

## **PROGRAM OVERVIEW :**

### **BACKGROUND**

The Mount Sinai School of Medicine has developed the *Shared Resource Facilities Program* (SRFs, also known as institutional cores) to provide substantial support and technology for research using innovative techniques. The SRFs currently occupy approximately 4,400 square feet of space in various laboratories around the main campus. The compact size of Mount Sinai makes it possible for all investigators to have essentially unlimited and easy access to these resources. We are using an additional approximately 5,800 square feet through a collaboration with researchers at the Bronx Veterans Affairs Hospital, a Mount Sinai affiliate, to house the *Mouse and Rat Phenotyping SRF* that is unique in the metropolitan NYC area.

Support for the Shared Resource Facilities by the Mount Sinai School of Medicine described below totals approximately \$3 million per year, of which user fee charges to investigators from their grants and other resources recoups approximately \$1.3 million. The school also contributes directly to the purchase of new equipment often matching funds from Departments or Centers or Instrumentation grants. This makes it possible to charge investigators reduced fees, which promotes increased use of the facilities, and to prevent duplication of these technologies in individual departments or laboratories. An important ancillary result is that the SRFs enhance the potential for collaboration in multidisciplinary research programs, since SRF directors can bring together investigators working in similar research areas. This also facilitates the adoption of new experimental approaches by PI's, especially in situations where crossover requiring basic science data is needed to underpin and to test clinical hypotheses. Thus, MSSM views its commitment to the SRFs as a significant part of its cost sharing.

A website was developed (<http://www.mssm.edu/research/resources/srf.shtml>) that is linked to individual SRFs and cores. On the individual websites, there is information about the services, fees, protocols for preparations and where appropriate, the opportunity to sign up for usage on a web-based calendar.

### **DESCRIPTION OF THE PROGRAM**

There are twelve (12) freestanding SRFs and each is directed by a scientist who is expert in the use of the technology and in educating investigators in their use. This may include advice on the design of experiments and on the accumulation and analysis of data. In addition to free standing SRFs, the new *Center for Genomics, Proteomics and Bioinformatics* was developed as an initiative to integrate and facilitate interactions between related SRFs and other cores at Mount Sinai (see SRF Organizational Chart below) and to greatly enhance the opportunities to conduct clinical and translational research as well as enhancing the quality of research conducted. This Center and all the SRFs, and relevant Departmental Cores are described below. As new technologies evolve these research capabilities will be incorporated into the the SRF network via a process of faculty peer review (Executive Scientific Advisory Committee) and sound business plan ( Dean's Office Review). This two tiered review will ensure that proposed SRFs will enhance the institutional research mission and use our resources efficiency. Established SRFs will be reviewed on a 3 year cycle for continued support, using a combination of internal and external reviewers. In addition all SRFs are reviewed semi-annually for operational needs via meetings with the SRF Advisory Committees, SRF Director, and Dean's office, Associate Dean for Research Resources (ADRR). Corrective action plans will be developed for poorly functioning SRFs at the semi-annual reviews. This level of accountability will ensure that our SRFs are state of the art, functioning in support of research goals, and prudent fiscal investments.

## The Mount Sinai School of Medicine Shared Resource Facilities.

### 1. Biorepository Cooperative and Histology Service SRF (Susan Morgello, MD, Director)

The facility provides consultations to determine investigator requirements for human tissues in translational research, and then arranges procurement as feasible. After consulting with the investigators about their research needs, we determine the best mechanism to obtain samples and implement their collection. This is made possible by the location of this SRF in the Mount Sinai Department of Pathology, and its focus on anonymized "waste" samples that are in excess of routine diagnostic procedures. If collections are not feasible from diagnostic procedures in the Mount Sinai surgical or autopsy services, attempts are made to provide contacts for the investigator with other biorepositories or tissue collection units.

The facility also offers basic histology services, with capability to process, embed and section fixed and frozen tissues for the Mount Sinai community. We also prepare unstained slides suitable for a variety of applications (histochemistry, immunohistochemistry, *in situ* hybridization, LCM), as well as hematoxylin and eosin sections and simple histochemical stains for routine light microscopic evaluation with dedicated use of a tissue processor, embedding station, microtome, cryostat, and semi-automated tissue arrayer. We have recently added tissue microarrays that can be constructed either from materials procured by the SRF, or from research tissues provided by individual investigators.

PDFs provided on the SRF's website instruct and guide users on "Human Tissue and Fluids Handling Risks and Safety Precautions", "Human Specimen Single User Agreement" and "Commercial Use Policy and Disclosure". The SRF serves to educate investigators about the appropriate human subjects considerations when requests for human materials are made, thus assuring that all human tissue applications that it supports are in strictest compliance with HIPAA and IRB regulations. To date, the facility has been able to serve all investigators demonstrating compliance with the Mount Sinai IRB, and thus by extension, with state and federal regulations pertinent to utilization of human tissues.

Future Plans: Over the next 5-year period, the SRF will enhance its services in two ways: 1. by expanding the types of histologic services it provides, and 2. by developing an integrated IT approach to tissue procurement and tracking outcomes of analysis. For the former, both enhancing techniques (expanding the repertoire of histochemical stains), as well as acquiring and supporting technologies to automate analysis of microarrays will be developed. For the latter, the SRF is developing methods to integrate results of tissue analyses (rendered either in other SRFs or in individual investigator laboratories), so that a databank of tissue types annotated by multi-study outcomes will be developed. This will allow MSSM investigators to access information about tissue characteristics from studies preceding theirs and thus enhance the value and utility of our anonymized samples, and render them more attractive to researchers.

### 2. Flow Cytometry SRF Hans Snoeck, MD, PhD, Director.

The Flow Cytometry SRF provides instrumentation and expertise for automated cytofluorimetric analysis and the sterile sorting of specific cell types. The equipment of this facility is state-of-the art; it consists of three high-speed cell sorters equipped with three lasers, a single deposition unit, and three analytical flow cytometers, one of which has a capacity to analyze up to 18 colors and is equipped with a high throughput sampler.

Major instruments provide for cell sorting by the SRF operator and/or the director, a MoFlo high-speed cell sorter, an Influx high-speed cell sorter and a FACSVantage SE high-speed cell sorter with DIVA electronics. For cell analysis, the equipment is open to anyone who has taken a training session. We have a FACScan single laser, a FACScalibur dual laser, and a five-laser LSRII Special Order Flow cytometer with high throughput samples and DIVA electronics.

Future Plans: This SRF facility is currently being expanded to include a BSL3 cell sorter (completion Spring 2009). This instrument will allow the sorting of unfixed human samples, including samples from HIV patients. The need for safe sorting of live human cells is increasing rapidly along with the emphasis on translational research. Sorting of human samples on cell sorters in conventional rooms is widely deemed unsafe because the sorting process generates an aerosol, and carries the risk of the transmission of pathogens to users and operators. Currently, only human samples that have been tested for HIV, HCV, HTLVI and HBV by the blood bank are sorted in this facility. Patient samples that have not been tested for at least these pathogens cannot be processed. The establishment of a BSL3 cell sorting facility, which will be funded by the institution, is absolutely critical to the efforts of the institution in translational research, in particular in the areas of stem cell biology, immunology and infectious disease.

### 3. Hybridoma SRF Thomas Moran, PhD, Erin Petersen, Co-Directors.

The facility offers assistance and expertise to investigators requesting the preparation of monoclonal antibodies to a desired antigen. The hybridoma production includes the immunization of animals, cell fusions, screening via ELISA, cloning, isotyping, and cryopreservation. The facility also offers peptide linkage to carrier molecules, genetic immunizations, additional screening options such as transient transfection immunostaining, and large scale growth of hybridoma supernatant for antibody purification. Antibodies are generated using a protein or peptides antigen for immunization or by using only the DNA encoding the protein (genetic immunizations) or by viruses expressing proteins of interest on their surfaces. Although there are commercial sources, we continue to serve special needs by applying these new technologies to investigator-generated projects. For example, we generated monoclonal antibodies to the pandemic 1918 influenza virus without the need for having the virus.

Future Plans: Based upon a survey of investigator interest, this SRF will add Luminex technology, which allows investigators to multi-plex or simultaneously analyze, up to 100 analytes in supernatant from a single microplate well. The user can custom select and measure a broad range of mouse, human, rat, and non-human primate cytokines, chemokines, growth factors, and cell signaling proteins. This technology has several advantages over traditional methods of gathering such data, particularly in clinical and translational studies since studies involving human samples often have highly limited sample volume. Only a small sample volume is required for measurement of many different analytes using Luminex technology. More data will now be able to be extracted and analyzed from each sample that is collected. Additionally, with the ability to perform one inclusive experiment, variation between experiments is eliminated and a greater data consistency is achieved. This novel technology covers many areas of research because of the broad range of analytes available.

### 4. Image-Based High Content Screening SRF Dan Felsenfeld, PhD, Marek Mlodzik, PhD, Directors.

This newly established SRF, now in its initial phase of organization, provides high-throughput screening techniques based on microscopy and spectroscopy to the Mount Sinai community. Imaging-based assays, once restricted to cell and developmental biology, have become a critical component in a broad spectrum of basic and clinical research. The development of novel fluorescent probes combined with improvements in robotics and computer-assisted feature recognition, has facilitated the development of commercial microscopes capable of high-throughput evaluation of image-based assays.

Microscopy-based assays permit the detection of molecular events in the context of their cellular environment and complement other high-throughput genomic and proteomic techniques that examine primarily changes that occur *en mass*. Those technologies can't detect local changes in cell physiology that are obscured when cell homogenates are used as a starting point for assays. Microscopy directly measures physiological events reflected through changes in protein distribution or cell morphology. For instance, using fluorophore-conjugated reporters that alter their subcellular distribution in response to physiological signals, it is possible to quantify changes in cell physiology on a single-cell basis. Similarly, fluorescent reporters that alter their spectra based on the concentration of a signaling molecule or activity of a specific kinase permit the detection of a wide variety of signaling pathways in their cellular context. In combination with new automated microwell-based microscopes, these reporters permit the evaluation of libraries of compounds or siRNA reagents on a high-throughput basis using changes in cell-structure as the primary method of evaluation.

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This SRF therefore complements existing high throughput methods at Mount Sinai. Staff will assist end users in assay design, equipment automation, programming and automated feature recognition. We estimate that we will be able to evaluate a library of 14,000 small compounds or siRNA (small interfering RNA) pools over the course of 3-5 days. siRNA libraries are directed primarily at identifying the critical components of pathways under consideration (drug targets). Compound libraries will be screened to identify drug candidates that modulate those targets. At full capacity, we expect to complete 10-14 full screens per year, including assay design and optimization, primary screens and reevaluation of positive samples.

Major instruments include a new Molecular Devices Imagemex Ultra Confocal Imaging System, the central resource of the SRF, is equipped with lasers capable of exciting a wide variety of fluorophores (405nm, 488 nm, 561nm and 635 nm), including all major variants of green fluorescent protein. This machine, in combination with feature recognition software (metaXpress) permits the evaluation, in a 96-or 384-well format, of libraries of compounds or siRNA reagents. Additionally, the facility offers access to a Perkin Elmer Fusion ratiometric plate fluorometer/luminometer that permits high-throughput assays using spectroscopic reporters, including FRET-based probes. Finally, the SRF will include on-site facilities for robotic fluid handling to permit automated formatting of assay plates.

The ability to carry out assays based on microscope-derived data will provide a unique opportunity for PI's to develop experimental approaches that would be cost prohibitive for an individual lab. Currently, our researchers use facilities at other New York or Boston institutions. We expect that these large-scale screens will lead to the identification of drug candidates or targets essential to translational research. The establishment of this new facility, expected to be fully functional in the second quarter of 2008, has been made possible through \$630,000 in seed funds from the Dean's office of Mount Sinai.

Future plans: Following an initial start-up phase, the SRF will focus its efforts in two directions. 1. The establishment of a library of fluorescent reporters designed to permit the rapid development of new assay systems for examining the role of known signaling pathways in disease processes and 2. The development of methods for examining time-resolved signaling events in cells using photo-activatable ligands for cell-surface receptors. The use of activatable ligands in particular will permit the examination of rapid, transient events that often escape detection using current methodology

### 5. In-Vivo Molecular Imaging SRF Cheuk Ying Tang, Ph.D., Director.

The In-vivo Molecular Imaging Laboratory based on the IVIS 200 offers in-vivo biophotonic imaging services for real-time imaging to monitor and record cellular and genetic activities within a living organism at multiple time-points. This technology provides a more accurate picture and more efficient use of animals.

The laboratory is equipped with the top of the line Xenogen IVIS-200 imaging system with the fluorescence XFO-12 option which can image 5 mice simultaneously under isoflurane anesthesia. A set of spectral filters covering wavelengths from 420nm to 740nm allows for more precise localization of the target source. The fluorescent option provides for a wide range of excitation and detection wavelengths. The system is located behind the IMI barrier of the animal facility where the majority of users house their animals. Although the IVIS-200 is designed for in-vivo imaging application, it can also be used for in-vitro experiments with cell cultures that complement studies performed in the Microscopy SRF (see below).

The IVIS-200 imaging system is equipped with a workstation for post-processing and quantitative analysis. The system is networked to the hospital backbone and data can be electronically transferred to the researcher's laboratory. A dedicated animal technologist performs all the imaging procedures and post processing of data. The facility provides technical assistance as well as consultation for investigators interested in using the facility.

Future Plans: We plan to upgrade this unit by the end of 2007 to the IVIS Spectrum for better 3D localization as well as more accurate fluorescent data with reduced background signal. Recently a high-end instrumentation

grant was submitted for a 7T small animal MRI. This system will complement the optical data with anatomical information from the same animal.

6. Microscopy SRF Victor Friedrich, Ph.D. Rumana Huq, M.S., Co-Directors

The facility provides high-quality advanced microscope systems, image analysis software, and microscopy expertise for live cell, live animal, and fixed specimen imaging and supports studies that range in scale from tissue structure to molecular interactions. A staff of two fulltime biomedical engineers and a scientific director provide consultation services on imaging and image analysis protocols, give hands-on training, and maintain and develop the instrumentation. Advanced techniques in use include FRET, automated cell migration and process growth analysis, and second-harmonic imaging. The facility served 110 Mount Sinai laboratories in the past year, with more than 4000 user sessions and more than 7000 hours of equipment use. In 2007, in response to increasing needs for confocal microscopy (as documented by the number of user hours and user fees), the Dean provided funds to purchase a new confocal microscope and matched investigators' contribution to upgrade an existing confocal.

Major instruments for image acquisition include four confocal microscope systems: a Zeiss LSM510 Meta CLSM; Leica SP-5 CLSM upright system; a Leica high-speed SP-5 CLSM inverted system with stage environmental chamber; and a BioRad/Zeiss Radiance 2000 MP single- and multiphoton CLSM. Three widefield microscope systems, equipped with high quality digital cameras, perform fluorescence, brightfield, and DIC imaging. Structured illumination (Zeiss ApoTome®) is available for increased axial resolution Computer-controlled, automated long-term time-lapse recording of living cells is accomplished with an Olympus IX-70 based microscope system which includes motorized X, Y, Z movement, motorized shutter and motorized filters, fluorescence and brightfield optics, and a stage incubator to maintain live cells over periods as long as several days. Additional equipment supports short-term (hours) imaging of live cell preparations on any of the microscope systems in the facility, using Bioptechs FCS2 closed chamber and ΔTC3 open chamber environmental control systems and Bioptechs objective heater system.

Transmission electron microscopy of tissue sections is performed with a Hitachi H7000 transmission electron microscope and scanning electron microscopy is available in the Department of Pathology.

In an adjacent SRF-associated laboratory there are two live-cell inverted microscopes one of which has an optical-gradient laser trap (laser tweezers) and the other high-speed fluorescent microscope has been modified to include both total-internal reflection fluorescence (TIRF) microscopy and spinning disk confocal microscopy. This microscope also includes a laser for photo-bleaching and photo-activation that permits bleaching or uncaging of GFP variants and the resolution of molecular interaction on a cellular and subcellular level. Both microscopes permit climate control and routine bright-field microscopy.

Image analysis on the SRFs computers provides deconvolution for increased resolution, 2D and 3D image rendering and visualization, and multiple modes of image analysis including fluorescence colocalization. Software packages to accomplish these include ImageJ, Volocity, Metamorph, Amira, Autodeblur and Adobe Photoshop.

Future Plans: Recently surveyed needs of investigators indicate a need for improved technology for live cell, live animal, and molecular interaction imaging in the next five years. For live cell imaging, we will acquire a spinning disk confocal microscope with motorized stage movement. The spinning disk system exposes cells to lower levels of excitation, reducing phototoxicity and allowing the investigator to perform time-lapse imaging over much longer intervals than is possible with the scanning laser confocal microscope. We expect this to be used for *in vitro* studies of metastatic disease in combination with information on cell motility and protein localization. For live animal imaging, we will apply for funding for a new multiphoton confocal CLSM system. This system will have at least four external detectors for observation of interactions between four or more cell populations marked with different colors to be observed in living organs such as lymph nodes and spleen. It will also be equipped with an electronically tunable laser, to facilitate optimization of multiprobe visualization and of other modalities that take advantage of intrinsic characteristics such as second harmonic generation and visualization of native

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fluorescence. We will also introduce FCS (Fluorescence Correlation Spectroscopy) and FLIM (Fluorescence Lifetime Imaging), currently available at Mount Sinai. This new technology offers a five or more fold improvement in resolution over current CLSMs, allowing imaging of structures such as synaptic vesicles, which are currently "submicroscopic". The ability to visualize the formation and translocation of molecular complexes are key events in intracellular signaling cascades, and acquisition of this technology will further research in this area. In addition, we will evaluate STED (STimulated Excitation Depletion) confocal systems as they become available.

### 7. Microvascular Surgery SRF Peter Boros, MD, PhD Jonathan S. Bromberg, MD, PhD, Directors.

The facility provides microsurgical services for many other research laboratories and departments including our Transplantation Institute. The facility has extensive experience in standard microsurgical procedures, as well as innovative techniques relevant to many areas of biomedical research. For example, our staff researchers developed murine models of both orthotopic tracheal and small bowel transplantation, procedures that are virtually unique to our institution. The staff also teaches basic and advanced microsurgical techniques to researchers, fellows, surgical residents and medical students.

The facility is staffed by two full-time microvascular surgeons who perform a broad range of microsurgical procedures in rodents. The facility performs state of the art and fully compliant microsurgical procedures. These procedures encompass a variety of complex transplant and vascular procedures in rodent models, as well as other microsurgical procedures important to medical research. The procedures performed on rats and/or mice over the last three years include transplantation of liver (orthotopic), small intestine (orthotopic), kidney, pancreatic islets, heart (heterotopic), vascular conduits (vena cava, aorta), and trachea (orthotopic). General techniques performed include vector administration, catheter placement, skin grafting, vascular intubation, and injection. Other surgical procedures that are performed include partial hepatectomy, bile duct ligation/cannulation, thymectomy, splenectomy, generation of parabiotic animals, coronary artery ligation and stereotaxic surgical procedures. Investigators are encouraged to work with the facility to develop novel procedures and techniques to expand the competencies of the Microvascular SRF so as to provide novel assays and procedures for independent investigators.

Future Plans: Although demonstration and training for specific procedures are currently available, our investigators have indicated in a recent survey that they would send their lab members, fellows and post-docs for a microsurgical training course. We plan to organize and offer courses on basic techniques within the next year.

### 8. Mouse Genetics SRF Kevin Kelley, Ph.D., Director.

The Mouse Genetics Research Facility provides state-of-the-art facilities for the production of transgenic and knockout mice, as well as related rodent embryology techniques. These include 1) Pronuclear Injection- we microinject purified DNA constructs for the production of transgenic mice. This includes injection of a single transgene construct that has been prepared by the investigator. A minimum of 2 transgenics or 20 live births (or embryos), whichever comes first, is prepared for each set of injections charged to an investigator. Standard transgenic founders are established in either B6C3 hybrids or FVB/N inbreds. Pronuclear injection of other strains can be much less efficient but is performed for an additional surcharge. 2) ES Cell Injection we microinject selected embryonic stem (ES) cell clones to establish chimeric mice for the production of "knockout" mouse lines and includes injection of 129/Sv derived ES cells into C57Bl/6 blastocysts. We also perform 3) Rederivation of mouse lines infected with various mouse pathogens to allow these lines to be shipped to collaborators at other institutions or to allow them to be moved into cleaner, barrier facilities at Mount Sinai. 4) Sperm Cryopreservation/Recovery to reduce the need for constant maintenance of lines that are not essential for current research needs. Two levels of service for sperm cryopreservation will be offered: Basic Sperm Cryopreservation after isolation from a single, genotyped male and Sperm Cryopreservation Plus, which in addition to visual observation of sperm density and motility, in vitro fertilization (IVF) of wild-type eggs will be performed to assess the viability of the frozen sperm. This approach is used for mouse lines which are part of an active research program, or which are likely to be recovered at some point in the future. 5) IVF Recovery Mouse Genetics SRF will recover lines from which sperm has been frozen by IVF followed by recovery surgeries of fertile eggs into pseudopregnant female mice.

Future Plans: Two new services will be added within the next five years: 1) Embryo cryopreservation. This is especially useful for PI's who have lines with complicated genetics, such as double knockouts on an inbred background, which cannot be recovered from frozen sperm without additional intercrossing and extensive genotyping. 2) Lentiviral infection of early embryos to produce transgenic mice. This is becoming an increasingly useful tool in the field, especially for the study of siRNA effects *in vivo*. Preliminary experiments conducted by the SRF have indicated that it is feasible and would be beneficial for many studies of gene regulation.

9. Mouse and Rat Phenotyping Facility Joseph D. Buxbaum, Ph.D. and Gregory Elder, M.D., Co-Directors. This facility can quickly and comprehensively elucidate the phenotypic profile of laboratory animals following modification by genetic, pharmacological, surgical, or other means. Knockout and transgenic animals are increasingly common experimental models and the facility serves researchers by characterizing phenotypes of these animals as completely as possible, determining not only whether modification affects the predicted systems but how it alters other systems as well. This leads to a better understanding of how genetics underlie developmental, behavior and disease and of the mechanisms underlying genetic modification-induced phenotypic changes. In addition, experts are available to aid in experimental design.

This SRF has two components in a state-of-the-art phenotyping center. The behavioral component has equipment and expertise for detailed analyses of behavior, including learning and memory, motor, reproductive, social, and other complex behaviors. The morphological component has equipment and expertise to carry out detailed pathological analyses and our staff includes an expert rodent neuropathology.

Future Plans: It is anticipated that a great increase in disease models involving genetically modified mice will occur with the completion of the human genome and the rapid breakthrough in gene discovery through genome-wide expression and association analyses. In addition, as Mount Sinai is expanding its role in high-throughput screening for lead compounds, we anticipate a need for moderate-throughput behavioral assays to evaluate the impact of lead compounds. For both of these reasons we are planning an expansion of the facility. Recruitment of a veterinary pathologists with expertise in rodent pathology will be a primary focus. This recruitment will be a collaborative effort between the Center for Comparative Medicine/ Surgery, Department of Pathology, and the Mouse and Rat Phenotyping Facility. We are implementing a moderate-throughput learning and memory screen based on fear conditioning and we are porting our assays to higher throughput architectures. In addition, we are developing bioinformatic tools to aid users in data mining.

10. Human Embryonic Stem (hESC) Facility: Sunita D'Souza, Ph.D. Director

The Human Embryonic Stem Cell core facility has been established to facilitate the transfer of this technology to the Mount Sinai community and other NY State affiliated institutions. The objectives of the facility are to provide undifferentiated hESCs, mouse embryonic fibroblasts (MEFs) and/or hematopoietic, cardiac and endoderm progenitors. The facility will also train faculty, postdoctoral fellow, and students in the maintenance and differentiation of hESCs. Recent developments in the field have demonstrated the ability to reprogram adult human cells to an ES cell-like state using only 3-4 genes, thus avoiding some of the major ethical issues associated with the transfer of adult nuclei into oocytes. Therefore, a part of the core will be dedicated to assisting investigators with the development of novel induced pluripotent stem cell lines (iPSC). Karyotyping, reagent preparation, media, and other associated resources will also be provided by the hESC SRF to assist in the development of this technology. This SRF is jointly supported by a New York State Stem Cell grant (NYSTEM)

11. In vivo Irradiator SRF Kevin Kelly, Ph.D. Director

The use of gamma irradiation to the whole body irradiation in animals (rodents) and/or cells has been a major research model for many years. The Mount Sinai Medical center hosts two Shepard, Cesium source, irradiators in support of this research. Due to recent regulatory and Homeland Security concerns the two irradiators were brought under the SRF program. As a result a dedicated technician has been hired and trained to oversee the

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equipment but more importantly to assist researchers with their studies. Rather than training new post-docs and students on the use of the machine(s), the technician performs all exposures. The result has been greater consistency and reduced down time for the machines. These machines are housed within the central vivarium due to the proximity of the animals used in the various studies. A separate entrance has been designed such that non animal users are not required to enter the main animal barriers.

12. Microarray, PCR, Bioinformatics SRF Co-Directors – Stuart Sealfon, M.D.; Tehua Tearina Chu, Ph.D  
This state-of-the-art genomic technology center is devoted to facilitating access to cutting edge instrumentation and expertise needed to perform successful large-scale, high through put genomic/ proteomic experiments. The facility provides access to high throughput robotic instruments for liquid handling, high throughput real-time PCR, large-scale microarray technology including array fabrication of custom genomic or proteomic arrays, and Affymetrix Genechip processing of expression array, genotyping array and tiling array, as well as basic and advanced data analysis / statistics / bioinformatics support, and access to various analysis software tools. The facility also offers complete publication of quality RNA sample-to-results custom services for real-time PCR mRNA quantification in large scale (many samples, many genes) or small scale experiments.

### STRUCTURE AND GOVERNANCE OF THE SHARED RESOURCE FACILITIES PROGRAM

The SRFs are overseen by the Associate Dean for Research Resources, Reginald W. Miller, D.V.M, DipACLAM. Operational oversight of the SRFs, is through a dual, peer review mechanism. Each SRF has a dedicated Scientific Advisory Committee that includes Dr. Miller and either the Dean for Basic Research (John Morrison, PhD, Prof. Neurosciences) or the Dean for Translational Biomedical Sciences (Hugh Sampson, M.D.). In addition, the advisory committee also has 3-5 members chosen from its user group by Dr. Miller. Every three years, each SRF is reviewed by adding 1-2 external reviewers (suggested by SRF directors) to the standing advisory committee. These triennial reviews include review of publication credits, technology, and personnel expertise. These reviews will assist the institution in determining continued support of current SRF. Fiscal oversight and administrative support for the SRFs is provided through the office of the Associate Dean for Translational Research and Operations, Phyllis Schnepf via Ms. Kruti Mohan, MBA. Dr. Miller works closely with this group to monitor the finances of the SRFs. Each SRF is directed by an expert who provides research services, educates investigators on the use of the technology, and helps them develop studies using new technologies in support of their research projects. A senior member of the veterinary staff also serves as ex-officio on all the advisory committees of animal-based SRFs. Advisory committees meet semi-annually to evaluate and recommend improvements and updates to the SRF technology and services.

Proposed new SRFs are reviewed by: 1) Executive Scientific Advisory Committee – for scientific merit in support of institutional research goals; 2) Engineering / Facilities - for infrastructure needs in support of new technologies; 3) Dean's Office- for business plan, final approval incorporating recommendations from two previous reviews. Reviews must be completed in 90 days of submittal. New SRFs are given three years to succeed (see Triennial review above). The Executive Scientific Advisory Committee will be composed of Institute Directors (CTRI) and SRF Directors.

In general, operating costs for SRFs are covered by institutional funding (30-40%) and user fees (60-70%). Instrument capital costs are not recovered through user fees but rather through instrumentation grants, Dean's funds or Departmental contributions and matching funds from the Dean.

Departmental Cores are governed by their individual departments and have a history of ready access on a fee-for-service basis to the Mount Sinai community. The Departmental Cores that operate under the umbrella of the CPGB subscribe to the same principles as the SRFs in that they are open to any MSSM investigators without distinction between MSSM and Departmental users with regards to access, priority or price.

**Departmental and Center Cores (D&CC): Research Resources in addition to the Institutional SRFs.**

These laboratories are based in and administered by individual departments or centers that provide specialized services to investigators who are programmatically connected or to others on a fee-for-service basis. Structure and governance of each is determined by the home department or center.

1. Gene Targeting Facility (Black Family Stem Cell Institute) Kevin A. Kelley, Ph.D., Director.

The facility creates knock-out or knock-in models for homologous recombination in mouse embryonic stem (ES) cells. Investigators provide targeting constructs designed to introduce specific changes into the gene(s) of interest and the staff electroporates these targeting constructs into ES cells and selects transfected colonies. Once colonies are identified that contain the altered gene, clones are expanded from a master plate. After expansion, the clones are injected into mouse embryos by the Mouse Genetics SRF staff (SRF #8 above) to create mouse lines carrying the selected genetic modifications.

2. Human Gene Linkage and Genetics Assessment (Department of Genetics and Genomic Sciences) Robert J. Desnick, M.D., Ph.D. Bruce Gelb, MD, Co-Directors.

This Core provides expertise for the mapping of human genes. Both traits with simple Mendelian modes of inheritance and traits with complex patterns of inheritance can be studied. The Core facility can determine genotypes for highly polymorphic markers that systematically cover the entire genome for linkage and association analysis. Subsequent to the detection of linkage, the Core can determine genotypes for additional markers to determine the minimum obligate region that must contain the gene of interest. Expert assistance is available for study design, sample procurement, establishment of long-term lymphoid lines and linkage data analysis and for all positional cloning and molecular genetic technology to investigators engaged in basic, translational and clinical research on the genetic basis of human diseases. There are three components of this core: **MOLECULAR DIAGNOSTICS** for human diseases with a genetic component using identification of common mutations by PCR techniques (detected with restriction enzymes, mutation-specific oligonucleotides, or DNA sequencing), and/or family studies using gene-specific or closely linked RFLPS. The **HUMAN GENE MAPPING** facility provides somatic cell hybrid panels and/or DNA isolated from these panels for the chromosomal mapping of human genes. In addition, filters can be prepared containing various restriction digests of each hybrid panel for subsequent Southern hybridization analysis with species-specific cDNA and/or oligonucleotide probes. Hybrid cells containing specific gene rearrangements also are available for many human chromosomes and are useful for regional chromosomal assignments. The **HUMAN CELL CULTURE** facility supplies cultured human fibroblasts from skin biopsies and of cultured human lymphoid cells from venous blood samples and will freeze-down, and store lines.

3. Molecular Modeling (Department of Structural and Chemical Biology) Mihaly Mezei, Ph.D., Director.

The Core specializes in techniques for the display and analysis of macromolecular structures of proteins and nucleic acids. It offers molecular modeling capabilities at several levels. Access is provided to several important databases, e.g., the RCSB Protein Data Bank (PDB), Cambridge Crystallography Data Bank (CSD), Genbank, EMBL, and Swissprot. Sequence analysis and comparison tools provide the display, editing, transforming and analysis of protein and nucleic acid sequence data. Macromolecular associations, e.g. protein-protein or protein-DNA interactions, are studied with the aid of high-resolution graphics display systems: optimal interactions can be determined, and conformational searches can be performed.

The computers in the facility include several Silicon Graphics (SGI) workstations, a 12-CPU multiprocessor server (SGI Power Challenge), a 'farm' of several 4CPU SGI O200 servers and Compaq Alpha servers, all networked. The graphics workstations are accessible 24 hours a day. Assistance in the use of the Core is also available in the form of a facility guide, extensive documentations, on-line tutorials, help facilities, and consultations.

4. Cancer Registry (Department of Urology) Simon Hall, M.D., Director.

The Cancer Registry assists physicians by developing and maintaining a computerized database relevant to the diagnosis, treatment and lifetime follow-up of cancer patients cared for at the Mount Sinai Hospital. The Cancer

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Committee of the Medical Board provides important guidance and direction in the areas of policy, procedure and clinical data quality.

The information collected by the Registry provides a foundation for clinical oncological investigations and medical education. The comprehensive database, begun in January 1989, is also used by basic science researchers in studies of cell biology, genetics, and epidemiology of specific types of cancers. Investigators wishing to utilize the Cancer Registry are asked to fill in a form specifying the nature and purpose of their study. The Registry's staff will then search the computerized database and prepare a written report containing the requested information.

### 5. Tumor Cytogenetics (Department of Pathology) Vesna Najfeld, Ph.D., Director.

The Core provides consultation in cancer cytogenetic techniques and performs cytogenetic analysis for clinical and basic science researchers including the identification of chromosome abnormalities in hematological disorders using both the chromosome and FISH (fluorescent in situ hybridization) studies. FISH provides localization of gene(s) on human chromosomes. Automatic karyotyping is provided on a microscope/CCD camera setup. Cytogenetic analysis of cells from tumors and other tissues is performed for investigators to determine whether the conditions *in vivo* favor the proliferation of cell populations with a particular chromosome rearrangement, or whether chromosome changes have taken place during growth *in vitro*. In long-term cultures of human derived cell lines, karyotyping is used to determine if inter-species contamination has occurred.

### 6. Cytopathology (Department of Pathology) David Burstein, M.D., Director.

The primary activity of the Core is diagnosis of cancer, precancerous lesions and infectious diseases. It renders to clinical and basic science researchers diagnostic evaluation of their samples from various organs and tissues, as well as of cells from body fluids: CSF, urine and effusions. Viable tumor cells identified in effusions may be adaptable to growth in cell culture *in vitro*; body cavity fluids of appropriate, consenting patients are thus made available to investigators wishing to culture tumor cells and study them and whatever they shed/secrete into media. Since cytological evaluation of fine needle biopsies frequently precedes surgical excision of tumors the Core can provide these diagnoses to investigators interested in particular cancer types thus permitting them to arrange for obtaining tumor tissue during subsequent surgical procedures. The Core is equipped for cytopathology and immunoperoxidase.