ALBERT EINSTEIN COLLEGE OF MEDICINE

STRATEGIC RESEARCH PLAN UPDATE 2010

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Introduction

A Vision for the Einstein Research Enterprise

Beginning in 2006, the leadership and research community of the Albert Einstein College of Medicine have undertaken a dynamic strategic planning process that is predicated on a vision for Einstein's future in which:

- Einstein research is characterized by true collaboration and synergy between basic, translational, and clinical investigators.

- Einstein research informs both our educational mission in training the next generation of physicians and scientists, and our clinical agenda in partnership with our medical center affiliates.

- Einstein research leads to measurable improvement in the health of our Bronx community, of our nation, and of people throughout the world.

The initial planning process resulted in the publication of a Strategic Research Plan[1] in April 2007 that proposed the development of new scientific directions and innovative research resources and infrastructure in seven science and technology theme areas and eight major health-related focus areas. In 2010, a planning process was undertaken to review progress made in response to the Plan (see Appendix, page 20, for Progress Report on Implementation), identify issues that may have limited implementation in any areas, and propose new or amended opportunities for ongoing development of the Einstein research enterprise.

Updating the Strategic Research Plan

To ensure that the direction of the Einstein research enterprise remains current and on course, the Dean initiated a process to update the 2007 Strategic Research Plan. The objectives were to review progress, identify stumbling blocks, and determine which areas require expansion or a change in direction. The update process also provided an opportunity to identify new areas of investigation whose importance or existence was unappreciated during the 2006-2007 strategic planning process. The update process was tempered by fiscal realities and required Einstein faculty and leadership to prioritize where best to invest the College's resources to maintain and grow Einstein research.

An Inclusive Process for Updating the Strategic Plan

To provide a foundation for the update planning process, a brief survey was distributed to all department chairs and center directors as well as new key recruits (totaling over

[1] The April 2007 Strategic Research Plan is available at http://www.einstein.yu.edu/researchsp/page.aspx.

120 faculty members) in November 2009. Chairs and directors were asked to envision how their department or center could contribute to Einstein's future in the areas of recruitment, technology, program projects, and collaborations. Ideas were solicited for areas of research, "big science" multidisciplinary collaborative research programs, and new and emerging technology areas that should be pursued at Einstein. Finally, respondents were asked to identify areas of research that could be developed with the enhanced clinical opportunities afforded by the new Einstein-Montefiore affiliation and to suggest ways for facilitating such research.

After the survey results were compiled, working groups composed of a chairperson and seven to ten faculty members from across the College were appointed in seven theme areas:

- Basic Biological Research
- Behavioral, Social Science, and Effectiveness Research
- Computational and Informatics Research
- Einstein-Montefiore Interface
- Genetics and Epigenetics Research
- Imaging
- Stem Cell Research

Prioritizing Items for Strategic Development
Chairs and members of the working groups, as well as additional faculty members and senior leadership from the Office of the Dean, convened at a one-day retreat on April 26, 2010 to discuss and prioritize the theme-related proposals. After presentation and discussion of all working group proposals, retreat participants identified the highest priority items for further development. Implementation of these initiatives was expected to provide critical new resources and/or infrastructure that will broadly enhance the effectiveness and competitiveness of Einstein investigators in a variety of health foci and across the spectrum of basic, translational, and clinical research.

After further discussion by the Dean's Office staff, the following high-priority initiatives were identified for development and inclusion in the Strategic Research Plan Update:

- Automated Technologies for Stem Cell Research
- Metabolomics
- High-Throughput Systems for shRNA and chemical genomics screening
- Integrated Imaging Resource/Multi-Modal Image Analysis
- Clinical Research Enterprise/Einstein-Montefiore Interface
    - Co-Funding of Clinical Researchers
    - Clinical Trials Infrastructure
    - Co-Funding of Databases, Repositories and Information Technology
- Center for Social Science, Behavioral, and Effectiveness Research
- Genomics/Epigenomics/Computational Biology

This update to the Strategic Research Plan describes the opportunities, needs, and examples of applications to human health for each of these priority initiatives.

Automated Technologies for Stem Cell Research

The Opportunity: Established in May 2010, the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research provides a cohesive and supportive environment for stem cell investigators at Einstein and facilitates the recruitment of new researchers and the coordination of shared stem cell core resources. *The new Institute represents an opportunity to create a large, globally relevant, multifaceted center that could dramatically increase the efficiency of bench to bedside translation of stem cell research.*

The Need: By providing state-of-the-art automated technologies for stem cell research, the Gottesman Institute will increase Einstein's competitiveness for new collaborative funding opportunities from the National Institutes of Health, as well as from the Empire State Stem Cell Program. Full implementation of automated technologies for human stem cell research will require:

- Equipment to grow embryonic (ES) and induced pluripotent (iPS) stem cells in large volume.
- Two technicians to perform genetic manipulations of ES and iPS cells.
- Robotics expertise to service and program automated instrumentation on campus, including a full-time associate and full-time technician.

Application to Human Health: Major areas of strength in stem cell research at Einstein include embryonic and fetal stem cells, normal and malignant hematopoietic stem cell biology, and liver stem cells with a focus on liver failure, hemophilia, and other diseases. Other disease-specific stem cell research programs involve the three germ layers, i.e., mesoderm (cardiac stem cells), endoderm (pancreas) and ectoderm (eye development, schizophrenia, Huntington's disease).

Metabolomics Core Facility

The Opportunity: Researchers across Einstein incorporate metabolomics—the study of all products of metabolism in a specified cell, tissue, organism, or biological condition—as a central approach to understanding fundamental biology and its perturbation in disease. Interest and usage of the recently-established Einstein Metabolomics Core is also spreading at a national level, with inquiries from other institutions including Mount Sinai, Columbia, and Vanderbilt. *Expansion and technical development of the Metabolomics Core Facility will provide critical infrastructure for multiple research centers and programs and will create new opportunities for collaborative research.*

The Need: To expand the capacity of the Metabolomics Core Facility as an efficient and highly functional resource for multiple Einstein Centers and research programs and, importantly, as a regional facility with the potential for NIH support, the Core must incorporate additional equipment and personnel. Current needs include:

- *Personnel*: mass spectroscopy technician; mass spectroscopist; research technician
- *Equipment*: Leco GC/Tof; Seahorse XF24 Flux analyzer; MALDI station; Nanomate

Application to Human Health: Einstein researchers are using metabolomics approaches to study the regulation of mTOR, a protein that appears to be central to a variety of cellular processes, such as growth, proliferation, motility, and response to nutrient availability, among others. MTOR function or dysfunction has been implicated in a variety of human diseases and conditions, including cancer, fragile X syndrome, parasite infection, aging, and diabetes.

shRNA Functional Genomics Facility

The Opportunity: Until recently, identifying the critical genes responsible for many diseases was dependent on a time-consuming gene-by-gene analysis of their role in cellular function and disease. With each cell capable of expressing the 20,000 known human genes, this tedious sequential approach would have taken hundreds of investigators years to identify genes that cause diseases. Two major breakthroughs have now provided scientists with shortcuts to dramatically reduce the number of investigators and the time needed for these studies:

- First, a technology was devised that could specifically turn off any gene in a cell. This technology used artificial short interfering RNA (siRNA) with gene-specific sequences expressed by a lentivirus vector as a short hairpin RNA (shRNA) structure to selectively silence the expression of the corresponding gene.

- Second, powerful robotics platforms were developed that can perform automatic, continuous and highly efficient processing of thousands of biological samples in parallel. These robotics systems provide us with the ability to analyze tens of thousands of microculture wells.

Combining these approaches would enable us to selectively turn off every gene in a cell and then examine its effect on cellular behavior. Each gene can potentially direct the production of a distinct protein. Consequently, every cell in the body has the capacity to produce tens of thousands of different proteins with diverse functions. However, for each cell only a fraction of these genes are turned on and permitted to produce their protein. The unique function of the cell is determined by the summation of the activated genes and the specific proteins they produce. For example, a cell in the liver has many genes that are turned on which are relevant to liver function that are not turned on in cells in other organs of the body such as the heart, brain or kidney. We do not know the identity of many of the genes that confer unique organ-specific function to cells.

In addition, sometimes things go wrong. A gene that should be turned on in a cell is turned off or, conversely, a gene that should be turned off in a cell is turned on. This deregulated gene function can cause the cell to behave abnormally and develop cancer or autoimmune diseases. *The proposed shRNA Functional Genomics Facility has the potential to transform Einstein's capacity to identify the individual genes responsible for many diseases and cellular processes.*

The Need: Investment in the infrastructure that is required to develop this high-performance research platform, which is present in only a handful of medical and research centers in the world, would provide a powerful new resource for Einstein research. Establishing a state-of-the-art shRNA Functional Genomics Facility will require a facility director, robotic equipment, and molecular supplies.

Application to Human Health: Just as Google revolutionized our ability to access individual facts from the thousands of terabytes of information on the web, the proposed Einstein shRNA Functional Genomics facility has the potential to transform our capacity to identify the individual genes responsible for many diseases including cancer and autoimmune disorders. For example, by individually silencing every gene expressed in breast cancer cells with a library of shRNAs, researchers can identify which gene(s) needs to be turned off to eliminate the cells' malignant behavior. This information can then be used to identify new targets for drug development to treat breast cancer.

Chemical Genomics Facility

The Opportunity: Where does one start when there are infinite possibilities? The atomic structures that could be possible drugs of the future number beyond the grains of sand on the earth. And yet less than one thousand pharmaceuticals are now in use to improve the quality of human life. Converting the exciting new discoveries of Einstein's scientists into drug therapies is a high priority. We can speed discovery by screening atomic libraries for interaction with new drug targets. We plan to use robotics, and diverse chemical libraries to provide Einstein researchers access to new starting points in drug discovery. With each of the thousands of possible human drug targets being discovered from advances in genome science, testing each against the infinite number of possible atomic structures would take forever. We are developing new ways to speed the process and thereby accelerate drug discovery.

Major advances in finding the starting point for drug development are now possible by three new resources.

- First, atomic diversity libraries are available from established chemical supply companies. Einstein scientists have generated a unique library that contains atomic fragments commonly found in drugs.
- Second, Einstein's new Macromolecular Therapeutics Development Center permits researchers to produce new biological targets to permit atomic library testing.
- Third, powerful robotic analyzers can perform precise, continuous and highly efficient processing biological targets against thousands of drug fragments.
- Fragment 'hits' are pieced together like pieces of a jig-saw puzzle to build a new drug-candidate to fit each target.

Combining these approaches will allow Einstein scientists to discover new agents that can be tested in cells and animals on the path to new drug development. A new target for drug development often comes from genetic information. For example, mutations in cellular proteins that cause cells to grow without restraint are common causes of cancer. This mutation is found only in the tumor tissue, making the tumor different from normal human cells. This abnormal protein is a causative agent of the cancer and becomes a target for drug design. Where to start the process? First, each member of a diverse chemical library is tested on the drug-screening robot to find which members of the library interact with the target. Einstein has already made substantial investments in technologies that provide "read outs" of interactions between drug fragments and biological targets. These include our state-of-the-art facilities in x-ray crystallography, nuclear magnetic resonance (NMR) and mass spectrometry. The initial hit from the diversity library is analyzed to see how the drug fragment is interacting with its target. The lead discovery in fragment design often reveals a partial fit, like filling a glove with only a two fingers. But by knowing this structure, researchers can discover how to expand the drug fragment so that the other finger-sites are occupied and thereby give powerful inhibitors. When these are tested in cancer cell cultures, inhibitors that have the desired effects with minimal side effects become drug candidates.

Synergism with Other Einstein Discovery Research Einstein has recently invested in new technology to gene-silence every gene in cells, one at a time. Genetic silencing will identify genes in abnormal states, including cancer. These can be used as targets for the development of new therapies. Gene regulation studies can identify abnormal or cancer cells that no longer exhibit malignant behavior and thereby establish which gene was turned off in order to return the malignant cell to normal. That gene product (often a protein) becomes a target for drug discovery research.

The Need: Trained chemists and supplies, specifically appropriate chemical libraries. Robotics equipment obtained for high-throughput screening with shRNA (see above) will be used here as well providing economies of scale.

Application to Human Health: Investment in this high-performance research platform – which is only present in a handful of medical and research centers in the world – and which includes a chemical library unique to Einstein, will provide our investigators with the ability to identify the drug fragments whose structures can be grown into more powerful inhibitors with drug potential for diseases including cancers, immune-mediated disorders and new antibiotics.

Integrated Imaging Resource/Multi-Modal Image Analysis

The Opportunity: Comprehensive analysis of disease states requires the surveillance of tissues and organs at the macroscopic level combined with the ability to "zoom in" on cellular and even intracellular detail. To enhance clinical practice, different imaging modalities with varying spatial resolutions must be used to acquire and integrate data. Einstein currently has significant expertise and infrastructure in a range of imaging modalities covering all physical scales in living tissue, including: *in vivo* single molecule or cells; tissue microenvironments; and organ function and architecture. These resources position Einstein at the forefront in the development of multi-modal imaging technology. *By creating an **Integrated Imaging Resource**, Einstein can take a leading role in the development of multi-modal imaging technology and analysis to extend the application, resolution, and interpretation of clinical imaging beyond what is currently possible.*

The Need: Establishing an Integrated Imaging Resource would allow Einstein researchers to continuously image living tissues from nanometer to centimeter scale. The Resource will include the Biophotonics Center, the Gruss Magnetic Resonance Research Center, PET/SPEC/CT, and IVIS facilities and Electrophysiology resources already or about to be in place. Their integration and synergy will require the development of a Molecular Development Center**,** composed of chemists and molecular scientists focused on developing novel biomaterials for imaging and therapy. This Center will help adapt bench science to animals and to human patients in the clinic. In addition, a Multi-Modal Image Analysis Resource**,** by registering and combining the data from individual imaging modalities, will allow the physical scales imaged by each to be bridged leading to the translation of basic science and increases in scope of measurement and resolution to be exploited for clinical use.

Establishing a fully functional Integrated Imaging Resource will require:

- Recruitment of faculty to participate in the Integrated Imaging Resource
- Dedicated HPC computing cluster to support a new registration-analysis core
- Integration of the use of the recent NIH-awarded animal MicroPET/SPECT/CT instrument and a small animal bioluminescence IVIS instrument with MRI and multiphoton imaging
- 1 Hyperpolarizer and coil technology for C13, F19, and N15
- Human scale PET/SPECT/CT or PET/MR
- Enhanced housing for animals
- FACS capability for sorting eukaryotic cells and bacteria for probe development
- Renovated space for multimodal imaging and molecular development personnel
- A bridge technology postdoctoral training program.
- Engineers and molecular probe developers to build interfaces between imaging modalities and to support the Molecular Development Center.

Application to Human Health: Using magnetic resonance imaging, fluorescence mediated tomography, intravital microscopy, and integrated data analysis, researchers found that tumors selectively manipulate a subpopulation of monocytes to increase their motility and migrate to tumor sites where they differentiate into macrophages or dendritic cells. Then, the cells release factors that promote tumor progression. Cancer biologists and medical oncologists are now using these imaging modalities to define the functions of tumor cells in specific microenvironments and discover interaction networks of cells and molecular factors in living tissues.

Clinical Research Enterprise/Einstein-Montefiore Interface

The Opportunity: With the funding by NIH of the Einstein-Montefiore Institute for Clinical and Translational Research, and the strategic alignment of Einstein's enhanced research capabilities with Montefiore's integrated clinical care delivery system, there is a unique opportunity to create a powerful clinical research enterprise that leverages the strengths of both institutions and delivers on the promise of personalized medicine in the genomics era. Einstein and Montefiore are moving from collaborative but separate institutions to a joint clinical and translational research enterprise. One of the strategic priorities of the Einstein research plan is to create a robust Einstein-Montefiore research interface.

The Need: Three components are critical for the next stage:

I. Enhancing clinical trials capacity
II. Clinical Researcher co-recruitment with Montefiore
III. Establishing a robust Biorepository, databases, and IT strategy

Each is described in greater detail below:

Joint Office of Clinical Trials-

Clinical trials have expanded within the practice community and increasingly outside the US since sponsors have often opted to select trial sites outside of major US medical centers. This is because of the perceived lack of responsiveness within the academic community in negotiating contracts, moving protocols through IRBs, and the poor enrollment. Such a bias, though legitimate, has minimized the participation of academic medical centers in the ever-growing business of randomized trials.

Given the size and scale of the clinical enterprise and faculty at Montefiore and Einstein, there is a real potential for a many-fold expansion of industry-sponsored and federally funded clinical trials. A Montefiore-Einstein office of clinical trials will formalize an infrastructure providing local, national and global leadership in clinical trials, evidence-based health care and comparative effectiveness research, and be a locally and nationally recognized leader proving the efficiency of trials conducted at an academic medical center. Additionally, there are opportunities for development of sponsored clinical research including investigator-initiated and collaborative projects, coordinating center roles, centralized reading centers and data management sites, and collaborative consortia leveraged by our membership in the CTSA.

We are now in a unique position to expand clinical trials—the strengthening and deepening of affiliation between Einstein and MMC has promoted the recognition that clinical research is, of clinical care, not a thing apart, but the flip side of general

excellence in patient care. Furthermore an expanded clinical trials capability will synergize with the Cancer Center, other disease-specific facilities such as gynecologic oncology, diabetes, aging, sleep disorders, epilepsy, and the Institute for Clinical and Translational Research to provide platforms and resources for supporting many aspects of the clinical research enterprise. clinical research being emphasized in both Montefiore and Einstein strategic plans; a compelling critical mass of inpatient and outpatient facilities; a diverse patient population; a common and expanding medical information system; and a large network of ambulatory care settings. Finally, the partnership with the Biomedical Research Alliance of NY (BRANY) enables Montefiore-based care providers unique resources to engage in clinical research. Clinical trials will build on the collaborative nature exhibited by Einstein and Montefiore in the past and help to cement the research plans for the future.

Clinical Researcher Recruitment-

A coordinated approach to the recruitment of clinical investigators will be key to expanding the research base. Major recruitments of clinical leadership in the past several years has yielded new opportunities in cardiovascular surgery, pediatric cardiology, pulmonary medicine, organ transplantation, ophthalmology, critical care, cancer, adult cardiology, and pediatric diabetes. Existing clinical programs—radiation oncology, family medicine, hepatology, rheumatology, infectious diseases, and otorhinolaryngology, among others—are also positioning their faculty to take advantage of the growing infrastructure for clinical research. There is also a robust pipeline of young investigators supported through career development awards, funded by both the NIH and Einstein's Men's Division philanthropic program. Nevertheless, going forward we will need to recruit additional clinical investigators in key areas. Such recruitments must take into consideration the support for faculty salaries designated for clinical care as well as research, follow guidelines for co-funding support staff, and commitments to the infrastructure such as space and core resources, including biostatisticians and data management.

Biorepository, Databases and Information Technology Strategy-

Through the Einstein-Montefiore ICTR and other efforts, we have already established specialized biorepositories and databases for areas including liver disease/primary liver cancer, cervical and ovarian cancer, and head and neck cancer. Community-based cancer databases have also been established by Bruce Rapkin and colleagues. But there is a need to move beyond these few specialized areas if we are to take full advantage of the clinical/translational research opportunities at the Einstein-Montefiore interface.

A foundational component of this joint plan for clinical and translational research is the development of methods and policies for cross-institutional access to data. Data originate in both clinical care settings and in research environments. Access to this data is of significant value to both institutions as well as the collective partnership. For Einstein, the primary benefit is support for the expansion into clinical and translational (both "bench to bedside" and "bedside to community") research; for Montefiore, it is in support of the expansion from healthcare delivery to clinical research. Particularly in the context of new mandates in health care reform, the electronic health record (EHR) is a platform for both enhancing care as well as conducting research. In most instances, the same data are required to meet both needs, since patient care and biomedical research are bridged by common data elements.

Building a single research enterprise requires two key components of which several elements are already underway. The first is the development of an information technology infrastructure to allow the appropriately protected, unimpeded flow of data between the institutions. The second is the creation of a coherent environment for the management of research data. Our vision is to create a cross-campus technology environment/platform to support research in the broadest sense. To be specific, linkage of research data—including a major emphasis on biospecimen-based methods such as genomics and proteomics—provides an opportunity for laboratory-based investigators to ask and answer important human health questions. This will lead to increased competitiveness and greater institutional recognition. For the clinical enterprise, the enhanced datasets can be used for augmented healthcare quality improvement and for increased operational efficiency and cost-effectiveness, thereby benefiting operations. In addition, it furthers Montefiore's reputation as a world-class institution, allowing it to attract clinicians and clinician-researchers that will advance the combined organizational imperatives. Finally, as genetic data increasingly becomes an integral part of healthcare delivery, Montefiore will be prepared to meet the promise of personalized medicine.

There are many investigators/projects that are stuck in "second gear" where access to clinical data prevents further progress, grant applications, or publications. Providing an information and technology infrastructure that supports unimpeded data assembly for biospecimen research, data exchange, data sharing, and wider integration with basic science laboratories will enable more efficient and effective healthcare and research. The investments will lead to successful integration of information and workflow between patient care and clinical research. This plan will ensure that we remain competitive at the level of data integration required by the CTSA and NIH in general.

This comprehensive technology platform will provide connectivity, hardware, software and a team of experts to the Einstein and Montefiore research community at large. Leveraging this infrastructure, investigators can remain focused on the acquisition,

analysis and interpretation of data. In order to achieve this vision, the following will be priorities: expanded support for computing environment in partnership with Montefiore, needs assessment and evaluation of the Einstein-Montefiore research partnership, data management for investigators, and a clinical trials management system to enable the expansion of multicenter trials.

Application to human health: Investment in the Clinical Research enterprise at the Einstein-Montefiore interface will have a positive impact on our progress in addressing virtually all of the major health focus areas identified in our original strategic research plan. Einstein research strengths and platform technologies (Genomics, Epigenomics, shRNA, Transcriptomics, Proteomics, Metabolomics, chemical genomics) interface with key elements of an enhanced clinical research enterprise (EMR, Montefiore's Clinical Looking Glass, and External Databases, Images (pathology/CT, MRI, PET), clinical trials,) to address improved diagnosis, treatment and prevention of human disease.

(*Note: Many elements required for implementation of the final two priority initiatives: "Einstein Center for Health and Society" and "Institute for Clinical Genomics and Epigenomics" are addressed in a more general way in the preceding description of the "Clinical Research Enterprise/Einstein-Montefiore Interface" initiative. To avoid redundancy, these will not be repeated in the descriptions that follow, but it should be emphasized that investment in the Clinical Research Enterprise could be leveraged to achieve many of the goals of these two priority initiatives.)*

Einstein Center for Health and Society

The mission of the proposed Einstein Center for Health and Society (ECHS) is to advance community, family and individual health through research that is grounded in basic and applied social science theory. The ECHS aims to identify the behavioral, social, and biomedical pathways that give rise to poor health and health disparities, to develop interventions to improve health and reduce disparities, and conduct comparative effectiveness research.

The Center will have a diversified portfolio of exceptional research led by its own social science researchers, but it will be a campus-wide resource as well. It will provide consultation to investigators and students who seek to conduct social science research, use social science methods, or integrate social science constructs in their work. In addition, the Center will lead a collaborative initiative that will address a four-part substantive agenda. This forms its first five year plan and shapes its investments. The Center's four main scientific goals are:

1. **To build capacity and competitiveness of social science researchers through constructing a database infrastructure in partnership with Montefiore.**
2. **To conduct social research on population and community health in the Bronx**
3. **To identify and address the causes of health disparities in the Bronx**
4. **To advance the science and practice of program evaluation and comparative effectiveness research**.

<u>The Need</u>:

Recruits, equipment, support staff and space needed to implement this initiative will not be detailed here, as noted above.

<u>Application to Human Health:</u>

Behavioral and social factors are key determinants of some of the major diseases affecting not only the population of the Bronx, but the U.S. as a whole. Diabetes, congestive heart failure, and smoking-associated emphysema and lung cancer are notable examples. Investment in the Einstein Center for Health and Society offers the prospect of addressing these and other diseases in a way that cannot be achieved through laboratory-based biomedical research alone.

Institute for Clinical Genomics and Epigenomics (ICGE)

The goals of bringing the results of basic science to the bedside are best served within an organizational entity that integrates resources to focus attention on the translational applications of our genomics and epigenomics infrastructure. The proposed ICGE would be the resource to which researchers and clinicians alike bring their ideas for how human diseases could be studied collaboratively.

Several of the elements required to complement the function of the ICGE are addressed in the "Clinical Research Enterprise" initiative. These include:

- Assistance with IRB submissions
- Study design in terms of patient cohort numbers and characteristics
- Funding of pilot projects
- Assistance with patient consenting and sample collection processes
- Development of clinical sample repositories and clinical databases.
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Other elements are unique to the ICGE:

- Design of molecular assays, including novel and cost-effective approaches
- Provision of core facility services to perform assays in a high-throughput manner
- Data analysis and interpretation
- Advice on how associations can be validated using model organism approaches

<u>The Need:</u>

Again, we will not detail specific equipment, recruitment, support staff and space needs here to the extent that they are addressed in the "Clinical Research Enterprise" initiative. Particular attention will need to be paid to robust linkage of the new clinical research enterprise elements to the ICGE. Additional elements required for establishing the ICGE include expansion of next generation genome sequencing capacity, recruitment of highly qualified computational and statistical geneticists, consideration of development of a model organism core facility, and investment in technologies needed for a structural epigenomics program.

<u>Application to Human Health:</u>

While the payoff from sequencing the Human Genome to date has been limited in terms of meaningful translation to human health/disease, there is no doubt that as genome sequencing becomes much cheaper and more routine, applications to personalized medicine in cancer treatment, pharmacogenomics and other areas will flourish. Establishing the ICGE offers Einstein and Montefiore the opportunity to become leaders in this effort.

Looking to the Future

Implementing the initiatives proposed in this Strategic Research Plan Update will help propel Einstein to the forefront of research on the role of genes, the environment, and interactions between the two in human health and disease. Collectively, these initiatives will support a robust scientific environment that spans the gamut from clinical and translational research in cooperation with patients and the community to state-of-the-art technologies to study human health and biology at the molecular and cellular level. The resources, technologies, and collaborative opportunities provided by the proposed initiatives will broadly benefit researchers across the Einstein campus and enable research on countless human diseases.

The Gene-Environment Paradigm in Health and Disease

Biomedical and behavioral research has uncovered many, diverse factors that affect human health in complex and often still-unknown ways. Now, researchers are studying how myriad genetic, behavioral, and environmental risk factors interact with each other to cause disease and, conversely, how these factors sometimes work together to protect a person's health. As more knowledge is gained, researchers will use this information to improve health in multiple ways. Being able to accurately predict who will develop a particular disease could allow individuals to undergo preventive treatment, if available, take steps to mitigate their environmental risk factors, or be monitored for early diagnosis of disease onset, which can improve prognosis of some diseases. Researchers can also use knowledge of disease risk factors and their interactions to target molecular pathways for the rational development of new drugs and therapies. Finally, understanding specific disease risk factors represents a major step toward fulfilling the promise of personalized medicine—clinicians would be able to identify specific genetic and non-genetic factors that triggered disease in an individual patient and use that information to select optimal strategies for prevention and treatment. Personalized medicine has the potential to increase therapeutic benefit, minimize adverse effects, and potentially reduce medical costs by avoiding treatment that would not be effective in a particular patient.

Einstein Research – From the Patient to the Laboratory and Back Again

A major priority of this strategic plan is strengthening the ***Clinical Research Enterprise*** that links Einstein and Montefiore. A robust clinical research and clinical trials program that efficiently interfaces with the 1.4 million patients who receive care at Montefiore each year is essential for research on the genetic, behavioral, and environmental causes of diseases. Improvements to information technology and data access between the two institutions will improve the capture and analysis of patient information while ensuring appropriate protection of patient privacy. Researchers can mine these data to identify factors that are associated with specific diseases or subtypes of diseases. The clinical research infrastructure and an expanded clinical research faculty base will also help Einstein researchers to access patient biosamples for research on genetic and

molecular biomarkers of disease. The ***Integrated Imaging Resource/Multi-Modal Image Analysis*** initiative will allow researchers to collect an added dimension of data on patients and disease states by imaging tissues and organs across a wide range of physical scales from cells to the whole body.

Shared facilities proposed in this strategic plan will enable Einstein researchers to study gene-environment triggers of disease from a molecular viewpoint. The ***Metabolomics Core Facility*** will provide technologies that allow researchers to identify the thousands of metabolites in a particular cell or tissue, including biosamples collected from patients. Metabolic profiling can be used to detect physiologic changes caused by a chemical, pharmaceutical drug, dietary or nutritional change, infection, or gene mutation. Thus, metabolomics technologies are critical to understanding how gene-environment interactions affect cellular processes and lead to disease. Similarly, the ***shRNA Functional Genomics Facility*** will provide a high-throughput technology that researchers can use to scan more than 20,000 genes to identify the ones that are associated with specific diseases. This facility will greatly accelerate the search for disease-causing genes and genetic mutations.

Discovery of genetic and environmental factors will, in turn, allow researchers to identify molecular and cellular processes that go awry in specific diseases and find new targets for therapeutic intervention. The ***Chemical Genomics Facility*** affords Einstein scientists an opportunity to participate in the earliest stages of drug development—the discovery of novel chemical structures that can interfere with disease-related pathways. Likewise, the ***Automated Technologies for Stem Cell Research*** will enhance Einstein's capacity for the development of stem cell-based therapies and the use of stem cells to screen new drugs. Ultimately, new drug candidates or cell-based therapies can be taken back through the Einstein-Montefiore clinical research enterprise to evaluate their ability to treat disease and improve health.

Summary

This strategic plan update presents a comprehensive strategy for ensuring that Einstein researchers have the resources, technologies, support staff, and collaborative scientific environment that are necessary for leading-edge biomedical and behavioral research. When fully implemented, these initiatives will provide a clear path for research from the clinic and community to the laboratory and back again, thus reinforcing Einstein's commitment to improving human health through research.

APPENDIX

Implementing the 2007 Strategic Research Plan: A Progress Report

In the past 3 years, significant progress has been made in implementing the recommendations of the Strategic Research Plan. The College has recruited new faculty that complement and expand existing research focus areas, established new institutes and centers to promote collaboration and provide shared resources in several research fields, and acquired state-of-the-art technologies to ensure that Einstein research programs remain current and competitive. Selected programs that have been newly implemented or expanded in response to the Strategic Research Plan are described below.

Structural Biology

Structural biology, particularly determination of three dimensional protein structure using X-ray crystallography, was a major science/technology focus of the 2007 strategic plan. A Protein Production facility was established in the Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion under the scientific direction of Dr. Steve Almo. Building on this technology investment, and with Dr. Almo's leadership, Einstein has now been awarded three separate multimillion dollar grants: a multicenter "glue grant" to study enzyme function, a project with Dr. Stan Nathenson on structural genomics of the immune system, and leadership of the NIH's Structural Genomics initiative.

Department of Systems and Computational Biology

The Strategic Research Plan described the importance of the emerging fields of computational biology and systems biology. These disciplines provide vital tools and approaches for studying complex biological systems and processes, such as the immune system, neural networks, and evolutionary biology. The strategic plan noted that the existing program-based structure for computational and systems research had not fostered the development of a cohesive research effort in these disciplines among the Einstein faculty or the development of an effective educational program in these areas. The creation of a new academic department was proposed as a means to provide an appropriate organizational structure to support research, collaboration, and education in the computational and systems biology fields at Einstein.

In 2008, a Department of Systems and Computational Biology was established with Dr. Aviv Bergman, an Einstein professor of pathology and neuroscience since 2004, as its Founding Professor and Chairman. The new department defined its mission as "advancing the understanding of living systems as a whole by promoting a new approach to biology that combines theoretical and experimental approaches aimed at explaining how the higher-level properties of complex biological systems materialize from the interactions among their parts." The department developed a graduate student curriculum on the role of systems, theoretical, and computational biology in modern

biomedical research that received degree granting accreditation from NY State, and has begun to enroll graduate students. Recruitment of new faculty to the department is underway, and is being coordinated with recruitment of computational biologists in the Genetics Department.

Institute for Clinical and Translational Research /Clinical and Translational Science Award

The Strategic Research Plan emphasized the need for Einstein to cultivate a vigorous translational and clinical research program in order to remain competitive in the current funding climate for biomedical research. In partnership with the Montefiore Medical Center, Einstein created an Institute for Clinical and Translational Research (ICTR) that aimed to remove barriers that often inhibit investigators from translating basic science discoveries into clinical applications. The ICTR was designed to provide necessary resources and infrastructure for clinical and translational research in all health-related fields, as well as to support training, education, and career development of clinical and translational researchers.

In 2008, Einstein received a $22 million, 5-year Clinical and Translational Science Award (CTSA) from the National Institutes of Health (NIH) to support the ICTR. The CTSA grant links Einstein to a consortium that in 2010 expanded to 55 clinical and translational research centers across the United States. Thus, the Einstein research community has a voice in the NIH-led efforts to transform the conduct of biomedical research across the country in ways that improve human health and enhance the efficiency and quality of clinical and translational research. Locally, the ICTR promotes multidisciplinary collaboration among Einstein and Montefiore investigators and enhances community participation and engagement in clinical research activities.

Einstein-Montefiore Interface for Clinical Research

The natural affinities between Einstein and its major clinical affiliate—Montefiore Medical Center (MMC)—have been critical to re-engineering our clinical and translational research programs. Under the leadership of the new President of Montefiore, Dr. Steven Safyer, Einstein and Montefiore faculty engaged in a strategic planning process aimed at medical center priorities in health care delivery. Emerging from this process, the Montefiore Strategic Plan of 2009 identified the partnership with Einstein around research and education as its highest priority. A historic agreement between the two institutions signed in 2010 codifies the shared responsibilities for the clinical research enterprise, with Einstein assuming a major role in supporting research at all MMC campuses. Alignment of the medical center priority areas in health care has become a touchstone for recruitment of new faculty and the creation of clinical centers of excellence in cardiovascular diseases, transplantation, cancer, diabetes/obesity, and child health. The partnership between Einstein and Montefiore thus merges research with the health care mission into a joint academic health and science center in the Bronx. A recent $4M grant awarded to Dr. Mark Einstein, Marla Keller, Betsy Herold and

other colleagues to conduct a clinical trial of a microbicide against the human papilloma virus causing cervical cancer typifies the synergies that can be achieved through alignment of Einstein's research capabilities and Montefiore's integrated clinical care delivery system.

Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion

A major driving force for the 2007 Strategic Research Plan was the recruitment of investigators and programs to fill the new Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion. Beginning in January 2008, Einstein began a series of aggressive internal and national searches for faculty leaders and investigators in the priority areas identified in the 2007 Strategic Plan. Over the course of two years, 14 investigators were recruited to Einstein to be housed in the Price Center/Block Pavilion. The capstone of the recruitment was the selection of a director for the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research in 2010 to be housed in the Price Center/Block Pavilion. Detailed descriptions of the programs now located in the Price Center/Block Pavilion can be found the 2009 and 2010 Annual Reports.[2]

Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research

The Strategic Research Plan highlighted Einstein's unique resources and historic strengths in stem cell research and regenerative medicine, particularly in the areas of liver research, hematology, and neurology. The Plan recommended the development of an institute to support and promote stem cell research across the college. Such an institute was envisioned as a means to support individual investigator research, as well as foster multidisciplinary studies by increasing communication and collaboration among investigators and providing shared resources, technologies, and training opportunities.

In 2008, a generous gift from Ruth L. and David S. Gottesman enabled the establishment of an institute for stem cell and regenerative medicine research. The Gottesman Institute for Stem Cell and Regenerative Medicine Research provides a more cohesive and supportive environment to nearly two dozen stem cell investigators focusing on a diverse range of health-related focus areas, including liver failure, cancer, and heart disease. In 2010, Einstein recruited a renowned stem cell investigator, Dr. Paul Frenette, to direct the new Institute. Dr. Frenette has made significant contributions to the understanding of the hematopoietic stem cell microenvironment and sickle cell disease. Dr. Frenette will explore new research directions, encourage new collaborations among the faculty, recruit new stem cell investigators, and oversee the

[2] Albert Einstein College of Medicine Annual Reports can be accessed at: http://www.einstein.yu.edu/home/publications/index.asp

establishment of shared resources. Over the past few years, Einstein stem cell researchers have also attracted significant new funding from the NIH (including a $9.5M lab renovation grant) and the New York State Stem Cell Research Program (NYSTEM; >$14M in grants) to support its stem cell research programs, as well as the modernization of stem cell laboratories and shared resource facilities.

Human Genetics/Translational Genetics Division and the Center for Epigenomics

The Strategic Research Plan identified an opportunity for Einstein to develop a well coordinated, integrated program in human genetics and epigenetics research to enhance translational research and promote collaboration across the College. Particular needs included a translational genetics center to establish critical resources, services, and technologies for genetics researchers, as well as the recruitment of a new departmental chair to provide leadership for the support and expansion of human genetics research at Einstein.

The re-named Department of Genetics launched a trajectory of renewed growth and development in 2008 with the recruitment of a new Chairman, Dr. Jan Vijg, an expert in genomic instability, aging and disease. Two new divisions, the Division of Translational Genetics and the Division of Computational Genetics were added to a Division of Molecular Genetics. New faculty with expertise in human genetics and the development of innovative genomics tools have been recruited. A new Center for Epigenomics was created with a gift from Ruth L. and David S. Gottesman to provide cutting-edge assays and technologies for research on how the normal epigenome becomes dysregulated in human disease. Collectively, these new organizational structures, faculty, and shared resources have revitalized genetics and epigenetics research at Einstein.

Gruss Magnetic Resonance Research Center

In response to the recommendations of the Strategic Research Plan, the Gruss Magnetic Resonance Research Center (MRRC), first established in 2000 with a generous gift from the Gruss-Lipper Foundation, has been upgraded and outfitted with state-of-the-art imaging equipment. New resources include the first Philips 3T TX MRI system to be installed in the United States, a completely renovated Varian 9.4T MRI magnet for animal imaging, and brand-new computing infrastructure for faculty, staff, students, and visiting researchers. To oversee the MRRC expansion and ongoing activities, Einstein appointed two nationally recognized researchers in the field, Dr. Craig Branch and Dr. Michael Lipton, as director and associate director of the Center. With their guidance, the Center supports imaging research in a variety of health-related areas, as well as research on the development of new imaging technologies.

Major Faculty Recruitment and Infrastructure Support for Health-Related Focus Areas

The Strategic Research Plan identified several over-arching health-related focus areas that represented historic research strengths at Einstein, as well as priorities for national and global health research efforts. Many of these focus areas encompass research on

diseases and conditions that disproportionately affect the Bronx community, including diabetes, cancer, and HIV/AIDS. Over the past 3 years, Einstein has successfully recruited new scientific leadership and secured significant funding to support research programs and shared resources in a range of health-related fields.

Aging: In 2010, Einstein was designated an NIH Nathan Shock Center of Excellence in the Basic Biology of Aging, one of only five such centers across the United States. The new center, led by Dr. Nir Barzilai, enhances Einstein's productive Institute for Aging Research by providing unique research resources and advanced technologies, as well as seed funding for new investigators in the field. The successful application for the Nathan Shock Center builds on Einstein's strong base of research in the basic biology of aging, including program project grants awarded to Dr. Barzilai (genes and longevity), Dr. Ana Maria Cuervo (role of autophagy in aging), Dr. Jan Vijg (genome instability and cellular aging), and a clinical/translational program project awarded to Dr. Richard Lipton (Einstein Study of Aging).

Cancer: In 2008, a generous donation from Marilyn and Stanley M. Katz was used to create a major new research program within the Albert Einstein Cancer Center. The Marilyn and Stanley M. Katz Comprehensive Cancer Prevention and Control Program directed by Dr. Bruce Rapkin supports Einstein scientists in designing new methods for promoting the health of Bronx residents. The program includes population studies to identify lifestyle and environmental factors that cause cancer, as well as cancer prevention initiatives focusing on smoking cessation, exercise, healthy nutrition, and preventing obesity.

Cardiovascular Disease: A generous gift from Zygmunt "Zygi" Wilf and his family enabled the establishment of the Wilf Family Cardiovascular Research Institute in 2009 to support research on cardiovascular disease, the leading cause of death worldwide. As Director of the new Institute, Dr. Richard Kitsis is assembling a core group of existing and to-be-recruited faculty in basic, clinical, and epidemiological disciplines who will focus on better understanding cardiovascular disease and using that knowledge to develop new treatments and improve health.

Diabetes, Obesity, and Other Metabolic Diseases: In 2008, Einstein recruited Dr. Jeffrey Pessin to direct the Einstein Diabetes Research and Training Center (DRTC), one of the first and longest running NIH-supported diabetes research centers in the country. Under Dr. Pessin's leadership, Einstein expanded its robust diabetes research program by recruiting several new outstanding diabetes investigators to the Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion. Recognizing Einstein's continuing excellence in diabetes research, the NIH renewed funding for the DRTC in 2010 with a 5-year, $9.5 million grant, as well as supplemental funding for equipment and additional pilot and feasibility studies.

Infection and Immunity: The NIH renewed funding for the Einstein-Montefiore Center for AIDS Research (CFAR) in 2008 with a 5-year, $8.5 million grant, reaffirming its position as one of the leading centers for AIDS research in the United States. Under the

leadership of CFAR director Dr. Harris Goldstein, the grant provides support for Einstein's research programs in HIV biology and therapeutics; HIV-associated pathogens and HIV-related epidemiology; and behavior and substance abuse. The grant also enabled the expansion of AIDS-related research and treatment programs in Rwanda, Ethiopia, South Africa, India, and Guatemala. The latter reflect Einstein's contributions to global health research focusing not only on HIV but also TB which often complicates and exacerbates HIV infection. Over $8M in NIH grants were recently awarded to Drs. Sarita Shah and Neel Gandhi for studies of drug resistant TB and TB/HIV coinfection in South Africa. Major recent NIH grants to Dr. William Jacobs (Genetics of TB) and Dr. Kami Kim (Systems biology of toxoplasma) further emphasize Einstein's increasing strength in infectious disease research. Such strength is of strategic importance in an era of newly emerging and reemerging infectious diseases, as well as the threat of bioterrorism. The latter involves more than just potential infectious agents, and in that context, a $10.8M NIH award to radiation oncology investigator, Dr. Chandan Guha, to develop measures to counteract radiation-induced gastrointestinal syndrome is equally important.

Liver Diseases: The Einstein-Montefiore Division of Hepatology was formally established in 2007 as a joint endeavor between Albert Einstein College of Medicine and Montefiore Medical Center, and under the direction of its founding director, Dr. Allan W. Wolkoff. The Division provides state-of-the-art diagnosis and treatment of liver disease and provides a formal bridge between basic and clinical research efforts. Its activities are integrated with those of the Marion Bessin Liver Research Center, and it has a close and ongoing relationship with the Department of Surgery's Division of Transplantation and the Department of Pathology's Division of Gastroenterology and Liver Pathology. Recent initiatives have included establishment of a liver transplantation program, development of a tissue and blood biorepository, and inclusion of a program in therapeutic cell transplantation technologies. Recently, the Division of Hepatology was merged into a unified Division of Gastroenterology and Liver Diseases under the direction of Dr. Wolkoff. The unified Division is expected to broaden translational research efforts to include areas such as colon and pancreatic cancer.

Neuropsychiatric Diseases: Established in 1956, Einstein's Children's Evaluation and Rehabilitation Center (CERC) provides evaluation, diagnostic, and treatment services for infants, children, adolescents, and adults who have developmental disorders such as autism, attention-deficit hyperactivity disorder, cerebral palsy, and hearing impairments. In 2009, CERC recruited its first research director, Dr. John Foxe, who studies autism and childhood schizophrenia. Dr. Foxe plans to hire new faculty who specialize in developmental disorders, increase collaborative studies between CERC physicians and the scientists in other Einstein departments, and enroll more CERC patients in clinical studies. Under the leadership of Drs. Steven Walkley and Foxe, the Intellectual and Developmental Disabilities Research Center in the Rose F. Kennedy Building will integrate CERC-based research with the outstanding neuroscience research base, and take advantage of other major investments in Pediatrics, Genetics, Imaging, and Stem Cell research cores.

Reproductive Medicine and Health: In 2009, the NIH awarded Einstein a $7.5 million grant to establish a Specialized Cooperative Center Program in Reproduction and Infertility Research (SCCPIR). According to its director, Dr. Jeffrey Pollard, the new program focuses on basic studies of endometrial biology and reproductive neuroendocrinology, with a particular emphasis on the reproductive health needs of the local Bronx community. Einstein's SCCPIR is one of only 13 such centers across the United States and the only one in New York State.