Stem Cell Research in New York State: *A Snapshot*

NYSTEM

NEW YORK STATE STEM CELL SCIENCE

New York State Department of Health Wadsworth Center

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PART I

EXECUTIVE SUMMARY

STEM CELL RESEARCH IN NEW YORK STATE: A SNAPSHOT

Executive Summary

This report summarizes data obtained from responses to written surveys and structured personal interviews with stem cell scientists in New York State between June and October, 2007. The findings are accompanied by a directory of the scientists interviewed. The objectives of this initial inquiry were threefold: (i) identify institutions and scientists in New York State with ongoing stem cell research programs; (ii) develop an overview of the scope and directions of these researchers' activities and (iii) solicit the views of the stem cell science community in New York regarding the potential scope and mechanisms of funding by NYSTEM. Letters were sent to 42 institutions that were identified through publicly available funding and publication records as having relevant research efforts. Overall, from 28 responding institutions we received feedback from 162 principal investigators (PI) at 23 institutions in time for inclusion in this report. The first interviews took place July 20 and the most recent visit was October 4; in this span of 10 weeks we interviewed investigators from 21 institutions representing all geographic areas of the state.

Importantly, this inquiry identified a strong community of stem cell scientists across the state, as judged by publications and external funding, with diverse interests and expertise, who are well positioned to take immediate advantage of the opportunities that will be provided by NYSTEM. Within the limits of our surveys and interviews, we estimate that more than 200 scientists head laboratories conducting stem cell related research, and that roughly two-thirds of these have a major focus in some aspect of stem cell science. Our survey demonstrated that 52% of PIs have NIH funding. Based on an examination of public databases in 2006, the research scientists have attracted $39.5 million in National Institutes of Health (NIH) funding for stem cell research, as well as substantial foundation, industry and other types of support for which no comprehensive figures are available. Based on survey responses, their work has resulted in at least 115 patents and 16 licenses. Moreover, we estimate that approximately 1,000 scientists, trainees and support staff are currently employed in their academic and private laboratories conducting stem cell research. The data provide fuel for the need for traineeships. At present, only 58% of PIs have graduate students working on stem cells. The situation is similar but slightly better with postdocs as 67% of PIs report having a postdoc.

Stem cell research in New York is broad in scope and highly collaborative, as about 80% of the investigators reported at least one collaboration. One objective of our inquiry was to ascertain the scope of this research within New York State and determine if there are dominant themes or specific areas of strength. Based on data from 162 scientists, the largest fractions had a focus on cancer, neural disease or aging. Other major topics included hematopoietic and musculoskeletal disease and diabetes. The data also showed that many investigators are engaged in studies of fundamental aspects of stem cell biology. Of the 162 respondents, nearly half reported that their research significantly concerned basic stem cell biology.

The types and sources of stem cells that researchers use in their studies are diverse. The majority of investigators use rodent or other non-human sources to supply stem cells for their research. However, nearly half of the investigators use stem cells of human origin, most of whom employ non-embryonic derived cells of a variety of types: hematopoietic and mesenchymal stem cells from marrow and umbilical cord blood, amniotic stem cells, and organ-specific cells derived from skin, cardiac, liver, kidney and other sources. Also included in this list are cancer stem cells. A smaller but still significant fraction of investigators use human embryonic stem cells (hESCs) in their work, or hold approved protocols and plan to use hESCs in the immediate future. Of 39 investigators, 24 reported using only NIH-approved ("registry") hESC lines and 15 reported using "non-registry" lines. Investigators planning to derive new stem cell lines from embryos deemed non-viable, were included in the "non-registry" hESC group. Several of those involved in hESC work were doing so only through collaborations with investigators at other institutions, and only about half of those using hESCs in their work reported that it represented a large fraction of their effort.

In terms of funding preferences, there was strong, but not universal agreement for the use of an investigator-initiated NIH R01-like grant mechanism that would provide substantial funding to individual laboratories for multiple years. Many also favored an additional mechanism of investigator-initiated funding analogous to the NIH R21 vehicle which encourages higher risk with the promise of greater reward. Many interviewees supported institution-based multi-investigator grants in which several researchers at one institution, or investigators at several institutions, collaborate on complementary aspects of a particular research problem. There was considerable support for individual postdoctoral fellowships or young investigator grants as a mechanism for bringing new talent into the stem cell field. Likewise there was considerable enthusiasm for short -term funding for "sabbaticals" in which investigators could visit another laboratory (inside or outside NYS) to acquire specific training in stem cell science or a field that would benefit particular aspects of stem cell research. In contrast, there was little support for institutional training grants, in which graduate students or postdocs are supported en masse, often to work in assigned labs.

It is clear that the area of hESC research has been constrained by inadequate federal support, and that an important focus of NYSTEM should be to enhance opportunities for hESC studies within appropriate ethical guidelines as established by the Board. Concurrent with this opinion, there was unanimity among these researchers that NYSTEM funding should not be restricted to hESC work, since it is unknown at this time which human stem cell types (embryonic or adult) will be best suited for application to particular diseases. Several investigators involved in translational research noted that there is a major gap in available federal funding for pre-clinical studies that move important findings from animal models to human systems. New York State funding for advanced biotechnology core facilities was identified as important by a number of individuals. In particular, researchers working with non-registry hESC indicated that the duplication of equipment required by current federal funding restrictions was a hardship.

Stem Cell Research In New York State: A Snapshot

I. Introduction

This report summarizes data obtained from responses to written surveys and structured personal interviews of 162 stem cell scientists in New York State between June and October, 2007. The findings are accompanied by a directory of the scientists interviewed. The objectives of this initial inquiry were threefold: (i) identify institutions and scientists in New York State with ongoing stem cell research programs; (ii) develop an overview of the scope and directions of these researchers' activities and (iii) solicit the views of the stem cell science community in New York regarding the potential scope and mechanisms of funding by NYSTEM. The observations contained in this document, represent the opinions of current New York State scientists and academic leaders as to the areas of promise, targets for future research funding, and how improvements in infrastructure, recruitment and training of young and established investigators can be best achieved through state funding for stem cell research

The data were collected and analyzed by staff from the Wadsworth Center led by David Anders, Ph.D. and including Carmen Mannella, Ph.D., Marti McHugh B.A., David L. Martin, Ph.D. and Jeffrey Kennedy, M.D.

II. Methodology and Scope

Letters were sent to 42 institutions that were identified through publicly available funding and publication records as having relevant research efforts. They were invited to participate by submitting lists of their investigators whose research included a broadly defined stem cell focus. A questionnaire was sent to responding institutions requesting a number of essential elements of information and soliciting opinions on scientific and funding mechanisms. Third, visits to responding institutions were arranged, whenever possible to allow for follow-up discussions with individual investigators.

This study was initiated in June, 2007. Overall, from 28 responding institutions we received feedback from 162 investigators at 23 institutions in time for inclusion in this report. A majority of the responding researchers reported that stem cell research was a major focus in their laboratories. The first interviews took place July 20 and the most recent visit was October 4; in this span of 10 weeks we interviewed investigators from 21 institutions representing all geographic areas of the state (Fig. 1).

The response to our request for information was excellent. Notably, those responding included the 15 institutions with most stem cell research activity as estimated by available data on relevant research funding. There were several limitations to our study however. Most significantly, although this effort was intensive and inclusive, it was not comprehensive. As indicated above, not all institutions responded to our initial query. Thus, an unknown number of stem cell investigators were unintentionally omitted from this first survey. Second, because of the compressed time frame, we were not able to visit every institution that hosts some stem cell research, and not all stem cell investigators were available to meet with us during our scheduled visits.

Third, this is a new and dynamic field with ongoing recruitments bringing in new investigators while others depart to take positions elsewhere. Lastly, our initial analysis did not extend to the commercial sector, primarily because much of that information is not publicly available. In view of these limitations we intend to make this an ongoing effort.

III. The potential of stem cell research and NYSTEM

Stem cells, which ultimately give rise to all of the differentiated cells, tissues and organs in the body, offer the potential of treatments for many diseases and injuries that result in suffering, disability and premature death for millions. For the purposes of this report we consider two broad classes of stem cells and stem cell research: *embryonic stem cells* (ESCs) and *adult stem cells*. ESCs are derived from a very early stage of development, the *blastocyst*, and are *totipotent*, meaning that they can give rise to every tissue type present in the adult (as well as the extraembryonic tissues necessary for implantation of the embryo). In the course of development, the progeny of these ESCs differentiate through a series of well-characterized steps to form the various tissues and organs present in the adult. However, a few, unique post-embryonic cells maintain the ability to divide extensively and to give rise to multiple cell types within a given tissue, and these are referred to as *adult* — or *somatic* — *stem cells*. Hematopoietic stem cells, which have been studied for over 30 years, give rise to the full complement of cells found in blood and are the best known example.

Stem cell biology is relevant to almost all aspects of biomedicine and disease, including developmental abnormalities, degenerative diseases, immune dysfunction and even cancer. With the rapid growth in understanding of basic aspects of stem cell biology, the potential use of stem cells in other types of tissue repair is being widely investigated. In addition to applications in regenerative medicine, stem cells can provide in vitro resources to study the nature of certain human disease states at the cellular level, in ways that have not been possible. Such studies provide critical new approaches for drug discovery and for understanding the impact of environmental insults and injury during development. Finally, stem cells may give rise to some kinds of cancers, with major implications for cancer therapies. A better understanding of the relationship between stem cells and cancers will enable improved treatments and greater protection from devastating side effects.

Despite great progress in recent years, these are still early days in the medical application of stem cells to human disease problems. So what are the major challenges to be addressed? When we queried scientists about the most important research problems in the stem cell field, a number were repeatedly mentioned. First, much remains to be understood about the sources and properties of stem cells. Several approaches that could be used to produce histocompatible, pluripotent ESC or ESC-like cells are being developed including somatic cell nuclear transfer (SCNT) into oocytes or zygotes, parthenogenesis where the embryo contains only maternal chromosomes, and most dramatically by “reprogramming” somatic cells using co-expression of transcription factors. Although demonstrated in animal models, except for parthenogenesis, the application of these approaches to human cells remains to be worked out. Bona fide ESCs remain the gold standard for all such studies. Likewise, new types of adult stem cells continue to be described, but as yet many of these have been incompletely characterized and so their potential for disease research and therapy is unclear.

Second, application of cellular therapies will require advances in maintaining “stemness” during expansion, and in directing stem cell differentiation into desired cell types. Again, many of these approaches must be worked out in animal models. This may be aided by a better understanding of the epigenetic and transcriptional mechanisms that underlie pluripotency and self-renewal.

Similarly, understanding the role of the microenvironment or "niche" and specific signaling mechanisms in regulating the properties and differentiation of stem cells remains an important problem. Therapeutic development remains mostly in the preclinical stage and only a few early clinical trials have been initiated. Thus, the consensus was that much fundamental work remains in order to translate the science into effective human therapies.

There is great excitement in the scientific community about the potential of the Empire State Stem Cell Fund to enhance stem cell science in New York State and to accelerate progress toward the ultimate goal of new treatments for devastating human diseases, and all of the participants generously shared information about the current focus of their research, as well as their ideas and opinions for NYSTEM which are summarized in the next sections.

IV. Findings

Institutions and scientists. New York State is home to more than 40 large and small, prominent, biomedical research institutions. These institutions clearly recognize the potential utility of stem cells in addressing human disease problems. In recent years they have moved to increase support for stem cell science and clinical applications through new recruitments. Several institutions have created new cross-department stem cell centers to enhance institution-wide interactions. Some institutions possess unique resources or technologies that could enhance the effectiveness of other, complementary programs. Strong non-governmental organizations have also provided leadership and support for stem cell research, particularly in areas where federal funding is restricted or insufficient as it is in research using newly generated human embryonic stem cells (hESCs). Nevertheless, these private resources are quite limited. NYSTEM provides an exciting opportunity to enhance the strengths of stem cell research in New York State and ultimately help speed the realization of its potential benefits.

Importantly, this inquiry identified a robust community of stem cell scientists across the state, as judged by publications and external funding, with diverse interests and expertise, who are well positioned to take immediate advantage of the opportunities that will be provided by NYSTEM. Within the limits of our surveys and interviews, we estimate that more than 200 scientists head laboratories conducting stem cell-related research, and that roughly two-thirds of these have a major focus in some aspect of stem cell science. The years of experience in stem cell research reported by the PIs ranged from less than one, to more than 40, the average being 8.7 and the median 6 years. Our survey demonstrated that 52% of PIs have NIH funding (Table 1). Based on an examination of public databases in 2006, the research scientists have attracted 39.5 million dollars in NIH funding for stem cell research, as well as substantial foundation, industry and other types of support for which no comprehensive figures are available. Based on survey responses, their work has resulted in at least 115 patents and 16 licenses. Moreover, we estimate that approximately 1,000 scientists, trainees and support staff are currently employed in academic and private laboratories conducting stem cell research (Table 2). Because this is a rapidly growing area of biomedicine, and because industry commitment to the development of stem cell science is increasing as fundamental understanding matures, we anticipate these numbers will grow substantially over the coming decade. The data shown in Table 2 also provide evidence of the need for traineeships. At present, only 58% of PIs have graduate students working on stem cells. Those PIs with graduate students have an

average of 2.1 students. The situation is similar but slightly better with postdocs, as 67% of PIs report having a postdoc. Those PIs with postdocs have an average of 2.7. Stem cell research in New York is highly collaborative, as about 80% of the investigators reported at least one collaboration. Three reported 10 or more collaborations and 20 reported five or more. The largest number of collaborations reported by a single PI was 14 (Table 3).

As detailed below, New York State scientists, working in diverse areas of specialization, contribute substantially to progress being made world-wide on the roles and potential therapeutic applications of stem cells in neurological disorders and injuries, cardiovascular disease, diabetes, skin and musculoskeletal disorders, cancer, and immune dysfunctions and aging, as well as crucial research into basic stem cell biology. They employ many different types of stem cells, including hESCs , in their investigations.

The scope and focus of stem cell research in NYS. By its nature, the overall scope of stem cell research is diverse. One objective of our inquiry was to ascertain the scope of this research within New York State and determine if there are dominant themes or specific areas of strength. We categorized stem cell researchers by the disease groups on which their efforts are focused (Fig. 2). Note that in this classification, individual investigators were in some cases assigned to more than one category (e.g. “hematopoietic” and “cancer”). Based on data from 162 scientists, the largest fractions had a focus on cancer (39), or a neural disease or aging focus (37). Other major topics included hematopoietic (21) or musculoskeletal disease (19) and diabetes (10). Within each of the broad categories, studies addressed a variety of specific disease-related problems. For example, the neural category includes researchers with interests in Parkinson’s, Alzheimer’s, amyotrophic lateral sclerosis and spinal muscular atrophy, multiple sclerosis, dystonia, mood disorders and spinal cord injury, among others. Not surprisingly perhaps, the distribution of stem cell investigators among different fields roughly reflects the research funding opportunities represented by those fields. Thus, it appears that the research interests of New York State stem cell scientists are distributed broadly, and there is no single predominant theme. Nonetheless, there is sufficient overlap in the research interests of New York State stem cell scientists that productive inter- and intra-institutional collaborative interactions have occurred, and, with appropriate funding opportunities, would be fostered.

Another observation from these data is that many investigators are engaged in studies of fundamental aspects of stem cell biology. Of the 162 respondents, nearly half reported that their research significantly concerned fundamental aspects of stem cell biology. These areas include growth control, regulation of self-renewal and differentiation, transcriptional and epigenetic programs, and the role of the stem cell microenvironment, or niche, in determining stem cell fate. It is widely held that a better understanding of the basic cellular, genetic, molecular and physiologic mechanisms underlying stem cell function is needed before scientists will be able to manipulate stem cells to desired ends. It is noteworthy that these “basic” scientists employed a variety of complementary approaches involving different technologies and model systems, thereby providing a comparative basis for establishing general principles and identifying the most useful models to address specific problems.

The types and sources of stem cells that researchers use in their studies are diverse (Fig. 3 and Table 4). The majority of investigators (120 of 162) use rodent or other non-human sources to supply stem cells for their research. However, nearly half (80) of the investigators use stem cells of human origin, most of whom (55) employ non-embryonic derived cells of a variety of types: hematopoietic and mesenchymal stem cells from marrow and umbilical cord blood, amniotic stem cells, and organ-specific cells derived from skin, cardiac, liver, kidney and other sources. Also included in this list are cancer stem cells. A smaller but still significant fraction of investigators (39) use hESCs in their work, or hold approved protocols and plan to use hESCs in the immediate future. Of these 39 investigators, 24 reported use solely of NIH-approved ("registry") hESC lines and 15 reported using "non-registry" lines. Investigators planning to derive new stem cell lines from embryos deemed non-viable, were included in the "non-registry" hESC group. Several of those involved in hESC work were doing so only through collaborations with investigators at other institutions, and only about half of those using hESCs in their work reported that it represented a large fraction of their effort. Finally, only a very few laboratories in New York State presently have the capability to create and work with new hESC lines.

Special resources and technologies. It was clear from our discussions with the stem cell researchers that their institutions are home to a wide array of state-of-the-art scientific core facilities for large-scale cell culturing, cellular and whole-animal imaging, high-throughput genomic and proteomic analysis, structural biology, drug-screening, nanofabrication, bioinformatics, and high-end computation. However, the availability of these enabling technologies varies considerably from institution to institution, and it is not always clear whether particular cores are accessible to investigators from other institutions.

New York State has a network of high-technology research centers supported through various state programs (many through NYSTAR), as well as federally supported national biotechnology resource centers, that can contribute valuable capabilities and expertise to stem cell research. These include, but are not limited to, centers for bioinformatics and disease modeling in Buffalo (UB); a new supercomputer center in Troy (RPI); centers for nanotechnology in Ithaca (Cornell) and Albany/Troy (SUNY and RPI); centers for genomics in Albany/Rensselaer (SUNY) and NYC (Columbia); centers for bioengineering in Troy (RPI) and biotechnology in NYC (Yeshiva), Binghamton (SUNY) and on Long Island (SUNY and CSHL); national imaging resources in Ithaca (Cornell), Albany (Wadsworth) and Long Island (Brookhaven), along with other imaging centers in NYC (e.g. Columbia); and the statewide structural biology consortium, the New York Structural Biology Center on the CUNY City College campus. There is some question whether the capabilities and accessibility of these state and federally funded centers are sufficiently well-known to the general science community and, in particular, to the stem cell community in New York State.

V. Observations and recommendations from the NY stem cell research community

Through the use of surveys and structured personal interviews we queried investigators active in the field of stem cell research for their opinions regarding the mechanisms of funding that might have the greatest impact and about the nature and scope of the research to be supported by NYSTEM. The following is a synopsis of these discussions.

Funding Preferences

1. The researchers were unanimous in urging that the stem cell program be science-driven, and that funding should be determined by a peer-review process to assure that the best scientific as well as innovative proposals are supported. Although specific areas of focus varied among the scientists surveyed, there was uniform agreement that there is a critical need for research that will advance the basic understanding of stem cells, novel technologies, and ultimately the translation of fundamental knowledge to the clinic. This broader view of the field of stem cell research, in terms of promising new therapeutics coming from unexpected areas, is entirely consistent with the aims of the authorizing legislation.

2. There was strong, but not universal agreement for the use of an investigator-initiated NIH R01-like grant mechanism that would provide substantial funding (in the range of $200,000 to 400,000 per year) to individual laboratories for multiple years (3-5). This kind of funding has long been the cornerstone of federal biomedical research support, providing investigators with financial resources needed to make significant progress in a reasonable timeframe, while providing a degree of flexibility needed to rapidly respond to new developments in their fields.

3. Many favored an additional mechanism of investigator-initiated funding analogous to the NIH R21 vehicle which encourages higher risk with the promise of greater reward. Such grants support exploration of novel, innovative ideas with little or no preliminary data, essential for RO1 grants. Because of the uncertainties inherent in these proposals, the awards are smaller (in the range of $100,000 to $200,000 per year) and of shorter duration (1 or 2 years), with additional funding contingent upon achieving milestones. These grants promote thinking “outside the box”, with positive preliminary results providing the basis for subsequent R01 funding. Researchers also felt that these kinds of grants provide critically needed opportunities for new investigators to establish themselves, and for established investigators in related areas to enter the stem cell field.

4. Many interviewees supported institution-based multi-investigator grants in which several researchers at one institution, or investigators at several institutions, collaborate on complementary aspects of a particular research problem, usually enabled by specific advanced technical expertise or resources at a particular institution(s). Such “program project” grants aim to create synergies via the shared focus and mingling of expertise. There is a growing emphasis at the federal level on broader, multidisciplinary or interdisciplinary, multi-institutional consortia, often involving cooperative agreements with active involvement of the funding institutes in setting directions. There was strong consensus among the scientists that this type of research cooperation already is essential in the field of stem cell research. Therefore the idea to establish “NYSTEM centers” as consortia organized around particular diseases or biological challenges, with external advisory boards assessing progress and helping to set directions, was a research funding theme that many of the institutions we visited had already considered. This was seen as a better method for sharing of resources and likely to expedite more rapid progress translating programs to the clinic.

5. There was considerable support for individual postdoctoral fellowships or young investigator grants as a mechanism for bringing new talent into the stem cell field. It would be important that the host laboratories be assessed for the training and career supportive environment that they provide. Likewise there was considerable enthusiasm for short -term funding for “sabbaticals” in which investigators could visit another laboratory (inside or outside NYS) to acquire specific training in stem cell science or a field that would benefit particular aspects of stem cell research. In contrast, there was little support for institutional training grants, in which graduate students or postdocs are supported *en masse*, often to work in assigned labs.

6. A smaller percentage of interviewees suggested that NYSTEM might be used to support programs for targeted recruitment of established investigators to the state. One example would be to create well-funded appointments (salaries of $250-400,000 per year, lab support of $500,000 per year, with $1-2 million start-up packages) for recruiting the directors of NYSTEM centers. This approach is consistent with the manner in which major universities and medical centers recruit "stars" who will play major roles in new initiatives. Several of the larger institutions have already set aside considerable funding to achieve these goals. Although this is an advantage of larger institutions, one can envision that cooperative research grants requiring multi-institutional investigators will enable other institutions to benefit from shared expertise and the growing influx of new, more senior investigators.

The role of ESC research in the NYSTEM Agenda.

1. The discussions with stem cell researchers also centered on their impressions of the role that the New York State initiative should have in hESC research. It is clear that this area of research has been constrained by inadequate federal support, and that an important focus of NYSTEM should be to enhance opportunities for hESC studies within appropriate ethical guidelines as established by the Board.

2. Concurrent with this opinion, there was unanimity among these researchers that NYSTEM funding should not be restricted to hESC work, since it is unknown at this time which human stem cell types (embryonic or adult) will be best suited for application to particular diseases. Major new advances are occurring broadly through many different areas of human stem cell research, and therapeutics are likely to arise from unanticipated areas of research. Advances are occurring in development biology, genetics, cell signaling as well as areas of imaging and nanotechnology. The use of animal model systems was also considered essential to allow comparative studies that are needed to move the field forward quickly. It is important to note that researchers working with hESC were among those expressing these opinions about human adult stem cells and animal models. In the words of one established hESC researcher: "it would be a big mistake to limit all the funding to human ES cell work".

3. As outlined in section III, these are early days in the medical application of stem cells. Many researchers stressed that NYSTEM should address the tremendous gaps in basic understanding of stem cells that must be filled to realize their full potential to treat human disease. One investigator drew the analogy with biomedical research in general: "the dynamic created by investing in earlier, more basic studies and encouraging translation toward the clinic is what has brought success and treatments". A counterbalance to this widely held view was the warning expressed by some that NYSTEM should not fund mediocre science just because it involves stem cells, or research in which stem cells were used out of convenience or because they are topical (i.e., fundable), with no intent to address the grand challenges that stand in the way of translation of stem cell research to the clinic.

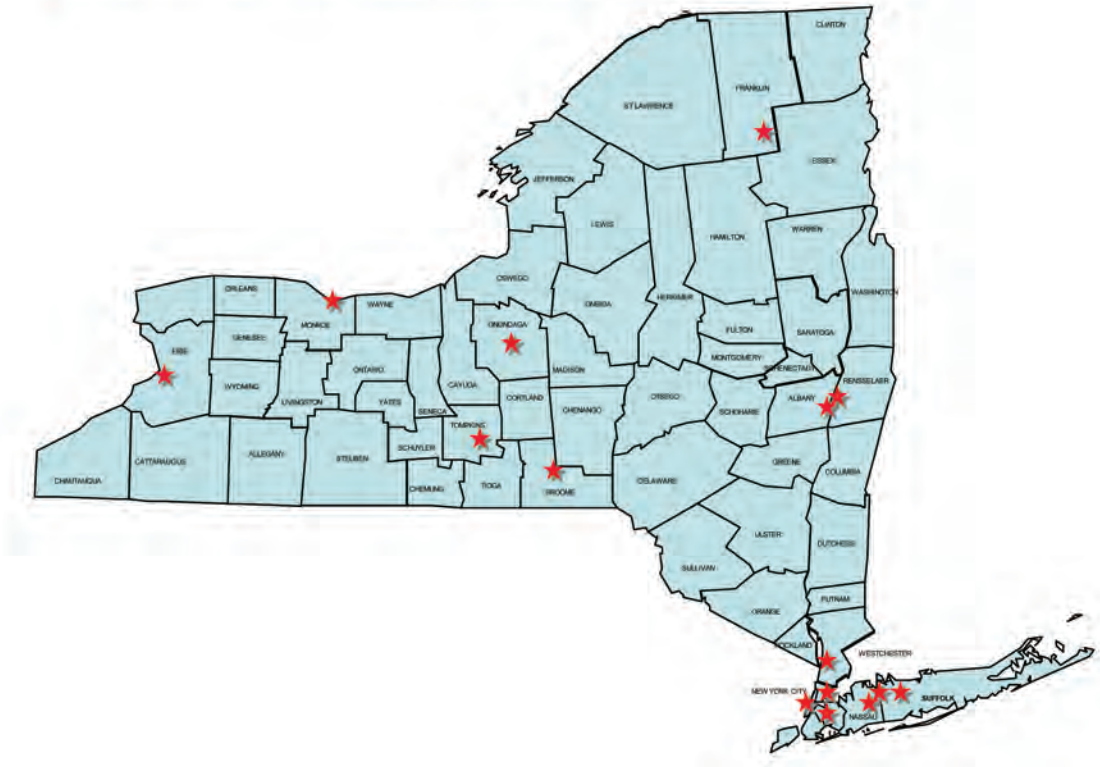
4. Several investigators involved in translational research noted that there is a major gap in available federal funding for pre-clinical studies (moving important findings from animal models to human systems) and Phase I clinical trials for promising therapies. They urged NYSTEM to provide support for this kind of research, which is often considered low priority by basic science-oriented NIH study sections.

5. New York State funding for advanced biotechnology core facilities was identified as important by a number of individuals. In particular, researchers working with non-registry hESC indicated that the duplication of equipment required by current federal funding restrictions was a hardship. They would benefit from lab facilities built with non-federal dollars that generated and characterized these cells, as well as shared facilities with advanced imaging and analytic capabilities. There was a general interest in more advanced scientific core facilities, depending on the particular strengths and weaknesses of the researchers' home institutions. These needs may be met, in part, by a wider dissemination of information about existing state and federally supported centers (see section IV).

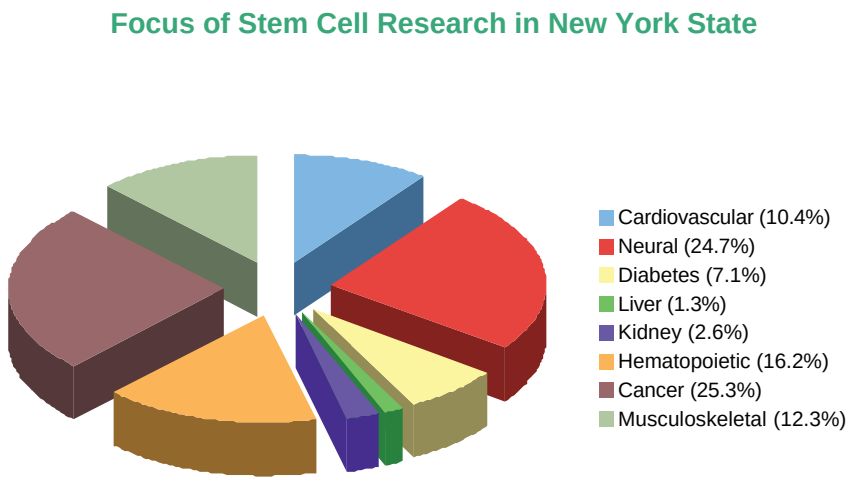
6. The importance of scientific conferences in stimulating advances in a new field like stem cell science was stressed by many. These meetings would help to create a sense of community among NYSTEM-supported investigators, facilitate exchanges of ideas, and help in identifying potential collaborators. We received several ideas of particular note that should be considered.

    a. An annual meeting for New York State stem cell scientists structured along the lines of a Gordon Conference
    b. Gatherings specific for New York State scientists and their outside collaborators within a large national or international meeting.
    c. Mini-symposia that focus on key areas of technology development, new laboratory methods and education.

Figure 1: Institutions visited during this study



Institutions visited
Albany Medical College
Albert Einstein College of Medicine
Brookhaven National Laboratory
Cold Spring Harbor Laboratory
Columbia University College of Physicians and Surgeons
Cornell University
Memorial Sloan-Kettering Cancer Center
Mount Sinai School of Medicine
New York Medical College
New York University School of Medicine
Rensselaer Polytechnic Institute
Roswell Park Cancer Institute
State University of New York, University at Albany
State University of New York, University at Buffalo
State University of New York, Downstate Medical Center
State University of New York, Stony Brook University
State University of New York, Upstate Medical University
The Rockefeller University
Trudeau Institute
University of Rochester School of Medicine & Dentistry
Weill Cornell Medical College



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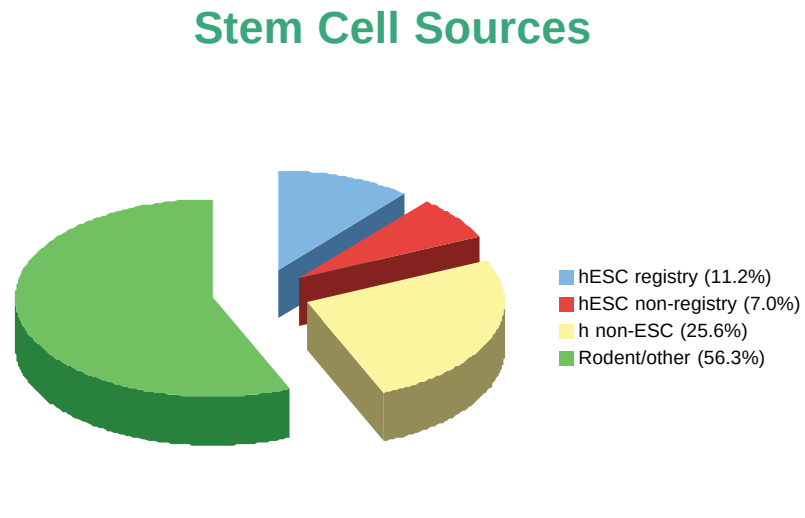

Figure 3:

Table 1: Sources of funding for New York State stem cell researchers

Sources of Funding	
	Number of PIs
NIH	69
Other Federal	16
NYS	17
NGO	40
Industry	10
Other	34

Table 2: Composition of stem cell laboratories

Staffing of Stem Cell Research Laboratories		
	Number of PIs Reporting Staff in Each Category	Total Number of Staff Reported in Each Category
Senior Scientists	52	100
Post-doctoral	88	237
Graduate Students	77	158
Visiting Scientists	24	32
Technical Support	74	129
Other	26	84
Total employment reported		740

Average number of staff per PI is 5.6.

Table 3: Collaborative nature of stem cell research in New York State

Number of PIs Reporting Collaborations in Stem Cell Research	
With scientists at home institution	76
With scientists at another institution	73
Did not report collaborations	26

Table 4: Type of stem cells used in research

Types of Stem Cells Being Investigated	
Type	**Number of PIs Using**
Human stem cells	
Embryonic stem cells	39
Federally approved hESC	24
Non-approved hESC	15
Non-embryonic stem cells	47
Mesenchymal	16
Hematopoietic	8
Epidermal	6
Neuronal	1
Adipose	1
Endothelial	1
Cord blood	6
Other	28
Non-human stem cells	
Embryonic stem cells	55
Non-embryonic stems cells	77

Many investigators are using more than one type of stem cell.

PART II

DIRECTORY OF PRINCIPAL INVESTIGATORS ENGAGED IN STEM CELL RESEARCH IN NEW YORK STATE

Principal Investigators

Principal Investigators

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Professor Abeliovich's lab is studying aspects of dopamine neuron development, function, and survival. This lab uses a simple, in vitro clonal cell culture model system: embryonic stem (ES) cell differentiation. ES cells can mature in vitro through roughly the same series of developmental events as the more complex in vivo process. They are probing molecular regulatory events, ultimately with an intererest in replacement therapies for Parkinson's disease. In a second line of inquiry, Abeliovich is studying dopamine neuron survival in the context of rare genetic mutations that have been linked to familial forms of Parkinsonism.

MacLeod, D., Dowman, J., Hammond, R., Leete, T., Inoue, K., and Abeliovich, A. The familial Parkinsonism gene LRRK2 regulates neurite process morphology. Neuron 52 (2006)., 587-593.

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Martinat, C., Shendelman S., Jonason, A., Leete, T., Beal, M.D., Yang, L., Floss, T. & Abeliovich, A. (2004). Sensitivity to oxidate stress in DJ-1-deficient dopamine neurons: and ES-derived cell model of primary Parkinsonism. PloS Biol 2, e327.

Link Back to PI List

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Dr. Abraham's lab demonstrated that controlling reactive oxygen species (ROS), via the induction of heme oxygenase-1 (HO-1), increased stem cell longevity, as measured in long term bone marrow cultures, and showed that the proper stromal microenvironment is essential for stem cell renewal and differentiation. Abraham's laboratory is conducting clinical trials using stem cells to treat heart failure and stem cells transduced with an IFN gene to treat cronic myelogoneys leukemia and believes that the use of whole bone marrow, not just CD34+ cells may be ideal.

Asija A., Peterson S.J., Stec D.E., Abraham N.G. Targeting Endothelial Cells with Heme Oxygenase-1 Gene Using VE-Cadherin Promoter Attenuates Hyperglycemia-Mediated Cell Injury and Apoptosis. Antioxid Redox Signal. 2007 Sep 20 [Epub]

Nader Abraham , Amit Asija , George Drummond , Stephen Peterson, Heme Oxygenase -1 Gene Therapy: Recent Advances and Therapeutic Applications Curr Gene Ther. 2006 Apr ;7 (2):89-108. Review

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Julio A. Aguirre-Ghiso, Ph.D.
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It is thought that tissue stem cells may be the ones that, when mutated, result in cancer growth. Tumor stem cells (TSCs), like their normal counterparts, are thought to be able to enter a state of quiescence. This property might explain the pause in progression observed in cancer patients deemed cured and recurrence might result from the ability of quiescent TSCs to resume proliferation in secondary sites. Professor Aguirre-Ghiso's research is aimed at understanding the switch between the proliferation and quiescence programs of TSCs. Aguirre-Ghiso believes it is most likely linked to a reversible silencing of a self-renewal program. These studies may be helpful in the design of strategies to maintain TSCs quiescent or eradicate them through specific targeting.

Sharon J. Sequeira, Aparna C. Ranganathan, Alejandro P. Adam, Bibiana V. Iglesias, Eduardo F. Farias and Julio A. Aguirre-Ghiso. Inhibition of Proliferation by PERK Regulates Mammary Acinar Morphogenesis and Tumor Formation. PLoS ONE. (2007) Jul 18;2:e615.

Mio Shinohara, Alexei V. Mikhailov, Julio A. Aguirre-Ghiso and Conly L. Rieder. ERK1/2 activation is required for timely progress through early G2 but it is not directly involved in the G2/M or M/A transitions in mammalian cells. Molecular Biology of the Cell. (2006) Dec 1st. 17: 5227-5240.

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Iannis Aifantis, Ph.D.
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The main focus of Professor Aifantis's laboratory is the study of the mechanisms of hematopoietic stem cell (HSC) differentiation and transformation. The research is focused on three signaling pathways, Notch, Hedgehog (Hh) and SCF ubiquitin ligase signaling cascades, and their role in stem cell biology and function. Notch is a receptor/transcription factor initially identified in Drosophila melanogaster that is remarkably conserved during evolution. The studies have found that Notch not only affects stem cell commitment to the T lymphocyte lineage but also transform the cells to induce fatal T cell acute lymphoblastic leukemia (T-ALL). Aifantis is studying the signaling pathways responsible for the oncogenic transformation of stem cells to identify cancer-initiating stem cells in T-ALL. Dr. Aifantis is using both loss and gain of function animal models to study the role of Hh signaling in HSC differentiation and self-renewal.

Aifantis, Iannis; Vilimas, Tomas; Buonamici, Silvia. Notches, NFkappaBs and the making of T cell leukemia. Cell cycle. 2007; 6: 403.

El Andaloussi, Abdeljabar; Graves, Stephanie; Meng, Fanyong; Mandal, Malay; Mashayekhi, Mona; Aifantis, Iannis. Hedgehog signaling controls thymocyte progenitor homeostasis and differentiation in the thymus. Nature immunology. 2006; 7: 418.

Reschly, Erica J; Spaulding, Christina; Vilimas, Tomas; Graham, W Vallen; Brumbaugh, Rachel L; Aifantis, Iannis; Pear, Warren S; Kee, Barbara L. Notch1 promotes survival of E2A-deficient T cell lymphomas through pre-T cell receptor-dependent and -independent mechanisms. Blood. 2006; 107: 4115.

Link Back to PI List

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Stem cells are characterized by low cycle time, which has allowed us to identify such cells in the mature kidney. These putative stem cells are located mostly outside the renal tubule and are concentrated in the papilla of the kidney, potentially under the urinary epithelium of the papilla. Clonal analysis of these cells shows that they can differentiate into epithelial, neuronal, and other uncharacterized cells. Induction of ischemic renal failure resulted in increased proliferation of these papillary cells. Injection of these cells under the renal capsule led to their incorporation into various tubule segments. It is likely that these stem cells sense a “damage” signal from the cortex resulting in proliferation followed by migration to the site of injury.

Al-Awqati Q, Oliver JA. (2002) Stem cells in the kidney. Kidney Int 61(2):387-95

Oliver, JA, Maarouf O, Cheema, FH, Al-Awqati Q. (2004). The renal papilla is the “niche” for adult kidney stem cells. J. Clin. Invest. Sep: 114: (6): 795-804.

Takito, J., Al-Awqati Q. Conversion of ES cells to Columnar Epithelia by Hensin and Squamous Epithelia by Laminin. J. Cell Biol. 116:1093-1102.

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The focus of Professor Andreadis's research is vascular tissue engineering with bone marrow stem cells, specifically treatment of burns and chronic wounds using bioengineered skin, and tissue engineered blood vessels for treatment of cardiovascular disease. Despite significant progress in design of biomaterials for vascular tissue engineering, the source of cells remains a major problem. Isolation of autologous cells from the patient requires invasive surgery and injures the donor site. Most important, the proliferative capacity and functional properties of vascular smooth muscle cells are limited, especially when they originate from older donors, the population mostly in need of vascular prostheses. Andreadis has developed a novel method for isolating smooth muscle progenitor cells from ovine bone marrow (termed BM-SMPC) using a tissue specific promoter (alpha-actin promoter) and fluorescence activated cell sorting.

S.T. Andreadis (2004) Gene transfer to epidermal stem cells: implications for tissue engineering. Expert Opinion on Biological Therapy 4(6): 1-18.

D.J. Geer, D.D. Swartz and S.T. Andreadis (2004) An in vivo model of wound healing based on transplanted tissue engineered skin. Tissue Engr. 10(7-8): 28-37

D.J. Geer and S.T. Andreadis (2003) A novel role of fibrin in epidermal healing: plasminogen-mediated migration and selective detachment of differentiated keratinocytes .J. Invest. Dermatol. 121(5): 1210-1216.

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Stelios T. Andreadis, Ph.D.
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The focus of Professor Andreadis's research is vascular tissue engineering with bone marrow stem cells, specifically treatment of burns and chronic wounds using bioengineered skin, and tissue engineered blood vessels for treatment of cardiovascular disease. Despite significant progress in design of biomaterials for vascular tissue engineering, the source of cells remains a major problem. Isolation of autologous cells from the patient requires invasive surgery and injures the donor site. Most important, the proliferative capacity and functional properties of vascular smooth muscle cells are limited, especially when they originate from older donors, the population mostly in need of vascular prostheses. Andreadis has developed a novel method for isolating smooth muscle progenitor cells from ovine bone marrow (termed BM-SMPC) using a tissue specific promoter (alpha-actin promoter) and fluorescence activated cell sorting.

S.T. Andreadis (2004) Gene transfer to epidermal stem cells: implications for tissue engineering. Expert Opinion on Biological Therapy 4(6): 1-18.

D.J. Geer, D.D. Swartz and S.T. Andreadis (2004) An in vivo model of wound healing based on transplanted tissue engineered skin. Tissue Engr. 10(7-8): 28-37

D.J. Geer and S.T. Andreadis (2003) A novel role of fibrin in epidermal healing: plasminogen-mediated migration and selective detachment of differentiated keratinocytes .J. Invest. Dermatol. 121(5): 1210-1216.

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Dr. Anversa's lab specializes in studying cardiovascular disease and focuses especially on the "Aging of the Heart" and related physiology. As a cardiovascular researcher Anversa reported that the heart contains stem cells that have the ability to regenerate heart muscle, or create new muscle tissue and blood vessels to replace damaged or old ones. Anversa has isolated these rare cells in the hearts of rats and injected the cells into the hearts of other rats that had suffered a heart attack. The team discovered that seventy percent of the damaged heart muscle was repaired. Anversa and colleagues are planning human trials of a novel therapy that could change the way the heart disease is treated.

Linke A, Muller P, Nurzynska D, Casara C. Torealla D, Nascimbene A, Castaldo C, Cascapera S, Bohm M, Quaini F, Urbanek K, Leri A, Hintze TH, Kajstura J, Anversa P. Stem cells in the dog heart are self-renewing, clonogenic, multipotent and regenerate infarcted myocardium improving cardiac function. Proc. Natol, Acad Sci. USA 102 (25):8966-8971, 2005.

Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E, Urbanek K, Leri A, Kajstura J, Nadal-Ginard B, Anversa P. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 114:1-20, 2003.

Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, Kajstura J, Leri A, Anversa P.Chimerism of the transplanted heart. N England J Med 346:5-15, 2002.

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Margaret H. Baron, M.D., Ph.D.
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Professor, Gene And Cell Medicine
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Professor Baron's laboratory is interested in research related to: development of the hematopoietic and vascular systems of the mouse embryo; regulation of stem cell proliferation, survival, and differentiation; gene regulation during development; development and differentiation of the primitive and definitive endodermal lineages; modulation of postnatal and adult hematopoietic and vascular development; and angiogenesis.

Mohn D, Chen S, Dias D, Weinstein D, Dyer MA, Sahr K, Ducker CE, Zahradka KE, Keller G, Zaret KS, Gudas L, Baron MH. The mouse Mix gene is activated early during differentiation of ES and F9 stem cells and induces endoderm in frog embryos. Developmental Dynamics 2003; 226:446-459.

Baron MH. Molecular Regulation of Embryonic Hematopoiesis and Vascular Development: A Novel Pathway. J Hematotherapy & Stem Cell Research 2001; 10:587-594.

Baron MH. Induction of Embryonic Hematopoietic and Endothelial Stem/Progenitor Cells by Hedgehog-Mediated Signals. Differentiation 2001; 69:175-185.

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Multiple Myeloma (MM), the second most common bone marrow cancer, is prevalent in Brooklyn, and remains incurable. Dr. Batuman's laboratory recently showed that increased tumor neovascularization mediated by endothelial progenitor cells (EPCs) powerfully enhances tumor progression in MM. More recently, genome-wide comparisons of EPCs and tumor cells show that these cells are genetically identical, and indicate that both cell types originate from a common MM stem cell clone. Utilizing leading-edge genomic and bioinformatic approaches to characterize MM stem cells, Batuman aims to identify novel and more effective means to suppress tumor progression, prolong survival, and ultimately achieve a cure for this disease.

Braunstein M, Özçelik T, Bagıslar S, Smith ELP, Akyerli CB, and Batuman OA. Endothelial progenitor cells display clonal restriction in multiple myeloma. BMC Cancer 6:161-170, 2006.

Kahn DM, Braunstein M, Smith ELP, Klueppelberg U, Özçelik T, and Batuman O. Endothelial progenitor cell clonality and response to treatment in multiple myeloma. J Clin Oncol 24:17546A, 2006.

Zhang H, Vakil V, Smith ELP, Chen L, Braunstein M, Maroney J, Dai K, Berenson JR, Hussain M, Özçelik T, Norin AJ, Akman HO, Klueppelberg U, and Batuman OA. Circulating endothelial progenitor cells in multiple myeloma: implications and significance. Blood 105:3286-3294, 2005.

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Robert Benezra, Ph.D.
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Professor Benezra's lab is analyzing the role of the Id proteins in stem cell self-renewal and the maintenance of pluripotency. The Id proteins inhibit the activity of transcription factors thereby controlling cell fate decisions during embryogenesis and adult life. Embryonic, neural and hematopoietic stem cells have all been shown to require Id proteins to block premature commitment to a more differentiated cell state. The downstream targets of Id activity vary depending on the stem cell in question. Benezra's current efforts focus on analyzing the effects of stem cell depletion on normal adult physiology in cancer.

Jankovic, V., Ciarrocchi, A., Boccuni, P., Deblasio, T., Benezra R., and Nimer, S. (2007) Id1 restrains myeloid commitment, maintaining the self-renewal capacity of hematopoietic stem cells. PNAS 104: 1260-1265.

Fraidenraich D, Stillwell E, Romero E, Wilkes D, Manova K, Basson CT, Benezra R. (2004) Rescue of cardiac defects in id knockout embryos by injection of embryonic stem cells. Science. 8;306(5694):247-52

Benezra, R. (2001) Role of Id proteins in embryonic and tumor angiogenesis. Trends in Cardiovascular Med. 6:237-41.

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Kristin P. Bennett , Ph.D.
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Professor Bennett is collaborating with colleagues to understand, characterize and predict stem cells and the stem cell niche using powerful machine learning and data mining methods applied to genomic, proteomic, kineomic, mass-spectometry traditional assay and image data. Bennett has a particular interest in osteogenic differentiation. The team's analysis of proteomics data introduced the concept of gene focus as a basis of stem cell differentiation.

Klees RF, Salasznyk RM, Vanderberg S, Bennett K, Plopper GE. Laminin-5 activates extracellular matrix production and osteogenic gene focusin in human mesenchymal stem cells. Matrix Biol. 2007 Mar; 26(2):106-14.

Salasznyk, RM, Westcott AM, Klees RF, Ward DF, Xiang Z, Vanderberg, Bennett K, Plopper GE. Comparing the protein expression profiles of human mesenchymal stem cells and human osteoblasts using gene ontologies. Stem Cells and Development. 2005, 14(4): 354-366.

Salaszynyk, R.M., R.F. Klees, S. Vanderberg, K. Bennett and GE. Plopper. Focusing of gene expression as the basis of stem cell differentiation. Stem Cells Dev. 2005 Dec; 14 (6): 608-20

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Muscular dystrophies are clinically and molecularly heterogenous diseases characterized by progressive wasting of skeletal muscle and lack of mobility. Dr. Bhagavati's lab is interested in developing cell based therapies for these and other muscle disorders. Bhagavati is focused on identifying and isolating mouse skeletal muscle specific stem/progenitor cells by targeting reporter genes by homologous recombination to the earliest genes known to be expressed in developing skeletal muscle progenitors, such as Pax3, Pax7 and Myf 5. The lab is working to generate myogenic stem cells, from developing ES cells, by cell-cell fusion studies. Myogenic stem cells isolated in this way will be analyzed for their in vitro proliferative and differentiation characteristics and potentially promising cell populations will be tested for their capacity to generate skeletal muscle after transplantation into dystrophic mice.

S.Bhagavati & Weimin Xu. Generation of skeletal muscle from transplanted embryonic stem cells in dystrophic mice. Biochem and Biophysical Res Comm, 333, July 29, 644-649, 2005

S.Bhagavati & Weimin Xu. Isolation and enrichment of skeletal muscle progenitor cells from mouse bone marrow. Biochemical & Biophys Res Comm. 318, 119-124, 2004.

Link Back to PI List

Nina Bhardwaj, M.D., Ph.D.
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Dr. Bhardwaj's laboratory is interested in understanding the functional role and immunogenicity of antigens that are expressed in cancer cells, including cancer stem cells. NY-ESO-1 is a protein that is expressed only in germ line tissues or in cancer cells, including cancers of the skin (melanoma), lung, ovary and breast. Expression of this protein occurs in late stage disease and is often associated with a strong immune response, however, there is no information on its function, or its regulated expression in dedifferentiated tissues. As expression may be limited to "cancer stem cells", removal of these cells through therapeutic immune approaches now being tested in the clinic may control tumor growth. Another project focuses on the differentiation of cellular immune adjuvants (dendritic cells) through manipulation of stem cells (CD34+ cells) to improve vaccination against cancer antigens.

Velazques E.F., Jungbluth A.A., Yancovitz M, Gnjatic S, Adams S., O'Neill D., Zavilevish K, Albukh T., Christos P, Mazumdar M, Pavlick A, Polsky D, Shapiro R, Berman R, Spira J, Busam K, Osman I Bhardwaj, N. Expression of the Cancer Testis (CT) Antigen NY-ESO-1 in Primary and Metastatic Malignant Melanoma Correlation with Serology and Prognostic Factors. Cancer Immun. 2007; 7:11.

O'Neill, D and Bhardwaj N. Generation of autologous peptide and protein pulsed dendritic cells for patient specific immunotherapy. Methods in Molecular Medicine. 2005: 109: 97-112.

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John Boockvar, M.D.
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Dr. Boockvar directs Cornell's Neurosurgical Laboratory for Translational Stem Cell Research which is working to advance stem cell research to aid patients with neurosurgical disorders. Dr. Boockvar's laboratory interests focus on neural stem cells using the epidermal growth factor receptor (EGFR). The lab is investigating the link between brain tumor formation and adut human central nervous system stem cells. They are interested in understanding the differential sensitivity of patients with glioma to EGFR inhibitors like erlotinib. By manipulating normal and tumor derived stem cell EGFR signaling, Boockvar studies neural stem cell migration and invasion as this has relevance to glioma and to intracerebral transplantation paradigms in other disorders such as stroke and spinal cord injury.

Ayuso, A., Graham, C., Greenfield JP., Boockvar, JA. (2006). The duality of EGFR signaling and neural stem cell phenotype: Cell enhancer or cell transformer? Current Stem Cell Research and Therapy, 1, 231-238.

Boockvar JA, Kapitonov D, Schouten J, Counelis GJ, Kapoor G, Bogler O, Snyder E, McIntosh T, O?Rourke DM. Constitutive (2003) EGFR signaling confers a motile phenotype to neural stem cells. Molecular and Cellular Neuroscience 24, (4): 1116-1130.

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Cancer stem cells (CSCs) determine all major biological features of the tumor, including its response to treatment. Professor Botchkina's research is focused on the identification, enrichment and characterization of CSCs of different cancer types. The team is searching for drug molecules with the potential to kill CSCs and to develop new drugs which can provide a long-term cure for cancer cytotoxic effects including high intravenous dozes of ascorbate, ICB&DD second generation taxoids, and nitroaspirin compounds. The Botchkina Lab has developed an in vitro model for CSC-targeted drug testing.

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Eric Bouhassira, Ph.D.
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The goal of Professor Bouhassira's research is to learn how to produce large amounts of therapeutically useful cells with an adult phenotype by forced differentiation of human embryonic stem cells. Bouhassira's lab has chosen the erythroid lineage as a model because it has two unique advantages as a translational target: red cells don't express the HLA genes, eliminating most of the histocompatibility issues, and red cells are enucleated and therefore cannot cause cancer. Industrial production of red cells would be of great significance because while current supplies are very safe, they remain vulnerable to new pathogens, and because local shortages occur in many part of the world.

Olivier EN, Rybicki AC, Bouhassira EE (2006). Differentiation of Human Embryonic Stem Cells Into Bipotent Mesenchymal Stem Cells. Stem Cells. 2006 Apr 27 [Epub ahead of print]

Olivier EN, Qiu C, Velho M, Hirsch RE, Bouhassira EE (2006). Large scale production of embryonic red blood cells from human embryonic stem cells. Exp Hematol. 2006 Dec; 34 (12):1635-42.

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Peter R. Brink, Ph.D.
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Stem cells represent a novel approach to organ repair. Critical to this delivery system is the ability of these cells to integrate into tissues via gap junctions. Brink's lab demonstrated that human mesenchymal stem cells can deliver a pacemaker gene creating a biological pacemaker in the canine heart by forming gap junctions. Their research efforts, which include electrical and mechanical repair of the heart as well as cancer therapy , focus on this cell-to-cell communication. Besides mesenchymal stem cells, Brink is studying cardiac stem cells, and through recent collaborations, amniotic stem cells and human embryonic stem cells as well.

Plotnikov AN, Shlapakova I, Szabolcs MJ, Danilo P Jr, Lorell BH, Potapova IA, Lu Z, Rosen AB, Mathias RT, Brink PR, Robinson RB, Cohen IS, Rosen MR. Xenografted adult human mesenchymal stem cells provide a platform for sustained biological pacemaker function in canine heart. Circulation. 2007 Aug 14;116(7):706-13. Epub 2007 Jul 23.

Potapova IA, Gaudette GR, Brink PR, Robinson RB, Rosen MR, Cohen IS, Doronin SV Mesenchymal stem cells support migration, extracellular matrix invasion, proliferation, and survival of endothelial cells in vitro. Stem Cells. 2007 Jul;25(7):1761-8. Epub 2007 Mar 29.

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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 the study of early human embryonic development.

James, D., Noggle, S.A., Swigut, T., and Brivanlou, A.H. (2006). Contribution of human embryonic stem cells to mouse blastocysts. Developmental Biology, 295(1):90-102.

Sato, N., Meijer, L., Skaltsounis, L., Greengard, P., Brivanlou, A.H. (2004). Maintenance of Stemness in Embryonic Stem Cells through Activation of Wnt Signaling by a Novel GSK-3 Inhibitor, BIO. Nature Medicine 10, 55-63.

Brivanlou, A.H., Gage, F.H., Jaenisch, R., Jessell, T., Melton, D., Rossant, J. (2003). Cellular and Molecular Standards for the Study of Human Embryonic Stem Cells (hESCs). Science 300, 913-916.

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John B. Brunski, Ph.D.
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There is a long history of interest in biomechanical conditions and their role in cell differentiation. Since the skeleton is a structural, load-bearing system, Dr. Brunski is interested in how the tissues that make up the skeleton are capable of sensing mechanical stimuli in their local environment, interpreting these stimuli, and responding in a biologically appropriate fashion. In particular, Brunski and colleagues have been examining how skeletal progenitor cells respond to mechanical stimuli in a clinically-relevant model of bone regeneration around specially-designed implants, where in vivo strain fields can be experimentally controlled.

Leucht P, Kim JB, Wazen R, Nanci A, Brunski J, Helms JA. Effect of mechanical stimuli on skeletal regeneration around implants. Bone 2007 Apr;40(4):919-930.

Leucht P, Kim JB, Currey J, Brunski J, Helms JA. (2007) FAK-mediated mechanotransduction in skeletal regeneration. PLoS One. April 2007, Issue 4, e390.

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The Cairo laboratory is engaged in investigations of dendritic cell biology, T-cell regulatory cell immunology, NK cell therapeutics and genomics of hematological malignancies. The Cairo clinical research team leads investigations in reduced intensity allogeneic stem cell transplantation, phase I therapeutics and chemoimmunotherapy of leukemias and lymphomas. Dr. Cairo has developed an experimental procedure that expands the use of umbilical cord blood, a rich source of stem and immune cells, in transplantation for childhood leukemia and solid tumor patients. This procedure would enable children who relapse or have residual disease to undergo additional cord blood cell immunotherapy.

Ayello, J., van de Ven, C., Fortino, W., Wade-Harris, C., Satwani, P., Baxi, L., Simpson, L.L., Sanger, W., Pickering, D., Kurtzberg, J., and Cairo, M.S. Characterization of cord blood natural killer and lymphokine activated killer lymphocytes following ex vivo cellular engineering. Biology of Blood and Marrow Transplantation 2006: 12:608-622.

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Recent studies demonstrate that the microenvironment or niche regulates stem cell behavior. Since niche components are potential targets for therapies aimed at controlling stem cell behavior, definition of the niche is a novel strategy to achieve stem cell manipulation. Focusing on hematopoietic stem cells in the bone marrow, Professor Calvi has identified osteoblasts as hematopoietic stem cell regulators. Dr. Calvi's research now seeks to define the molecular signals between osteoblasts and hematopoietic stem cells, and to manipulate those signals to expand stem cells. To this end, the lab has defined in vivo systems in which osteoblastic signals expand specific subsets of stem cells, improving survival after bone marrow injury

Calvi LM, Adams GB, Weibrecht K, Weber JM, Olson DP, Knight MC, Martin RP, Schipain E, Diviet P, Bringhurst FR, Milner LA, Kronenberg HM, Scadden DT. (2003) Osteoblastic cells regulate the hematopoietic stem cell niche. Nature 425:841-846.

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The human retina does not regenerate nerve cells that are lost due to trauma or diseases such as macular degeneration and diabetes. This lack of cellular regeneration contributes directly to the persistent visual deficits and blindness associated with such disorders. The retinas of some animals however, including fish, contain stem cells that permit substantial cellular repair. Professor Cameron's lab is actively investigating the stem cells and molecular mechanisms that enable the adult fish retina to regenerate nerve cells. The ultimate goal is to harness these biological mechanisms to repair damaged human retina and other parts of the central nervous system.

Yuro P, Cameron DA, (2005). Responses of muller glia to retinal injury in adult zebrafish. Vision Research 45:991-1002.

Tyler MJ, Carney LH, Cameron DA (2005) Control of cellular pattern formation in the vertebrate inner retina by homotypic regulation of cell fate decisions. Journal of Neurosience 25:4565-4576.

Cameron DA, Middleton FA, Gentile, K, Yurco P (2005). Gene expression profile of intact and regenerating zebrafish retina. Molecular Vision 11:775-791.

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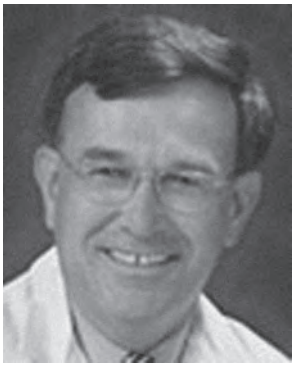

John Canty, M.D.
Albert & Elizabeth Rekate Chair in Cardiovascular Disease
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Dr. Canty heads the University's Center for Research in Cardiovascular Medicine. The center conducts translational research in patients with coronary artery disease as well as in animal models of chronic ischemia heart disease. The team is doing pioneering work investigating the mechanisms involved in sudden cardiac death, a condition caused by a catastrophic disruption in heart rhythm resulting in ventricular fibrillation. Other areas of investigational strength include the development of gene transfer and adult stem cell therapy treatments for ischemic heart disease and the implementation of high-throughput molecular biological approaches to identify mechanisms of acquired cardiovascular disease.

Suzuki, G. Lee, T.C. Fallavollita, J.A. Canty, J.M., Jr. Adenoviral gene transfer of FGF-5 to hibernating myocardium improves function and stimulates myocytes to hypertrophy and reenter the cell cycle. Circulation Research; 2005; 96; 767-775.

Gangasani, A. Sidhu, S. Fallavollita, J.A. Korotchkina, L. G. Suzuki, G. Patel, M.S. Canty, J.M., Jr. Cardiac pyruvate dehydrogenase complex (PDC) deficiency in mice leads to myocardial hypertrophy and cardiomyopathy. Circulation; 2005; 112(II); II-21-II-22.

Luisi AJ Canty, J.M., Jr. deKemp, R.A. Haka, M.S. Toorongian, S.A. Fallavollita, J.A.; Patients with ischemic cardiomyopathy eligible for ICD therapy demonstrate extensive sympathetic denervation out of proportion to previous infarction.. Circulation; 2005; 112; 472-472.

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Pluripotent embryonal carcinoma (EC) cells derived from adult male germ cell tumors (GCTs) represent a unique resource to molecularly define lineage differentiation pathways and identify novel genes. EC cell lines share pluripotentiality with embryonic stem (ES) cells. Furthermore, both ES cells in culture and many GCTs show characteristic gains 12p and/or 17q which aid in maintenance of pluripotency. Being of unlimited proliferation potential, EC cells are an excellent alternative resource to study regulation of self-renewal and pluripotency. Professor Chaganti's program is directed at understanding the role of stem cells in malignancy and regulation of self-renewal and pluripotency.

Chadalavada, R.S., Houldsworth, J., Olshen, A.B., Bosl, G.J., Studer, L., Chaganti, R.S.K. Transcriptional program of bone morphogenetic protein-2-induced epithelial and smooth muscle differentiation of pluripotent embryonal carcinoma cells. 2005. Funct. Integr. Genomics. 5: 59-69.

Korkola, J.E., Houldsworth, J., Chadalavada, R., Olshen A.B., Dobrzynski, D., Reuter, V.E., Bosl, G.J., and Chaganti, R.S.K. Down-regulation of stem cell genes, including those in a 200kb gene cluster at 12p13.31 is associated with in vivo differentiation of human male germ cell tumors. 2006. Cancer Res. 66:820-827.

Chadalavada, R.S.V., Korkola, J.E., Houldsworth, J., Olshen, A.B., Bosl, G.J., Studer, L., Chaganti, R.S.K. Constitutive gene expression predisposes morphogen-mediated cell fate responses of NT2/D1 and 27X-1 embryonal carcinoma. 2007. Stem Cells 25: 771-8,

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Dr. Chaudhry's research focuses on cardiac regeneration, the role of cell cycle regulation of cardiomyocytes and endogenous cardiac progenitor cells. Chaudhry's lab has found that cyclin A2 is a critical gene mediating cardiomyocyte mitoses even after birth when expressed in the heart of transgenic mice. After a myocardial infarction (MI) is induced these mice are able to repair their hearts with significantly restored cardiac function. There is molecular and cellular evidence of "de novo" cardiogenesis. The formation of new cardiomyocytes appears to involve side-population (SP) stem cells which may be differentiating into cardiomyocytes after injury is induced. As a translational strategy, the lab has delivered cyclin A2 cDNA in an adenoviral vector to adult, genetically naive rat hearts after MI and observed significant restoration of cardiac function with evidence of cardiomyocyte proliferation. Present and future goals include investigations of the mechanisms of proliferation observed in these two, distinct small animal models.

Cheng RK, Asai T. Tang, Dashoush Nh, Kara RJ, Costa KD, Naka Y, Wu EX, Wolgemuth DJ, Chaudhry HW. Cyclin A2 Promotes Cardia Regeneration after Myocardial Infarction and Prevents Heart Failure. Circulation Research, 2007 Jun 22; 100 (12): 1741-8.

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Moon I. Cho, Ph.D.
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Periodontitis is a chronic inflammatory disease that damages the periodontal tissues and thus is the main cause for the loss of teeth. Professor Cho's research has focused on development of an effective, reliable and reproducible stem cell therapy capable of achieving periodontal regeneration. The Cho lab proposes to isolate, expand in vitro and transplant autologous hair follicle bulge stem cells, as they have an origin from neural crest like periodontal tissue-forming cells and the ability to differentiate into fibroblasts. Further, they are abundant and easily accessible by a minimally invasive surgery. Cho anticipates this adult stem cell therapy will ensure immediate repopulation of fibroblasts and thus successful periodontal regeneration.

Steele-Perkins G, Butz KG, Lyons GE, Zeichner-David M, Kim HJ, Cho MI, Gronostajski RM. Essential role for NFI-C/CTF transcription-replication factor in tooth root development. Mol Cell Biol. 23:1075-84, 2003.

Dey, R., Son, H.-H., and Cho, M.I. Isolation and partial sequencing of potentially odontoblast-specific/enriched rat cDNA clones obtained by suppression subtractive hybridization. Archs. Oral Biol. 46:249-260, 2001.

Chien, H.-H., Lin, W.-L. and Cho, M.I. Down-regulation of osteoblastic cell differentiation by epidermal growth factor receptor. Calcif. Tiss. Int. 67:141-150, 2000.

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Unlimited potency makes stem cell therapy an exciting area of medical research, yet their properties in vitro and especially in vivo have not been comprehensively defined. Using a novel direct-writing method at RPI, we will fabricate combinatorial libraries of scaffold, biomolecule, and stem cell constructs with single-cell spatial resolution. These tissue-constructs, with varying composition and geometry, will define stem cell properties, leading to custom-designed tissue replacements built with autologous cells. Professor Chrisey's laboratory is working to characterize effects of physical/biochemical stimuli on stem cells, and how these factors direct their differentiation and development and build stem cells into improved prototype tissue replacement constructs.

D.B. Chrisey, A. Pique, R.A. McGill, J.S. Horwitz, B.R. Ringeisen, D.M. Bubb, P.K Wu. Laser Deposition of Polymer and Biomaterial Films, Chemical Review 103 (2), (2003) 553-576.

B.R. Ringeisen, H. Kim, J.A. Barron, D.B. Krizman, D.B. Chrisey, S. Jackman, R.C.Y. Auyeung, and B.J. Spargo, Laser Printing of Pluripotent Embryonal Carcinoma Cells, Tissue Engineering 10, (2004) 483-491.

T.M. Patz, R. Modi, R. Narayan, and D.B. Chrisey. Two-Dimensional Differential Adherence and Myoblast Alignment Driven Fabrication of Engineered C2C12 Muscle Organoids, Materials Science & Engineering B: Solid-State Materials for Advanced Technology (2005) 242-247.

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Angela Christiano, Ph.D.
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Dr. Christiano has initiated a comprehensive program of cellular transplantation and reprogramming that holds great promise toward advancing the feasibility of successfully treating a broad spectrum of disorders of the skin, as well as providing a source of easily accessible multipotent adult stem cells to regenerate other organs. Her lab will exploit the inductive properties of adult hair follicle dermal cells combined with 3D culture and tissue engineered scaffolds to induce new hair follicles. The lab will use adult hair follicle epidermal stem cells and hair follicle dermal stem cells to create a skin equivalent that leads to scarless wound healing.

O'Shaughnessy, R.F.L., Yeo, W., Gautier, J., Jahoda, C.A.B., Christiano, A.M. The WNT signaling modulator, Wise, is expressed in an interaction-dependent manner during hair follicle cycling. J. Invest. Dermatol. 2004;123:613-621
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Bazzi, H., Kljuic, A., Christiano, A.M., Panteleyev, A.A. Intragenic deletion in the Desmoglein 4 gene underlies the skin phenotype in the Iffa Credo "hairless" rat. Differentiation 2004; 72:450-464.

Bazzi H., Getz A., Mahoney M.G., Ishida-Yamamoto A., Langbein L., Wahl J.K., Christiano A.M. Desmoglein 4 is expressed in highly differentiated keratinocytes and trichocytes in human epidermis and hair follicle. Differentiation 2006; 74:129-140.

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The focus of Professor Cimato's research is to identify novel therapies for the treatment of cardiovascular disease. Cimato has identified cardiovascular progenitors as they diverge from the mesoderm in murine and human embryonic stem cells (ESCs). Future work will determine the mechanisms that control differentiation and growth of these cells to vascular and cardiac cell fates, and will determine if transplantation of human ESC derived cardiovascular precursors or endothelium can effectively revascularize ischemic myocardium. A second, related area of interest is adult, autologous endothelial progenitors. Recent work has shown that peripheral blood cells identified by expression of VEGFR2, CD 133 and CD34 but NOT CD45 identifies endothelial progenitors from venous blood. The research goal is to determine if these cells can be obtained and expanded from pigs with chronic myocardial ischemia and dysfunctional myocardium, and effectively used as autologous therapy.

Cimato, T.R., Jessup, M. (2002) Recipient selection in cardiac transplantation: contraindications and risk factors for mortality. J Heart Lung Transplant. Nov 21 (11):1161-1173.

Cimato TR, Tang J, Xu Y, Guarnaccia C, Herschman HR, Pongor S, Aletta JM. (2002) Nerve growth factor-mediated increases in protein methylation occur predominantly at type I arginine methylation sites and involve protein arginine methyltransferase 1. J Neurosci Res. Feb 15;67(4):435-42.

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Dr. Clarkson's laboratory is continuing to dissect the intracellular signaling pathways that are altered by BCR/ABL fusion genes, which are the primary and probably the sole initial genetic abnormalities responsible for the clinical manifestations of chronic myelogenous leukemia (CML), Ph+ALL (acute lymphoblastic leukemia), and chronic neutrophilic leukemia. CML is a clonal disease initiated in an early hematopoietic progenitor or stem cell that is primarily characterized by a highly consistent reciprocal translocation, t (9;22), resulting in a chimeric BCR/ABL fusion gene that is probably responsible for the manifestations of the initial phase of the disease. BCR/ABL fusion proteins have constitutively elevated protein tyrosine kinase activity; and the degree of elevation is directly correlated with the proteins' transforming abilities both in experimental systems and in the severity of clinical manifestations.

Strife A, Wisniewski D, Liu C, Lambek CL, Darzynkiewicz Z, Silver RT, and Clarkson B. Direct evidence that Bcr-Abl tyrosine kinase activity disrupts normal synergistic interactions between kit ligand and cytokines in primary primitive progenitor cells. Mol Cancer Res. 2003;1:176-185.

Clarkson B, Strife A, Wisniewski D, Lambek CL, Liu C. Chronic myelogenous leukemia as a paradigm of early cancer and possible curative strategies. Leukemia. 2003;17:1211-1262.

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Retinoblastoma is a childhood eye cancer that forms due to the mutation of the RB1 gene and loss of Rb protein. Cells that express a stem cell marker called Nestin were detected in retinoblastoma tumors. Dr. Cobrinik's lab posited that these Nestin+ cells might form a stem cell niche in the tumors that play a role in retinoblastoma tumorigenesis. The lab has identified the stem cell-like cells in retinoblastomas as astrocytes and Müller glia and shown that these cells promote tumor cell growth and survival. Because retinoblastoma cells resemble neoplastic cone precursors, the lab is examining whether the normal interaction of glia with cone cells is co-opted to promote retinoblastoma tumorigenesis. This work will define interactions of stem cell-like cells and neoplastic tumor cells in retinoblastoma tumorigenesis.

Cobrinik D, Francis RO, Abramson DH, Lee TC. (2006) Rb induces a proliferative arrest and curtails Brn-2 expression in retinoblastoma cells. Mol Cancer. 12;5:72.

Lee TC, Almeida D, Claros N, Abramson DH, Cobrinik D. (2006).Cell cycle-specific and cell type-specific Invest Ophthalmol Vis Sci. Dec;47(12):5590-8.

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Dr. Cohen is investigating electrical and mechanical regeneration of cardiac function. 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 mechanical function in the heart.

Potapova I.A., Gaudette G.R., Brink P.R., Robinson R.B., Rosen M.R., Cohen I.S., Doronin S.V. Mesenchymal stem cells support migration, extracellular matrix invasion, proliferation, and survival of endothelial cells in vitro. Stem Cells. 2007 Jul;25(7):1761-8. Epub 2007 Mar 29.

Gaudette G.R, Cohen I.S. Cardiac regeneration: materials can improve the passive properties of myocardium, but cell therapy must do more. Circulation. 2006 Dec 12;114(24):2575-7.

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Barry S. Coller, M.D.
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Dr. Coller's laboratory is developing Platelet Therapy using ES Cell-Derived Megakaryocytes. The ability to generate multiple cell types from embryonic stem (ES) cells in culture offers an unprecedented opportunity to generate an unlimited supply of cells for transplantation for the treatment of a broad range of diseases. Patients treated with chemotherapy or radiation therapy commonly require platelet transfusions and some patients eventually develop reactions to transfused platelets. Thus, a source of platelets derived from embryonic stem cells would be very valuable, especially if they could be prepared with the same tissue type as the recipient. Dr. Collier aims to optimize the differentiation of embryonic stem cells into platelets and to develop animal models to assess their function.

Mitchell, W.B., Li, J., French, D.L., Coller, B.S. aIIbb3 biogenesis is controlled by engagement of aIIb in the calnexin cycle via N15-linked glycan. Blood, 107:2713-2719, 2006.

Mitchell, W.B., Li, J., Murcia, M., Valentin, N., Newman, P.J., Coller, B.S. Mapping early conformational changes in aIIbb3 during biogenesis reveals a potential mechanism for aIIbb3 adopting its bent conformation. Blood 109:3725-3732, 2007.

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Dr. Coonrod is investigating the role of stored mammalian maternal egg factors in reprogramming the embryonic genome. In particular, the Coonrod lab is interested in understanding how maternal transcripts are translated in the early embryo and then orchestrate nuclear reprogramming events shortly after fertilization. This work has a direct link to stem cell biology, given that the totipotent zygote gives rise to pluripotent stem cells and that donor oocytes will be utilized to reprogram patients somatic cells to generate functional stem cells.

Vitale,A.M., Calvert, M,E., Mallavarapu, M., Yurttas, P., Perlin , J, Herr, J., Coonrod, S.A. (2007) Proteomic profiling of murine oocyte maturation. Mol Reprod Dev. 74(5):608-16.

Liu M., Oh A., Calarco P., Yamada M., Coonrod, S.A., Talbot, P. (2005) Peptidylarginine deiminase (PAD) is a mouse cortical granule protein that plays a role in preimplantation embryonic development. Reprod. Biol. Endocrinol. 3(1):42

Wright, P.,W., Bolling, L.C., Calvert, M.E., Sarmento. O., Berkeley, E., Shea M., Hao Z, Jayes, F., Bush, L., Shetty ,J., Shore, A., Reddi, P., Tung, K, Samy, E, Allietta, M, Sherman, N., Herr J., and Coonrod SA (2003) ePAD, an oocyte and early embryo-abundant peptidylarginine deiminase-like protein which localizes to egg cytoplasmic sheets. Dev Biol. 256:74-89.

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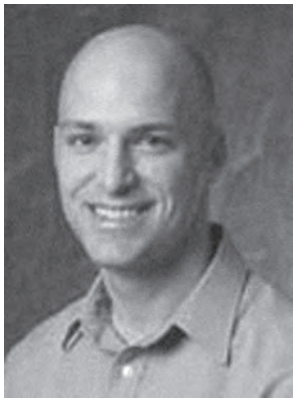

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Using a novel direct-writing method at RPI, Dr. Corr is fabricating combinatorial libraries of scaffold, biomolecule, and stem cell constructs with single-cell spatial resolution. These tissue-constructs, with varying composition and geometry, will define stem cell properties, leading to custom-designed tissue replacements built with autologous cells. The lab is working to characterize effects of physical/biochemical stimuli on stem cells, and how these factors direct their differentiation and development and to build stem cells into improved prototype tissue replacement constructs.

Best TM, Shehadeh SE, Leverson GE, Michel JT, Corr DT, Aeschlimann D. Analysis of changes in mRNA levels of myoblast- and fibroblast-derived gene products in healing skeletal muscle using quantitative reverse transcription-polymerase chain reaction. J Orthop Res 2001; 19:565-572.

Corr DT, Leverson GE, Vanderby RJr, Best TM. A nonlinear rheological assessment of muscle recovery from eccentric stretch injury. Med Sci Sports Exerc 2003; 35(9):1581-1588.

Aarimaa V, Rantanen J, Best T, Schultz E, Corr D, Kalimo H. Mild eccentric stretch injury in skeletal muscle causes transient effects on tensile load and cell proliferation. Scan J Med Sci Sports 2004; 14(6):367-372.

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The Cowin Laboratory focuses on the role of beta-catenin during breast development and in breast cancer. The lab has developed a mouse expressing activated beta-catenin in the mammary gland and showed that this induces precocious alveolar development and breast cancer. The work indicates that beta-catenin acts downstream of hormones to stimulate the proliferation of breast stem cells and the survival and of their immediate progenitors. Cell-type specific activation of beta-catenin regulates ductal/alveolar cell fate, expansion and the induction of distinct types of breast tumors. Dr. Cowin is investigating the relationship between specific stem/progenitor cell expansion and tumor phenotype and characterizing novel breast stem cell biomarkers.

Zhang X, Podsypanina K, Huang S, Mohsin SK, Chamness GC, Hatsell S, Cowin P, Schiff R, Li Y. Estrogen receptor positivity in mammary tumors of Wnt-1 transgenic mice is influenced by collaborating oncogenic mutations. Oncogene. 2005 Jun 16;24(26):4220-31.

Liu B.Y., Kim Y.C., Leatherberry V., Cowin, P., Alexander, C.M. Mammary gland development requires syndecan-1 to create a beta-catenin/TCF-responsive mammary epithelial subpopulation. Oncogene. 2003 Dec 18;22(58):9243-53.

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Lisa Daily, Ph.D.
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Dr. Daily's work focuses on deciphering the mechanisms of transcriptional regulation in early embryogenesis. The lab initially found that the transcription factor Sox2 is expressed in ES cells and that it acts synergistically with Oct4 to activate FGF4 gene expression in ES and embryonal carcinoma (EC) cells, and the early embryo. This was the first report of a functional interaction between these two factors that has subsequently been shown to form a core component of the transcriptional circuitry of ES cells. Professor Daily's research aims to extend the understanding of transcriptional regulation in ES cells beyond the Sox/Oct network. The lab has developed a new technology that will allow the high throughput identification of ES cell-specific promoters and enhancers whose analyses will reveal novel ES cell-specific transcriptional activators.

Dailey L., and Basilico (2001) Coevolution of HMG domains and Homeodomains and the generation of transcriptional regulation by Sox/Pou complexes. J Cell. Physiol. 186:315-328.

Ambrosetti, D-C., Scholer, H.R., Dailey, L., Basilico, C. (2000) Modulation of the activity of multiple transcriptional activation domains by the DNA binding domains mediates the synergistic action of Sox and Oct-3 on the fibroblast growth factor 4 enhancer. J. Biol. Chem 275:23387-23397

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A feature of many genetic diseases is that mutations in widely expressed genes cause tissue-specific illness. One example is DYTl dystonia, a disease caused by an in-frame deletion (Deltagag) in the gene encoding torsinA. Dauer's lab discovered that neurons from both torsinA null and homozygous disease mutant "knockin" mice contain abnormal nuclear membranes. The membrane abnormalities develop in post-migratory embryonic neurons and subsequently worsen with further neuronal maturation, a finding evocative of the developmental dependence of DYTl dystonia. Observations demonstrate that neurons have a unique requirement for nuclear envelope (NE) localized torsinA function. The lab has isolated torsinA embryonic stem (ES) cells and demonstrated that they develop NE blebs when differentiated into neurons, but show no NE abnormality when differentiated into myocytes. This ES-based system is being used to identify the features that make neurons uniquely susceptible to torsinA loss-of-function.

Goodchild RE, Dauer W. (2004) Mislocalization to the nuclear envelope: an effect of the dystonia-causing torsinA mutation. Proc Natl Acad Sci USA. 101:847-52.

Rideout HJ, Dietrich P, Savalle M, Dauer W, Stefanis L. (2003) Regulation of alpha-synuclein by bFGF in cultured ventral midbrain dopaminergic neurons. J Neurochem. 84(4):803-13.

Dauer W, Przedborski S. (2003) Parkinson's disease: mechanisms and models. Neuron. 39:889-909.

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Lucian Del Priore, M.D., Ph.D.
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Professor Del Priore's goal is to use stem cell transplantation to treat age-related macular degeneration and peripheral retinal degenerations. Retinal degenerations are the leading cause of blindness in the world. This team is inducing hESC to differentiate into retinal pigment epithelium (RPE) or neural retinal cells by seeding the hESC onto human Bruch's membrane (BM) explants prior to transplantation into animal models of human retinal degeneration. This is the first time human BM will be used for this purpose. Simultaneously they are initiating studies on isolation of tissue-specific stem cells from the eye, and investigating the efficacy of transplanting tissue-specific and differentiated hESC into animal models of retinal degenerations.

Tezel TH, Del Priore LV, Berger AS, Kaplan HJ. (2007) Adult Retinal Pigment Epithelial Transplantation in Exudative Age-related Macular Degeneration. Am J Opthalmol., 143:584-595.

Del Priore LV, Kuo YH, Tezel TH. (2002) Age-related changes in human RPE cell density and apoptosis proportion in situ. Invest Ophthalmol Vis Sci;43:3312-3318.

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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 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. Her laboratory is 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.

F. Doetsch (2003) The glial identity of neural stem cells. Nature Neuroscience, 6 1127-1134.

F. Doetsch (2003) A niche for adult neural stem cells. Current Opinion in Genetics and Development, 13, 543-550.

F. Doetsch, L. Petreanu, I. Caille, J.M. Garcia-Verdugo and A. Alvarez-Buylla (2002). EGF converts transit amplifying neurogenic precursors in the adult brain into multipotent stem cells. Neuron, 36, 1021-1034.

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Professor Dordick's lab is interested in developing high-throughput tools for stem cell research. This relates to the development of cell microarrays that can be used to screen small molecules and growth factors for stem cell expansion and differentiation. Dordick and colleagues are developing methods to study millions of stem cells on devices the size of a standard microscope slide. Ultimately, they aim to develop new compounds that can be used to selectively alter stem cell physiology and evaluate their use in therapeutics.

M.Y. Lee, C.B. Park, J.S. Dordick, and D.S. Clark (2005), Metabolizing Enzyme Toxicology Assay Chip (MetaChip) for High Throughput Microscale Toxicity Analyses
Proc. Natl. Acad. Sci. USA 102, 983-987.

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The stem cell research in Professor Dziak's lab involves the use of bone marrow stem cells for regeneration of bone. In many cases where there is a large effect due to trauma and/or osteoporosis, there is also a deficit of precursor cells evolving from osteoprogenitor stem cells. In these situations, which occur quite frequently, the addition of a bone matrix scaffold to support endogenous repair is not sufficient for complete healing, and the addition of stem cells can greatly enhance the healing process. Their research has led to the development of a nanocalcium sulfate scaffold into which bone marrow stem cells can be incorporated to most effectively enhance bone regeneration and repair of a large defect.

Kamer AR, El-Ghorab N, Marzec N, Margarone JE 3rd, Dziak R. Nicotine induced proliferation and cytokine release in osteoblastic cells. Int J Mol Med. 2006 Jan;17(1):121-7.

Bateman J, Intini G, Margarone J, Goodloe S, Bush P, Lynch SE, Dziak R. Platelet-derived growth factor enhancement of two alloplastic bone matrices. J Periodontol. 2005 Nov;76(11):1833-41.

Perinpanayagam H, Martin T, Mithal V, Dahman M, Marzec N, Lampasso J, Dziak R.
Alveolar bone osteoblast differentiation and Runx2/Cbfa1 expression. Arch Oral Biol. 2006 May;51(5):406-15. Epub 2005 Oct 25.

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Grigori Enikolopov, Ph.D.
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Dr. Enikolopov studies signals that regulate distinct steps in the cascade converting stem cells, into differentiated cells in different tissues focusing on the nervous system. Enikolopov's lab is generating new animal models to study stem cells in the brain and other adult tissues. These models enable the lab to isolate stem cells to examine the requirements of such cells for tissue maintenance, response to injury, repair, or transplantation. The team is interested in how production of new neurons in the adult brain may be linked to mood regulation and antidepressant therapies. They developed a new approach for identifying and quantifying cellular targets of neurogenic stimuli to determine cell populations targeted by antidepressants in the adult brain.

Packer, M., Stasiv, Y., Benraiss. A., Chmielnicki, E., Grinberg, A., Westphal, H.,Goldman, S., and Enikolopov, G. (2003). Nitric oxide negatively regulates mammalian adult neurogenesis. Proc. Nat. Acad. Sci. USA, 100, 9566-9571.

Gleiberman, A.S., Encinas, J.M., Mignone, J.M., Michurina, T., Rosenfeld, M.G., and Enikolopov, G. (2005) Expression of nestin-GFP transgene marks oval cells in the adult liver. Dev. Dynam., 234, 413-421.

Encinas, J.M., Vaahtokari, A., and Enikolopov, G. (2006) Fluoxetine targets early progenitor cells in the adult brain. Proc. Nat. Acad. Sci. USA 103, 8233-8238.

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James Fallavollita, M.D.
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The Fallavollita lab is studying myocardial responses and adaptations to chronic ischemia. The laboratory has developed a porcine model of chronic hibernating myocardium to examine flow and function with particular attention to inotropic and vasodilatory reserve. They are also studying the metabolic and molecular adaptations to ischemia and have confirmed alterations in high glucose uptake and sarcoplasmic reticulum calcium regulatory gene expression in a chronic model. The work has shown that hibernating myocardium is characterized by apoptotic cell loss with compensatory hypertrophy. These experiments have been complemented by a series of acute experiments following a period of prolonged moderate ischemia or “short-term hibernation”, prior to the development of hibernating myocardium. Dr. Fallavollita is evaluating alterations in flow, function, oxygen consumption, glucose uptake, sarcoplasmic reticulum calcium regulatory gene expression, glucose transporter expression and troponin degradation.

Suzuki, G., T-C. Lee, J.A. Fallavollita, and J.M. Canty, Jr. (2005) Adenoviral gene transfer of FGF-5 to hibernating myocardium improves function and stimulates myocytes to hypertrophy and reenter the cell cycle, Circulation Research, 96, 767-775.

Vacanti, V., E. Kong, G. Suzuki, K. Sato, J.M. Canty, Jr., and T-C Lee (2005) Phenotypic changes of adult porcine mesenchymal stem cells induced by prolonged passaging in culture, Journal of Cellular Physiology, 205, 194-201.

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Professor Feng has been working with mouse embryonic stem (ES) cells for ten years to generate various genetic changes in mice to model human diseases. He has generated animal models of depression and epilepsy. The Feng lab is currently focused on Parkinson's disease, by generating animal models of this disorder using mouse ES cells. The future aim of his lab is to work on human ES cells, and introduce disease-causing mutations into these cells and differentiate them into dopaminergic neurons. These experiments, Feng believes, will allow future study of the impact of genetic and environmental factors linked to Parkinson's disease on actual human neurons, which may have different properties than mouse neurons.

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J. Feng (2006). Microtubule: a Common Target for Parkin and Parkinson's Disease Toxins. Neuroscientist. 12:469-476.

Q. Jiang, Z. Yan, and J. Feng (2006). Neurotrophic factors stabilize microtubules and protect against rotenone toxicity on dopaminergic neurons. J. Biol. Chem. 281:29391-29400.

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Dr. Feuer has employed human hematopoietic stem and progenitor cells (HSC/HPCs) in his research since 1992. His particular expertise involves generating “humanized” SCID mice (SCID-hu) by intravenous injection of human HSC/HPCs. These mice support the development and maturation of a human immune system comprising T-and B-lymphocytes as well as monocyte/macrophages. SCID-hu mice can be infected with human oncogenic viruses and serve as a unique small animal model to study how viral infection predisposes human stem cells to become leukemic. In the near future, Dr. Feuer plans to utilize human embryonic stem cells (hESCs) to evaluate the differentiation profiles following injection into SCID mice using glucose transporter expression and troponin degradation.

Tripp A., Liu Y., Sieburg M., Montalbano J., Wrzesinski S., Feuer G., (2003) Human T-Cell Leukemia Virus Type 1 Tax Oncoprotein Suppression of Multilineage Hematopoiesis of CD34+ Cells In Vitro Journal of Virology, 12152-12164, Vol. 77, No. 22.

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Microenvironmental conditions are critically important in tumor induction and progression, and mediate the establishment of metastases at preferential target sites. Dr. Fischbach-Teschel is exploring diversified tissue-engineered model systems and polymeric growth factor delivery strategies. The lab's research aims at elucidating microenvironmental events that currently impair the prognosis of cancer patients towards development of new drug delivery systems for more effective treatment of cancer. This work involves gaining a better understanding of the role of microenvironmental conditions in the malignant transformation of adult stem cells as well as in the modulation of normal stroma derived progenitors towards a cell type that supports tumor malignancy.

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Neubauer, M., Fischbach, C., Bauer-Kreisel, P., Lieb. E., Hacker, M., Tessmar, J., Schulz, M.B., Goepferich,A., and Blunk,T. (2004). Basic fibroblast growth factor enhances PPARgamma ligand-induced adipogenesis of mesenchymal stem cells. FEBS Lett (577) 277-283

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Dr. Fishell is studying directed differentiation of ES cells related to cortical interneuron identities towards neuronal replacement strategies. The strategy is two fold, beginning with established ES cell lines where the EGFP reporter is under the control of the Dlx5/6 locus. This locus is activated broadly in Gabergic populations, including cortical interneurons. The lab complements this by engineering the expression of transcription factors required for cortical interneuron development in ES cell lines and uses extrinsic factors known to function in the specification of cortical interneuron precursors, such as FGF8 and Shh. Validation of method is accomplished through a complementary in vitro/in vivo strategy. The in vitro strategy makes use of cortical interneuron feeder layers, previously shown to allow cortical interneuron precursors to attain their mature characteristics. In vivo transplantation methods are used to reintroduce engineered “cortical interneurons” to ascertain ability to integrate into a functional nervous system.

Machold RP, Kittell DJ, Fishell GJ. (2007) Antagonism between Notch and bone morphogenetic protein receptor signaling regulates neurogenesis in the cerebellar rhombic lip. Neural Development, 2:5.

Balordi, F., Fishell, G., (2007). Mosaic removal of hedgehog signaling in the adult SVZ reveals that the residual wild-type stem cells have a limited capacity for self-renewal. J Neurosci. 27(52):14248-59.

Klein C., Fishell, G., (2004). Neural stem cells: progenitors or panacea? Dev Neurosci. 82-92.

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Professor Fuchs has developed a strategy for purifying the population of adult mouse stem cells from their natural niche in the hair follicle. These cells undergo self-renewal, replenish hair follicles during cycling, and repair both sebaceous glands and epidermis in response to injury/loss of their resident progenitor cells. The Fuchs lab has shown that when introduced into the cytoplasm of unfertilized oocytes, mouse skin stem cells can become reprogrammed to generate all tissues of the animal. The team has also identified the mechanisms underlying how hair follicle stem cells become activated to regenerate a new hair with each cycle, and showed that when uncontrolled, the very mechanisms underlying stem cell activation result in hair follicle tumors, including pilomatricomas, trichofolliculomas and most likely basal cell carcinomas.

Blanpain C, Fuchs E. (2007) p63: revving up epithelial stem-cell potential. Nat. Cell Biology. Jul;9(7):731-2.

Li J, Greco V, Guasch G., Fush E., Mombaerts P. (2007) Mice cloned from skin cells. Proc Natl Acad Sci USA, Feb 20; 104(8):2738-43. Epub 2007 Feb 13.

Fuchs, E. (2007) Scratching the surface of skin development. Nature, 445 (7130):834-42.

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Sarah Gaffen, Ph.D.
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Professor Gaffen's laboratory is interested in understanding the molecular basis for signal transduction by the immune cytokine IL-17. IL-17 is produced by a novel subset of T helper cells termed "Thl7" cells, which have recently been shown to drive pathology in most, if not all, autoimmune diseases. Conversely, IL-17 is critical for host defense against numerous infectious organisms, largely through regulation and expansion of the neutrophil lineage. Although produced by T cells, IL-17 acts on non-immune cells such as bone marrow stromal cells, fibroblasts and epithelial cells to promote an innate immune response. Therefore, this cytokine bridges adaptive and innate immune functions.

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Yu, JJ, Ruddy, MJ, Wong, GC, Baker, PJ, Smith, JB, Evans, RT and Gaffen, SL (2007) An essential role for IL-17 in preventing pathogen-initiated bone destruction: Recruitment of neutrophils to inflamed bone requires IL-17 receptor-dependent signals. Blood 109:3792-3802.

Shen, F, Ruddy MJ, Plamondon, P and Gaffen, SL (2005) Cytokines link osteoblasts and inflammation: Microarray analysis of IL-17- and TNFalpha-induced genes in bone cells. J Leuk Biol. 77:388-399.

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Lin Gan, Ph.D.
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Dr. Gan's research is centered on identifying transcription factors and regulatory pathways required for neuronal differentiation in two model systems: the mammalian retina and inner ear. The Gan lab is currently investigating the regulatory pathways comprised of three major classes of transcription factors: the basic helix-loop-helix (bHLH), the LIM-domain, and the Class IV POU-domain transcription factors. Using genetically modified mice, the lab has shown that these three classes of transcription factors function in transcription factor cascades to regulate the patterning and cell fate specification in retinal and inner ear structures.

Shibasaki K, Takebayashi H, Ikenaka K, Feng L, Gan L. (2007) Expression of the basic helix-loop-factor Olig2 in the developing retina: Olig2 as a new marker for retinal progenitors and late-born cells. Gene Expr Patterns. Jan;7(1-2):57-65.

Yan DH, Wen Y, Su LK, Xia W, Wang SC, Zhang S, Gan L, Lee DF, Spohn B, Frey JA, Hortobagyi GN, Hung MC. (2004).A delayed chemically induced tumorigenesis in Brca2 mutant mice. Oncogene. Mar 11;23(10):1896-901.

Yang Z, Ding K, Pan L, Deng M, Gan L. (2003). Math5 determines the competence state of retinal ganglion cell progenitors. Dev Biol. Dec 1;264(1):240-54.

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Lee Ann Garrett-Sinha, Ph.D.
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Professor Garrett-Sinha is interested in the role of Ets proteins in regulating the normal development of hematopoietic cells, and the role of Ets family members in tumor formation and progression. Ets-1 is one of the Ets genes that has been shown to be over-expressed in a large number of different types of human cancers. Human tumors that over-express Ets-1 tend to be more aggressive and metastatic than Ets-1 negative tumors. To explore the relationship between Ets-1 expression and tumor formation and metastasis, this lab has recently developed a transgenic mouse model, in which they can inducibly express Ets-1 in a variety of tissues at different stages of development. The induction of Ets-1 in the epithelial cells of stratified squamous epithelial tissues in adult mice resulted in a dramatic hyper-proliferative phenotype and altered terminal differentiation of the tissues. These results support a role for Ets-1 in mediating early events in squamous cell carcinogenesis.

Clements, J.L., John, S.A., and Garrett-Sinha, L.A. (2006) Impaired generation of CD8+ thymocytes in Ets-1-deficient mice. J Immunol. 177:905-912.

Wang, D., John, S.A., Clements, J.L., Percy, D.H., Barton, K.P. and Garrett-Sinha, L.A. (2005) Ets-1 deficiency leads to altered B cell differentiation, hyper-responsiveness to TLR9 and autoimmune disease. International Immunology, 17:1179-1191.

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Adult stem cells can be reprogrammed to give rise to new lineage descendants as the result of changes in the microenvironment. Moreover, such instructive signals may impose stem cell features on other cells. This has raised several issues in stem cell biology. Is this plasticity restricted to stem cells or all nucleated cells? To what extent does microenvironment impose “stemness” on cells? Can a damaged stem cell be replenished by pre-existing stem cells or can differentiated progeny acquire “stemness” ? Professor Ghazizadeh is interested in using epidermal repair and regeneration as a unique model to address these issues in stem cell biology.

Ghazizadeh, S., Taichman, L.B., (2001) Multiple classes of stem cells in cutaneous epithelium: a lineage analysis of adult mouse skin EMBO J. 20:1215–1222.

Ghazizadeh, S., Taichman, L.B., (2005) Organization of stem cells and their progeny in human epidermis. Invest. Dermatol. (124:367-372.

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Professor Goff is best known for the development of retroviruses as a genetic system. He has used mutagenesis to define the functional domains of the viral protease, reverse transcriptase, and integrase in the life cycle. His lab was also the first to express enzymatically active reverse transcriptase in bacteria, and to localize its two major enzymatic activities. Goff has been particularly active in applying the yeast two-hybrid method to study interactions between viral and cellular proteins and to identify novel host factors for virus replication. His group has recently begun using somatic cell genetics to directly identify new cellular components utilized early in retrovirus infection.

Orlova, M., Yueh, A., Leung, J., and Goff, S.P. (2003) Reverse transcriptase of moloney murine leukemia virus binds to eukaryotic release factor 1 to modulate suppression of translational termination. Cell 115, 319-331.

Wang, M.Q., Kim, W., Gao, G., Torrey, T.A., Morse, H.C., III, DeCamilli, P., and Goff, S.P. (2003) Endophilins interact with moloney murine leukemia virus Gag and modulate virion production. J. Biol. 3, 4.

Evans, M.J., Rice, C.M., and Goff, S.P. (2004) Phosphorylation of Hepatitis C virus NS5A modulates its protein interactions and viral RNA replication. Proc. Natl. Acad. Sci. USA 101, 13038-13043.

Link Back to PI List

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Professor Goldman is working to define time-and location-specific patterns of glial and neuronal development and to understand the roles of environmental and lineage-controlled factors in specifying cell fate. Using viral gene transfer, transgenics, and culture systems, his research is defining the migration of precursor cells from germinal zones of the perinatal rodent forebrain and cerebellum and the development of these precursors into neurons and glia. By studying precursor migration in real time in living slices, the lab has determined a number of ways to change migration patterns with pharmacological agents and growth factors. They also study cycling precursor cells in the adult CNS to understand their fates under normal and pathological situations. For example, cycling precursors in adult white matter can differentiate into myelinating oligodendrocytes after demyelination. His lab studies Alexander disease, a degenerative disorder of white matter caused by mutations in the astrocyte intermediate filament protein, GFAP.

Angelastro J, Mason JL, Goldman J.E., Greene L., (2005) Downregulation of AFT5 is required for differentional of neural progenitor cells into astrocystes. J. Neurosci., 25: 3889-3899.

Brenner, M., Johnson, A.B., Boespflug-Tanguy, O., Rodriguez, D., Goldman, J.E. Messing, A. (2001). Mutations in glial fibrillary acidic protein (GFAP) associated with Alexander disease. Nature Genetics, 27: 117-120.

Staugaitis, S.M., Zerlin, M., Levine, J.M., Hawkes, R., and Goldman, J.E., (2001) Aldolase C/Zebrin II expression in neonatal rat forebrain reveals cellular heterogeneity within the subventricular zone and early astrocyte differentiation. J. Neurosci., 21: 6195-6205.

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Steven Goldman, M.D., Ph.D.
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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.

Goldman SA (2007) Disease Targets and Strategies for the Therapeutic Modulation of Endogenous Neural Stem and Progenitor Cells. Clin Pharmacol Ther. 2007 Aug 22.

Lin JH, Takano T, Arcuino G, Wang X, Hu F, Darzynkiewicz Z, Nunes M, Goldman SA, Nedergaard M (2007) Purinergic signaling regulates neural progenitor cell expansion and neurogenesis. Dev Biol. 302:356-66.

Roy NS, Cleren C, Singh SK, Yang L, Beal MF, Goldman SA (2006) Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat Med. 2006 12:1259-68.

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Studies performed in the Goligorsky laboratory in the last five years have established the role of endothelial progenitor cells (EPC) in rescuing the kidney subjected to ischemia/reperfusion; demonstrated the pathways of EPC mobilization and engraftment post-ischemia; provided evidence in support of renal resident mesenchymal stem cells, their motility and renoprotective action and established the role of glial cell-derived neurotrophic factor in stimulating migration and antiapoptotic properties of mesenchymal stem cells. Currently, Dr. Goligorsky is exploring the mechanism whereby alarm signaling, an innate immune response, mobilizes stem cells to the source of such signals, the mechanisms of stem cell premature senescense and the proteomic phenotype of dysfunctional endothethial cells and their progenitors.

Arriero M., Brodsky, S.V., Gealekman, O., Lucas, P. , Goligorsky, M.S. (2004) Adult skeletal muscle stem cells differentiate into endolthelial lineage and ameliorate renal dysfunction after acute ischemia. Am J Physiol 287:F621-F627.

Patschan D., Plotkin M., Goligorsky M.S. (2006). Therapeutic use of stem and progenitor cells in actue renal injury: ca ira, Curr Opin Pharmacol, 6: 176-183.

Plotkin,M., Goligorsky, M.S. Mesenchymal Cells from Adult Kidney Support Angiogenesis and Differentiate into multiple Interstitial Cell Types Including Erythropoietin Producing Fibroblasts. Am J Physiol, 291:F902-F912, 2006.

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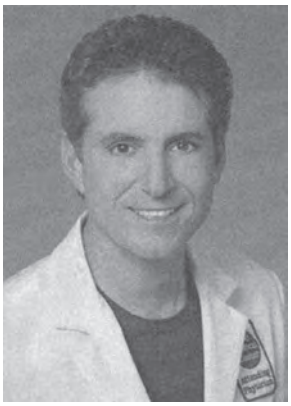

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The NYU Fertility Center, is currently pursuing two hESC projects with IRB approval. The first project is to generate novel disease models from genetically abnormal embryos as diagnosed by Preimplantation Genetic Diagnosis, focusing on fatal, prevalent, and incurable conditions such as Tay-Sachs and cystic fibrosis. Second, to generate novel types of hESC lines from individual cells of discarded frozen embryos which are most undifferentiated or lineage-allocated, allowing for the development of enhanced stem cell differentiation protocols and the study of totipotency, lineage allocation, and plasticity in human embryonic cells. Patients are currently being recruited and experimental conditions established by mouse ES cells.

Grifo JA, Flisser E, Adler A, McCaffrey C, Krey LC, Licciardi F, Noyes N, Kump LM, Berkeley AS. (2007) Programmatic implementation of blastocyst transfer in a university-based in vitro fertilization clinic: maximizing pregnancy rates and minimizing triplet rates.
Fertil Steril. Aug; 88(2):294-300. Epub 2007 May 25.

Moffa F, Comoglio F, Krey LC, Grifo JA, Revelli A, Massobrio M, Zhang J. (2002) Germinal vesicle transfer between fresh and cryopreserved immature mouse oocytes. Hum Reprod. Jan;17(1):178-83.

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Professor Gronostajski's lab uses mouse Embryonic Stem Cells (mES) to make mice with mutations in the genes for the Nuclear Factor I transcription factors. They have cultured mES cells to make homozygous mutant cells from heterozygous cells, to delete genes in targeted mES cells using Cre-recombinase, and to create embryoid bodies to promote differentiation of mES cells into multiple cell lineages. Gronostajski's lab is culturing mouse neural stem cells (NSC) to assess changes in NSC number in some of our NFI knockout mice and investigating the effect of loss of NFI genes on the differentiation of NSCs into neural and glial cells.

Ling G., Hauer C.R. Gronostajski R.M, Pentecost BT, Ding X., (2004) Transcriptional Regulation of Rat CYP2A3 by Nuclear Factor 1: Identification of a novel NFI-A isoform, and evidence for tissue-selective interaction of NFI with the CYP2A3 promoter in vivo.
J Biol Chem; Jul; 279(27); 27888-27895.

Bachurski C.J., Yang G.H., Currier T.A, Gronostajski R.M., Hong D., (2003) Nuclear factor I/thyroid transcription factor 1 interactions modulate surfactant protein C transcription.; Mol Cell Biol., Dec; 23(24); 9014-9024.

Messam CA, Hou J, Gronostajski RM, Major EO; Lineage pathway of human brain progenitor cells identified by JC virus susceptibility.; Ann Neurol; 2003 May; 53(5); 636-646.

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The Gross laboratory has been studying the renin-expressing cell found in association with the developing renal vasculature during kidney organogenes is. Purification and expression profiling of the cells has led to the hypothesis that the
cell expression signature is that of an 'activated pericyte' and that the transientexpression of renin observed during kidney vascular development specifically marks the window for the activated state of this mural cell lineage. Interestingly, the expression profile strongly resembles profiles published previously for putative mesenchymal stem cells. This, in turn, may offer insight into the role served by the reactivation of renin expression that is observed in vascular adventitial cells during injury and repair in adults. Current studies are aimed at testing these hypotheses.

Pan L, Glenn ST, Jones CA, and Gross KW. (2005). Activation of the rat renin promoter
by HOXD10•PBX1b•PREP1, Ets-1, and the intracellular domain of Notch. J Biol Chem 280:20860-20866.

Pan L, Xie Y, Black TA, Jones CA, Pruitt SC, Gross KW. (2001) An Abd-B class Hox/Pbx recognition sequence is required for expression from the mouse Ren-1c gene. J Biol Chem 276:32489-32494.

Jones CA, Hurley MI, Black TA, Kane CM, Pan L, Pruitt SC, Gross KW. (2000) Expression of a renin/green fluorescent protein transgene in mouse embryonic, extra-embryonic and adult tissues. Physiol Genomics 4:75-81.

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The dynamics of stem cell compartments of normal tissues and tumors determines the therapeutic and adverse effects of anticancer treatments. Our group develops pharmacological agents capable of selective protection and stimulation of normal stem cells, particularly in radio- and chemo-sensitive tissues. We found that human microbial parasites can produce factors capable of induction of proliferation and mobilization into peripheral blood of multipotent hematopoietic stem cells. This class of agents has the potential to radically improve the therapeutic index of currently used therapeutic regimens by stimulating recovery of cancer patients suffering from the side effects of cancer treatment.

Strom, E., Sathe, S., Komarov, P.G., Chernova, O.B., Pavlovska, I., Shyshynova, I., Bosykh, D.A., Burdelya, L.G., Macklis, R.M., Skaliter, R., Komarova, E.A. and Gudkov, A.V. (2006) Inhibition of p53 binding to mitochondria by small molecule is sufficient for radioprotection in vivo. Nature Chem. Biol., 2, 474-9.

Burdelya, L.G., Komarova, E.A., Hill, J.E., Browder, T., Tararova, N.D., Marvrakis, L.,DiCorleto, P.E., Folkman, J. and Gudkov, A.V. (2006). Inhibition of p53 Response in Tumor Stroma Improves Efficacy of Anticancer Treatment by Increasing Antiangiogenic Effects of Chemotherapy and Radiotherapy in Mice. Cancer Res.,66, 9356-61.

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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.

Zhang M., Joseph, B., Gupta S, Guest I, Sell S, Son K.H., Koch K.S., Leffert H.L. (2005) Xenoengraftment and hepatocytic differentiation of embryonic mouse STO cell lines in the livers of non-immunosuppressed adult rats. Stem Cells. 23: 186-199.

Qui C., Hanson e, Olivier E, Inada M, Kaufman D, Gupta S, Bouhassira E.E. (2005) Differentiation of human embryonic stem cells into hematopoietic cells by coculture with human fetal liver cells recapitulates the globin switch that occurs early in development. Exp Hematol. 33:1450-1458.

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Anna-Katarina Hadjantonakis, Ph.D.
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The long-term goal of the Hadjantonakis laboratory is to understand the critical events underlying cell lineage specification and morphogenesis in the mammalian embryo. Central to this goal is the identification of stem and progenitor cell populations resident within the early embryo. In parallel they are also investigating the reprogramming of differentiated cells. To address these questions they are using tools of mouse functional genomics, including transgenesis and targeted mutagenesis in embryonic stem (ES) cells and mice, microarray analysis and optical imaging.

Eakin, G.S. and Hadjantonakis, A.-K. (2006) Production of chimeras by aggregation of embryonic stem cells with diploid or tetraploid mouse embryos. Nature Protocols 1:145-153.

Rhee, J.M., Pirity, M.K., Lackan, C.S., Long, J.Z., Kondoh, G., Takeda, J. and Hadjantonakis, A.-K. (2006) Live imaging and differential localization of lipid-modified green fluorescent protein variants in embryonic stem cells and mice. Genesis 44:202-218.

Long, J.Z., Lackan, C.S. and Hadjantonakis A.-K. (2005) Genetic and spectrally distinct in vivo imaging: embryonic stem cells and mice with widespread expression of a monomeric red fluorescent protein. BMC Biotechnology 5:20.

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MicroRNA expression patterns are often characteristic of specific cell types. The mouse mammary epithelial cell line, Comma-1D, contains a sub-population of self-renewing stem cells, which can reconstitute the mammary gland. Hannon has purified this population and determined its microRNA signature. Several microRNAs, including miR-205 and miR-22, are highly expressed in mammary stem cells, while others, including let-7 and miR-93, are depleted. Let-7 sensors can be used to prospectively enrich self-renewing populations, and enforced let-7 expression induces loss of self-renewing cells from mixed cultures. Remarkably, tumor-initiating cells, purified from human cancer cell lines, share the microRNA signature of mammary stem cells.

Kim J., Inoue K., Ishii J., Vanti W.B, Voronov S.V., Murchison E., Hannon G., Abeliovich A. (2007). A MicroRNA feedback circuit in midbrain dopamine neurons. Science Aug 31;317(5842):1179-80.

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Dr. Hansis is working to understand the molecular mechanisms defining totipotency and cell differentiation in humans in order to expand knowledge about reprogramming. He is studying totipotency and the very first steps of cell differentiation in early human embryos to analysis marker genes such as Oct-4 and –HCG. Hansis has observed that blastomeres seem to differ in their potency and can be regarded as lineage-specific stem cells as early as the 4-cell stage. The allocation of these stem cells to specific fates might follow a pattern reminiscent of animal and vegetal poles. On the opposite end of the developmental spectrum, differentiated human cells can be used as a means of studying nuclear reprogramming. Intact human 293T kidney cells and primary leukocytes were reprogrammed towards a more undifferentiated state by Xenopus laevis egg extract. Based on the results, more efficient reprogramming protocols might allow for the generation of fully differentiated or undifferentiated human cells for clinical application.

Hansis C., Totipotency, cell differentiation and reprogramming in humans. Reproductive BioMedicine Online 2006, 13:551-557.

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Stem cells show great promise in neuroscience in a number of areas. They help scientists to explain how specific types of neurons are specified and differentiated and advance the understanding of how these new neurons migrate and form appropriate synapse. Their potential to generate neurons for transplantation to replace neurons that have died or become damaged as a consequence of diseases such as Parkinson's, Huntington's and ALS is promising. A number of scientists at Cornell, Rockefeller and Sloan-Kettering are working with neuronal stem cells and are interested in GABAergic, dopaminergic and motoneuronal phenotypes. The goal is to produce fully functional and differentiated neuronal populations from stem cells that have the appropriate biochemical properties. However, the neuronal phenotype can only be fully evaluated by examining the electrophysiological characteristics of the neurons generated from stem cells, and it is in this area that the Harrison laboratory is collaborating with these groups.

Lee H., Shamy G.A., Elkabetz Y., Schofield C.M., Harrison N.L., Panagiotakos G., Socci N.D., Tabar V. and Studer L. (2007) Directed differentiation and transplantation of human embryonic stem cell-derived motoneurons. Stem Cells 25, 1931-1939.

Perrier A.L., Tabar V., Barberi T., Rubio M.E., Bruses J., Topf N., Harrison N.L., and Studer L. (2004) Derivation of midbrain dopamine neurons from human embryonic stem cells. Proceedings of the National Academy of Sciences, U.S.A., 101, 12543-12548.

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Professor Hen's research is aimed at understanding the mechanism of action of medications that are currently used to treat depression and anxiety-related disorders. Although selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed antidepressants and anxiolytics, their mechanisms of action, and particularly the reason for their delayed (4-6 weeks) onset of therapeutic efficacy, are largely unknown. The general hypothesis that his team is studying is that the generation of new neurons from a pool of undifferentiated stem cells located in a part of the brain called the hippocampus is responsible for the delayed onset of action of SSRIs.

Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R. Paradoxical influence of hippocampal neurogenesis on working memory. Proc Natl Acad Sci U S A. 2007; 104(11): 4642-6.

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Link Back to PI List

Christopher E. Henderson, Ph.D.
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Work in the Henderson lab focuses on the study of motor neuron development to understand mechanisms underlying amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). This lab has studied the signaling pathways involved in motor neuron death during development and has brought to light a novel mechanism potentially involved in ALS. Purified motor neurons in culture have allowed the lab to identify not only polypeptide neurotrophic factors required for normal motor neuron survival, but also compounds from chemical libraries that can enhance neuronal survival or axon growth. Henderson's lab uses specialized in vitro and in vivo approaches to pursue objectives and aims to study the development of specific groups of motor neurons within the spinal cord, using chemical libraries to probe the mechanisms of key events including differentiaion, growth and survival in neuronal development and pathology.

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Junghans,D., Chauvet, S., Buhler, E., Dudley, K., Sykes, T., and Henderson, C.E.(2004). The CES-2-related transcription factor E4BP4 is an intrinsic regulator of motor neuron growth and survival. Development 131:4425-4434.

Helmbacher, F.,Dessaud, E., Arber, S., deLapeyrière, O., Henderson,C.E., Klein, R.,and Maina, F. (2003). Met signaling is required for recruitment of motor neurons to PEA3-positive motor pools. Neuron 39:767-777.

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Fritz A. Henn Ph.D., M.D.
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Dr. Henn's laboratory is interested in the role of neurogenesis in the hippocampus as it relates to major depressive disorder. The lab is looking at animal models of depression and assessing the role of neurogenesis in altering depressive behavior. Henn's team has found changes in neurogenesis can be dissociated from depressive behavior suggesting neurogenesis is not etiologically important in this disorder. To prove this in the human model we have developed, with colleagues at Cold Spring Harbor Laboratory and Stony Brook School of Medicine, a method to measure neurogenesis in vivo in patients which will facilitate direct answer to this question.

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Different sarcomas of a certain histological subtype or even different areas in the
same tumor display various levels of maturation. This observation has changed the traditional view of the “sarcoma cell-of-origin” (a mature cell that ‘de-differentiates’
during the neoplastic process) for a mesenchymal progenitor that transforms before accomplishing differentiation. Professor Hernando has recently reported the generation of mice that faithfully reproduce the transition from smooth-muscle (SM) hyperplasia to leiomyosarcoma-genesis. Using this mouse model, the derived mesenchymal stem cells and human sarcomas, this lab plans to identify the sarcoma “cell of origin”, isolate and characterize potential ‘cancer stem cells”, and investigate the relationship between these two entities.

Dickins RA; McJunkin K; Hernando E; Premsrirut PK; Krizhanovsky V; Burgess DJ; Kim SY; Cordon-Cardo C; Zender L; Hannon GJ; Lowe SW. (2007) Tissue-specific and reversible RNA interference in transgenic mice. Nature genetics. 39: 914.

Hernando E; Charytonowicz E; Dudas ME; Menendez S; Matushansky I; Mills J; Socci ND; Behrendt N; Ma L; Maki RG; Pandolfi PP; Cordon-Cardo C. (2007) The AKT-mTOR pathway plays a critical role in the development of leiomyosarcomas. Nature Medicine. 13: 748.

Hernando, E. (2007) MicroRNAs and cancer: role in tumorigenesis, patient classification and therapy. Clinical & translational oncology. 9: 155.

Link Back to PI List

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Brain tumors in humans have stem cells central to their biology and therapeutic response. Dr. Holland's laboratory has created histologically and genetically accurate mouse models of gliomas and medulloblastomas. These mouse models also replicate the resistant stem cells and their perivascular niche found in humans. They are studying the biology of therapeutic response in these stem cells relative to the bulk of the cells in the tumor. This system is more experimentally tractable than studying patient samples and the results are transferable to human brain tumors. Based on their data they are performing clinical trials in brain tumor patients here at MSKCC.

Fomchenko EI, Holland EC. Stem cells and brain cancer. Exp Cell Res. 2005 Jun 10;306(2):323-9. Epub 2005 Apr 14.

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Adult stem cells within many tissue-types are under intense investigation, but additional basic understanding of their establishment, behavior and maintenance is required to realize their potential for therapeutic use and to assess their relationship to cancer. Invertebrate model organism stem cells are relatively easily manipulated in vivo and can help uncover basic principles that underlie analogous systems in humans. Professor Hubbard's research uses the C. elegans germ line as a model to study the control of stem cell proliferation. These studies employ genetic, molecular and cell-biological techniques to analyze germ cell behavior in normal and mutant conditions that alter proliferation.

D. J. Killian and E. J. A. Hubbard, (2005). C. elegans germline patterning requires coordinated development of the somatic gonadal sheath and the germ line. Developmental Biology 279:322-335.

J. Maciejowski, N. Ugel, B. Mishra, M. Isopi, E. J. A. Hubbard (2006) Quantitative analysis of germline mitosis in adult C. elegans. Developmental Biology 292:142-151.
Hubbard, E.J.A. (2007).

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Silviu Itescu, M.B.B.S.
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Professor Itescu's research covers the off-the-shelf utility of allogeneic adult mesenchymal progenitor cells (MFCs). These cells have a low cost, can be easily culture-expanded under GMP conditions, have regulatory controls for release and potency criteria allowing for uniformity of product, are 1000 fold purer than other cell types and can be used to treat unrelated patients without the need for immunosuppression. The research has demonstrated proof-of-principle safety and efficacy of these cells in a variety of indications covering cardiovascular, eye disease, orthopedic and bone marrow transplantation. Itescu is focused on understanding the basic mechanism for how these cells exert their effects and how to harness their potential and translate the findings to clinical practice.

Xiang G, Schuster MD, Seki T, Kocher AA, Eshghi S, Boyle A, Itescu S. (2004) Down-regulation of Plasminogen Activator Inhibitor 1 Expression Promotes Myocardial Neovascularization by Bone Marrow Progenitors. J Exp Med. 200(12):1657-66.

Schuster MD, Kocher AA, Seki T, Martens TP, Xiang G, Homma S, Itescu S. (2004) Myocardial neovascularization by bone marrow angioblasts results in cardiomyocyte regeneration. Am J Physiol Heart Circ Physiol. 287(2):H525-32.

See F, Thomas W, Way K, Tzanidis A, Kompa A, Lewis D, Itescu S, Krum H. (2004) p38 mitogen-activated protein kinase inhibition improves cardiac function and attenuates left ventricular remodeling following myocardial infarction in the rat. J Am Coll Cardiol. 44(8):1679-89.

Link Back to PI List

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Bone marrow-derived stem cells have been shown to differentiate into endothelial, vascular smooth muscle and cardiac muscle cells. In the porcine model of hibernating myocardium there is an increase in myocardial CD 133+ cells. The number of these cells increases in response to treatment with HMG-CoA reductase inhibitors or statins. Professor Iyer has investigated the bone marrow, peripheral blood and myocardial levels of CD133+, VEGFR2+ and CD117+ hematopoietic stem cells in response to low dose or high dose Pravastatin in normal swine. There is a concordant dose-dependent increase in the number of CD113+/VEGFR2+ cells in the bone marrow, peripheral and myocardium of normal swine.

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Stem cells are essential to plants, since they permit the indeterminate growth cycle and continual initiation of organs during development. Stem cell regulation is also an important contributor to crop yield and biomass. The Jackson lab is studying mechanisms of cell-cell communication that are essential for stem cell maintenance. Dr. Jackson has discovered a novel pathway of direct intercellular transport of transcription factor proteins and mRNAs, which appears to be critical for stem cell maintenance. The lab has also isolated genes that regulate the balance between stem cell proliferation and differentiation, and are studying their mode of action.

Lucas, W.J., Bouche-Pillon, S., Jackson, D., Nguyen, L., Baker, L., Ding, B., and Hake, S. (1995). Selective Trafficking of KNOTTED1 and its mRNA Through Plasmodesmata. Science 270: 1980-1983.

Shiobara, F.T., Yuan, Z., Hake, S., and Jackson, D. (2001). The fasciated ear2 gene encodes a leucine-rich repeat receptor-like protein that regulates shoot meristem proliferation in maize. Genes Dev. 15: 2755-2766.

Giulini, A., Wang, J., and Jackson, D. (2004). Control of Phyllotaxy by the Cytokinin Inducible Response Regulator Homologue ABPHYL1. Nature 430: 1031-1034.

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Thomas M. Jessell, Ph.D.
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Dr. Jessell's research has focused on the development of functional circuitry in the vertebrate central nervous system. Using the sensory-motor reflex circuit in the spinal cord as a model system, his work has defined many of the cellular and molecular mechanisms and principles that determine the formation of neuronal connections and the assembly of functional circuitry. His studies have shown how insights from normal pathways of neuronal specification can be used to direct embryonic stem cells to form functional neurons that can integrate into brain circuits. These findings have profound implications for the reconstruction of circuits that have been damaged through trauma or neurodegenerative disease.

Yoshida Y., Han B., Mendelsohn M., Jessell T.M. (2006) Plexin A1 Signaling Directs the Segregation of Proprioceptive Sensory Axons in the Developing Spinal Cord. Neuron Dec 7;52(5):775-88.

Kramer, I., Sigrist, M., de Nooij, J.C., Taniuchi, I., Jessell, T.M., and Arber, S. (2006) Runx transcription factor signaling contributes to the emergence of specific sensory neuron subpopulations. Neuron 49, 379-393.

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The Joyner laboratory studies the potential of mouse adult stem cells to repair tissues or contribute to cancer, and the role of Hedgehog signaling in these processes. They have developed a method (Genetic Inducible Fate Mapping) to mark and follow stem cells expressing the Hedgehog target gene Gli1. In the prostate, they study the ability of Gli1-expressing mesenchymal cells to contribute to regeneration following castration or to tumor metastasis. In the lung, they study the potential of Gli1-expressing mesenchymal cells to contribute to airway remodeling in asthma. In the skin, spinal cord and forebrain, they study the response of Gli1-expressing cells to various injuries.

Ahn, S. and Joyner, A.L. (2005) Quiescent adult neural stem cells are targets of Sonic hedgehog signaling. Nature, 437: 894-897.

Joyner, A.L. and Zervas, M. (2006) Genetic fate mapping in mouse: establishing genetic lineages and defining genetic neuroanatomy in the nervous system. Developmental Dynamics, 235:2376-85.

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Recent studies have shown that cancer stem cells are important to several different tumor types, and represent critical targets for therapy. The concept of cancer stem cells is best characterized in the blood-forming (hematopoietic) tissues, where a stem cell origin for leukemia has been well described. Professor Jordan's research seeks to identify differences between normal and malignant hematopoietic stem cells, and to use such differences as a means to preferentially target cancerous cells for destruction. To this end, this lab has demonstrated that human leukemia stem cells can be induced to undergo programmed cell death upon treatment with specific types of drugs, while normal stem cells are spared.

Jordan, C.T., Guzman, M.L., and Noble, M. (2006). Cancer stem cells. New England Journal of Medicine, Invited review, 355:1253-1261.

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Ravi Kane, Ph.D.
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Stem cells in vivo reside in a complex microenvironment that presents them with
numerous signals that regulate their behavior and functions. Understanding how these factors influence stem cell fate is a major challenge of stem cell biology. Designing strategies to control stem cell function is also critical for applications of stem cells in tissue engineering and regeneration. The aims of research efforts in the Kane group are to develop and apply tools for elucidating gene function in stem cells and to develop bioactive materials - soluble ligands, biofunctionalized surfaces, and three-dimensional scaffolds – for controlling stem cell function.

Basha, S.; Rai, P.; Poon, V.; Saraph, A.; Gujraty, K.; Go, M.; Sadacharan, S.; Frost, M.; Mogridge, J.; Kane, R. S. (2006) Polyvalent Inhibitors of Anthrax Toxin that Target Host Receptors. Proceedings of the National Academy of Sciences, USA, 103, 13509-
13513.

Rai, P.; Padala, C.; Poon, V.; Saraph, A.; Basha, S.; Kate, S.; Tao, K.; Mogridge, J.; Kane, R. S. (2006) Statistical Pattern Matching Facilitates the Design of Polyvalent Inhibitors of Anthrax and Cholera Toxins, Nature Biotechnology, 24, 582.

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Donald W. Landry is the Interim Chair of Medicine and Director of the Division of Experimental Therapeutics. He is the leading proponent of an alternative method for the production of human embryonic stem cells that relies on harvesting live, normal cells from embryos that by objective, peer reviewed criteria have died of natural causes. By conducting natural history studies on human embryos engendered for the purpose of reproduction, he is precisely defining death in embryos based on arrested growth. Cells harvested from dead embryos would be covered under the established ethics undergirding essential organ donation from deceased donors.

Landry DW, Zucker H. (2004) Embryonic death and the creation of human embryonic stem cells. J. Clin. Invest. 114:1184-6.

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Dr. Lacy's research on a mouse development has identified a previously unrecognized player in the regulation of stem/progenitor cell differentiation - nuclear pore complex (NPC) composition. Her laboratory research seeks to elucidate the role of NPC composition by defining the requirement for Nup133, one of the NPC's 30 protein components, in stem and progenitor cells of the embryo and adult. The lab will ask:
Do embryonic progenitor cells require Nup133 to execute commitment to a terminal differentiation pathway? Do NPCs of differentiated cells lack Nup133, to stabilize their gene expression profile? Do NPCs of adult stem cells lack Nup133 as protection against inadvertent responses to differentiation signals, while derivative progenitor cells express Nup133 to facilitate differentiation?

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Suzanne Laychock, Ph.D.
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The research interest of Professor Laychock's laboratory is understanding the cellular mechanisms regulating insulin secretion from beta cells of Islets of Langerhans of the pancreas, and the expansion of beta-cell populations to meet the needs for transplantation approaches to treatment of diabetes mellitus. The long-term goal of this work is to improve the survival and function of transplanted pancreatic islets by enhancing islet post-transplantation angiogenesis and beta-cell survival and mitogenesis. Laychock is attempting to establish culture conditions that reduce apoptotic potential and produce endothelial cell and beta-cell growth and organization in isolated islets. This research has direct applicability to islet beta-cell progenitor (stem cell) research since the identification and expansion of beta-cells is a high priority in anticipation of transplantation.

Laychock, S.G., Sessanna, S.M., Lin M-H, Mastrandrea, L.D. (2006) Sphingosine 1-phosphate affects cytokine-induced apoptosis in pancreatic islet beta-cells. Endocrinology 147:4705-4712.

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Bone marrow-derived mesenchymal stem cells (MSCs) can contribute to the regeneration of human tissue. This healing power of MSCs is mediated by their mutilineage potential as well as growth factor/cytokine production capacity, and constitutes the basis for their use in regenerative medicine. Cardiovascular therapeutic potentials of MSCs are being investigated by using two different animal models: porcine hibernating myocardium and hamster dilated cardiomyopathy. Genetic engineering is being used to boost the competency and to increase the versatility of MSCs. Cell implantation strategies are being optimized to achieve maximal therapeutic benefits. Immune privileged MSCs may facilitate future therapeutic applications in an allogeneic or xenogeneic fashion.

Lin H, Shabbir A, Molnar M, Lee TC. Stem cell regulatory function mediated by expression of a novel mouse Oct4 pseudogene. Biochem. Biophys. Res. Comm. 355:111-116.

Wang X, Hu Q, Mansoor A, Lee J, Wang, Z, Lee TC., Zhang J. (2006). Bioenergetic and functional consequences of stem cell based VEGF delivery in pressure-overload swine hearts. Am J Physiol Heart Circ Physiol. 290:H1393-1405.

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Ruth Lehmann, Ph.D.
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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. Lehmann's lab 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.

Renault, A.D, Sigal J.Y., A. Morris A.J. and Lehmann R. (2004) Soma-germ line competition for lipid phosphate uptake regulates germ cell migration and survival. Science. 305 (5692):1963-6.

Gilboa , L. and Lehmann R. (2004) Repression of primordial germ cell differentiation parallels germ line stem cell maintenance. Current Biology 14 (11):981-986.

Gilboa, L. and Lehmann R. (2006) Soma-germ line interactions coordinate growth and homeostasis in the Drosophila gonad. Nature. 443(7107):97- 100.

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Rudolph L. Leibel, M.D.
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Current research activities include efforts to identify genes related to obesity and/or Type 2 Diabetes in mice and humans. The lab has particular interest in the molecular physiology of the energy homeostasis and glucose/insulin metabolism. The lab expertly use naturally occurring and transgenic rodent models to identify candidate molecules, and in vetting these candidates in large numbers of human subjects using high throughput methods (DHPLC, fluorescence-based SNP detection). The lab shares responsibility with the Columbia Genome Center for the creation and maintenance of the Columbia University microarray facility (CUMAP) and has personnel expert in the relevant molecular and information science.

Kowalski, T.J., Liu, S-M, Leibel, R.L., Chua, S.C. (2001) Transgenic complementation of Leptin Receptor Deficiency-Rescue of the obesity/diabetes phenotype of LEPR-null mice expressing a LEPR-B transgene. Diabetes. 50:425-435.

Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, RL, and Ferrante, A. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest. 112:1796-1803.

Phan, LK, Chung, WK, and Leibel, RL. (2006). The Mahoganoid mutation (Mgrn1md) improves insulin sensitivity in mice with mutations in the melanocortin signaling pathway independently of effects on adiposity. Am J Physiol Endocrinol Metab. 291(3):E611-20.

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The interests of Dr. Ihor R. Lemischka's laboratory are focused 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.

Ivanova N, Dobrin R, Lu R, Kotenko I, Levorse J, DeCoste C, Schafer X, Lun Y, Lemischka IR. (2006) Dissecting self-renewal in stem cells with RNA interference. Nature. 442(7102):533-8. Epub 2006 Jun 11.

Lemischka, I.R. (2005). Stem cell biology: a view toward the future. Ann N Y Acad Sci. 1044:132-8.

Lemischka, I.R. (2002). A few thoughts about the plasticity of stem cells. Exp. Hematol. (8):848-52.

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The STAT3 transcription factor appears to play a fundamental role in trophoblast stem cells (TSC) and the development and maintenance of the trophectoderm and extraembryonic ectoderm lineages. The trophoblast lineage is derived from a stem cell population of the early embryo that gives rise to all embryo-derived cells of the placenta. Like the cells of the inner cell mass, TSC have the capacity for unlimited proliferation in vitro, for differentiation into a number of distinct cell types, and can contribute to placental tissues in vivo. Dr. Levy is working to characterize the role of STATS in the trophoblast lineage. This work may provide new molecular insight into fundamental mechanisms of implantation and placentation.

Levy, D.E., Loomis, C.A. (2007) STAT3 Signaling and the Hyper-IgE Syndrome. N Engl J Med. 2007 Sep 19; [Epub ahead of print].

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Professor Ligon's lab is working to understand one of the key elements of cellular
structure - the microtubule network. This dynamic network not only provides structural support for all cellular functions, but it also serves as an essential cellular organizing principle. For example, in stem cells, asymmetric cell divisions in the stem cell niche are crucial for fate determination. It is thought that interactions between the microtubule network and the cell cortex orients the mitotic spindle and allows for these asymmetric divisions, but the precise molecular mechanisms of these microtubule-cortex interactions are not known. Through her research Ligon is working to elucidate these mechanisms.

L.A. Ligon, S. Karki, M. Tokito, and E.L.F. Holzbaur, Dynein Binds to _-Catenin and May Tether Microtubules at Adherens Junctions, Nature Cell Biology, 3(10) 913-917, 2001.

S. Karki, LA Ligon, J. DeSantis, M. Tokito, and E.L.F. Holzbaur, PLAC-24: A Novel Protein that Binds to Dynein and Localizes to Cell-Cell Contacts, Molecular Biology of the Cell, 13(5) 1722-34, 2002.

L.A. Ligon and E.L.F. Holzbaur, Microtubules Tethered at Epithelial Cell Junctions by Dynein Facilitate Efficient Junction Assembly, Traffic 8 (7) 808-819, 2007.

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Professor Linhardt's laboratory specializes in glycobiology, glycochemistry and glycotechnology. They are experts in glycosaminoglycans and proteoglycans found in the extracellular matrix, having critical roles in cell adhesion, migration, differentiation and signaling. The laboratory has had an integral role in understanding the structure-activity of the signal transduction complex. Linhardt's team is actively involved in glycomics research specifically aimed at understanding how glycome changes with stem cell differentiation. This work in nano-biotechnology has involved the separation of carbohydrate-nanomaterial composites with specific chemical, mechanical and electrical properties for optimal interaction with mammalian cells with the goal of preparing functionalized matrices to control cell differentiation.

Ibrahimi, O.A., Yeh B.K., Eliseenkova, A.v., Zhang, F., Olsen, S.K., Igarashi, M., Aaronson, S.A., Linhardt, R.J., Mohammadi, M. (2005). Analysis Of Mutations in FGF and a Pathogenic Mutation in FGFR Provide Direct Evidence in Support of the Two-End Model for FGFR Dimerization. Molecular and Cell Biology, 25, 671-684.

Linhardt, R.J., Toida, T. (2004) Role of Glycosaminoglycans in Cellular Communication. Accounts of Chemical Research, 37, 431-438.

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Dr. Lucas is investigating pluripotent mesenchymal stem cells (PPMSCs) to accomplish tissue regeneration. Lucas has isolated PPMSCs isolated from skeletal muscle or dermis and expanded ex vivo without differentiation. These cells can be induced to form cartilage, bone, skeletal muscle, cardiac muscle, fat, and the cellular components of blood vessels in vitro. In vivo, the cells respond to endogenous inductive factors to form the tissues at the site of implantation. MSCs have the potential to regenerate tissues derived from the mesodermal developmental lineage, which include skeletal muscle, blood vessels, heart, cartilage, tendons, ligaments, bone, hematopoietic tissue, and breast tissue. Projects underway in the Lucas lab include exploring the differentiation and proliferation potential of PPMSCs, exploring the use of PPMSCs in regeneration models for and using PPMSCs to study early genetic and molecular events in differentiation.

Schultz S.S., Abraham S., Lucas P.A. (2006) Stem cells isolated from adult rat muscle differentiate across all three dermal lineages. Wound Repair Regen.14(2):224-31.

Vourc'h P., Lacar B., Mignon L., Lucas, P.A., Young, H.E., Chesselet, M.F. (2005) Effect of neurturin on multipotent cells isolated from the adult skeletal muscle.
Biochem Biophys Res Commun. 24;332(1):215-23.

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David C. Lyden, M.D., Ph.D.
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Dr. Lyden is a major contributor to the study that showed that bone marrow harbors the cells that are essential to building the lining of tumor blood vessels, a finding which may lead to more targeted treatment for cancer, including the use of antibodies to block the mobilization of bone marrow cells. Most recently, Lyden co-authored work demonstrating that bone-marrow-derived vascular stem cells contribute to angiogenesis and growth of certain tumors.

Garcia-Barros, M., Paris, F., Cordon-Cardo, C., Lyden, D., Rafii, S., Haimovitz-Friedman, A., Fuk, Z., Kolesnick, R. (2003) Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science, 300 (5622) 1155-9.

Rafii, S., Lyden D., Benezra, R., Hattori, K., Heissig, B. (2002). Vascular and hematopoietic stem cells: novel targets for anti-angiogenesis therapy? Nature Reviews-Cancer 2(11); 826-35.

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The primary interest of Professor Maletic-Savatic's laboratory is to discern the mechanisms that determine the fate and function of neural stem cells (NSC) and to apply that knowledge to a variety of human brain diseases. In animal studies, transgenic mice are used to visualize NSC in the living brain by high-resolution multiphoton microscopy, and metabolomics to track them by micro MRI spectroscopy. Maletic-Savatic is investigating how electrical stimulation affects lineage preference when NSC differentiate, and how microglia controls NSC survival rate. The lab's discovery of a specific NSC metabolomic biomarker has enabled them to visualize NSC in the human brain. They are conducting studies to identify mobilization of NSC in human neurological disorders, such as multiple sclerosis, and to discern their role in development of human depression.

Mignone JL, Roig-Lopez JL, Fedtsova N, Schones DE, Manganas LN, Maletic-Savatic M, Keyes WM, Mills AA, Gleiberman A, Zhang MQ, Enikolopov G. (2007). Neural potential of a stem cell population in the hair follicle. Cell Cycle 6(17):2161-70. Epub 2007 Jun 13.

Manganas LN, Maletic-Savatic M. (2005). Stem cell therapy for central nervous system demyelinating disease. Curr Neurol Neurosci Rep 5 (3):225-31.

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Professor Mao has expertise in several lineages of stem cells and their application in de novo formation or regeneration of tissues and organs. His research has shown that a synovial joint condyle can be formed in vivo with two stratified layers of cartilage and bone, both derived from a single population of mesenchymal stem cells. The Mao lab has demonstrated that synergistic actions of mesenchymal and hematopoietic stem cells lead to vascularized tissue and organ formation. The team has demonstrated that stem cells can be tracked in vivo and in real time using bioconjugated quantum dots and nanoparticles. Recently, they have shown that vascularized soft tissue can be generated from adult stem cells, providing the possibility to heal defects resulting from facial and breast cancer with stem cells.

Moioli EK, Hon, L, Mao JJ. (2007) Inhibition of osteogenic differentiation of human mesenchymal stem cells. Wound Repair and Regeneration 15:413-421.

Mao JJ, Giannobile, WV, Helms JA, Hollister, SJ, Krebsbach, PH, Longaker, MT, Shi, S. (2006). Craniofacial Tissue Engineering by Stem Cells. J Dent Res 85(11):966-979.

Moioli EK, Hong L, Guardado J, Clark PA, Mao JJ. (2006). Sustained release of TGFbeta3 from PLGA microspheres and its effect on early osteogenic differentiation of human mesenchymal stem cells. Tissue Eng. 12(3):537-46.

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Robert Martienssen, Ph.D.
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The shoot meristems of plants comprise stem cells, peripheral derivatives and primordial initials from which leaves, branches and flowers arise. Ramosa1 in maize and symmetric Leaves1 (AS1) in Arabidopsis inhibit stem cell fate mediated by Ramosa2 in maize, which is an AS1 target in Arabidopsis. AS1 coats mitotic chromosomes indicating a role for chromatin which Professor Martienssen is examining using profiling and genetic analysis. His research has shown that RNA interference maintains heterochromatin during S phase which has implications for stem cell proliferation and renewal in both animals and plants.

Irvine, D, Zaratiegui, M., Tolia, N., Chitwood, D., Goto, D., Vaughn, M., Joshua-Tor, L., and Martienssen, R. (2006). Argonaute slicing is required for heterochromatic silencing and spreading. Science 313, 1134-1137.

Vollbrecht, E. Springer, P.S., Goh, L., Buckler, E., and Martienssen, R. (2005). Architecture of floral branch systems in maize and related grasses. Nature 436, 1119-1126.

Byrne M.E., Barley R., Curtis M., Arroyo J.M., Dunham M., Hudson A. and R. Martienssen (2000) Asymmetric leaves1 mediates leaf patterning and stem cell function in Arabidopsis. Nature 408, 967-971.

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Carol Ann Mason, Ph.D.
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Professor Mason has identified program genes that are important for cell identity in the developing retina, the light-sensitive tissue at the back of the eye. These genes direct retinal axon growth through the optic chiasm, where retinal fibers redistribute to one or the other side of the brain toward visual targets. This circuit is crucial for binocular vision. Current experiments involve in utero gene delivery into the normal and albino mouse retina to rescue defects in visual system circuitry. With these studies, Mason's lab works to develop gene therapy and cell transplantation to reduce visual defects in humans.

Petros, T.J., Williams, S.E. and Mason, C.A. (2006) Temporal regulation of EphA4 in astroglia during murine retinal and optic nerve development. Mol.Cell. Neurosci. 32:49-66

Manzini, M.C, Joseph, D.J., MacDermott, A.B., and Mason, C.A. (2007) Differential effects of AMPA receptor activation on survival and neurite integrity during neuronal development. Mol.Cell. 35:328-338.

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Margot Mayer-Prosche, Ph.D.
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The discovery of novel precursor cells involved in generation of the glial cells of the eNS opened multiple avenues of research in the Mayer-Prosche laboratory. Glial cells are formed via their precursor cells at specific windows during development where they perform critical functions specific to particular developmental stages. These windows of precursor cell function coincide with windows of vulnerability of brain development to many extrinsic insults. Professor Mayer-Prosche's research focus is to determine how disturbances of stem and precursor cell function contributes to human disease and whether precursor cells can be exploited for use in repair strategies.

Strathmann, F., Xi Wang and M. Mayer-Proschel. (2007) Identification of two novel glial-restricted cell populations in the embryonic telencephalon arising from unique origins BMC Dev. Biol 7:33.

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Mark F. Mehler, M.D.
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Dr. Mehler's stem cell interests are centered on defining the regional localization and the biological properties of neural stem cells during embryonic and postnatal development and in the mature and the aging mammalian brain. Stem cells are also being utilized as "biological probes" to elucidate the pathogenesis of a spectrum of complex and poorly understood acquired and genetic nervous system disorders. These insights have allowed the laboratory to "reprogram" specific regional stem and progenitor cell subpopulations both in vitro and in vivo to acquire the cellular properties of specific neuronal and glial subtypes invariably affected in different classes of neurological diseases. The overall aim of these studies is to identify innovative approaches to brain repair by activation/molecular modulation of latent neural stem cell pools throughout the neuroaxis to engage in selective regeneration of those cell types and neural network connections that have been compromised in specific disease states in the adult brain.

Gokhan, S., Mehler, M.F. (2001). Basic and Clinical Neuroscience Applications of Embryonic Stem Cells. The New Anatomist 265:142-156.

Van De Water, T., Kojima, K., Tateya, I., Ito, J., Malgrange, B., Lefebvre, P.P., Staecker, H., Mehler, M.F. (2004). Stem Cell Biology of the Inner Ear and Potential Therapeutic Applications, In: Adult Stem Cells, Turksen, K. (ed.), Humana Press, New Jersey, pp. 269-288 (2004).

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Anand N. Mhatre, M.D., Ph.D.
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The long-term objective of Professor Mhatre's laboratory is to apply adult stem cells as therapeutic vectors for treating hearing loss resulting from degeneration of the cochlear sensory hair cells and/or the primary auditory neurons. The stem cells used in these studies carry a marker gene for unambiguous and rapid identification in the implanted cochlea. Both in vitro and in vivo models are used to assess and identify the induction signals provided by specific growth factors and microenvironments - specific cells and tissues - in effecting differentiation and targeting of the stem cells in the implanted cochlea. Structural and functional integration of the implanted stem cells is assessed through histopathological and auditory testing of the implanted cochlea, treated with ototoxins to induce sensory cell degeneration and hearing loss.

Mhatre AN, Li J, Kim Y, Coling DE, Lalwani AK. (2004) Cloning and developmental expression of nonmuscle myosin IIA (Myh9) in the mammalian inner ear. J Neurosci Res. 76(3):296-305.

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Alea A. Mills, Ph.D.
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The Mills laboratory is currently focused on assessing the role of tumor suppressor CHD5 in stem cells. They discovered that CHD5 functions as a tumor suppressor by serving as a master switch for a tumor suppressive network. CHD5 facilitates expression of Ink4/Arf, a locus that is also regulated by Bmi1, a protein that plays a key role in both neural and hematopoietic stem cells. Their findings suggest that CHD5 competes with Bmi1 to modulate stem cell fate/renewal. A second area of research interest is how the p53-related protein p63 affects cancer stem cells. Mills has shown that p63 depletion compromises proliferation by inducing a program of cellular senescence, thereby providing tumor protection while simultaneously contributing to aging. Current efforts are providing mechanistic insight into how p63 negatively impacts senescence to promote proliferation of epithelial stem cells, the cell type responsible for the most common human malignancy--carcinoma. These studies will help to elucidate the genetic basis of stemness.

Keyes WM, Wu Y, Vogel H, Guo X, Lowe SW, Mills AA.(2005) p63 deficiency activates a program of cellular senescence and leads to accelerated aging. Genes Dev. 19(17):1986-1999.

Bagchi A, Papazoglu C, Wu Y., Capurso D, Brodt M, Francis D, Bredel M, Vogel H, Mills AA. (2007) CHD5 is a tumor suppressor at human 1p36. Cell 128: 459-475.

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Ana Milosevic, PhD
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Glioblastoma, the most common brain tumor, is composed of a heterogeneous population of cells, some of which are the progeny of tumor-initiating cell and others are recruited into the tumor. Majority of cells in the tumor mass are expressing stem cell and immature glia markers. Our interest is to characterize the relevant cell subpopulations in the tumor mass as a first step to developing a targeted therapy. We will achieve this by combining the glioblastoma model developed in the Holland laboratory at MSKCC with the method of the polysome profiling developed in the Heinz laboratory at RU. We will use this technology to determine the actively translated mRNAs in stem cells, which in turn would provide immense insight into the biology of these cells and their role in cancer biology.

Mhatre AN, Li J, Kim Y, Coling DE, Lalwani AK. (2004) Cloning and developmental expression of nonmuscle myosin IIA (Myh9) in the mammalian inner ear. J Neurosci Res. 76(3):296-305.

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Vivek Mittal, Ph.D.
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Professor Mittal's laboratory is interested in the analysis of BM-derived stem/progenitor cells that contribute to cancer progression. The lab will focus on the role of bone marrow-derived endothelial stem/progenitor cells in angiogenesis-mediated progression of primary tumors, initiation of metastasis and development of micrometastasis to macrometastases. The clinical translation of these cells will be evaluated with respect to both their prognostic and therapeutic value. The utility of specific bone marrow stem cell populations in regenerating ischemic heart and limbs will be studied.

Ruzinova, M.B., R.A. Schoer, W. Gerald, J.E. Egan, P.P. Pandolfi, S. Rafii, K. Manova, V. Mittal, and R. Benezra (2003). Effect of angiogenesis inhibition by Id loss and the contribution of bone marrow derived endothelial precursor cells in spontaneous murine tumors, Cancer Cell. 4: 277-289.

Nolan, D.J., Ciarrocchi, A., Mellick, A.S., Jaggi, J.S., Bambino, K., Gupta, S., Heikamp, E., McDevitt, M.R., Scheinberg, D.A., Benezra, R. and Mittal, V. (2007) Bone marrow-derived endothelial progenitor cells are a major determinant of nascent tumor neovascularization. Genes and Development, 21,1546-1558.

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Hiroshi Mitusmoto, M.D., D.Sc.
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Dr. Hiroshi Mitsumoto is interested in research that involves patient care and works to find the cause and treatment of ALS. He participates in a number of clinical trials of ALS and helps his colleagues to lead major, NIH-funded clinical trials. He is interested in exercise in patients with ALS, in terms of improving muscle strength and ALS function, but concurrently, he is involved in researching the effects of cycle exercise to experimentally generate oxidative stress in patients. He is participating in the nuclear transfer of ALS patient fibroblasts to fertilized human oocytes to generate the patient's ES cells.

Levy G, Kaufmann P, Buchsbaum R,Montes J, Barsdorf A, Arbing A, Battista V, Zhou X, Mitsumoto H, Levin B, Thompson JLP. (2006). A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS. Neurology 66:660–663.

Mitsumoto H, Floyd A, Tang MX, Kaufmann P, Battista V, Hristova A, Pullman SL. (2006). Transcranial magnetic stimulation for upper motor neuron involvement in amyotrophic lateral sclerosis (ALS). Suppl Clin Neurophysiol. 59:327-32.

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Kateri A. Moore, D.V.M., Ph.D.
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The interests of Dr. Kateri Moore's laboratory are focused on a cellular and molecular understanding of the hematopoietic stem cell niche. Previously, Moore's lab developed a molecular profile of an in vitro surrogate stem cell niche and established the Stromal Cell Database containing these data. From this profile they have identified many candidate molecular mediators of hematopoiesis that may be clinically relevant in manipulating stem cell populations in vitro prior to in vivo transplantation therapy. The lab is also using genetically modified mice as model systems to both manipulate and visualize stem cells in vivo under normal homeostasis and after perturbation.

Moore, K. A. ,Lemischka, I.R. (2006). Stem Cells and Their Niches. Science, 311:1880-1885.

Hackney, J.H., Charbord, P, Brunk, B., Stoeckert, C., Lemischka, I.R., Moore, K.A., (2002). A molecular profile of a hematopoietic stem cell niche. Proc. Natl. Acad. Sci., U.S.A., 99:13061-6.

Ivanova, N.I., Dimos, J.T., Schaniel, C., Hackney, J.A., Moore, K.A., Lemischka, I.R., (2002). A Stem Cell Molecular Signature. Science 298:601-604.

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Malcolm A.S. Moore, D. Phil.
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Dr. Moore's interest in hESC is in developing methods of differentiating these to hematopoietic stem cells, T lymphocytes, endothelial cells and cardiomyocytes that could be used therapeutically. Professor Moore's interest in cancer stem cells in leukemia, myeloma and solid tumors is to identify differences (genetic, epigenetic, functional) between normal and malignant stem cells and develop therapies that selectively target cancer stem cells.

Shi-Jiang Lu S-J, Feng Q, Caballero S, Chen Y, Moore MAS, Grant MB, Lanza RB. Generation of Functional Hemangioblasts From Human Embryonic Stem Cells. Nature Methods. 2007;4:501-9.

Moore MAS, Dorn DC, Schuringa JJ, Chung KY, Morrone G. Constitutive activation of Flt3 and STAT5A enhances self-renewal and alters differentiation in normal and hematopoietic stem cells. Exp Hematol 2007, 35 (Suppl 1.);105-116.

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Rebecca Morris, Ph.D.
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Dr. Morris is isolating the target cells in skin carcinogenesis with the goal of understanding the regulation of adult stem cell number and proliferative potential in normal and abnormal epidermis. Her laboratory has recently developed a transgenic mouse model for visualizing the progeny of hair follicle stem cells as they develop into skin tumors. She is currently determining whether the hair follicle progeny become tumor stem cells. Other studies in the Morris laboratory are focused on the role of bone marrow derived stem cells in the pathogenesis of skin cancer, and development of culture systems for human hair follicle stem cells.

Popova NV, Morris RJ. (2004) Genetic regulation of mouse stem cells: identification of two keratinocyte stem cell regulatory loci. Curr Top Microbiol Immunol. 280:111-37.

Kljuic A, Bazzi H, Sundberg JP, Martinez-Mir A, O'Shaughnessy R, Mahoney MG, Levy M, Montagutelli X, Ahmad W, Aita VM, Gordon D, Uitto J, Whiting D, Ott J, Fischer S, Gilliam TC, Jahoda CA, Morris RJ, Panteleyev AA, Nguyen VT, Christiano AM. (2003) Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell 113(2):249-60.

Popova NV, Teti KA, Wu KQ, Morris RJ. (2003) Identification of two keratinocyte stem cell regulatory loci implicated in skin carcinogenesis. Carcinogenesis 24(3):417-25.

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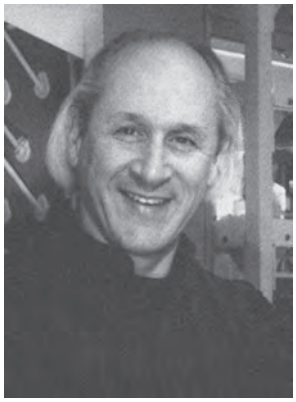

Mark Noble, Ph.D.
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Noble's central goal is the creation of a comprehensive approach to stem cell medicine that extends far beyond the use of cell transplantation for tissue repair. Professor Noble's research includes cell discovery, identification of optimal cell types for tissue repair, analysis of developmental maladies, discovery of universal principles of division and differentiation control, and physiological analysis of stem/progenitor cell function. He also analyzes biological and molecular effects of toxicant exposure on the developing nervous system, analysis of adverse side effects of chemotherapy on the nervous system and development of new approaches to cancer treatment that cause less harm to normal cells.

Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M., Noble, M. (2006) CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J. Bio. 5:22.

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Benjamin Ohlstein, M.D., Ph.D.
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Professor Ohlstein is using lineage labeling to identify intestinal stem cells in Drosophila midguts, which give rise to enterocytes and enteroendocrine cells. As in vertebrates, Notch signaling is required to produce an appropriate fraction of enteroendocrine cells. Unlike other Drosophila stem cells, intestinal stem cells (ISCs) do not reside in a niche with a specific partner stromal cell and may be controlled differently than other stem cells. Ohlstein's goals are to determine the mechanisms that regulate maintenance of ISCs and the differentiation of their daughters into daughter cells. Ohlstein's studies will also serve as an excellent model for understanding these mechanisms in the vertebrate gut.

Buszczak M. Paterno S. Lighthouse , Bachman J, Planck J, Owen S, Skora AD, Nystul TG, Ohlstein B, Allen A, Wilhelm JE, Murphy TD, Levis RW, Matunis E, Srivali N, Hoskins RA, Spradling AC. The Carnegie protein trap library: a versatile tool for Drosophila developmental studies. Genetics. 2007 Mar; 175 (3): 1505-31. Epub 2006 Dec 28.

Ohstein B., Spradling A. Multipotent Drosophila intestinal stem cells specify daughter cell fates by differential notch signaling. Science 2007 Feb 16: 315 (5814 988-92.

Ohlstein B, Spradling A. The adult Drosophila posterior midgut is maintained by pluripotent stem cells. Nature. 2006 Jan 26; 439 (7075): 470-4. Epub 2005 Dec 7.

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Juan Oliver, M.D.
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Dr. Oliver is working in the laboratory to provide analysis of molecular mechanisms involved in renal vascular development; isolation of growth factors and adhesion molecules involved in this process. Oliver's clinical research is focused on analysis of mechanisms involved in vasodilation of shock.

Oliver JA, Maarouf O, Cheema FH and Al-Awqati Q. (2004). The renal papilla is the "niche" for adult kidney stem cells. Journal of Clinical Investigation 114:795-804.

Oliver JA. (2004) Adult renal stem cells and renal repair. Current Opinion in Nephrology and Hypertention 13: 17-22.

Oliver JA, Barasch J, Yang J Herzlinger D, Al-Awqati Q. (2002) Metanephric mesenchyme contains embryonic renal stem cells. American Journal of Physiology 283:F700-F809.

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Catherine Ovitt, Ph.D.
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Radiation treatment of head and neck cancers, and autoimmune diseases such as Sjögren's syndrome, cause irreversible cellular damage in the salivary glands that usually renders them atrophic. The long-range goal of our work is to identify and characterize salivary gland progenitor cells, for use in the repopulation of damaged glands. We have identified a distinct population of cells with the potential to differentiate into the major cell types of the salivary gland. Current research is focused on the role of these precursor cells in both differentiation and regeneration of the salivary gland; and on developing techniques to cultivate, expand and transplant them, in order to test their ability to contribute to gland repair.

Chen, J., Bush, J.O., Ovitt, C.E., Lan, Y., Jiang, R.T., (2007) The TGF-beta pseudoreceptor gene Bambi is dispensable for mouse embryonic development and postnatal survival. Genesis. Aug; 45 (8):482-6.

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Patrick Paddison, Ph.D.
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Paddison's research aims to; identify genes required for self-renewal and lineage specification in embryonic and adult stem cells using in vitro functional genetic approaches, identify genes promoting stem cell-driven cancers; and study the application of RNAi technology for the creation of desirable cell types for cell replacement therapies. Dr. Paddison is working to apply RNAi in mouse embryonic stem cells to functionally dissect self-renewal and lineage specification using focused gene sets. The lab is expanding screens for genome-wide coverage and incorporating human ES cells, neural stem cells, and glioma stem cells.

Paddison, P. J., Caudy, A. A. and Hannon, G. J. (2002) Stable suppression of gene expression by RNAi in mammalian cells. Proc. Natl. Acad. Sci. USA. 99:1443-1448.

Silva, J.M., Li, M.Z., Chang, K., Ge, W,, Golding, M.C., Rickles, R.J., Siolas, D., Hu, G., Paddison, P.J., Schlabach, M.R., Sheth, N., Bradshaw, J., Burchard, J., Kulkarni, A., Cavet, G., Sachidanandam, R., McCombie, W.R., Cleary, M.A., Elledge, S.J., and Hannon, G.J. (2005) Second-generation shRNA libraries covering the mouse and human genomes. Nat Genet. 37:1281-8.

Schaniel, C., Li, F., Moore, T., Lemischka, I., & Paddison, P.J. (2006) Delivery of short hairpin RNAs into mouse embryonic stem cells. Nature Methods 3:397-400.

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James Palis, M.D.
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Dr. Palis' aim is to elucidate the cellular and molecular events underlying the initiation of hematopoiesis in the mammalian embryo by investigating the ontogeny of unipotential and multipotential hematopoietic progenitors and their origin from hemangioblast precursors. The Palis lab has identified an embryonic erythroid precursor with extensive self-renewal properties. These studies will ultimately produce insights into the ontogeny, regulation and expansion of the hematopoietic system and lead to improved treatment of marrow failure syndromes and leukemias.

Palis J, Chan RJ, Koniski A, Patel R, Starr M, Yoder MC. (2001). Spatial and temporal emergence of high proliferative potential hematopoietic precursors during murine embryogenesis. Proceedings National Academy of Science USA 98:4528-4533.

McGrath KE, Koniski AD, Malik J, Palis J. (2003) Circulation is established in a step-wise pattern in the mammalian embryo. Blood 101:1669-1676.

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Janet L. Paluh, Ph.D.
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Our knowledge of the hESC 3D microenvironment in culture remains extremely basic and is a prerequisite for robust biomedical therapies. We have minimal information on homogeneity or heterogeneity of this population, whether subtle dedifferentiation and differentiation are occurring and how intercellular cues generate intracellular changes. By time lapse microscopy, Professor Paluh will generate a spatiotemporal map of individual stem cell behavior in the hESC colony to allow tracking of immediate responses to cues and the subsequent alterations to cells when stimulated towards differentiation. Initial analysis uses cytoskeletal biomarkers. A more comprehensive library of biomarkers for high throughput studies will be developed.

Mayer, C.L., Filopei, J., Batac, J., Alford, L. and J.L. Paluh (2006) An extended signaling pathway for Mad2p in anaphase includes microtubule organizing center proteins and multiple motor-dependent transitions. Cell Cycle. 5: 1456-1463.

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Virginia Papaioannou, Ph.D.
Professor, Genetics & Development.
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Professor Papaioannou is studying the genetic control of early mammalian development, from the first cleavage of the fertilized zygote through implantation, gastrulation, and early organogenesis. The lab uses mouse embryonic stem cells to produce mutations by genetic engineering. In addition, two projects in the Papaioannou lab are related directly to stem cells. One is the derivation of human stem cell lines from clinically dead human embryos obtained from in-vitro fertilization centers. The second is testing the potential of mouse embryo pancreatic stem cell/precursors in the treatment of type 1 diabetes using a mouse model.

Naiche, L. A., Harrelson, Z., Kelly, R. and Papaioannou, V. E. (2005). T-box genes in vertebrate development. Annual Review of Genetics 39:219-239. 116.

Jerome-Majewska, L. A., Jenkins, G. P., Ernstoff, E., Zindy, F., Sherr, C. J. and Papaioannou, V. E. (2005). Tbx3, the ulnar-mammary syndrome gene, and Tbx2 interact in mammary gland development through a p19Arf/p53-independent pathway. Developmental Dynamics 234:922-933.

Kelly, R. G., Jerome-Majewska, L. A. and Papaioannou, V. E. (2004). Regulation of branchiomeric myogenesis by the del22q11.2 candidate gene Tbx1. Human Molecular Genetics 13:2829-2840.

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George Plopper, Ph.D.
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The Plopper laboratory is primarily concerned with determining how cellular adhesion to extracellular matrix (ECM) molecules elicits specific cellular responses, including growth, differentiation, and migration. This lab works with human mesenchymal stem cells adhering to purified ECM proteins as our model system. Our general hypothesis is that adhesion to ECM molecules activates a subset of intracellular signaling pathways associated with integrin receptors, and that this signaling controls cell behaviors by modulating the organization of the cytoskeleton. Collectively, these studies should increase understanding of the mechanisms governing hMSC differentiation and how to capitalize on this knowledge in tissue engineering applications.

Ward, D.F., Salasznyk, R.M., Klees, R.F, Backiel, J., Agius, P., Boskey, A., Bennett, K., and Plopper, G.E. (2007) Mechanical strain enhances ECM induced cell fate determination and promotes osteogenic differentiation of human mesenchymal stem cells through the ERK MAPK pathway. Stem Cells & Development, 16(3): 467-480.

Salasznyk, R.M., Klees, R.F, Vandenberg, S., Bennett, K, and Plopper, G.E. (2007) Laminin-5 activates extracellular matrix production and osteogenic gene focusing in human mesenchymal stem cells. Matrix Biology, Mar;26(2):106-14.

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An increasing number of neurological diseases are thought to be caused or exacerbated by defects in glial cells. Consequently, Professor Proschel has focused on the study of glial precursor cells. His research program encompasses three distinct, yet complementary areas of interest: the cell-biological analysis of neurological diseases with an emphasis on the role of neural precursors, the molecular analysis of the astrocyte lineage (including signals that promote the generation of astrocyte precursors and distinct classes of astrocytes), and the application of glial progenitors and their derivatives for treatment of neurological diseases, including spinal cord injury.

Li Z, Dong T, Pröschel C, Noble M. (2007) Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. PLos Biol.5(2):e35.

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Steven Pruitt, Ph.D.
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Dr. Pruitt's laboratory is studying both embryonic and somatic stem cells. Much of the work on somatic stem cells is being performed using mouse models where the central focus of the work is on understanding the role of these cells in age-related dysfunctions including cancer. Since many age-related changes are ultimately attributable to genomic instability, an important focus of this work is on mechanisms responsible for accurate replication of the genome and the role that a stem cell based tissue organization plays in minimizing the burden of repeated replication cycles. Work on embryonic stem cells, both mouse and human, focuses on mechanisms of cell lineage determination and the interaction of these mechanisms with changes required for oncogenic transformation.

Pruitt SC, Bailey KJ, Freeland A. (2007) Reduced Mcm2 Expression Results in Severe
Stem/Progenitor Cell Deficiency and Cancer. Stem Cells. Aug 23; [Epubahead of print].

Maslov AY, Bailey KJ, Mielnicki LM, Freeland AL, Sun X, Burhans WC, and Pruitt SC. Stem/progenitor cell specific EGFP expression driven by the endogenous Mcm2 promoter. Stem Cells. 2006; [Epub ahead of print]; Stem Cells 2007 Jan;25(1):132-8.

Maslov AY, Barone TA, Plunkett RJ, Pruitt SC. Neural stem cell detection, characterization and age related changes in the sub-ventricular zone of mice. (2004). J Neurosci 24:1726-1733.

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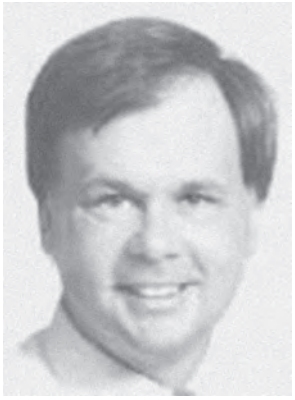

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Activation of undifferentiated mesenchymal stem cells and committed progenitors in the marrow space and periosteum of bone is one of the initial steps in skeletal repair. Recently, much research has been aimed at devising ways to modulate the stromal cells with the ultimate goal of controlling skeletal metabolism, including the processes of fracture repair. With relevance to identifying a new agent to accelerate the healing process, parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) have been documented to be potent in the expansion of progenitor populations and the regulation of differentiation of these cells. An emerging concept regarding the role of PTH/PTHrP in chondrogenesis and endochondral bone formation states that both of these hormones play an important role in regulating the pool of undifferentiated mesenchymal stem cells available for growth plate expansion and fracture callous formation.

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The major focus of the Rafii laboratory is to isolate and characterize known and novel adhesion and membrane-bound cytokines expressed by endothelium that regulate proliferation and adhesion of hematopoietic stem cells and their progenitors. To this end, they have utilized expression cloning strategy using BMEC and FLEC cDNA libraries to screen for known and novel adhesion/homing receptor and membrane-bound cytokines that regulate proliferation of hematopoietic progenitors. In collaboration with Dr. R. Crystal, adenoviral vectors overexpressing cytokines and adhesion molecules are being used to examine their function in long-term CD34+ progenitor-endothelial coculture studies. Direct introduction of adenoviral vectors expressing stem cell active cytokines into hematopoietic microenvironment provides novel approaches for the treatment of acquired or congenital hematological disorders.

Seandel, M., James, D., Shmelkov, S.V., Falciatori, I., Kim, J., Chavala, S., Scherr, D.S., Zhang, F., Torres, R., Gale, N.W., Yancopoulos, G. D., Murphy, A., Valenzuela, D. M., Hobbs, R. M., Pandolfi, P.P. & Rafii, S. (2007) Generation of functional multipotent adult stem cells from GPR125+ progenitors. Nature 449: 346-350.

Milde, T., Shmelkov, S.V., Jensen, K.K., Zlotchendo, G., Petit, I. & Rafii, S. (2007) A novel family of slitrk genes is expressed on hematopoietic stem cells and leukemias. Leukemia 21: 824-827.

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Boris Reizis, Ph.D.
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Stem cells manifest a unique capacity to differentiate into various cell types while maintaining their own number in an undifferentiated state. The unique property of continuous self-renewal is shared among different stem cell types, including pluripotent embryonic stem cells and adult tissue-specific stem cells such as hematopoietic stem cells. Dr. Reizis is investigating the mechanisms regulating stem cell self-renewal, including potential common mechanisms shared by embryonic and adult stem cells, as well as by cancer stem cells.

Caton M.L., Smith-Raska M.R., Reizis B. (2007) Notch-RBP-J signaling controls the homeostasis of CD8- dendritic cells in the spleen. J. Exp. Med. Jun 25 [Epub ahead of print]

Galan-Caridad J.M., Harel S., Arenzana T.L., Hou Z.E., Doetsch F.K., Mirny L.A., Reizis B. (2007). Zfx controls the self-renewal of embryonic and hematopoietic stem cells. Cell. 20 129 (2): 345-57.

Babbe H., Chester N., Leder P., Reizis B. (2007). The Bloom's syndrome helicase is critical for development and function of the alphabeta T-cell lineage. Mol. Cell Biol (5): 1947-59.

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Elizabeth A. Repasky, Ph.D.
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Professor Repasky's studies are aimed at understanding the role of pancreatic cancer stem cells in resistance to immune cell killing, and in particular, their sensitivity to Apo2L/TRAIL, a targeted therapy based on the molecule naturally expressed on activated T lymphocytes which can specifically cause tumor cell death by apoptosis. The lab has found that patient tumors exhibit a wide range of responses, from extremely sensitive to extremely resistant. The response however, can be enhanced by combining Apo2L/TRAIL with chemotherapy. The lab has observed that even in cases where the tumors underwent regression and remained sensitive to retreatment, tumors began to regrow when treatment was ended. The identification of pancreatic cancer stem cells led us to the intriguing speculation that cancer stem cells within these tumors may be particularly resistant to Apo2L/TRAIL, surviving and repopulating a recurring tumor. This is a critical question because although cancer stem cells have been identified in many tumor types, their significance in the clinical treatment of malignancies is, as yet, unknown.

Hylander, B.L., Pitoniak, R., Penetrante, R.B., Gibbs, J.F., Oktay, D., Cheng, J. and Repasky, E.A. (2005) The Anti-Tumor Effect of Apo2L/TRAIL on Patient Pancreatic Adenocarcinomas Grown as Xenografts in SCID Mice. J Translational Medicine 3:22.

Naka, T., Hylander, B.L., Rustum, Y.M., Widmer, M.B. and Repasky, E.A. (2002) Effects of tumor necrosis factor-related Apoptosis-inducing ligand alone and in combination with chemotherapeutic agents on patients' colon tumors grow in SCID mice. Cancer Res; 62:5800-5806.

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Rosemary Rochford, Ph.D.
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Professor Rochford has been using SCID mice to examine B cell lymphomagenesis. Rochford is also interested in expanding this model to develop humanized SCID mice support erythropoeisis and expansion of human red blood cells. With this model, the Rochford laboratory will test novel anti-malaria drugs in collaboration with Walter Reed Army Medical Center. There is currently no adequate animal model system for testing of anti-malaria drugs.

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Christopher Roman, Ph.D.
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Research focuses on transcription factors and receptors that control lymphocyte development and function, with the goal of identifying the normal molecular circuitry that becomes deranged in immunological diseases. A priority is the transcription factors TFE3 and TFEB, which are mutated in renal malignancies. Using approaches that include transgenic mice and hematopoietic stem cell transplantation, a major discovery was that TFE3 and TFEB are critical activators of CD40L expression necessary for protective antibody responses. These studies opened new avenues for research into better understanding and treating autoimmune diseases and B cell malignancies in which CD40L expression is abnormal and drives disease.

Huan C, Sashital D, Hailemariam T, Kelly ML, Roman CA. (2005). Renal Carcinoma-associated Transcription Factors TFE3 and TFEB Are Leukemia Inhibitory Factor-responsive Transcription Activators of E-cadherin. J Biol Chem. 280(34):30225-35. Epub 2005 Jun 30.

Guloglu, F. B., and Roman, C.A.J. (2006) Precursor B cell receptor Signaling Can Be Uncoupled from Surface Expression. J Immunol. Jun 1;176(11):6862-72.

Huan C, Kelly ML, Steele R, Shapira I, Gottesman SR, Roman C A. (2006). Transcription factors TFE3 and TFEB are critical for CD40 ligand expression and thymus-dependent humoral immunity. Nat Immunol. 7(10):1082-1091. Epub 2006 Aug 27.

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Michael Rosen, M.D.
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Dr. Rosen is investigating stem cell therapies for cardiac arrhythmias, myocardial regeneration and cancer therapy. For arrhythmias Rosen has developed hMSC-based pacemakers, to create a more physiologic outcome than electronic pacemakers. For cardiac regeneration he has enhanced the ability of hMSCs to follow a cardiac lineage, thereby recovering increased mechanical function. In cancer research the Rosen lab has developed an hMSC-based siRNA delivery system to enhance therapeutic targeting strategies. Dr. Rosen's research incorporates hMSCs, cardiac stem cells and most recently human embryonic stem cells as they seek the optimal cell type for each therapeutic need. All studies incorporate use of quantum dots as tracking agents.

Rosen MR. (2006) Are Stem Cells Drugs? The regulation of stem cell research and development. Circulation 114: 1992-2000.

Potapova I, Plotnikov A, Lu Z Danilo P Jr; Valiunas V, Qu J, Doronin S, Zuckerman J, Shlapakova IN, Gao J, Pan Z, Herron AJ, Robinson RB, Brink PR, Rosen MR, Cohen IS: (2004). Human mesenchymal stem cells as a gene delivery system to create cardiac pacemakers, Circ Res 94:952-959.

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Daniel Rosenbaum, M.D.
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The adult mammalian brain contains neural stem and progenitor cells that can proliferate, self-renew, and generate all of the cellular elements of the brain including neurons. During the past few years techniques have been developed which make it possible to isolate and expand, from developing or even adult CNS tissue, cells with properties characteristic of early neural multipotent progenitor or stem cells. These techniques have opened interesting new possibilities for the use of cells for CNS transplantation, neural replacement and brain repair. Rosenbaum's lab is initiating a project which will potentially bring the rapidly expanding area of progenitor cells to bear on the problems of stroke and cerebral ischemia.

Savitz, S.I., Dinsmore, J.H., Wechster, L.R., Rosenbaum, D.M., Caplan, L.R. (2004). Cell therapy for stroke. NeuroRx, 1:406-414.

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Todd K. Rosengart, M.D.
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Division of Cardiothoracic Surgery
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Significant clinical trial and pre-clinical experience exists in the Division of Cardiothoracic Surgery at Stony Brook suitable to the execution of stem cell trials. Dr. Rosengart and his research group share prolonged experience including the conduct of pre-clinical stem cell research and the design, (PDA) regulatory approval and completion of multi-center, collaborative studies. This experience includes Dr. Rosengart's participation in the design of an industry-sponsored study examining the use of skeletal myoblast implantation in open heart surgery patients ("MAGIC", Genzyme), and his oversight of cell therapy studies as part of the NIH -SCCOR in Cardiac Dysfunction DSMB. Dr. Rosengart's pre-clinical work includes his group's use of angiogenic "pre-treatment" of infarcted tissues to improve the survival and functionality of subsequently implanted stem cells.

Retuerto M.A., Beckmann, J.T. Carbray, J., Patejunas G., Sarateanu S., Kane B., Smulevitz, B., McPherson, D, Rosengart, T.K. (2007). Angiogenic pre-treatment enhances myocardial function following cellular cardiomyoplasty with skeletal myoblasts. J Thorac Cardiovasc Surg. 133:78-484.2.

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Zev Rosenwaks, M.D.
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Significant clinical trial and pre-clinical experience exists in the Division of Cardiothoracic Surgery at Stony Brook suitable to the execution of stem cell trials. Dr. Rosengart and his research group share prolonged experience including the conduct of pre-clinical stem cell research and the design, (PDA) regulatory approval and completion of multi-center, collaborative studies. This experience includes Dr. Rosengart's participation in the design of an industry-sponsored study examining the use of skeletal myoblast implantation in open heart surgery patients ("MAGIC", Genzyme), and his oversight of cell therapy studies as part of the NIH -SCCOR in Cardiac Dysfunction DSMB. Dr. Rosengart's pre-clinical work includes his group's use of angiogenic "pre-treatment" of infarcted tissues to improve the survival and functionality of subsequently implanted stem cells.

de Melo-Martin I, Rosenwaks Z, Fins JJ. (2006) New methods for deriving embryonic stem cell lines: are the ethical problems solved? Fertil Steril. 2006 Nov;86(5):1330-2.

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James E. Rothman, Ph.D.
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Stem cell differentiation is a complex, multi-factorial biological process, which the Rothman lab seeks to illuminate. Via genomic screens in embryonic stem cells, Dr. Rothman's goal is to decipher the transcriptional network orchestrating the initial stages of differentiation, thus enabling controlled differentiation into distinctive lineages. Working in the Columbia Genome Center High-Throughput Facility, Rothman is able to sort through literally millions of combinations of genes and morphogenes which will allow the overall pattern of control to reveal itself. His program of high-throughput stem cell biology should deliver a comprehensive overview, opening new approaches for the field, new practical opportunities, as well as key foundations for developing unifying concepts.

Rothman, J.E. (2002). Lasker Basic Medical Research Award. The machinery and principles of vesicle transport in the cell. Nature Med. 8:1059-1062.

Fix, M., Melia, T.J., Jaiswal, J.K. Rappoport, J.Z., You, D., Sollner, T.H., Rothman, J.E. and Simon, S.M. (2004). Imaging single-membrane fusion events mediatedd by SNARE proteins. Proc. Natl. Acad. Sci. USA 101:7311-7316.

Paumet, F, Rahimian, V., Di Liberto, M. and Rothman, J.E. (2005). Concerted Auto Regulation in Yeast Endosomal, t-SNAREs. J. Biol. Chem. 280: 21137-21143.

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Neeta S. Roy, Ph.D.
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The goal of this laboratory is to generate a clinical grade source for cell-replacement based therapies for neurodegenerative diseases like Parkinson's, Amyotrophic Lateral Sclerosis and Multiple Sclerosis. They are developing strategies for the induction of specific neural phenotypes from human embryonic stem cells (HESC) and their subsequent isolation. The lab is currently studying unique ligand/receptor targets, identified from gene expression profiles of adult and fetal human CNS derived cells, in their efficacy to drive HESC towards the desired neural phenotype. The transplantation potential of the cells, thus generated, is extensively studied in appropriate animal models.

Roy N.S., Nakano T., Jiang K., Xuing L., Nedergaard M., and Goldman S.A. (2005) Induction and Hb9 directed isolation of spinal motor neurons from human embryonic stem cells. Exptl. Neurology. 196:224-34.

Roy N.S., Cleren C., Singh, S. K., Yang, L., Beal M.F., and Goldman S.A. (2005) Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes Nat. Med. 12: 1259-68.

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Richard Rubenstein, Ph.D.
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The prion protein (PrP) is a normal cellular glycophosphatidylinositol anchored sialoglycoprotein encoded by the Prnp gene. PrP is expressed in many tissues (with relatively high levels in the brains of animals and humans) and has been shown to be necessary for clinical disease. PrP can display at least two conformations: a normal cellular conformation which is predominantly alpha-helical (PrP^{C}) and a pathological beta-pleated conformation (PrP^{Sc}) associated with prion diseases. Although prion diseases are characterized clinically as a result of neurodegeneration, PrP^{C} expression has been shown to exert a neuroprotective role. It is the goal of Rubenstein's lab to halt and reverse this neurodegeneration by establishing stem cells that are resistant to the infectious agent and using these stem cells in replacement therapy.

Stobart MJ, Parchaliuk D, Simon SLR, LeMaistre J, Lazar J, Rubenstein R, Knox JD. (2007). Differential expression of interferon responsive genes in rodent models of transmissible spongiform encephalopathy disease. Molecular Neurodegeneration 2: 5-17.

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Michel Sadelain, M.D., Ph.D.
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Dr. Sadelain is a geneticist working in the area of gene transfer, the notion of treating a disease by inserting a healthy gene in place of one that is malfunctioning or missing. Dr. Sadelain is trying to insert genes into bone marrow cells and T lymphocytes to reduce the risk of graft-versus-host disease, while preserving the antileukemic effect of the bone marrow transplantation. Another of Dr. Sadelain's goals is to enhance the use of T lymphocytes as therapeutic tools by targeting them to cancer cells, making sure that they go where they should in the body to kill tumor cells. Sadelain is seeking to improve gene transfer and gene expression in blood-forming cells and cells of the immune system. His ultimate goal is to use gene transfer mediated by retroviruses to create improved treatments for genetic disorders, such as sickle cell anemia, and for cancer.

May C, Rivella S, Callegari J, Heller G, Gainsler KML, Luzzatto L, Sadelain M. (2000). Therapeutic haemoglobin synthesis in _-thalassemic mice expressing lentivirus-encoded human _-globin. Nature 406: 82-86.

Samakoglu S, Lisowski L, Budak-Alpdogan T, Usachenko, Acuto S, DiMarzo R, Maggio A, Zhu P, Tisdale JF, Riviere, Sadelain M. (2006) A genetic strategy to treat sickle cell anemia by coregulating globin transgene expression and RNA interference. Nature Biotechnology. (1): 89-94.

Chang A, Stephan M, Sadelain M. (2006). Stem cell-derived erythroid cells mediate long-term systemic protein delivery. Nature Biotechnology. (8):1017-21.

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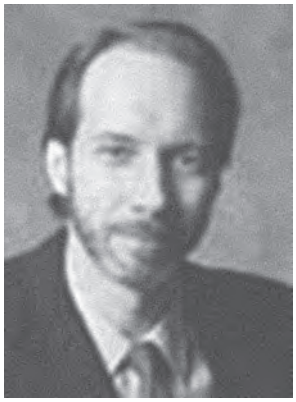

Thomas P. Sakmar, M.D.
Richard M. & Isabel P. Furlaud Professor
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Dr. Sakmar's research program focuses on the molecular mechanisms that control self-renewal and differentiation of stem cells. In collaboration with Prof. Ching-Hwa Sung of Weill-Cornell Medical College, Sakmar's lab has identified a novel G protein-regulatory molecule, AGS2/Tctex-l, which is enriched in neural stem cells of the developing neocortex. Dr. Sakmar's lab will characterize the functional interaction between AGS2/Tctex-1 and G proteins in neural stem cells and human embryonic stem cells (hESCs) and will elucidate the structural basis of the interaction to develop a screening strategy to search for small molecules that can modulate stem cell fate determination.

Sachdev, P., Menon, S., Kastner, D. B., Chuang, J. Z., Yeh, T. Y., Conde, C., Caceres, A., Sung, C. H. & Sakmar, T. P. (2007). G Protein beta-gamma subunit Interaction with the Dynein Light-Chain Component Tctex-1 Regulates Neurite Outgrowth. EMBO J 26:2621-2632.

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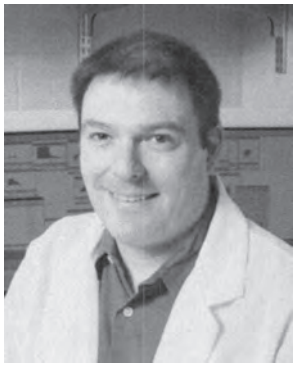

Derek Sant'Angelo, Ph.D.
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The mouse has proven to be an invaluable organism for investigation of the immune system. Significant differences with the human immune system have led to several missteps in translational efforts, however. Therefore, Dr. Sant'Angelo is interested in generating mouse models that have fully humanized immune systems. Secondly, Sant'Angelo's lab is interested in the potential of modifying T cell activities via gene transfer in an effort to enhance or limit immune responses.

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Stewart S. Sell, M.D.
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Dr. Sell's laboratory is investigating bone marrow derived stem cells to determine if these cells give rise to breast or liver cancer in animals. The lab is also exploring whether breast cancer stem cells from transgenic mice can be blocked by small molecular inhibitors or inhibitory RNA. Additionally, Sell is working to determine if premature aging in mutated p53 mice can be reversed by transplantation of bone marrow from normal mice, and can aging can be accelerated in normal mice by transplantation of bone marrow cells from premature aging mice. Beyond cancer and aging, they are examining tissue renewal to determine if a cell derived from fetal tissue stem cells (STO cells) are able to repopulate adult organs and to survive transplantation to immune-incompatible individuals.

Koch KS, Son K-W, Maehr R, Pellicciotta I, Ploegh, HL, Sanetti M, Sell S, Leffert HL. (2006). Immune-privileged embryonic Swiss mouse STO and STO cell-derived progenitor cells: MHC and cell differentiation antigen expression resemble those of human embryonic stem cell lines. Immunology. 119:98-115.

Sell S. (2006). Potential gene therapy for cancer stem cells. Current Gene Therapy. 6:579-591.

Sell S. (2006). Stem cells in hepatocarcinogenesis. Cell Science Reviews, ISN NO. 1742-8130.

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David A. Shafritz, M.D.
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Dr. Shafritz's research is directed at repopulating the liver with transplanted cells, using adult liver cells, activated adult liver progenitor cells, fetal liver stem/progenitor cells and embryonic stem cells. The Shafritz lab uses a variety of rat and mouse cell transplantation models with and without liver injury and are conducting preliminary studies with human cord blood cells and human ES cells. The lab's most significant finding to date is thirty percent repopulation of normal adult rat liver with fetal liver stem/progenitor cells that differentiate into mature hepatocytes and bile duct epithelial cells are structurally and functionally incorporated into the liver parenchyma for the lifetime of the recipient.

Shafritz, D.A., Oertel, M., Menthena, A., Nierhoff, D., Dabeva, M.D. (2006) Liver stem cells and prospects for liver reconstitution by transplanted cells. Hepatology. 43(2 Suppl 1):S89-98.

Gouon-Evans, V., Boussemart, L., Gadue, P., Nierhoff, D., Koehler, C.I., Kubo, A., Shafritz, D.A., Keller, G. (2006) BMP-4 is required for hepatic specification of mouse embryonic stem cell-derived definitive endoderm.. Nat Biotechnol. (11):1402-11. Epub 2006 Nov 5.

Dabeva, M.D., Shafritz, D.A. (2003) Hepatic stem cells and liver repopulation. Semin Liver Dis. 23(4):349-62.

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Michael Shelanski , M.D., Ph.D.
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Professor Shelanski's laboratory is investigating the mechanism of memory disruption and synaptic dysfunction in Alzheimer's Disease. The lab uses a combination of cell culture and transgenic animal approaches in an attempt to understand why the over-expression of the amyloid precursor protein (APP) or direct application of its active peptide, A-beta, inhibits intracellular signaling in neuronal cells and leads to alterations of electrical activity, dendritic spine morphology and behavior. In the past two years Shelanski's attention has been on the PKA-CREB signaling pathway and on the role of ubiquitin c-terminal hydrolase-L1 (Uch-L1) in regulating these events.

Rabacchi, S. A., W. J. Friedman, Shelanski, M.L. and Troy, C.M.. (2004). Divergence of the apoptotic pathways induced by 4-hydroxynonenal and amyloid beta-protein. Neurobiol Aging 25(8): 1057-6.

Lopez-Toledano, M. A. and M. L. Shelanski (2004). Neurogenic effect of beta-amyloid peptide in the development of neural stem cells. J Neurosci 24(23): 5439-44

Troy, C.M., Rabacchi, S.A., Hohl, J.B., Angelastro, J.M., Greene L.A., Shelanski, M.L. (2001). Death in the balance: alternative participation of the caspase-2 and -9 pathways in neuronal death induced by nerve growth factor deprivation. J Neurosci. 15;21(14)
5007-16.

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Warren Sherman, M.D., FACC, FSCAI
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Our two component research program involves, preclinical phase where we are working with catheter-based injection techniques to identify parameters of success in human myocardial-disease, and imaging methodologies for example, real-time MRI radio-contrast labeling. This phase has provided experience with different systems, cell-types, disease-models. Our second most-active areas, ES-derived cardiac precursors in acute injury, and, intramyocardial injection methods of complex cell-hydrogel preparations. The clinical component includes the "first-to-implant" autologous skeletal myoblasts by catheter into humans with congestive heart failure (CHF). Additionally, we have active stem-cell clinical trials focused on congestive heart failure, chronic myocardial ischemia and acute myocardial infarction.

Sherman, Warren. (2007). Myocyte replacement therapy: skeletal myoblasts. Cell Transplant. 16(9):971-5.

Sherman W, Martens TP, Viles-Gonzalez JF, Siminiak T. (2006). Catheter-based delivery of cells to the heart. Nat Clin Pract Cardiovasc Med. Mar;3 Suppl 1:S57-64.

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ES cells that grow as embryonic bodies (EB) have an advantage in that these cells have an unlimited capacity for self-renewal and potential to become cardiac progenitors and offer an alternative source of cells for transplantation therapy. Dr. Siddiqui is proposing to use EB-derived ES cells to obtain cardiac progenitors and analyze them for their ability to differentiate into cardiac myocytes for transplantation into the diseased heart of dystrophic mice or into the infracted region of ischemic heart. Siddiqui's strategy is to use a selectable marker gene, such as Nkx2.5, which is expressed in early cardiac mesoderm to obtain a pure population of Nkx2.5 positive ES cells. In a parallel study, the Siddiqui lab will use heart-targeted CLP-1 KO mice where the deregulated transcription activity is expected to produce new population of cardiac cells including the cardiac stem cells.

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Marcia Simon, Ph.D.
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Professor Simon's stem cell research has been linked to the production of therapies for the replacement and restoration of full thickness cutaneous, oral and ocular surface injuries. Simon and colleagues were the first to unequivocally demonstrate epidermal stem cell transplant and maintenance in a 6-year follow-up study of transplant patients. The Simon lab has since identified epidermal stem cell markers and have carried out phenotype studies of over 800 clones. Metabolic distinctions between the mesenchymal stem cells originating in subcutaneous fat and dermis have also been found and are being functionally evaluated. Finally, to facilitate translation of research into clinical practice, the lab is building a cGTP/cGMP facility production of clinical grade materials.

Matic, M., Brink, P., Simon, M. (2002). Epidermal stem cells do not communicate through gap junctions. DermatoM18:10-116.

Singer A and Simon M. (2006). Wound healing and skin substitutes. In: Stem cell and gene-based therapy: Frontiers in regenerative medicine, Battler A, Leor J (eds), London:Springer-Verlag, pp. 375-393.

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Satrajit Sinha, M.B.B.S., Ph.D.
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Professor Sinha's laboratory is interested in understanding the molecular mechanisms that underlie the development of skin's epidermis and its appendages from multipotent stem cells. The Sinha lab studies how skin stem cells achieve remarkable ability to both self-renew and to commit to proliferate and differentiate. The lab applies a wide array of powerful olecular, genetic and biochemical techniques to study skin cells primarily in transgenic mouse models. The fate of skin cells is governed in part by transcription factors, which are specialized proteins that control the molecular destiny of a cell by turning genes on and off. The team has developed several mouse models where the levels of critical transcription factors can be altered in the skin epithelium in a controlled fashion. These models allow for study of the underlying mechanisms that control the homeostasis of the skin epithelium and analysis of changes that lead to altered differentiation and development of skin diseases such as cancer.

Birkaya, B., Ortt, K., Sinha, S. (2007). Novel in vivo targets of _Np63 identified by a modified and improved chromatin immunoprecipitation approach. BMC Molecular Biology 8:43.

Romano, R. A., Birkaya, B., Sinha, S. (2007). A functional enhancer of keratin14 is a direct transcriptional target of _Np63. J Invest Dermatol 27(5):1175-86.

Nair, M., Bilanchone, V., Ortt, K., Sinha, S., and Dai, X. (2007). Ovol 1 represses its own transcription by competing with transcription activator c-Myb and by recruiting histone deacetylase. Nucleic Acid Research 35(5):1687-1697.

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Arthur I. Skoultchi, Ph.D.
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Dr. Skoultchi's laboratory investigates mechanisms controlling mammalian development. One project concerns the role of H1 linker histones in embryonic development. H1's control packaging of DNA and nucleosomes into the chromatin fiber. The lab has developed several H1 gene knock-out models in mice and mouse ES cells. The Skoultchi lab has demonstrated that H1 regulates methylation of imprinted genes which is crucial for proper embryonic development. Another project in this lab concerns the control of human ES cell proliferation and totipotency. Skoultchi is investigating which cell cycle regulators control human ES cell proliferation and whether these molecules also control their totipotency.

Fan, Y., T. Nikitina, J. Zhao, T. Fleury, R. Bhattacharyya, E. Bouhassira, A. Stein, C. Woodcock and A.I. Skoultchi (2005). Depletion of histone H1 in mammals alters global chromatin structure but causes specific changes in gene regulation. Cell 123(7): 1199-1212.

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Gary J. Smith, Ph.D.
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Dr. Smith focuses on the role of human prostate stem cells (PSC), and prostate tumor stem cells (PTSC), in the etiology and pathogenesis of prostate cancer. The Smith lab has identified the signature phenotypic characteristic of PSC causally associated with maintenance of the PSC/PTSC phenotype that allows isolation of viable cells. Purified populations of PSCs and PTSCs facilitate characterization of: commonalities/differences in gene expression/phenotype, reciprocal interactions between PSC/PTSC and their stem cell niche, PTSC role in metastases, and molecular targets for selective killing/differentiation. Prostate is the ideal model because differentiated prostate epithelial/cancer cells are eliminated by androgen deprivation, leaving stem cells intact.

Huss WJ, Gray DR, Greenberg NM, Mohler JL, Smith GJ. (2005). Breast cancer resistance protein-mediated efflux of androgen in putative benign and malignant prostate stem cells. Cancer Res. 1;65(15):6640-50.

Huss WJ, Gray DR, Werdin ES, Funkhouser WK Jr, Smith GJ. (2004). Evidence of pluripotent human prostate stem cells in a human prostate primary xenograft model. Prostate. 1;60(2):77-90.

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Professor Stackowiak's research focuses on potential treatments of neuronal degenerative conditions through activation of adult brain neurogenesis by endogenous stem cells (NSC). Stackowiak's laboratory has established a novel pathway that controls NSC development and nanotechnology-based gene therapy to promote in vivo neurogenesis. The goals are to identify molecular mechanisms for neurogenesis in adult brain and to establish gene therapeutic approaches for controlling neurogenesis following stroke or hearing loss. The lab is studying pluripotent human embryonic stem cells (HES) for differentiation into different types of functional neurons and strategies for integrating these cells in vivo for sensory processing, cognitive behavior and motor functions in our animal models.

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Singer A and Simon M. (2006). Wound healing and skin substitutes. In: Stem cell and gene-based therapy: Frontiers in regenerative medicine, Battler A, Leor J (eds), London:Springer-Verlag, pp. 375-393.

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Disruption of laminin gamma-l synthesis in mouse peripheral nerves leads to hindlimb paralysis. To assess stem cell rescue of this paralysis, the Strickland lab injected murine Adipose Derived Stem Cells into mutant sciatic nerves. ADSC treatment improved axon structure and function, and the mice showed hind limb improvement. After stem cell injection, endogenous Schwann cells and injected stem cells sorted and ensheathed axons. However, treatment of mutant nerves with laminin, non-multipotent laminin-producing cells, or laminin-deficient ADSCs did not rescue structure and function of the mutant nerve. Their results indicate that the transplanted adult stem cells served as both a source for new Schwann cells as well as a source of laminin.

ZL Chen, WM Yu, & S Strickland. (2007). Peripheral Regeneration. Annu. Rev. Neurosci. 30 209-233.

WM Yu, ML Feltri, L Wrabetz, S Strickland, & ZL Chen. (2005). Schwann cell-specific ablation of laminin gamma1 causes apoptosis and prevents proliferation. J. Neurosci. 25 4463-72.

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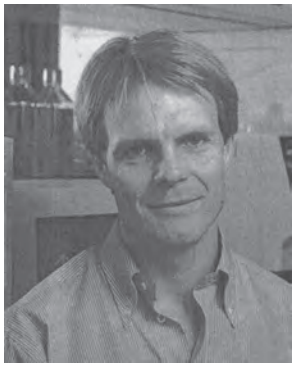

Lorenz Studer, M.D.
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The Studer laboratory has become one of the leading groups in mouse embryonic stem cell differentiation and hESC biology. Among the team's early key achievement were the first report on establishing and differentiating mouse ESCs via somatic cell nuclear transfer(ntESC lines), followed by a similar collaborative study, describing the derivation and in vitro directed differentiation of primate parthenogenic 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.

Barberi, T., Bradbury, M., Dincer, Z., Panagiotakos, G., Socci, N. D. & Studer, L. (2007). Derivation of engraftable skeletal myoblasts from human embryonic stem cells. Nature Med. 13: 642-648.
Tabar, V., Panagiotakos, G., Greenberg, E. D., Chan, B. K., Sadalain, M., Gutin, P. H. & Studer, L. (2005). Migration and differentiation of neural precursors derived from human embryonic stem cells in the rat brain. Nature Biotech. 23: 601-606.

Perrier, A. L., Tabar, V., Barbieri, T., Rubio, M. E., Bruses, J., Topf, N., Harrison, N. L. & Studer, L. (2004). Derivation of midbrain dopamine neurons from human embryonic stem cells. Proc. Natl. Acad. Sci. USA 101: 12543-12548.

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Dr. Stuhlmann's laboratory research program focuses on the identification and characterization of stem/progenitor cells of the endothelial cell lineage. While much attention has been paid to bone-marrow-derived endothelial progenitor cells, less is known about embryo-derived endothelial stem cells. Their research is aimed at the identification, cell lineage tracing, and therapeutic potential of endothelial stem cells derived during in vitro differentiation of ES cells and from angiogenic mesoderm of the yolk sac and the embryo proper. Their approach is to tag endothelial stem/progenitor cells that express the early endothelial gene Egfl7 with a fluorescent marker, thus allowing following the progenitors during cell lineage differentiation both in vitro and in vivo.

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Ching-Hwa Sung, Ph.D.
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One of the ultimate goals in adult stem cell research is to better understand the biology of these cells so that scientists may develop strategies to directly manipulate them without posing ethical questions raised by embryonic stem cells. Dr. Sung's lab is interested in the cell biology of stem cells in the central nervous system (CNS). Her lab discovered a novel marker Tctex-1 for the adult neural stem cells and showed its important role in the niche for neurogenesis. Strategies to purify and manipulate the genetic-tagged adult CNS stem cells and their therapeutic potentials in damaged brains and eyes are underway.

J.-Z. Chuang, T.-Y Yeh, C. Conde, F. Canavosio, F. Bollati, A. Caceres, and C.-H. Sung. (2005). Tctex-1 has a dynein-independent role in actin remodeling in neurite outgrowth. Developmental Cell 9: 75-86.

Dedesma, C., Chuang, J.-Z., Alfinito, P., and C.-H. Sung. (2006). Dynein light chain Tctex-1 identifies proliferating neural progenitors in adult brain. J. Comp. Neurol. 496: 773-786.

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Gen Suzuki, M.D., Ph.D.
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Dr. Suzuki has recently identified hematopoietic stem cells with high-dose HMG-CoA reductase inhibitors (statins) and ntracoronary injection of autologous mesenchymal stem cells (MSCs) increased cardiogenic stem cells in the myocardium. The quantity of myocytes reentering the growth phase of the cell cycle is proportional to the amount of primitive (CD 133 positive) hematopoietic stem cells which are mobilized in the heart. The Suzuki lab will test the hypothesis that synergism occurs with these two therapeutic approaches and can improve flow and myocardial function in swine with ischemic cardiomyopathy. The results of this translational research project will provide the experimental basis for the design of subsequent clinical trials to examine whether mesenchymal stem cells with statin background can ameliorate heart failure and improve myocardial perfusion in patients with ischemic cardiomyopathy.

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Susan L. Swain, Ph.D.
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Proinflammatory cytokines can overcome many aspects of the defects seen in aged naïve cells. When aged stem cells give rise to T cell progenitors in lymphopenic mice, the defects are much less prominent, suggesting that stem cell defects may also be reversible by inflammatory mediators. Dr. Swain's laboratory aims to identify the factors that regulate CD4 T cell and stem cell lifespan. The lab is working to determine the mechanisms by which increased lifespan of naïve CD4 T cells and stem cells lead to defective response. They are also working to determine the extent to which inflammatory mediators can overcome age-associated defects in stem cells and their progenitors.

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Link Back to PI List

Viviane Tabar, M.D.
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Dr. Tabar's laboratory works to develop novel human ES-based cell replacement strategies for the treatment of central nervous system disorders such as neurodegenerative disease and radiation injury models. The current areas of research are; therapeutic application of stem cells in animal models of neural disease; Parkinson's and Amyotrophic Lateral Sclerosis and radiation injury to the brain; animal models, cellular basis of radiation injury and replacement therapy via human ES cells.

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Sally Temple, Ph.D.
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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.

Lowry, N.A., Temple, S. (2007). Making human neurons from stem cells after spinal cord injury. PLoS Med. 4(2):e48.

Temple, S. (2003) Embryonic stem cell self-renewal, analyzed. Cell. 31;115(3):281-92.

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Marja Timmermans, Ph.D.
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Dr. Timmerman's lab aims to identify novel components in the genetic networks that regulate plant stem cell activity and distinguish stem cells from their differentiating descendants. Central to her work is the characterization of an HIRA-dependent epigenetic silencing mechanism that represses stem cell fate during organogenesis. The Timmermans lab is studying the fundamental properties of stem cell function, as contributions of HIRA and epigenetic chromatin states to stem cell homeostasis have recently also been recognized in animals and the roles of microRNAs as mobile signals operating in the stem cell niche. With the recognized importance of microRNAs in animal development and disease, experiments addressing their regulatory mechanisms and roles as development signals in plants are of general significance. Understanding the attributes of stem cells and their determinate descendants in evolutionary distinct systems will elucidate general properties that distinguish these cell types.

Nogueira, F.T.S., Madi, S., Chitwood, D.H., Juarez, M.T., and Timmermans, M.C.P. (2007)
Two small regulatory RNAs establish opposing fates of a developmental axis.
Genes & Dev.
21, 750-755.

Zhang, X., Madi, S., Borsuk, L., Nettleton, D., Elshire, R., Buckner, B., Janick-Buckner, D., Beck, J., Timmermans, M., Schnable, P., and Scanlon, M. (2007)
Laser microdissection of narrow sheath mutant maize uncovers novel gene expression in the shoot apical meristem. PLoS Genetics 3, 1040-1052.

Link Back to PI List

C. Dominique Toran-Allerand, M.D.
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Dr. Toran-Allerand's lab has identified in the postnatal and adult rodent brain a novel, developmentally regulated estrogen receptor named ER-X whose specific ligand, 17alpha-estradiol, is synthesized locally in the brain. They hypothesize that 17alpha-estradiol is the more important estrogen for the formation of new neurons (neurogenesis) and the mood-related behavioral responses attributed to estrogen and that the elevated brain levels of 17alpha-estradiol may act as an endogenous antidepressant. We are testing whether 17alpha-estradiol is comparable to, but more rapid in its action than, the antidepressant fluoxetine (Prozac). This research will lead to the development of novel, cell-based therapies for a broad range of cognitive and mood-related disorders.

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Stephen Tsang, M.D., Ph.D.
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Death of photoreceptor neurons in age-related macular degeneration (AMD) causes the loss of activities of daily living. AMD affects about 10 million Americans, twice as many as Alzheimer Disease and its incidence is expected to double by 2020. Dr. Tsang has established a mouse embryonic stem cell line engineered with a photoreceptor-specific reporter Pde6g::GFP construct to express a protein that fluoresces a bright green when stem cell-derived photoreceptors are created. The retinas fluoresce in the outer nuclear layer indicating the formation of new photoreceptors derived from embryonic stem cells.

Gouras, P., Kong, J., and Tsang, S. H. (2002). Retinal Degeneration and RPE Transplantation in Rpe65(-/-) Mice, Invest Ophthalmol Vis Sci 43, 3307-11.

Farber, D. B., and Tsang, S. H. (2003). Stationary night blindness or progressive retinal degeneration in mice carrying different alleles of Pde6 gamma, Front Biosci 8, S666-75.

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J Neurosci 26, 4472-4480.

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Emmanouhl S. Tzanakakis, Ph.D.
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Professor Tzanakakis's research is focused in the development of scalable culture systems for the expansion of embryonic stem cells (ESCs) in therapeutically useful quantities. The lab is exploring aspects of ESC self-renewal which are-critical for ESC propagation in vitro. The result is the development of a suspension bioreactor in which ESCs can be propagated without loss of their pluripotency. Additionally, the Tzanakakis lab is working on generation of pancreatic islet cells, especially insulin secreting D-cells, which can be used in cures for diabetes and has been successful in coaxing ESCs to adopt an endodermal fate by recapitulating aspects of early stages in embryonic pancreas development.

Lock LT, Tzanakakis ES. (2007). Stem/Progenitor cell sources of insulin-producing cells for the treatment of diabetes. Tissue Eng. 13(7):1399-412.

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Richard Vallee, Ph.D.
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Professor Vallee's lab works on the microtubule motor protein, which is involved in diverse cellular and subcellular activities. They are devoting attention to understanding the cellular and molecular basis for the human smooth brain disease, lissencephaly. This disease is caused by mutations in the LIS1 gene, the product of which regulates cytoplasmic dynein and participates in the proliferation and migration of neural precursor cells in the developing neocortex. In addition to extensive molecular analysis of LIS 1 and additional LIS1- and dynein-interacting proteins, NudE, NudEL, and NudC, they are imaging the migration and proliferation of LIS 1 -deficient cells in living brain. Vallee's team is in the process of working out the mechanism for the interkinetic nuclear oscillations exhibited by neural progenitor cells and the radial, glial-guided migration of their progeny and pursuing evidence from these studies for a novel mechanism controlling entry of the progenitors into mitosis.

Tsai, J.-W., Chen, Y., Kriegstein, A., and Vallee, R. B. (2005) LIS1 RNAi Blocks Neural Stem Cell Division, Morphogenesis, and Motility at Multiple Stages. J. Cell Biol 170(8): 935-945.

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Marcel R.M. van den Brink, M.D.
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Dr. van den Brink's laboratory studies the immunobiology of hematopoietic stem cell transplantation. Allogeneic hematopoietic stem cell transplantation (HSCT) is an important therapy for a variety of malignancies, including leukemias, lymphomas, and advanced solid tumors, such as renal cell carcinoma, as well as a number of nonmalignant diseases, such as aplastic anemia and severe combined immunodeficiency. The van den Brink laboratory uses murine HSCT models to study clinically important problems in HSCT and to test novel therapeutic strategies to ameliorate graft-versus-host disease, increase graft-versus-tumor activity, and enhance post-transplant immune reconstitution.

Schmaltz, D., Alpdogan, O., Kappel, B. J., Muriglan, S. J., Rotolo, J. A., Ongchin, J., Willis, L. M., Greenberg, A. S., Eng, J. M., Crawford, J. M., Murphy, G. F., Yagita, H., Walczak, H., Peschon, J. J. & van den Brink, M. R. M. T cells require TRAIL for optimal graft-versus-tumor activity. Nature Medicine 12: 1433-1437 (2002)

Alpdogan, O., Muriglan, S. J., Eng, J. M., Willis, L. M., Greenberg, A. S., Kappel, B. J. & van den Brink, M. R. M. IL-7 enhances peripheral T cell reconstitution after allogeneic hematopoietic stem cell transplantation. J. Clin. Invest. 112: 1095-1106 (2003)

Zakrewski, J. L., Kochman, A. A., Lu, S. X., Terway, T. H., Kim, T. D., Hubbard, V. M., Muriglan, S. J., Suh, D., Smith, O. M., Grubin, J., Patel, N., Chow, A., Cabrera-Perez, J., Radhakrishnan, R., Diab, A., Perales, M.-A., Rizzuto, G., Menet, E., Pamer, E. G., Heller, G., Zuniga-Pflucker, J. C., Alpdogan, O., & van den Brink, M. R. M. Adoptive transfer of T-cell precursors enhances T-cell reconstitution after allogeneic hematopoietic stem cell transplantation. Nature Medicine 12: 1039-1047 (2006)

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Andrea Viczian, Ph.D.
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Retinal precursor cells provide an important opportunity for treating retinal injuries and degenerations. Professor Viczian is interested in retinal stem cells and has recently found that primitive ectoderm isolated from frog embryos prior to gastrulation can be directed to retinal precursor cells capable of differentiating into every cell type necessary to form a functional eye. The goal of the Viczian lab's current project is to adapt our innovative approach to a mammalian system with the long-term objective of generating precursor cells in vitro capable of curing blindness.

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Dr. Vunjak-Novakovic is a Professor at Columbia University where she directs the program in stem cells and tissue engineering. She is also co-directing the NIH Tissue Engineering Resource Center. Her lab is working on biophysical regulation of adult and embryonic human stem cells, advanced bioreactors, and functional tissue engineering. The main emphasis is on cardiac muscle, vascularization, and osteochondral tissues, for application in regenerative medicine.

Vunjak-Novakovic G., Freshney, I. (2006). Culture of Cells for tissue engineering. J.Wiley.

Ferreira, L., Gerecht, S., Shieh, H., Vunjak-Novakovic, G., Langer, R. (2007) Bioactive hydrogel scaffolds for controllable vascular differentiation of human embryonic stem cells. Biomaterial 28 (17): 2706-2717.

Marolt, D., Augst, A., Vepari, C., Farley, M., Fajardo, R., Patel, N., Gray, M.L., Freed, L.E., Kaplan, D.L., Vunjak-Novakovic, G. (2006). Bond and cartilage tissue constructs grown using human bone marrow stromal cells, silk scaffolds and rotating bioreators. Biomaterials 27 (36): 6138-6149.

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Wnt signaling pathways, essential for embryogenesis, cell fate determination and
pattern formation, are the most important signaling pathways for embryonic development. Inappropriate activation of Wnt signals produces cancer. Wnt canonical pathway is applied to control cell fate, whereas Wnt noncanonical pathway is used to regulate cell movement and tissue polarity. Professor Wang's research is focused on signaling maps in both pathways, particularly how cellular messengers are formed and how they regulate key molecules in these pathways. Understanding the signaling mechanism is critical for the success in manipulation
of specific cell type differentiation and self-renewal of hESC.

Gao, Y. and Wang, H-y. (2006) Casein kinase 2 is activated and essential for Wnt/_-catenin signaling. J. Biol. Chem. 281, 183-18400.

Wang, H.-y., Kanungo, J., Malbon, C.C. (2002) Expression of Galpha12 (Q226L) induces P19 stem cells to primitive endoderm via MEKK1/4. J. Biol. Chem. 271:3530-3536.

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Hynek Wichterle, Ph.D.
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Professor Wichterle's lab utilizes in vitro differentiation of embryonic stem cells as a tool to study development of mammalian nervous system. They have developed robust protocols for the directed differentiation of mouse ES cells into distinct subsets of skeletal and autonomic motor neurons. ES cell-derived motor neurons acquire appropriate electrophysiological properties and innervate muscle targets upon transplantation into the developing neural tube. Currently, Wichterle is comparing distinct subtypes of ES-derived motor neurons, with the goal of identifying mechanisms that regulate motor neuron survival, axonal pathfinding and establishment of functional synapses. The lab is developing ES cell based models of motor neuron diseases to study pathological mechanisms and to develop cell based system for drug discovery.

Wichterle, H., Lieberam, I., Porter, J., and Jessell, T. (2002). Directed differentiation of embryonic stem cells into motor neurons. Cell 110: 385-397.

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E. Lynette Wilson, Ph.D.
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The goal of Wilson's laboratory is to identify and characterize normal prostate epithelial stem cells, to determine whether they are targets of malignant transformation and to define their relationship to prostate cancer stem cells. Wilson has identified prostate stem cells in the proximal region of murine prostatic ducts and isolated them based on their high expression of the Sca-1 antigen. They found that high levels of active TGF-beta in the proximal region maintain stem cell dormancy. An understanding of the biology of prostate stem cells will yield new insights into the initiation and maintenance of prostate cancer and pave the way to a better understanding of the etiology of prostate carcinoma and benign prostatic hypertrophy, as both diseases are considered to arise from the aberrant proliferation of stem cells.

Gotoa, K., Salma, S.N., Coetzeea, S., Xionga X., Burger P.E., Shapiro E., Lepor, H., Moscatellia, E., Wilson, E.L. (2006) Proximal Prostatic Stem Cells Are Programmed to Regenerate a Proximal-Distal Ductal Axis. Stem Cells. 24: 8 :1859 -1868.

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X. George Xu, Ph.D.
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Professor Xu's laboratory proposes to develop a novel computational platform for imaging and Monte-Carlo simulations of stem cells and cancer stem cells for potential applications in radiotherapy and radiation protection. An understanding of how stem cells respond to ionizing radiation such as x-rays, electrons and protons would provide unprecedented opportunity for protection against radiation-induced cancers such as leukemia and for more effective methods of radiation treatment of cancers. In radiotherapy, scientists have recently found that "cancer stem cells (CSCs)" play a previously unknown role in radiotherapy involving leukemia, breast tumors, human brain tumors, and bone tumors. However, there is currently little research in integrating the cell biology with advanced Monte Carlo based radiation transport simulations to develop better imaging and radiation delivery for cancer intervention. Professor Xu is interested in developing an in-vivo imaging and radiation dose modeling platform for characterizing CSCs for potential radiotherapy applications.

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Dr. Zou aims to understand the relationship of stem cells and their physical niches, and to identify the molecules that regulate homeostasis of stem cells. Results from her laboratory demonstrate that the chemokine CXCL12 not only functions as the major chemoattractant for hematopoietic stem cells (HSCs) homing into the stem cell niche but also regulates quiescence of HSCs. Their data further reveal a potential signaling circuit for regulating HSC quiescence that connects the signal from BM niche (CXCL12) with a HSC surface receptor (CXCR4) and a cell cycle regulator (p57KIP2). Current projects include investigating the role of p57kip2 in HSC quiescence using p57kip2 knockout mice and identification of the CXCR4 signaling components that regulate p57kip2 expression. Future studies will extend into other stem cells and cancer stem cells.

Bagri, A., Gurney, T., He, X., Zou, Y.-R., Littman, D. R., Tessier-Lavigne, M., and Samuel J. Pleasure, S. J. (2002) The chemokine SDF1 regulates migration of dentate granule cells. Development 129, 4249-4260.

Zou, Y.-R., Sunshine, M. J., Taniuchi, I., Hatam, F., Killeen, N., and Littman, D. R. (2001) Epigenetic silencing of CD4 in T cells committed to the cytotoxic lineage. Nature Genet. 29, 332-336.

Sun, Z., Unutmaz, D., Zou, Y.-R., Sunshine, M. J., Pierani, A., Brenner-Morton, S., Mebius, R.E., and Littman, D.R. (2000). Regulation of thymocytes survival and peripheral lymphoid organ development by an orphan nuclear hormone receptor. Science 288, 2369-2373.

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Stem cells have the ability to differentiate into specialized cells. A retinal stem cell, for example, may differentiate into a rod cell, a retinal ganglion cell, or any of the five other cell types of the mature retina. Retinal stem cells are also self-renewing. These two characteristics make retinal stem cells ideal for use in cell replacement therapies for treating blinding diseases. Professor Zuber's laboratory studies the molecular mechanisms driving the specification, proliferation and differentiation of retinal stem and progenitor cells. Zuber's goal is to identify factors necessary to reprogram more plentiful non-retinal cells to sight saving retinal stem cells.

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David A. Paterson
Lieutenant governor

Department of Health

Richard F. Daines, M.D.
Commissioner