highly specific for cells bearing the morphological and molecular phenotype of endothelial cells. Using this tissue specific reporter line, we have directly observed, in real time, endothelial specification and patterning, and devised a high throughput screening approach for the identification of molecular, spatiotemporal and biomechanical stimuli that foster the induction and maturation of hESC-derived endothelial cells that have angiogenic potential for the revascularization of ischemic tissue. We have developed a detailed protocol for increasing the relative yield of VECs from feeder and serum free differentiation cultures, and elucidated the ability for a small molecule inhibitor of TGF $\beta$  signaling to augment the degree of VEC differentiation as well as the proliferation of VECs following isolation and extended culture. These data not only provide a simple means of increasing VEC yield for pre-clinical studies, but also point toward a mechanistic role for TGF $\beta$  signaling in governing the specification and mitotic index of embryonic endothelium.

We have submitted a patent application governing the VEC-specific reporter construct and hESC line that we have generated and an article describing its use is currently under review at Nature Biotechnology.

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