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1. ANALYSIS

This report is prepared by the co-chair Drs Bertino (RCINJ-New Brunswick) and Rameshwar (NJMS-Newark), and members of the committee comprised of both physicians and basic scientists within RBHS and at other units of Rutgers University.

OVERALL GOALS: Creation of a comprehensive virtual institute, The Rutgers Institute for Regenerative Medicine (**Rutgers-IRM**) would comprise basic and clinical research, clinical care and educational activities related to tissue-specific stem cells and Regenerative Medicine. Our goal is to promote and coordinate interactions and initiatives amongst all basic and clinical Stem Cell scientists at Rutgers-RBHS. We will support multi-disciplinary projects that will develop basic research into the **signature areas** of hematopoietic, mesenchymal and neural stem cells, and we will facilitate the translation of basic science into clinical trials for stem cell therapies in heart, liver and inflammatory diseases, and for neuroscience activities related to neural regeneration in MS, Parkinson's disease and traumatic CNS injury, blindness and spinal cord injury. Four programmatic themes were identified in our preliminary assessment of clinical needs and our combined educational, research and clinical strengths. We will coalesce our resources to address these areas:

- 1) **Basic Research:** mechanistic studies on animal and human tissue specific stem cells;
- 2) **Bio and Material Sciences:** develop platforms for effective stem cell engineering;
- 3) **Drug Discovery:** develop high throughput drug screens with stem cell derived disease-relevant cell types (e.g. myelin cells from MS patients, dopaminergic neurons from Parkinson's; cancer stem cell organoids);
- 4) **Translational Research:** develop new treatment protocols such to facilitate transplantation (e.g., chimeric antigen receptors; the use of mesenchymal stem cells for cardiac, spinal cord injury).

2a. Existing Strengths

Overall: The committee identified many areas of strength in Stem Cell Biology at Rutgers schools.

(i) Our principal strength is the talented Stem Cell **scientists and physicians**, including those who are international experts in Stem Cell biology. The basic science component is coordinated through the Stem Cell Program of the Human Genetics Institute of New Jersey (HGINJ), which provides technical support, core facilities, pilot funding, and a seminar program. (ii) Many **facilities and resources** at the affiliated campuses, [Newark] the New Jersey Medical School (NJMS) and the Institute of Technology (NJIT), [New Brunswick] the Cancer and Child Health Institutes (CINJ, CHINJ), [Piscataway] the RW Johnson Medical School (RWJMS), Center for Advanced Biotechnology and Medicine (CABM) and the School of Public Health (SPH), and [Rutgers Bush Campus] the Keck Center for Collaborative Neurosciences, and the Human Genetic Institute of New Jersey (HGINJ). All locations have the relevant Core Facilities for basic research in stem cell biology. (iii) Our **educational** portfolio; many faculty are actively engaged in educational stem cell programs for undergraduate, graduate, postgraduate students, residents and fellows. (iv) The level of interactions; the faculty currently collaborates within Rutgers and with national and international academic institutions and biotechnology companies. (v) We also identified relevant clinical **transplant programs** at affiliated hospitals including those linked to New Jersey Medical School (liver, cardiac, kidney) and RWJUH New Brunswick (hematopoietic, pancreas, cardiac, kidney). The clinical program at Rutgers-CINJ (RWJUH) now uses hematopoietic stem cells for treatment of blood malignancies, supported by the hospital stem cell lab. Other programs that can immediately benefit from a cohesive regenerative medicine program include the NJMS/UH liver transplant program, the cardiac program (NJMS/UH), and the Keck center for spinal cord injury repair.

(i) **Faculty/Expertise:** Based on a search of the literature, grant funding and interviews with scientists the committee identified the following **areas of expertise** in stem cell research at Rutgers (RBHS included):

- Tissue specific stem cells: Cardiac, Hematopoietic, Neural, Ocular, Mesenchymal
- Molecular and cellular research on stem cells to study human diseases
- Direct reprogramming - generating specialized cells with or without iPS intermediates
- Animal models for regenerative medicine: mouse, rat, canine, zebrafish, *Drosophila*
- Anti-aging studies
- Cancer stem cells
- Cardiac repair

- Hematopoietic stem cell and cord blood transplantation for hematological malignancies
- Neural repair for Multiple Sclerosis, Parkinson's disease, spinal cord injury, traumatic brain injury
- Retinal degenerative disease

Collaborations: An effective Regenerative Medicine Institute requires strength in many subspecialties, and Rutgers has investigators encompassing the relevant areas of research. The Rutgers-IRM would facilitate collaborations between basic and clinical scientists across the Rutgers campus in the following key disciplines for effective translation of stem cell biology into clinical trials:

- Animal models (Rodent; Zebrafish)
- Bioengineering, Material sciences
- Biomedical sciences
- Cell biology
- Chemistry, Chemical Biology
- Engineering (bioinformatics; modeling; networks)
- Genetics (gene therapy; genome editing, models)
- Hematology/oncology
- Immunology/Inflammation
- Molecular biology
- Neural injury and repair
- Transplant biology

In addition, the Rutgers IRM would directly interact with and support other strategic initiatives at RBHS, including the neuroscience plan to focus on multiple sclerosis (MS) and CNS injury.

Target diseases: In addition to our signature focus on liver (fibrosis/cirrhosis), cardiac (ischemia, heart failure) and traumatic CNS injury, active areas of research that complement our patient populations and are potential targets for clinical trials include the following:

- Cancer, Diabetes, Immune (asthma, GvHD, arthritis, inflammatory bowel disease, Crohn's, diabetes)
- Inherited genetic diseases
- Neurodegenerative diseases (MS, Parkinson's, Autism)
- Pulmonary disorders, renal disease, retinal disorders
- Wound healing (soft tissue injury, anti-aging therapies)
- Retinal degenerative disease (age-related macular degeneration, glaucoma, retinitis pigmentosa)

Publications: A search of the literature revealed Rutgers faculty with outstanding publications in basic stem biology, translational and clinical sciences. Table 1 reflects this landscape and indicates ongoing collaborations among the Rutgers RBHS scientific community. The table is very likely an under-estimation of research because the outcomes of clinical trials on stem cells are not included as peer-reviewed publications.

Table 1. PubMed search for Stem Cell-related publications (last five years):

Search terms →→→	UMDNJ	NJMS	RWJMS	CINJ	RUTGERS
Stem Cell	97	141	52	37	124
Regenerative Medicine	12	16	8	1	15
Mesenchymal (MSC)	35	49	16	11	22
Hematopoietic (HSC)	21	29	5	6	9
Embryonic (ESC)	18	24	16	4	33
Induced Pluripotent (iPS)	4	4	2	1	8
Neural Stem Cells	9	1	1	1	30
Totals:	196	264	100	61	241

Grants: We identified 24 faculty involved in stem cell research with ~10 million dollars of annual federal funding. Rutgers investigators collectively have total annual funding ~15 million dollars for regenerative medicine/stem cell funding.

Basic and translational research and clinical trials on stem cells have attracted State funding from the NJ Commission (Stem Cell Research, Cancer Research; Spinal Cord Injury; Brain Injury), Federal agencies (NIH, NSF, DOA, DOD), funding societies (eg. ACS), Foundations (e.g., Leukemia and Lymphoma Society, NJ Health Foundation), Foundation Fighting Blindness, Inc and, Biotechnology companies (e.g. J&J, Celgene Cellular Therapeutics). In addition, legacy Rutgers funding includes the presence of the national NIMH and NIDA stem cell repositories and service labs at RUCDR Infinite Biologics, which is a multi-million dollar operation.

The diverse funding for basic and clinical research on stem cells as well as the sponsors (**Table 2, next page**) underscore the strength to make Rutgers a leader in bringing stem cells therapies to patients.

Table 2. Estimated summary of stem cell funding:

Areas of strength	Subjects/Titles/Clinical Trials	Sponsors
Stem Cell Support Centers	RUCDR/Center for Regenerative Medicine Service Agreement Armed Forces Institute of Regenerative Medicine (AFIRM) NIMH Center Repository Supporting Stem Cell Research	NIH DOD NIH
Anti-aging	Reprogramming Aging Stem Cells Genetics of aging	ReGen MT NIH
CNS myelin repair	Role of L1 Overexpressing Stem Cells in Myelination Genetic Dissection of Neuronal Regeneration in C. elegans Neurons from Blood-Derived Stem Cells: Model of A-T Neurodegeneration Olig2 Expression in Spinal Cord Development and Regeneration Retasking FDA-Approved Drug for Peripheral Nerve Regeneration Preclinical Study of Placental Stem Cells for Spinal Cord Injury Engineering Stem Cells to Promote Recovery after Spinal Cord Injury	MS Soc. NJCSCR A-T Child NJCSCR NIH Celgene NARSAD
Cancer and stem cells	BMI-1 inhibitors for prostate tumor stem cells Adult Stem Cell at Tumor Environments Division and Signaling in Lung Cancer Stem Cells Mesenchymal stem cell-derived exosome in breast cancer Molecular analyses of Mouse ES Cells and Their Derivatives Molecular characterization of Genetic Regulators of Cancer Stem Cell Nanomedicine in Neural Stem/Progenitor Cell for Spinal Cord Injury Defining Intestinal Stem Cell	DOD MS Soc. NIH DOD NJCST NIH NIH NJCCR
MiRNA and stem cells	Pre-differentiation of therapeutic stem cells using miRNAs MiRNA miR-290-295 in Blastocyst Derived Stem Cells and the Early Mouse Embryo MiRNA in Neural Stem Cell differentiation Bioinformatic Analysis of BetaLogics Human ESCs	NJCSCR NJCSCR NJCSCR Centocor
Mesenchymal stem cells	Mesenchymal Stem Cell Transplants in Spinal Cord Injury Gingiva Derived MSCs in Immunomodulation and tissue Regeneration	BrainSt. Penn SU
Hematopoietic stem cells	Stem cell origin in induced mutation of recovered T-cells Cell proliferation in Hematopoiesis	NJCST NIH
Regeneration/stem cell	Mobilized Stem Cells for Patients with Cirrhosis Phase I Study Plant Stem Cells Efficiency of Homologous Recombination in Human Stem Cells Bioinformatic Assessment of Stem Cells	Proteonomix USDA NJCSCR Celgene
Biomaterial/stem cells	REU Site: Cellular Bioengineering: From Biomaterials to Stem Cells Bimodal Delivery of L1 for Spinal Cord Regeneration Biomimetic Scaffolds for Targeted Peripheral Nerve Regeneration Guiding Axonal Regeneration and Piezoelectric Polymers 3D Microreactors for Stem Cell Differentiation Enhancement of Bone Regeneration through Cell-Based Strategies Stem Trix-Improved Growth Matrices for Stem Cell Propagation Recellularization of liver bioscaffolds	NSF NJCSCR NIH NJCSCR NJCSCR DOD OTTBD NIH
Tissue specific stem cells	Genomic and Molecular Genetics Approaches to Retinal Stem Cells Keratinocyte Stem Cell Regulatory Gene in the KSC2 Locus Zinc Homeostasis in Cardiac Stem Cells Transcription Factors for Hair Cell Regeneration Neural Stem Cell & Progenitor Clones Human ESC into Retinal Pigment Epithelial Successful Expansion of Umbilical Cord Blood Stem Cells	NIH NIH NIH HRF BMS M. Eye-Bank LRF
Educational stem cell programs	Center For Applied Training in Human ESC Biology Bioengineering of safe/efficient vector technology for stem cell IGERT: Integrated Science and Engineering of Stem Cells	NJCSCR NIH NSF

(ii) Core Facilities, Resources: In 2004 Trenton established the New Jersey Commission on Science and Technology, and generated a peer reviewed competitive stem cell grant funding initiative that has supported many labs at RU, CINJ, RWJMS and NJMS. Included in the funding stream were grants for **Core Facilities** that were established in the Keck Center on Busch campus and at RWJMS-Piscataway. The Commission also provided funds to support adult stem cell research as well as to remodel the cell processing facility, a clinical grade Good Manufacturing Process facility (**GMP**) at Rutgers-CINJ. The RUCDR, headed by Jay Tishfield has built a robust, federally-supported core facility to prepare all types of stem cells. In addition to Rutgers scientists, the group also serves scientists at the U. of Penn, Univ of Pittsburgh, Stanford University and other major universities. Thus, there is already a foundation for the Rutgers-IRM, and we now have arguably one of the largest and finest collections of Stem Cell biologists and Core Facilities in the country. We thus have all of the necessary infrastructure to provide the requisite tools, expertise and training to foster advances in stem cell research, sustain productive collaborations among investigators at RBHS and nationally, and translate science advances into clinical trials for regenerative medicine.

In addition to our world-class stem cell research laboratories and dedicated Stem Cell Core facilities, many other facilities are available to support stem cell research and clinical applications. These include biological mass spectrometry, multiple flow cytometry Core facilities, a research pharmacy, an electron microscopy core, MicroCT and phosphorimaging facilities, a biomolecular NMR facility, several confocal and electronic imaging centers, and housing facilities for both large and small animals (rodents, transgenic zebrafish). Other specialized resources that can further support stem cell research and clinical applications include the following:

- **Biomedical Informatics:** microarray, Next Generation Sequencing (NGS) for gene expression analysis.
- **Warehouse Services** (Rutgers-CINJ): information integration and data sharing data repositories provide access to clinical data, link research data sources and serve as a platform for translational research.
- **Chemical Informatics:** small molecule/peptide databases for screening to identify targets for therapeutics.
- **Biometrics Shared Resource:** software engineering and statistical analyses and computing resources.

iii) Clinical Resources:

Clinical Data Repository: The Office of Human Research Services (OHRS) at Rutgers CINJ shared resource provides hardware, software and a disaster recovery Clinical Trial Management System, for phase 1 and NIH-investigator driven clinical trials.

Epidemiology Services: infrastructure and design support for research tracking and analytical databases.

Network Hospital Portal: hospital networks affiliated with Rutgers-CINJ and NJMS provide clinical service for >1/3 of New Jersey residents. The database connects hospitals via the web and sites can host clinical trials.

Transplant Network: There is a plan for a Hospital consortium for organ transplants. The consortium will include University Hospital (liver), St Barnabas (kidney), Beth Israel and RWJUH (cardiac and hematologic malignancies). Their current need for immune suppression could be alleviated using MSCs generated from the GMP facility located at Rutgers-CINJ.

(iv) Education: Strong stem cell educational programs already exist in RBHS. The Newark NJMS course consists of an elective for medical students offering a certificate, and a concentrated graduate program in Stem Cell biology that allows residents, fellows and faculty to audit. This could be adapted across the entire Rutgers campuses. In Piscataway, a hands lab course on Stem Cell biology has been active on the Bush campus for several years, and there are Graduate courses on pluripotent stem cells (RU16:695:628), cell reprogramming (RU16:695:635) and multiple cancer stem cell courses in New Brunswick. As a first step an existing Regenerative Medicine elective in the Master of Biomedical Science Program can be made available to both NJMS and RWJMS students. The integrated courses in a regenerative medicine program will be offered at GSBS. This would promote more interactions of students and faculty in a fully integrated Rutgers-RBHS.

Seminar Series, Proceedings: Rutgers-IRM can host a seminar series as a platform to share information with the wider Rutgers community, by expanding the current seminar series held at both RCINJ and HGINJ and expand its outreach to the lay public by publishing mini-reviews in a Regenerative Medicine series using the format of the NY Academy of Science. This would inform the international scientific community of the strengths of stem cell research and regenerative medicine at Rutgers, and could potentially attract local (State)

and international biotechnology companies to the regenerative medicine resources available at Rutgers-IRM. It is expected that the center will submit 12 issues annually of ~ 5 pages each.

Community Outreach: The Rutgers-IRM program is poised to gain public support. There is an existing program in Newark, the Student Educational Society, whose members include graduate and medical students who have taken the stem cell courses. The society educates high schools, community colleges and the lay public at locals such as the Liberty Science Center about the potential applications of stem cells to treat disease. An office for Regenerative Medicine - Stem Cell Therapy education is planned at RWJUH to educate and recruit patients for stem cell trials. Outreach will also be done through the Rutgers-IRM web site, and connections with the affiliated hospitals and centers will offer patient an education program on Stem Cells. Additionally, the institute poster presentations at public events and community centers would increase visibility.

(v) Comparison with other Universities: The Rutgers-IRM virtual institute model that is proposed has been adapted by multiple universities including the Harvard Stem Cell Institute, Yale Stem Cell Center, Michigan Stem Cell Institute, the Stanford Stem Cell center, U of Pennsylvania and MD Anderson. All of these centers house an operational cell processing GMP facilities. Moreover, initiatives at states such as California, Connecticut, Maryland and Minnesota that provide funding for stem cell research have yielded significant growth in stem cell related biotechnologies. We firmly believe Rutgers has a unique opportunity to assume a leading role in the area of regenerative medicine through partnering with the state of New Jersey.

2b. CRITICAL GAPS

- (i) Faculty Recruitment:** There is a need to recruit additional outstanding faculty to provide basic and clinical science development for a clinical transplant program. Examples are clinical trials for myocardial infarction, heart failure, spinal cord injury, the study of graft versus host disease, modification of T-cells to target malignancies, and stem cell-based transplant programs to treat childhood cancer and non-malignant diseases. At present, patients from New Jersey who seek enrollment in such trials are being sent to Philadelphia and New York City, and Rutgers-IRM seeks to reverse this trend.
- (ii) A functioning Good Manufacturing Practice (GMP) stem cell processing facility.** This facility is critical for all clinical studies. The facility at the Rutgers-CINJ (New Brunswick) exists and has been remodeled to FDA standards, although it still needs FDA approval. This cell processing facility now requires resources to hire qualified personnel for FDA certification. This is a fully equipped, state-of-the-art stem cell production and drug processing facility. It is highly desired in this region and should generate revenue from biotechnology companies within New Jersey and surrounding states. However, the lack of funding to open the facility hampers the ability to initiate clinical trials, and companies who collaborate with scientists at RBHS are forced to translate the science to other centers with working GMP facilities.
- (iii) Technology Transfer:** The Rutgers-IRM will work closely with the Technology Transfer office to facilitate patents based on recent law changes and collaborative arrangements with the Pharmaceutical Industry. The Center would facilitate discoveries that could be patented and provide a revenue source.
- (iv) Scientific alignment:** During the committee discussions, it was clear that there is a lack of cohesion among basic and clinical stem cell scientists on the Newark and New Brunswick/Piscataway campuses. The establishment of a Rutgers-IRM monthly seminar series (discussed in Strengths) and an annual retreat could fill this critical gap. This would bring faculty, fellows, students and staff together to share information and establish collaborations to generate winning team science proposals.
- (v) Bench to Bed interactions:** Our clinical scientists believe a major hindrance to effectively develop clinical trials is the lack of interaction with the basic scientists, and Rutgers-IRM will promote such interactions.
- (vi) Logistics:** A shuttle service is needed between the Newark and New Brunswick campuses, and between the New Brunswick and Piscataway campuses. In addition, parking tags for faculty, students and staff should provide access to any campus. Both arrangements will facilitate collaborations and sharing of resources.
- (vii) Education:** Despite a strong educational strength in stem cell biology at Newark, the students in New Brunswick cannot cross register. There is a need to align the graduate program at RBHS to allow students to register for any of the stem cell courses. Improved collaborations could be garnered through

training grants with Rutgers investigators.

(viii) Clinical Resources: To date, there have been >1,000 hematopoietic stem cell transplants performed by Rutgers CINJ faculty. These transplants have occurred on a dedicated unit at RWJUH. This expertise could be used for other transplants in new center for cellular therapy. The unified unit can be expanded to provide the care for patients undergoing a broader scope and spectrum of stem and regenerative medicine cell therapies. This would include patients receiving: (1) cellular and non-cellular therapies for malignancies, immunodeficiency or autoimmune diseases; (2) hematopoietic stem cell transplants with novel cellular adjuncts; (3) cell and non-cellular therapies for heart, liver, orthopedic, neurologic, cardiac, vascular, autoimmune or other diseases.

2c. Opportunities for Collaborations:

(i) Basic Sciences: There are great opportunities for collaborative interactions in basic research.

Core Facilities: As discussed above (1a) the RBHS schools are home to many core facilities. Rutgers-IRM will promote their expanded use and fiscal stability through centralized administrative oversight and blanket service agreements, allowing discounted user fees to access these core facilities. Access to and communication with the RUCDR stem cell laboratory provides unique expertise and a great deal of resources with which to grow RBHS operations.

Academic Programs: There is an opportunity for the clinical departments to use Rutgers-IRM to recruit residents, fellows and junior faculty members. Similarly, GSBS will recruit strong graduate students, and the different schools will collaborate to strengthen current courses and teaching. Based on the expertise and international collaborations of the faculty, and the strong clinical departments, this program can become a unique and first-in-nation graduate program aligned with the activities of Rutgers-IRM, to offer Masters and Ph.D. degrees in Stem Cell Biology. This will generate and attract a new breed of exceptional young scientists and serve as a channel for international stem cell collaborations.

Training grants: The strength of Rutgers-IRM, particularly when combining clinical researchers with the existing base of stem cell biologists at RBHS and Rutgers, will encourage collaboration to prepare training grants that will train young investigators in stem cell research and substantially strengthen the standing of our academic programs to better compete for NIH funding.

(ii) Clinical Sciences: There are several investigators in clinical departments who have programs with stem cells. The center will allow these investigators to present their ideas/pilot data. This will encourage collaborations/team science to compete for national grants.

Consortium of hospitals: RBHS provides a unique opportunity to develop large scale clinical translational programs among the multiple affiliated hospitals. This serves a large patient population. There are opportunities for collaborations with other hospitals, such as the affiliations between Rutgers and the St Barnabas system, and RCINJ with several other affiliates.

Transplantation Programs: The Newark campus has a clinical liver transplant program and the New Brunswick campus has a hematopoietic transplant program. At present, these programs work independently. Rutgers-IRM will bring these two entities together to share findings/observations for improving overall transplantation, and provide expertise in emerging regenerative medicine clinical programs.

Trauma Centers: Trauma centers in Newark and New Brunswick Campuses are Level 1 with >5,000 patients. Investigators at both locations have also developed animal models to study trauma and use of stem cells to promote healing. There is an opportunity to improve trauma center collaboration with Rutgers-IRM in preclinical/trial settings.

Clinical trials: The lack of a well-functioning GMP facility has hampered initiation of some clinical trials of regenerative medicine. Rutgers- IRM would allow investigators to work collaboratively on trials to enhance recruitment, publications and funding. Specifically, Rutgers-IRM would be the 'umbrella' where the recruitment of patients from multiple RBHS units be facilitated.

(iii) Biotech, Pharmaceutical sciences: Most Pharmaceutical companies have now reduced on-site research and are actively seeking partnership with academia. Similarly, many Biotechnology companies are establishing themselves as virtual entities and are seeking partnership with academic institutions. The Rutgers-IRM would

be attractive for many companies because of proximity and our infrastructure, including the GMP facility and other core facilities, making it convenient for these companies to conduct clinical trials within Rutgers.

Drug Screening: Testing Stem Cell Products: The regenerative medicine center could use available stem cells and methods to develop stem cell banks with RUCDR for screening drugs for commercial entities, *in vitro* and *in vivo*. The latter would facilitate collaborations among scientists with *in vivo* models and expertise to humanize immune deficient mice (e.g., NSG). Established immune methods could be applied to test cell products for companies.

(iv) Applying stem cell strength to develop other areas within existing programs:

Mesenchymal stem cells: Stem cell biologists at throughout Rutgers who are experts in MSC biology could collaborate with clinical programs such as the stem cell transplant program in New Brunswick. This could lead to the development of a paradigm shift in how to manage immune-mediated hematological disorders.

Hematopoietic Stem Cells: Similarly, the strong hematology transplant group at RCINJ started collaborating with the cardiovascular centers in New Brunswick and Newark to develop effective trials.

Cancer Stem Cells: At the national and international levels, there is much interest to develop drugs to target cancer stem cells. The stem cell center will bring together cancer and stem cell biologists to utilize technologies such as cancer stem cell organoids developed at RCINJ for identification and patenting of novel cancer targets. These targets would also attract biotechnology companies to collaborate with Rutgers-IRM to develop strategies to test potential therapeutic compounds.

Anti-aging collaborations: Improved healthcare in the US has led to a longer lifespan, and both neurodegenerative and hematological disorders have clearly shown a relationship with aging. Rutgers-IRM will allow for collaborations between experts in aging and existing FM Kirby centers at Rutgers that are organized to study neural plasticity. Rutgers also has a current partnership with Advance Regen for restoration of aging mobilized peripheral blood stem cells.

Infectious Diseases: There is a strong research focus on infectious disease/inflammation at RBHS. The Rutgers-IRM will have experts with stem cells who could establish collaborations with groups such as the PHRI.