



Joan and Sanford I. Weill Medical College of Cornell University Environment and Resources

1. Overview and History

Joan and Sanford I. Weill Medical College of Cornell University (Weill Medical College, WMC) is committed to excellence in research, education, patient care, and the advancement of the art and science of medicine. The mission of the College is to provide the finest education possible for medical students and students pursuing advanced degrees in the biomedical sciences, to provide superior continuing education for the lifelong education of physicians throughout their careers, to conduct research at the cutting edge of knowledge, to improve the health care of the nation and the world, both now and for future generations, and to provide the highest quality of clinical care. The College is committed to the provision of health education, prevention, detection and treatment of disease, and the development of a research agenda and public health policy responsive and sensitive to the needs of the community. Weill Medical College is dedicated to the tripartite mission of education, research, and patient care.

Founded in 1898, and affiliated since 1927 with what is now New York-Presbyterian Hospital, Weill Medical College is the #18 ranked medical college in the country (*US News and World Report*, 2008). New York-Presbyterian Hospital is the #6 ranked hospital in the country (*US News and World Report*, 2008). Weill Medical College and Weill Graduate School of Medical Sciences are accredited by the Liaison Committee for Medical Education of the American Medical Association and the Association of American Medical Colleges.

Weill Medical College is one of 14 college/school units comprising Cornell University. The Medical College provides training and education for approximately 410 medical students, and in conjunction with the Weill Graduate School of Medical Sciences of Cornell University, provides training and education for 390 graduate students and over 320 post-doctoral fellows.

As of Spring 2006, Weill Medical College had 1048 full-time faculty members. Faculty members work throughout 8 basic science and 16 clinical departments.

The College is divided into basic science and patient care departments that focus on the sciences underlying clinical medicine and/or encompass the study, treatment, and prevention of human diseases. The basic science and clinical departments are located in multiple, tightly clustered buildings straddling York Avenue between 68th and 72nd Streets on Manhattan's Upper East Side. Several off-site buildings house administrative and clinical offices.

In the last decade, led by Dean Antonio Gotto Jr., M.D., Weill Medical College has increased its endowment to \$840 million, its operating budget to more than \$920 million, and nearly quadrupled the clinical revenue generated through its Physician Organization.

Total research support is in excess of \$200 million, of which \$133 million represents federal government and non-federal sponsored research grants, training grants, and fellowships. In addition to its affiliation with New York-Presbyterian Hospital, Weill Medical College and Graduate School maintain major affiliations with Memorial Sloan-Kettering Institute, Hospital for Special Surgery, The Rockefeller University, and the metropolitan-area institutions that constitute the New York-Presbyterian Healthcare Network.

2. Programs

Tri-Institutional MD-PhD Program

Weill Medical College, The Rockefeller University, and Memorial Sloan-Kettering Institute have formed an inter-institutional collaboration dedicated to joint MD/PhD training. The Program awards an MD degree from Weill Medical College and a PhD degree from either Weill Graduate School of Medical Sciences of Cornell University (formed by Weill Medical College and Memorial Sloan-Kettering Institute) or The Rockefeller University. Each year approximately 410 students apply for an average of 14 positions per year, which are fully funded by the NIH Medical Scientist Training Program. Faculty members at WMC, Rockefeller, and Memorial Sloan-Kettering are among the most distinguished medical and biomedical scientists in the world. The three institutions are home to more than 35 members of the National Academy of Sciences.

3. Facilities and Services

Laboratory Research Space

Weill Medical College has 330,000 net square feet (NSF) of research laboratory space. Over the past decade large portions of the research space have undergone major renovations. These renovations have provided many research programs with modern, state-of-the-art laboratories.

Clinical and Translational Science Center

The Clinical and Translational Science Center (CTSC) addresses the necessity of an integrated, comprehensive research support system that includes education, training and mentoring for clinical research investigators, coordinators and staff. The mission of the CTSC is to provide an environment that allows optimal use of our considerable multi-institutional assets and the diversity of our patient population to move translational research seamlessly from bench to bedside and to the community. The CTSC acts as a conduit through which essential resources, technological tools and education programs for all partners can be efficiently shared and managed.

Integral to Weill Cornell's Strategic Plan for Research, which was initiated seven years ago, the plan for the CTSC brought to fruition the integration of existing inter-institutional resources among neighbors on York Avenue and partner institutions in the immediate area. The resulting cluster of East Side institutions forms a unique and cohesive biomedical complex fulfilling the

NIH roadmap initiative of breaking down institutional silos and barriers separating scientific disciplines to accelerate the clinical application of basic science discoveries.

This center is funded through the Clinical and Translational Science Awards (CTSAs), a national consortium that is transforming how clinical and translational research is conducted. For more information about the national CTSA consortium please visit ctsaweb.org.

Animal Use Facilities

The Research Animal Resource Center (RARC) provides facilities, services, and information to facilitate effective research using laboratory animals. RARC currently serves on average 165 Principal Investigators with an average of 330 active projects. Animal research conducted at Weill Medical College utilizing includes research in cancer, neurobiochemistry, neurophysiology, stem cell biology, stroke, cardiovascular disorders, trauma, endocrinology and reproductive physiology, ingestive behavior, immunology, pharmacology, ophthalmology, and gene therapy.

The facilities are located on the Manhattan main campus and in two satellite sites in White Plains, NY. The Manhattan facilities are of single corridor design. Each facility is fully equipped with a cage wash center, diagnostic laboratory, biohazard containment facility (BSL-2 and 3), and a surgery suite that consists of areas for cleaning, preparing, and storage of instruments, animal prep, surgeon's scrub, and large capacity operating room facilities. Site 1 is equipped with a clean/dirty corridor system, four animal rooms, and a separate quarantine suite. Site 2 has eight animal rooms on two floors and a rodent surgery suite.

Library Resources

Among the many information resources available to WMC students and faculty are the Samuel J. Wood Library and the C.V. Starr Biomedical Information Center. The library houses over 1,500 printed journals, over 4,800 electronic journals, and over 150,000 archived volumes. The library is fully automated, featuring computer terminals that provide access to library collections from any networked computer and student workstation throughout the College. In addition, the Nathan Cummings Center at Memorial Sloan-Kettering Cancer Center, The Hospital for Special Surgery, The Rockefeller University and Cornell University in Ithaca collaborate to share databases, journals, and resources, effectively expanding access to available information. The library offers a variety of services, including computer -generated literature searches, translations, and inter-library loans. Medical graphics and photographic/audiovisual facilities provide a wide range of art, photographic, and audio-visual services.

4. Core Facilities

www.med.cornell.edu/research/rea_sup/

Recognizing the need to provide faculty with the tools to conduct state-of-the-art research, Weill Medical College has developed 21 core facilities. These facilities, from biomedical imaging to x - ray crystallography, are managed by scientist experts. They provide centralized access to equipment used by faculty in all departments, help to reduce duplication of resources, and allow the Medical College to remain at the forefront of biomedical research.

Biostatistics and Research Methodology

This core is comprised of a broad collection of services used to identify research questions, construct hypotheses, design investigative studies and data collection strategies, conduct statistical analyses of data, and interpret findings. The Biostatistics and Research Methodology Core has a proven track record in attracting funding for WMC laboratories. The inclusion of the core in a number of successful grant applications provides needed expertise to implement and conduct research projects in a cost effective manner. The existence of the Core not only strengthens grant proposals, increasing the likelihood of being funded, but also offers investigators an alternative to using outside consultants.

Facilities

Sophisticated computational resources are available to researchers including powerful hardware and advanced software technology. A state-of-the-art, high speed research workstation located on-site is linked to the departmental server and statistical software. Members of the Department of Public Health with expertise in a range of research methodology are available to investigators for consultation.

Services

The Core provides biostatistical services and methodological advice. Such consultative services include:

- Statistical analysis
- Sample size and power analysis
- Study design
- Protocol design/research planning
- Database design and management
- Questionnaire development
- Cost-effectiveness analysis
- Program evaluation

Cell Screening

The Core provides equipment and expertise to assist investigators in screening chemical compound libraries using cell-based assays and automated fluorescence microscopy. Fluorescence microscopy is a powerful tool for cell biology and biochemistry. It can provide information about subsets of cells and structures, and molecules and proteins within cells. In the past, the potential of this technique for providing the drug screener with this same wealth of information was limited by the inability to automate the process. Recent advances in instrumentation and software now make automated fluorescence imaging a practical tool in screening and drug discovery.

Facilities

The facility currently has a Discovery-1 High Content Screening System from Universal Imaging Corporation. For sample preparation, the facility has a Titertek Multidrop 384 Dispenser and a Bio-Tek ELx405 Select Plate Washer. For data storage and analysis, the facility has a dual-monitor Dell Workstation running MetaMorph Image Processing and Analysis Software and 450GB of OAC supported server space.

Services

- **Consultation:** Consultation on experimental design and the availability of chemical compound libraries.
- **Screening:** The facility can acquire images of cells stained with fluorescent or visible dyes in 24, 96, 384, or 1536-well microplates. A wide variety of fluorophores from UV to IR plus transmitted light can be imaged. Up to 16 different sites per well and as many as 45 plates can be screened automatically per run.
- **Data Analysis:** After data acquisition, analysis can be performed on our offline workstation or at any computer running the MetaMorph screening software.
- **Sample Preparation:** Preparation of assay plates, including dispensing of cells and reagents and washing the plates, can be performed using facility equipment.
- **Training:** The facility director will provide training in the use of the Discovery-1 screening system, the sample preparation equipment and the analysis software.

Citigroup Biomedical Imaging Center

The Biomedical Imaging Core Facility is dedicated to the development and support of emerging imaging technologies in biomedical research. Major equipment includes a 3.0 Tesla magnetic resonance imaging system, a combined positron emission tomography/computed tomography system, and a 19 MeV cyclotron and associated radiochemistry laboratories. Center staff includes applications scientists and technologists specifically devoted to the support of investigator initiated projects. Technologies available to researchers include:

The Magnetic Resonance Imaging and Spectroscopy (MRI/MRS) Facility supports high resolution imaging anywhere in the body. The instrument is used to study a wide range of diseases, from neurological and psychiatric disorders to cancer and vascular disease. Functional magnetic resonance imaging (fMRI) is a special type of MRI that provides a means for analysis of brain activity directly and non-invasively.

The Positron Emission Tomography/Computed Tomography (PET/CT) Facility is used for whole-body scanning or visualization of selected organs. PET/CT precisely measures physiologic function, detects metabolic changes in tissue, displays blood flow, tracks alternations in biochemical processes, and more.

The Cyclotron and Radiochemistry Facility produces positron-emitting radiolabeled pharmaceutical drugs designed and engineered to complement the pharmacokinetics of the clinical molecular target. The preparation of these unique drugs requires a source of radionuclides, and the tools for subsequent drug synthesis. The facility supports generation of specific short-lived, positron emitting radionuclides.

Services

The Biomedical Imaging Core Facility offers MRI and PET/CT scanner time that includes administrative and technologist support. Consultation, image processing, and applications development services are also offered. Currently supported applications include brain white matter tractography, functional magnetic resonance imaging, proton magnetic resonance spectroscopy, magnetic resonance angiography, radiofrequency resonator design, perfusion imaging, 18FDG PET imaging, and 15O water PET imaging.

Computational Genomics

The Computational Genomics Core provides access to state-of-the-art desktop bioinformatics software and computational tools for the analysis and management of gene expression data. The core also offers consulting services in various areas of bioinformatics and computational biology, and facilitates access to the larger infrastructure of the Institute for Computational Biomedicine.

Services

- **Analysis of gene expression data:** Provides users with commercial gene expression analysis programs (e.g., GeneSpring from SiliconGenetics) and general data mining and statistical tools.
- **Storage and organization of expression data:** The core provides and maintains GeNet (SiliconGenetics), a web-based micro-array data repository that facilitates sharing of microarray data. GeNet is seamlessly integrated with GeneSpring and helps individual labs store, archive and search microarray data produced during the course of their projects. Core personnel can assist users in organizing their gene expression data into formats suitable for publication, for deposition into and integration with publicly available databases.
- **Discovery through bioinformatics:** Gene expression profiles often highlight genes of unknown function. The core offers popular bioinformatics desktop tools, such as Vector NTI, Lasergene, Sequencher, Artemis, and ClustalX, to support a variety of sequence analysis tasks.
- **More resources for advanced projects, collaboration, and training :** The Institute for Computational Biomedicine (ICB) broadens the capabilities of the Computational Core by offering an advanced bioinformatics infrastructure, expertise in bioinformatics and computational biology methods and tools, workshops, and one-on-one training. ICB personnel provide users with guidance and consultation on the application of computation to biological research and are available for scientific collaborations when agreeable to all parties involved.

DNA Sequencing at Cornell University Biotechnology Resource Center at Ithaca

This Core is part of the Biotechnology Resource Center (BRC), the keystone in Cornell - Ithaca's service infrastructure in the biological sciences. This Core serves a very large community of researchers within Cornell University, including the Weill Medical College, but also in New York State, the US and abroad. Our DNA Sequencing Facility provided over 120,000 DNA Sequences to 1068 researchers (415 PIs) at 67 institutions in 14 countries in 2003 alone. This Core participates in grant applications both for shared instrumentation to enhance the Cores and in writing facility descriptions and letters of support for grant applications. Facility tours and exposure to the core technology for academic and industrial visitors are available in addition to participating in undergraduate and graduate academic courses.

Facilities

DNA Sequencing and Genotyping; Protein-expression Profiling, and Mass Spectrometry; and Microscopy, Imaging and Fluorimetry Computing is made available to all Cornell faculty.

Services

- DNA/protein purification
- Protein sequencing
- Protein-expression profiling
- Mass spectrometry
- DNA fragment analysis
- Sequence detection/real-time PCR
- Computer services
- Fermentation

Electron Microscopy

Electron Microscopy has been part of the research environment at WMC for over 40 years. Current applications concentrate on, but are not limited to, studies of developmental trends and the effects of genetic knockouts on specific cell types or organs. Localization of specific proteins using gold-labeled antibodies can give the next level information after preliminary studies have been done in light microscopy. The facility provides transmission and scanning electron microscopy services, including specimen preparation, embedding, thin and ultrathin sectioning and staining (TEM) and critical point drying, sputter and/or carbon coating (SEM).

Facilities

The facility has a JOEL 100CX-II transmission electron microscope equipped with a ASID unit enabling scanning EM, ultramicrotomes, a paraffin microtome, cryostat, 2 vacuum

evaporators, critical point dryer and sputter coater, a low temperature UV chamber for polymerization of acrylic resins for immuno EM, and an automated tissue processor for paraffin embedding.

Services

- **Consultation:** The staff provides consultation on experimental design approach.
- **Transmission Electron Microscopy :** Full sample processing from fixation through embedding, sectioning and microscopy is available.
- **Scanning Electron Microscopy:** Fixation, dehydration, critical point drying and sputter coating of small samples can be performed by the Core.
- **Microtomy:** Sectioning for electron microscopy is available. There is a second ultramicrotome available for those already versed in ultramicrotomy. Equipment is also available for the investigators' use to obtain paraffin and frozen sections for light microscopy. Ultrathin frozen sections for immuno EM are also available. Ultrathin Frozen Sectioning technique for immunolocalization at the EM level utilizes the Facility's new RMC MT7000 ultramicrotome equipped with the CRX cryo chamber.
- **Paraffin Embedding for Light Microscopy:** The TissueTek VIP 150 automated tissue processing unit and the accompanying embedding console is available for paraffin embedding for light microscopy applications.

Emergency Freezers

The Medical College has available two -80°C Revco freezers for emergency short term (i.e., approx. 1 week) use by investigators who experience a freezer breakdown that requires repair. This service is intended to help minimize the loss of valuable reagents and samples in the event of a -80°C freezer breakdown. Emergency protocols established by the Maintenance and Engineering Office should be followed in the event of a freezer emergency. To review these protocols, contact Engineering and Maintenance.

Flow Cytometry

We have entered into an agreement with the Hospital for Special Surgery to create a merged flow cytometry core facility containing the equipment from both facilities. WMC faculty will have full access to all the equipment. This merged facility is located in the Caspary Research Building of the Hospital for Special Surgery, on the ground floor in rooms G43 and G30.

Facilities

- Beckman-Coulter XL flow cytometer
- CompuCyte Laser Scanning Cytometer (LSC)
- Becton-Dickinson FACScan

- Becton-Dickinson FACSCalibur
- Becton-Dickinson Vantage cell sorter

Gene Therapy

The Belfer Gene Therapy Core Facility provides the infrastructure to carry out basic, translational and clinical research utilizing gene transfer.

Facilities

The Belfer Gene Therapy Core Facility is a new, fully equipped core facility devoted exclusively to developing and assessing gene transfer vectors. The Vector Core includes six independent cell culture rooms, bench and desk space for eight scientists, instrument room containing large equipment and office space. The Director supervises a technical staff of nine (seven technicians and two postdoctoral associates). The Vector Core includes analytical resources: quantitative PCR, 2 HPLC's, plate readers, automated liquid handling devices, phosphor-/fluoro-imager and appropriate computer support and backup. There is a database of the available vectors and plasmids with extensive sequence and restriction mapping data. The Good Manufacturing Practice (GMP) Core is comprised of the GMP facility which occupies approximately 2,400 square feet devoted exclusively to production of gene transfer vectors and gene modified cells for human therapeutic trials. There is office space and supporting laboratory space for analyses and quality control of GMP grade vectors including a room with a Biostat C fermentor. The design, construction, and validation of the GMP production facility is monitored and reviewed with the FDA to assure full compliance with all current GMPs. The GMP facility consists of a suite of three fully equipped production rooms, a staging area, gowning and degowning pathways arranged with a series of interlocking double-door pass-through devices and doorways. In conjunction with carefully maintained differential room pressure relationships and single pass HEPA filter air, standard operating procedures define the flow of material, personnel, and waste through the facility and particulates and equipment are monitored full time. In addition, there are separate rooms for QC released and quarantined materials, a cell bank and a quality control lab. There is an extensive set of standard operating procedures for the use, cleaning, and validation of equipment, and for the purchase, tracking, and storage of supplies and for training personnel.

Services

The Vector Core functions as a resource to investigators to provide centralized expert services and training in the design, creation, and production of gene transfer vectors, and to provide a characterized repository of gene transfer vectors and related reagents for use by investigators. The primary resource of the Vector Core is the expertise to efficiently design, construct and produce gene transfer vectors, including adenovirus (Ad), adenoassociated virus (AAV), lentivirus, retrovirus vectors, as well as non-viral vectors and plasmid vectors. New cDNA's of biological significance are continuously being acquired and used to make first generation and more advanced gene transfer vectors. The Vector Core maintains, and continually updates, standard operating procedures for the construction, production, and verification of gene transfer vectors. Many individual

steps of vector production have been optimized and new protocols and reagents are evaluated and incorporated into the standard operating procedures.

Genetically Engineered Mouse Phenotyping

The decoding of the human genome and advancements in the ability of scientists to manipulate the mouse genome have resulted in the generation of countless mouse models of human disease and tools to dissect the function of specific genes. It is expected that the numbers of genetically engineered mice carrying transgenes, targeted mutations, and chemically-induced mutations will only continue to increase.

The Genetically Engineered Mouse (GEM) Phenotyping Core exists to serve investigators at Memorial Sloan-Kettering Cancer Center, the Rockefeller University, and Weill Medical College by providing an extensive baseline phenotypic profile of genetically engineered mice. Such a comprehensive baseline characterization will be invaluable to investigators unfamiliar with normal mouse anatomy, histology, physiology and age - or strain-related background lesions. Furthermore, evaluating the entire mouse, as opposed to a specific tissue or organ system, will help to identify unanticipated phenotypic changes.

Services

Standard Genetically Engineered Mouse Phenotypic Profile Includes:

- **Hematology**
 - Complete Blood Count
 - White Blood Cell Differential
- **Clinical Chemistry**
 - 27 Biochemical Assay
- **Urinalysis**
 - Specific Gravity
 - Colorimetric Test for 10 Parameters
 - Sediment Analysis
- **Survey Radiographs**
 - Lateral and Dorsal -Ventral Views
- **Gross Necropsy**
 - Whole Mouse and Parenchymal Organ Weights
- **Extensive Microscopic Evaluation**
 - Digital Images of Macroscopic and Microscopic Lesions

- Electronic Report
- Interpretive Summary
- Recommendations for Ancillary Analyses

Other Services

Post mortem specimens from genetically engineered mice, or animals, tissues, and histology slides from other experimental studies may also be submitted for pathological evaluation.

In addition, complete histology services including tissue processing, paraffin embedding, sectioning and staining with routine stains such as hematoxylin & eosin and special histochemical stains are available. Unstained tissue sections specially processed and prepared for immunohistochemistry and in situ hybridization (to be performed by investigator) are also available upon request. The GEM Phenotyping Core has an MX-20 Faxitron (Faxitron X-ray Corporation, Wheeling, IL), which produces extremely high-resolution radiographs of small laboratory animals (mice and rats), as well as excised tissues and paraffin blocks. Specimens can be placed on adjustable shelves within a shielded and interlocked enclosure to obtain images magnified up to 5x.

Iodination

In order to comply with environmental regulations by minimizing all radioactive discharges, an activated charcoal hood designed to trap radioactive iodine was installed for use by investigators. The room is equipped with a state-of-the-art gamma counter for samples counting at the convenience of the investigator.

Facilities

A dedicated, secure hood rated for iodination purposes for use by licensed investigators at no charge.

Services

Iodination hood and gamma counter.

Mass Spectrometry

Weill Medical College has established a mass spectrometry (MS) core facility for analysis of protein structure. Routinely, MS can be used for precise determination of peptide/protein molecular mass as well as to identify contaminating impurities. Methods can be employed to identify unknown proteins and often to elucidate a protein's multimeric status, posttranslational

modifications, and sites of non-covalent association with small molecules or other proteins. Our MS core seeks to adapt evolving MS technologies to assist in tackling unique research problems that require protein structure analysis and identification.

The MS core was made possible by a series of shared instrument grant awards from the National Center for Research Resources of the NIH. The core supervisor, Dr. Ivan Haller, has a solid physical chemistry background and extensive mass spectrometric experience. He assists WMC users by advising on sample preparation, performing MS analyses, and interpreting MS data. An oversight committee, comprised of WMC faculty and users, periodically reviews the core to insure that it provides optimal benefit to users.

Facilities

This MS Core lab in D -412 has two types of mass spectrometers that provide complementary information on protein structure. These mass spectrometers are capable of Matrix-Assisted Laser Desorption Ionization - Time Of Flight (MALDI -TOF) mass spectrometry and Electrospray Ionization-tandem Mass Spectrometry (ESI -MS/MS). MALDI-TOF MS provides a sensitive, accurate and rapid procedure for determination of peptide/protein mass. Analyses are performed using an Applied Biosystems Voyager-DE PRO MALDI-TOF that was purchased in 2002. The instrument operates in both linear and reflectron mode and has a collision induced disassociation (CID) cell for enhanced fragmentation in post-source decay analyses. This instrument can provide mass information on peptides/proteins in the range of 500 to 200,000 Da, typically requires a few microliters of aqueous sample of < 1 μ M concentration (i.e., 1 pmole), and achieves 99.8% mass accuracy. When the sample is an unknown protein, it is frequently possible to identify it by peptide fingerprinting (i.e., computer-based matching of the observed peptides, following digestion with trypsin, vs. peptides predicted by in silico trypsinolysis of all known proteins from the species of origin). For samples in which the peptide/protein is known a priori, it is sometimes possible to identify sites with specific post-translational amino acid modifications. MALDI-TOF MS requires mixing samples with a matrix solution and applying it to a stainless steel sample target plate. Target plates are dried, introduced into the instrument and irradiated under high vacuum and fired at with a 337 nm nitrogen UV laser. With each laser shot, energy is absorbed by the matrix material and transferred to the sample, resulting in a plume of peptide/protein ions. The generated ions are then accelerated by a strong electrical field (20 -25K Volts) and travel through a field-free region toward a detector plate. The time interval from firing the laser until the resulting ions strike the detector (TOF) is a function of mass to charge ratio for each given peptide/protein ion. Mass of the unknown peptide/protein is deduced by averaging a requisite number of individual TOF measurements (20-1000, obtained by repeated laser firings at up to 20 times per second) and referenced to calibration standards of known mass. A limitation of MALDI/TOF is that the measured signal intensity is not linear with the quantity of introduced sample, and therefore the method is not applicable for determining concentrations of peptides/proteins in a mixture. Strengths of MALDI-TOF are its high sensitivity, broad mass range, relative tolerance to salts/buffers and suitability for the analysis of relatively complex mixtures.

ESI-MS/MS analyses are performed using either a triple quadrupole or ion trap type instrument. The triple quadrupole is a QUATRO -II (Waters Micromass) that was purchased in 1997. This instrument can measure mass/charge (m/z) over the range of 2 to 8,000.

Since mass spectrometers measure mass to charge ratio, not molecular mass per se, a pure protein gives multiple peaks on a quadrupole MS instrument, corresponding to one for each of its charge states. Thus, a 100kDa protein with 20 of its basic sites protonated will appear as a peak with an apparent mass of 5,000 Da. A factor contributing to the precision of mass detection by ESIMS/MS is that the mass of each of a proteins charge states contributes to the calculation of total mass. While the upper mass limit for a protein will depend on the number of charges it accepts, the practical limit is typically ~200,000 Da, with 99.98% mass accuracy. The ion trap MS is an Agilent XCTplus that was purchased in 2004. This instrument performs MSⁿ and is committed to high-throughput peptide sequencing. It is configured with a nanoLC system and nanospray -ESI source for sequence elucidation of low-abundance peptides (often < 100 fmol) in complex biologically-derived mixtures. Electrospray ionization (ESI) introduces desolvated ions into the high vacuum environment required for mass spectrometry from an atmospheric-pressure stream of droplets of polar molecules in a mixed aqueous/organic solvent. The stream of droplets is generated by passing the output of a syringe pump or the eluent of an HPLC through a fine stainless steel tip held at a high voltage. The triple quadrupole mass spectrometer (MS/MS) consists of two quadrupole mass analyzers separated by a collision cell. This configuration allows mass spectral analysis either directly on the ions originating in the ESI ion source (MS mode), or of the structural information-containing product ions generated by controlled fragmentation in the collision cell (MS/MS mode). ESI-MS/MS offers definitive information about protein structure; in some cases amino acid sequence and specific chemical modifications can be unequivocally deduced from the pattern of product ions generated. Additionally, since the technique uses soft ionization, it is possible to observe labile species, e.g., nitrosothiols, protein multimers and even biologically native non-covalent interactions which would be destroyed and therefore undetected in a MALDI-TOF MS experiment. Limitations of ESIMS/MS are the need for relatively high purity protein samples and a poor tolerance for electrolytes and detergents.

Services

Consultation.

Each research problem is unique. In order to clearly define an approach and MS technique may be most suitable to answer a given question, an initial free consultation is provided. If MS is appropriate, issues of experiment design, sample preparation, timing and the cost for project completion will be discussed.

MALDI-TOF. Three levels of MALDI-TOF MS service are offered:

- **Routine analysis of a synthetic peptide.** This service is for analysis of peptide molecular mass (crude synthetic or purified), where the user provides 10 pmol of peptide as a solid or solution (μM) without significant buffer or detergent contamination. This service is intended to assess the purity of the peptide and possibly to specify contaminating species. Samples are analyzed on a single matrix and a spectrum of peptide constituents are provided to the user.
- **Routine molecular weight determination of protein/peptide unknowns.** This service is intended to determine the accurate molecular mass of a purified/semi-purified unknown protein or derived proteolytic fragments. Samples are analyzed on up to three different matrices to enhance the detection of protein/peptide constituents.

Samples should be in 3-5 μl of water or low salt-containing buffer, preferably at a concentration of approximately 1-10 pmol/ μl . For tryptic digests of a protein from an organism with a sequenced genome, an optional computer search can be performed to identify an unknown protein by peptide fingerprinting.

- **Special handling analysis of protein/peptide unknowns.** This service is intended for research problems that require special attention and effort. It will be necessary in cases where resolution and/or detection sensitivity must be optimized, such as for the detection of low molecular mass protein modifications or when samples suffer from impurities or are available in limiting amounts.

ESI-MS/MS. This service affords an opportunity for protein structure determinations based on the pattern of product ions produced upon fragmentation of the species of interest. Routinely, ESI-MS/MS is used to verify the predicted sequence of an expressed recombinant protein (and to identify sites of unintended mutations), as well as to quantify the extent of chemical modifications introduced into a purified protein in vitro (e.g., phosphorylation, biotinylation, fluorescein labeling). Structural information on low mass, non-volatile polar compounds (synthetic or natural) can also often be provided. Non-routine application of ESI-MS/MS include identification of the nature and sites of in vivo protein modifications, protein multimeric status, cysteine residues engaged in disulfide bonds, amino acid sequence analysis, and non-covalent protein-protein interactions. It is also useful in microheterogeneity studies of isolated proteins, and can provide some tertiary structure information on native and partially denatured proteins. It should be appreciated that these non-routine applications of ESI-MS/MS utilize approaches that may be successfully applied in some, but not all cases. ESI-MS/MS samples should be provided in volatile polar/aqueous solvents containing less than 500 μM salt. Necessary protein quantities may range from 20 -500 pmol, depending on the specific information desired.

Microarray

Located in the Department of Microbiology & Immunology, the Microarray Core Facility (MCF) consists of Affymetrix GeneChip array instruments, a custom array system, ABI 7900HT Sequence Detection System, Agilent 2100 bioanalyzer and related bioinformatics tools, including software for image acquisition, microarray and SNP data analysis. The MCF helps biomedical researchers explore questions systematically by providing high throughput technology with flexibility and simplicity at low costs, for efficient extraction of biologically meaningful data.

Affymetrix GeneChip arrays

This platform can analyze all GeneChip probe arrays for gene expression analysis and DNA analysis. A broad range of whole genome arrays are available in Affymetrix product lines, including human genome array, human SNPs, mouse genome, rat genome, rat toxicology, rat neurobiology, drosophila genome, Arabidopsis genome, C. elegant genome, Yeast genome, E. coli and P. aeruginosa genome, and others. We can help you design your experiment and provide detailed protocols for both RNA and DNA sample preparations.

Custom array service

Custom arrays provide flexibility in the choice of arrayed elements, particularly for the preparation of smaller, customized arrays for specific investigations. The arrayed material can be complementary DNA (cDNA), oligonucleotide probes, and proteins, and the target area may be glass slides, porous nylon membrane, or other microplates. The custom array service supplies the Robotic 96-well/384-well transferring, spotting technology, hybridization and washing system, and an array reader.

Agilent 2100 Bioanalyzer

This piece of equipment replaces conventional gel electrophoresis and improves analysis of DNA, RNA, proteins and cells through automation for better accuracy and reproducibility, rapid visualization of sample quality and quantity, and high sensitivity with only a small amount of sample. Both RNA Nano and Pico chip kits are available in the core facility.

Beckman Biomek FX liquid handling robot

The FX system is a customizable, fully-automated, high throughput liquid handling robot with the ability to use 96 or 384 plates and to transfer from plate to plate with four formatting options 96-96, 96-384, 384-96, 384-384. The FX has span8 syringes for liquid handling in tubes, vials or plates for experiment setup and is ideal for large projects. The FX can be used for library manipulation, 96 well PCR setup, as well as library duplication.

Microarray data analysis

Our staff has a great deal of expertise in microarray data analysis. In the past few years, we have evaluated more than 12 software packages including GeneSpring, Spotfire, SAM, dChip, BRB, R-based tools from Bioconductor and some statistical packages, such as R and S-plus, etc. and helped each array user with data manipulation, including data visualization, normalization, statistical analysis and error modeling, pattern recognition, pathway and gene network, and data interpretation meaningful to biologists. We have also started to evaluate the tools and software for SNP data analysis since Affymetrix brought the 10K SNP chip to the research community. The core staff is available for consulting.

ABI 7900HT Sequence Detection System

In addition to standard PCR thermal cyclers, MCF also houses a real-time PCR instrument. The 7900HT System is the only real-time quantitative PCR system that combines 96- and 384-well plate compatibility and the TaqMan Low Density Array with fully automated robotic loading and also offers optional Fast real-time PCR capability. Using two automation software tools, Plate Utility and Automation Controller, most of the gene expression and SNP genotyping workflow is fully automated for high-throughput applications. Key applications include gene expression quantitation and the detection of single nucleotide polymorphisms (SNPs) using the fluorogenic 5' nuclease assay.

The Abby and Howard P. Milstein Synthetic Chemistry Core Facility

The Milstein Synthetic Chemistry Core Facility provides the equipment and expertise to assist investigators in several areas. Utilizing a newly renovated organic synthesis laboratory, we have the capacity to design and execute efficient and economical chemical syntheses. Additionally, assistance in the purification and identification of unknown metabolites can be provided. The

facility primarily serves Weill Medical College, but can occasionally extend its services to include the tri-institutional academic community.

Facilities

The Core Facility occupies 450 square feet and is supported by state-of-the-art resources. Standard benches are available for each scientist and include rotary evaporators with both low and high vacuum capacity, a fume hood with argon manifolds, and a Radleys StarFish™ multi-experiment workstation. In addition, the facility is equipped with a full array of chromatography and analytical equipment, including the following: Bīchi Sepacore binary gradient low/high pressure silica gel chromatography system; Waters ACQUITY SQD Ultra Performance LC-MS with simultaneous PDA and mass detection (up to 2000 amu); Varian preparative HPLC utilizing two PrepStar SD-1 solvent delivery modules, PDA detector and fraction collector; Varian 4000 GC-MS and autosampler, capable of internal, external and hybrid ionization; Bruker TENSOR 27 series FT-IR spectrometer equipped with a Diamond ATR for fast and easy IR sampling; SRS OptiMelt automated melting point system; Varian INOVA 600 MHz NMR spectrometer.

Services

- Consultation on experimental design and/or procedures, the availability of individual chemical compounds and/or reagents, and the feasibility of synthetic structures is available.
- Chemical synthesis of compounds that are not readily available.
- Synthesis of assay development tools and reagents including: fluorescently labeled compounds; affinity labeled compounds; cross linker-tethered molecules; labeled (¹³C, ²H, ¹⁵N) and radiolabeled (³H, ¹⁴C, ³²P, ¹²⁵I, etc.) compounds for preclinical and clinical pharmacological studies which cannot be directly addressed by the Radiochemistry Core facility.
- Synthesis of compounds in quantities that allow for in vitro and in vivo assays and secondary assays.
- Large-scale chemical synthesis of compounds with demonstrated biological activity in primary assays to provide material for further investigation.
- Structure-activity relationship (SAR) studies on validated pharmacophores in order to optimize targeting, specificity and bioavailability while minimizing toxicity.

Molecular Modeling

The Molecular Modeling Core Facility provides the latest technology in computer hardware and software to assist investigators in applying molecular modeling techniques to their research.

Facilities

Commercial modeling software packages such as Insight II, Cerius2, Quanta from Accelrys and individual software for visualization, docking, comparative modeling, quantum mechanics (QM), molecular mechanics (MM), and molecular dynamics (MD) simulation are available. New additions to our software list are the modules in Cerius2 for Computer Aided Drug (CADD) design which allow us to find the potential binding sites of proteins and design new and selective ligands that target those binding sites.

Services

In addition to access to the latest hardware and software, the Core also provides consultative and collaborative assistance in research efforts. This allows scientists with expertise in biochemistry and molecular biology but who are unfamiliar with computational methods to apply these techniques in their research. Staff can provide advice in the design of computational study approach, instruction in the use of the software and hardware, and assistance in the interpretation of data. Hands-on training in visualization, docking, comparative modeling and MD calculation is also available.

Nuclear Magnetic Resonance

NMR is the method of choice for investigation of disordered and partially folded proteins. There is a growing recognition that the disordered states of proteins play significant roles in important life processes. In the absence of fixed structure, antibodies, chaperones, and transport proteins and proteolysis machinery of the cell recognize proteins and peptides. Nascent structure in the unfolded state is known to impact pathologies associated with protein folding, ligand binding processes, mutations affecting protein stability and amyloid diseases.

Facilities

The facility provides nuclear magnetic resonance (NMR) instrumentation primarily for the investigation of the structure and dynamics of biological molecules. The facility consists of a Varian Unity Inova 600 MHz NMR spectrometer capable of state-of-the-art solution NMR experiments.

Services

Basic 1D and 2D NMR applications can be employed for assessing sample purity, chemical changes, binding events and the effects of mutations. More involved multidimensional NMR applications can be implemented for protein structure determination and dynamics investigations. The faculty associated with the NMR core has significant expertise in protein NMR applications aimed at investigating biologically relevant proteins with disordered structure. NMR is ideal for this purpose since protein possessing flexible regions is often difficult or impossible to structurally characterize crystallographically. NMR is uniquely suited to examine changes in the conformation, structure and mobility of proteins using solution conditions closely approximating the biological environment.

Optical Microscopy

This Core provides equipment and expertise to assist investigators in applying sophisticated optical microscopy techniques to their research. Fluorescence and transmitted light microscopy can provide information about the relationships of cells to one another and about the disposition of structures within cells. Images can be obtained in fixed cells and changes in living cells over time can be tracked using time-lapse imaging. Additionally, information about the 3-dimensional arrangement of structures within cells, both fixed and living, is accessible through the use of the Confocal Laser Scanning Microscope.

Facilities

The Core has a Zeiss LSM 510 laser scanning confocal microscope. This microscope has four detectors – 3 for fluorescence, 1 for bright field/differential interference contrast. It is illuminated by 3 lasers (argon, "green" helium-neon and "red" helium-heon) which supply excitation lines at 458 nm, 488 nm, 514 nm, 543 nm, and 633 nm, allowing simultaneous confocal imaging of 3 fluorophores (eg: FITC, Rhodamine and CY5) plus the bright field/DIC image.

The Facility also has a Zeiss Axiovert 200 widefield microscope for standard fluorescence and brightfield imaging. The Axiovert 200 is equipped with a MicroMax interline CCD camera and an assortment of fluorescence filter cubes that enable imaging of the most commonly used fluorophores (such as DAPI, FITC & GFP, Rhodamine, and CY5 & TOPRO-3) as well as transmitted light images in phase or differential interference contrasts. The microscope is controlled using MetaMorph software (from Molecular Devices).

Lastly, the Facility has an image processing workstation that runs both the Zeiss LSM proprietary software and the MetaMorph software for analysis of the images acquired on the microscopes.

Services

- Consultation. Consultation on experimental design and approach is provided by the Facility Manager and Director.
- Confocal Microcopy Imaging. The equipment in this facility includes a confocal microscope to be used for 3D image acquisition, and Dell and Silicon Graphics workstations to quantify, manipulate and render 3D fluorescence microscopy images.
- Training: The Manager will provide training in usage of the confocal microscope and the workstations. Training sessions are arranged in consultation with the Facility Manager.

Phosphorimaging

The Phosphorimager Core Facility, located in room A-022, consists of a Storm Model 860 and a Typhoon Triad. Both instruments are capable of scanning storage phosphor screens that have been exposed to radioactive samples as well as chemiluminescence and direct red or blue excited fluorescence. The Typhoon, which has greater sensitivity, can be used to scan for direct green excited fluorescence. In addition to storage screens, blots and gels can be scanned on both the Storm and Typhoon. The Typhoon is also capable of scanning a wider variety of objects, including microtiter plates, tissue sections and microarrays.

Applications include acquiring images of 1D or 2D gels, blots, tissue sections, etc. using either storage phosphor screens, chemiluminescence or specific fluorescent stains excited by red (633 nm), green (532 nm) or blue (488 or 457 nm) light. Protein or nucleic acid determination can also be done in microtiter plates when stained with relevant fluorescent dyes.

Data from any of the formats and either machine can be quantitated using available ImageQuant software.

Transgenic Mouse

WMC offers Transgenic Mouse Core services jointly with Sloan-Kettering Institute (SKI), and provides investigators access to many of the services offered at SKI's Transgenic Mouse Facility. A WMC transgenic core oversight committee is responsible for periodic review of the services and investigator satisfaction.

Facilities

This Facility produces transgenic and chimeric animals using, respectively, DNA constructs and embryonic stem (ES) cells provided by the investigator. It also cryopreserves embryos from transgenic, gene targeted, and congenic lines.

Detection and quantitation of radioactive decay on storage phosphor screens, fluorescence and chemifluorescence on gels, as well as western, southern and northern blots and arrays.

Services

- Consultation. Consultation on construct design, experimental strategy, and the establishment, maintenance and screening of transgenic lines is provided.
- Training. The Facility manager provides training in mouse husbandry and genetics, screening and analysis of transgenic and chimeric mice, ES cell culture, and dissection of pre- and post-implantation embryos.

X-Ray Crystallography

Structural information is critically important for understanding the function of macromolecules in normal physiological processes and in disease conditions. The information may also aid the discovery and optimization of potential therapeutic agents. X-ray crystallography is one of the most powerful methods in obtaining detailed atomic structures of macromolecules. This core is aimed at providing the equipment and expertise to assist investigators in obtaining crystallographic structures of macromolecules and in analyzing and visualizing protein structures. If for any reason you would like to know the atomic structure of your protein, whether it is a new protein with no known structure, a homologue of a protein with known structure, or a mutant of a protein with known structure, come and talk to the facility staff.

Facilities

The facility has state of the art equipment for diffraction data collection and structural analysis. This includes two Rigaku X-ray generators, two R-Axis IV imaging plate systems, and two cryo-devices for data collection at low temperatures. SGI graphics workstations are available for determination, display and analysis of protein structures.

Services

- **Consultation.** Consultation on every aspect of macromolecular crystallography including crystallization, structure determination and structural analysis may be provided.
- **Crystallographic Structure Determination.** Work on every aspect of macromolecular crystallography may be performed including crystallization, diffraction data collection and analysis, phase determination, structural refinement and structural analysis.
- **Structure Visualization and Analysis.** The SGI workstations are available to users for visualization and analysis of macromolecular structures. This includes structures downloaded from other sites.

X-Ray Development

Facilities

WMC offers an x-ray developing core facility for processing X-ray and autoradiographic film.

Services

The Facility Consists Of A KODAK X-O-MAT film processor that is available for use 24 hours per day, 7 days per week. Staff is available for emergencies, Monday through Friday, 9 a.m. to 5 p.m. Special note: all users will be assigned an access code that will allow entry to the facility. First-time users will be instructed in the proper use of the processor.

5. Hospital Affiliation

NewYork-Presbyterian Hospital

NewYork-Presbyterian Hospital is a 2,224 bed university teaching hospital based in New York City, jointly serving Weill Medical College and Columbia University College of Physicians and Surgeons. The Hospital provides state-of-the-art inpatient, ambulatory and preventive care in all areas of medicine at five major centers: Weill Medical College, Columbia University Medical Center in Northern Manhattan, Morgan Stanley Children's Hospital of NewYork-Presbyterian in Washington Heights and on the Upper East Side, the Allen Pavilion in the community of Inwood Manhattan, and the Westchester Division in White Plains, NY. NewYork-Presbyterian Hospital is the largest hospital in New York. The Hospital employs over 5,080 physicians holding faculty appointments at one or both medical schools and more than 14,700 non-physician healthcare providers and hospital employees. NewYork-Presbyterian Hospital is one of the most comprehensive health care institutions in the world, offering the latest advances in medical and computer technology to help ensure high quality, efficient, and cost-effective healthcare.

NewYork-Presbyterian Hospital is also the flagship hospital of an extensive healthcare network, which consists of more than 150 participating organizations including 32 hospitals, 6 long-term care facilities, 12 home health agencies, 3 specialty institutes, and 97 ambulatory care centers. Through the NewYork-Presbyterian Healthcare Network, the Hospital and its affiliates provide the most comprehensive, high quality services to residents of Manhattan, Brooklyn, Queens, and the Bronx, as well as Westchester, Long Island, New Jersey, Connecticut and several upstate New York counties. More than 12,000 attending physicians provide care in the System. Each System member is an affiliate of either Weill Medical College or Columbia University College of Physicians and Surgeons.

Note:

The institutional information in this document consists of numerous published documents from various sources. Some information is reprinted here in entirety, some documents have been paraphrased or reworded.

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Office of Grants & Contracts
Research & Sponsored Programs
646-962-8290
rasp@med.cornell.edu
<http://www.med.cornell.edu/research/gra con/>