THE ROCKEFELLER UNIVERSITY HOSPITAL

UPDATE

FALL • 2004

Hospital Five-Year GCRC Grant Renewed

Susan Richer, MPA, FACHE

The National Center for Research Resources (NCRR) of the National Institutes of Health (NIH) announced it will renew its five-year General Clinical Research Center (GCRC) grant to The Rockefeller University Hospital, ensuring its NIH funding through 2009. Although the size of the grant has not been finalized, NCRR notified the Hospital in June that its application had received an extremely favorable evaluation.

The hospital submitted its grant in February, and a team of thirteen NIH representatives conducted a site visit on May 11th. After initial welcoming remarks by Drs. Emil Gotschlich, Barry Coller, and Paul Nurse, the site visit began with a two-and-a-half hour "GCRC Program Overview," led by Dr. Jim Krueger. Individual segments were presented by Dr. Coller (describing training and education, including the Clinical Scholars program), Dr. Rhonda Kost (commenting on the role of the research subjects' advocate and human subjects protection), Kelly McClary (on the role of clinical research nurses), Dr. Gotschlich (discussing the Institutional Review Board), Alex Peshansky (on Informatics), and Knut Wittkowski (on biostatistical support and study design). Dr. Krueger's

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New Nursing Award to Delia Delarama

Peggy Hempstead

Delia T. Delarama, RN, MN, was awarded the Elizabeth A. Straight Nurses' Education Fund Award for Excellence in Research Nursing at the Nurses' Day celebration on May 7. The award recognizes Ms. Delarama's loyal service to medical research at The Rockefeller University Hospital and her commitment to the highest standards of patient care and collegiality. A permanent plaque acknowledging her contributions to clinical research at The Rockefeller University Hospital has been hung in the reception area of the Heilbrunn Outpatient Research Center.

The award, established in memory of Elizabeth A. Straight, Director of Nursing at the hospital from 1977 until 1990, is accompanied by a stipend of $2000 for continuing education in clinical research nursing. Kelly A. McClary, the current Director of Nursing and Patient Care Services, presented the award to Ms. Delarama, with the congratulations of the entire clinical research community.

As the first recipient of the award, Ms. Delarama embodies the qualities to which nurses aspire. In her 15 years at The Rockefeller University Hospital, she has worked in both the Inpatient Unit and the Outpatient Research Center, where she has served as a role model and mentor for nurses new to clinical research. Patients, investigators, and colleagues have

Delia Delarama

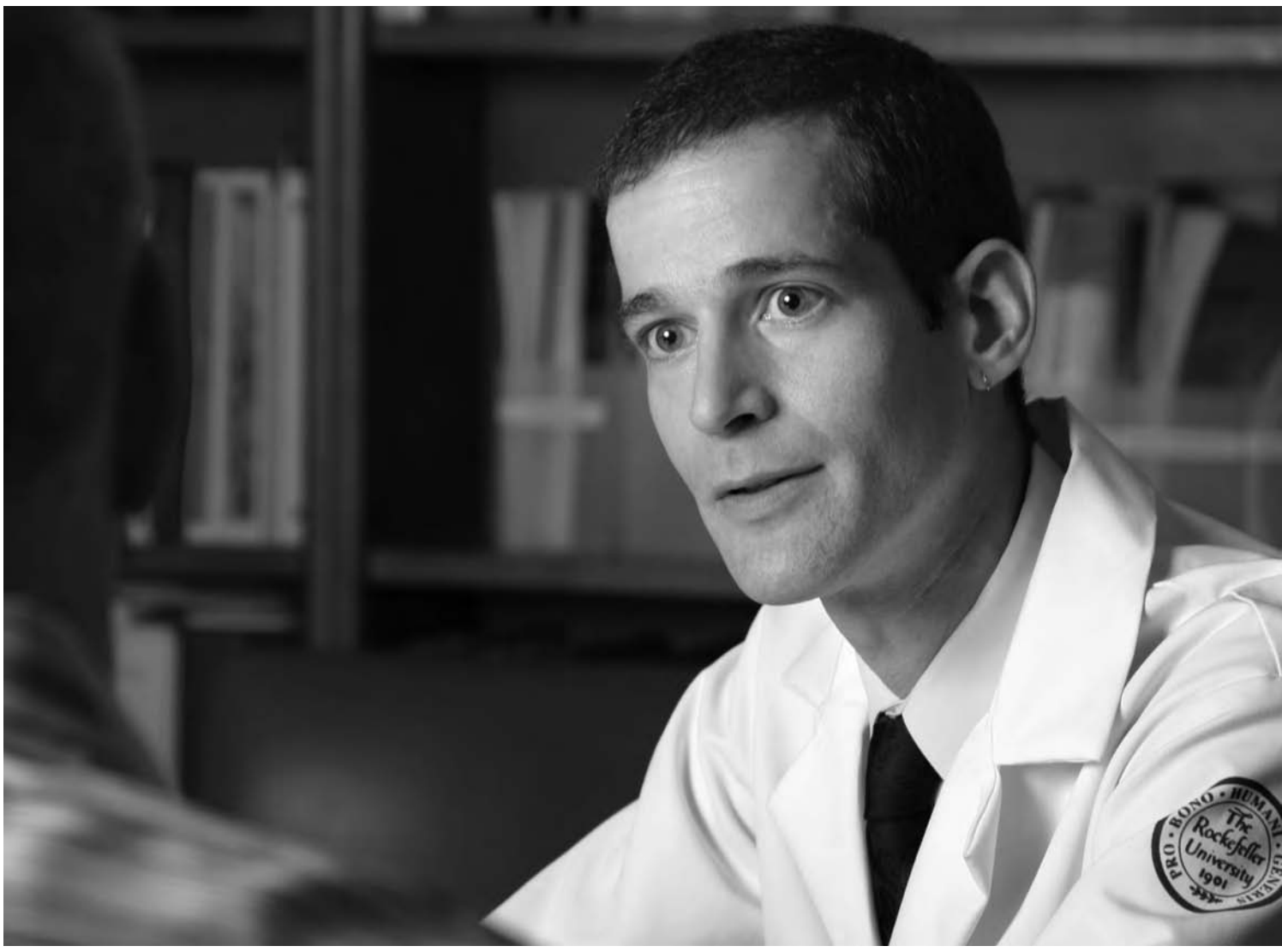
benefited from her competent and compassionate implementation of nursing and research principles.

The Elizabeth A. Straight Nurses' Education Fund Award for Excellence in Research Nursing will be awarded annually by a committee representing the spectrum of clinical research functions. For information about membership on the committee and to submit nominations for future awards, please contact Ms. McClary.

Getting to the Roots of Addiction

Gavin Bart
Laboratory of the Biology of Addictive Diseases

In February 1964, a young New York Hospital internal medicine resident crossed 68th Street to help Professor Vincent P. Dole, who was also joined at that time by a psychiatrist, Dr. Marie Nyswander, to study the number-one killer of New York City's youth – heroin addiction. Keen clinical observations led the team to hypothesize that rather than being a criminal behavior – the prevailing belief of the day – heroin addiction was a metabolic disease of the brain with resultant physiological and psychological manifestations caused by frequent and repeated cycles of heroin use and withdrawal. Using methadone, which they determined to be a long-acting opioid, to disrupt these cycles produced such dramatic effects that after only 16 patients, they realized that they had made an important breakthrough. Millions of patients worldwide continue to benefit from those initial studies.



Gavin Bart, Director of Clinical Research, Laboratory of the Biology of Addictive Diseases

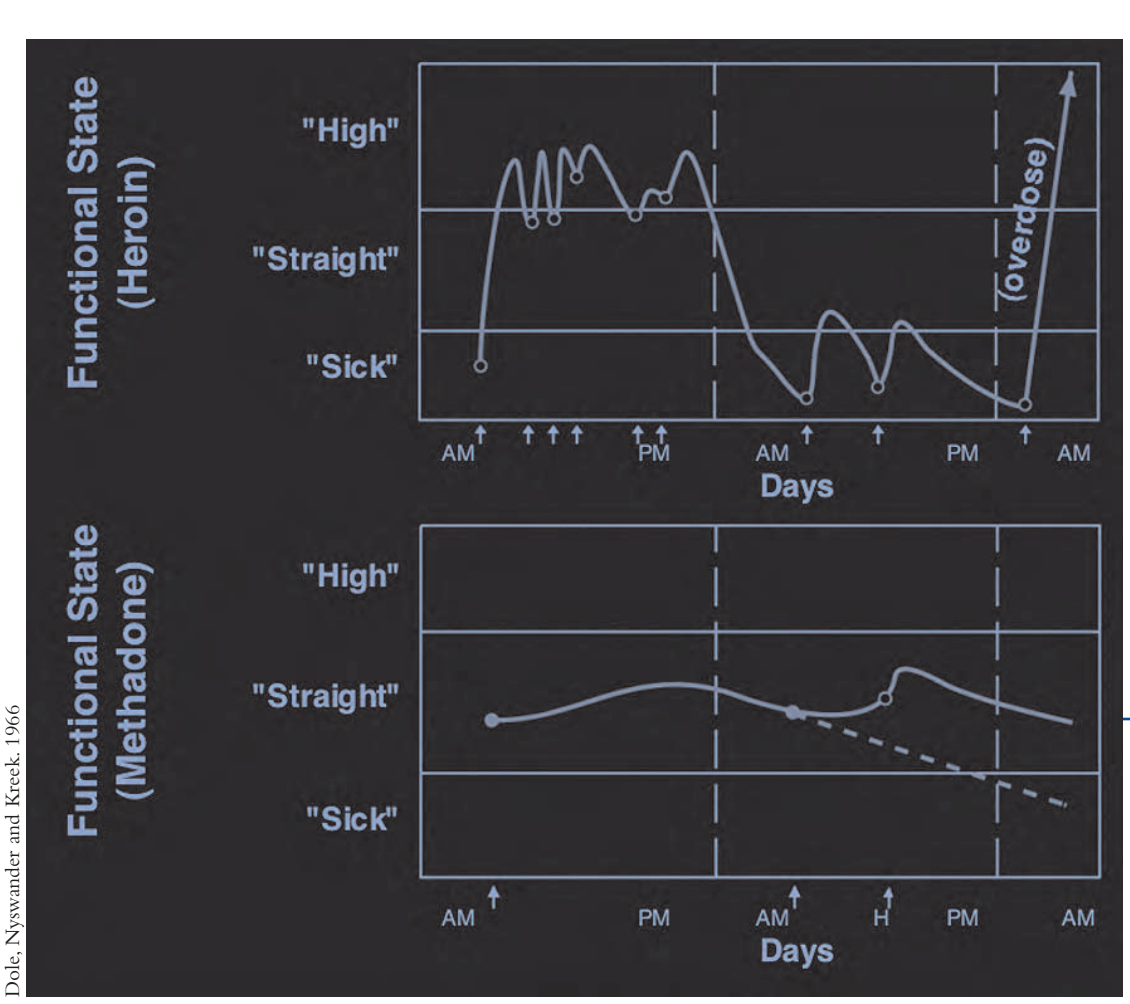
Forty years later, that young medical resident, Dr. Mary Jeanne Kreek, is Professor and Head of the Laboratory of the Biology of Addictive Diseases. Having completed the initial safety and efficacy studies of methadone, the Kreek lab (which I joined in 2000 as a Clinical Scholar) now focuses on the underlying factors that contribute to the development and persistence of specific addictive diseases: the physiological and molecular neurobiological effects of drugs of abuse, as well as genetic factors which may contribute from 30% to 60% of the risk of developing an addictive disease once a person is self-exposed to a drug of abuse.

Through animal and human research, our lab has been able to show that all drugs of abuse either directly or indirectly alter the endogenous opioid system, the brain's natural morphine-like proteins and their receptors. The lab has also shown that the endogenous opioid system modulates the function of our stress-responsive hormones. Together, these findings confirm what many have suspected from personal observation: that stress and addiction are intertwined.

Our lab has been focusing on changes in stress response during different stages of addiction. By studying how hormone response differs between normal volunteers, active addicts, and former addicts, we gain insight into the specific parts of the stress-response system affected by addiction, and whether and for how long these changes may persist. We have also been able to show that treatment of heroin addiction with methadone allows most of these changes to return to normal, whereas the few people who achieve abstinence without methadone continue to have several alterations in stress responsivity.

Our lab also studies how genes may alter our vulnerability to develop an addictive disease. Just as alcoholics have altered stress responsivity, we have been able to show that the non-alcoholic adult children of alcoholics also have alterations in stress responsivity. Part of these alterations exist at the level of the endogenous opioid system, and we have found specific changes in the genes of this system that are more likely to be observed in people with specific addictions than in the general population. While there is no one gene that causes addiction, we are finding several genes that may act in consort with each other to influence how the body responds to stress, the surrounding environment, and drugs of abuse. Teasing apart these complex interactions will guide our future research and, perhaps in another 40 years, we can reflect upon how research conducted at The Rockefeller University Hospital led to effective treatments not only for heroin addiction, but also for cocaine addiction, alcoholism, and other addictive diseases.

Gavin Bart received his M.D. degree from the University of Minnesota and completed his internal medicine residency at the Hennepin County Medical Center in Minneapolis. Having spent two elective rotations during residency in the Laboratory of the Biology of Addictive Diseases, he formally joined the lab as a Clinical Scholar from 2000 to 2003. He remains in the Laboratory of the Biology of Addictive Diseases, where he is Director of Clinical Research.



Dole, Nyswander and Kreek. 1966

Top: Diagrammatic summary of the functional state of a typical heroin addict. *Bottom*: Stabilization of a patient in a state of normal functioning during methadone maintenance treatment. Arrows represent heroin self-administration. Even after superimposed heroin self-administration, methadone maintained subject does not experience drug euphoria ("high") or withdrawal ("sick").

An Immunological Approach to Treating Multiple Myeloma

Keren Osman
Laboratory of Tumor Immunology and Immunotherapy

Multiple myeloma is a malignancy characterized by clonal proliferation of plasma cells in the bone marrow. It accounts for 1% of cancers and 10% of hematologic malignancies. Current therapies have been successful in controlling the disease only temporarily. Because multiple myeloma remains incurable, new therapeutic approaches are needed.

Since the cause of multiple myeloma is unknown, we are studying the development of multiple myeloma from a precursor disorder: monoclonal gammopathy of undetermined significance (MGUS). Some 25% to 30% of patients with MGUS develop multiple myeloma, but there are no reliable predictors indicating which patients will progress to overt malignancy. In fact, all of the cytogenetic changes that have been described in myeloma tumor cells have also been observed in plasma cells from MGUS patients. Furthermore, the gene expression profiles are similar in these two cell populations.

Since the cells of MGUS appear to have many of the hallmarks of multiple myeloma, we are analyzing whether it does not behave as a malignancy because it is being kept in check by the immune system. Our group is interested in studying the nature of the immune response against both MGUS and multiple myeloma in patients, which is facilitated by the fact that in these disorders, the tumor is in the bone marrow, where it is readily accessible.

Our studies involve the use of dendritic cells, which are potent antigen-presenting cells, to boost the antitumor immunity of patients with multiple myeloma and other cancers. We recently showed that a particular subset of immune cells called natural killer T cells (NKT) could be detected in the blood and bone marrow of patients with MGUS and multiple myeloma. NKT cells may have an immune regulatory role, and have an important role in mediating antitumor immunity, both in the laboratory and in animal studies. In our studies, we found that NKT cells isolated from the blood and bone marrow of patients with myeloma, while present, were dysfunctional; in sharp contrast, NKT cells from patients with MGUS retained normal function.

Moreover, the functional defect in NKT cells in myeloma patients could be reversed *in vitro* by using dendritic cells treated with α-galactosyl ceramide (α-GalCer), a glycolipid that binds to NKT cells. NKT cells that are activated by binding α-GalCer can efficiently kill multiple myeloma cells, as well as other tumor cells. Furthermore, activation of NKT cells may lead to increased numbers of NKT cells and cytotoxic T-cell activation, which may also result in antitumor activity. To assess the role of NKT cells in malignancy, we therefore embarked on a phase I trial to test the safety and tolerability of dendritic cells treated with α-GalCer to increase NKT cells in patients with cancer.

As a Clinical Scholar at The Rockefeller University Hospital, I am helping to conduct this study. We see our patients in the Heilbrunn Outpatient Research Center and as inpatients at The Rockefeller University Hospital. We collect the immune cells of patients who are eligible for our trial by performing

Keren Osman

leukapheresis, which separates white blood cells from other blood cells and returns the other cells to the patient. The white blood cells isolated by the leukapheresis procedure are then used to grow the dendritic cell vaccines for the trial.

Our patients receive three intravenous injections of dendritic cells prepared from their own white blood cells at monthly intervals. We monitor their immune systems by studying their blood and (in some cases) their bone marrow cells at various time points before, during, and after the injections, to assess the numbers and function of NKT cells. So far, we have treated a number of patients and are recruiting others. We hope that what we learn in this clinical trial will lead to a deeper understanding of the role that the immune system plays in controlling cancer and, in turn, to the creation of novel approaches to preventing and treating cancer.

Keren Osman completed her undergraduate studies with high honors at Swarthmore College, where she majored in history and religion. She attended medical school at Mount Sinai School of Medicine, and completed her residency in internal medicine there as well. She then went on to do her fellowship training in hematology and oncology at Memorial Sloan-Kettering Cancer Center. While there, she participated in clinical research employing new agents for the treatment of plasma cell diseases and employing traditional agents in novel ways. Because of her interest in plasma cell diseases, she decided to work with Dr. Madhav Dhodapkar as a Clinical Scholar in the Laboratory of Tumor Immunology and Immunotherapy. In recognition for some of her work at The Rockefeller University Hospital, she was the recipient of a Young Investigator Award from the American Society of Clinical Oncology last spring.

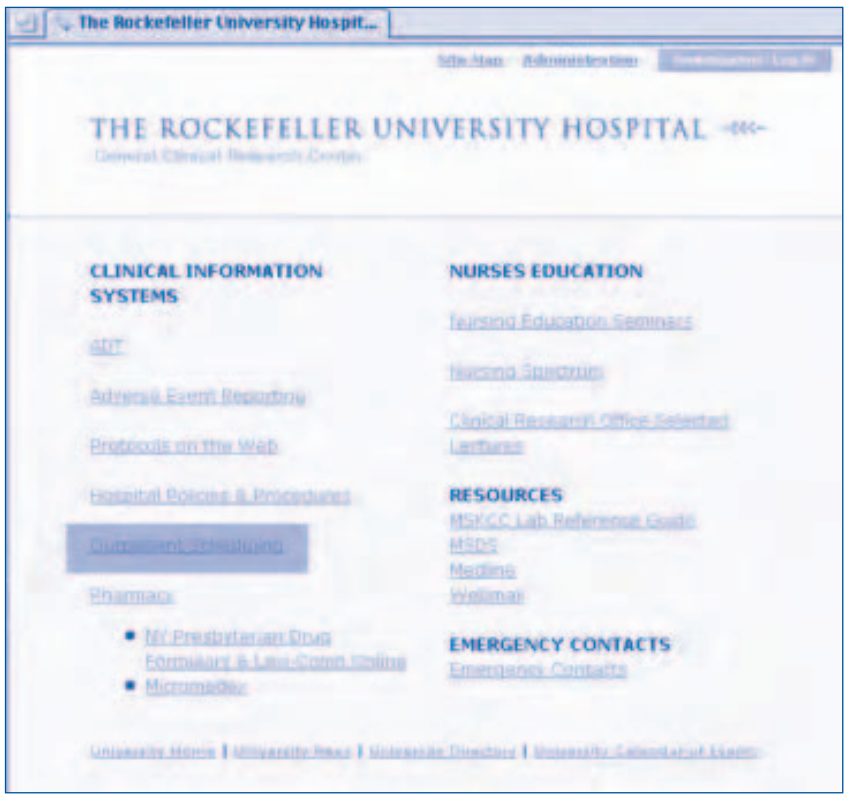
Online Scheduling Now Available for Outpatient Research Center

Peggy Hempstead

Investigators now have a new option for scheduling patients in the Outpatient Research Center (OPRC) of the hospital. Instead of faxing a Scheduling Request Form to the unit clerk, the investigator may now schedule patients online via the Outpatient Scheduling System on the Clinical Desktop (www.rucares.org/nurses/nurses/php). This program allows investigators to make appointments and to give the OPRC staff information such as meal requirements, protocol notes, or parking needs.

The appointment schedule may be edited to accommodate changes or corrections, and it gives investigators the convenience of viewing their appointment schedules online. Investigators can schedule their patients independently until 3:45 PM. Appointments made after this time must be called in (x8404) or faxed (x8405). Each exam room in the OPRC is equipped with a computer that allows easy access to all of these functions. To obtain a password and learn how to access the system, please call Peggy Hempstead at x8105.

Pre-registration of new patients is an excellent way to save your patients time. You may pre-register patients by contacting Oneida Ortiz, the Admissions Officer, at x8419. She will ask you the patient's name, demographics, contact information, and the date and time of the scheduled appointment. This information will be entered in the database, so that when your patient arrives, the chart will be prepared and a medical record number will already be assigned.



New Smell Study: In Search of the Genetic Basis of Odor Perception

Andreas Keller and Leslie B. Vosshall
Laboratory of Neurogenetics and Behavior

The enjoyment of a fine wine, the odor of a ripe cheese, the memory of a long-lost grandmother brought back by the scent of her perfume, or the alarm we feel when we smell smoke are all produced by a functioning olfactory system. Although it is debated exactly how many different odors a given human can detect, the number is likely to be in the range of hundreds or thousands.

Despite this, there are enormous individual differences in how we interpret these smells. Given almost any odor, some people will find it pleasant, others unpleasant. Ripe cheese or garlic may smell delicious to some, but repulsive to others. Some will describe a given smell as weak, others as quite intense.

The scientific basis of this variation has not been well-studied. Some assume it is the simple consequence of our individual experiences: the culture we were raised in, the foods we ate, the local customs we practiced. Despite the clear evidence for culture-based preferences for food and aromas, the nature-versus-nurture debate for smell remains unresolved. For example, young infants respond selectively to some odors, suggesting that some olfactory responses do not require any prior experience. There is anecdotal evidence that all animals are exquisitely sensitive to sulfur-containing compounds, perhaps because they signal the presence of fire. Given the importance of the nature/nurture debate, there have been surprisingly few studies of possible biological determinants of odor perception.

Leslie B. Vosshall and Andreas Keller, Laboratory of Neurogenetics and Behavior

One interesting starting point to investigate this important question is to study the genetic basis of specific anosmias – the inability of a given person to smell a certain odor while having an otherwise "normal" sense of smell. For example, some of us can smell methanethiol, the metabolite that is excreted in our urine after eating asparagus, whereas other people cannot.

What might be the underlying biological basis of these interesting differences in perception? The failure to smell certain musk odors is extremely common in human populations, and has even been reported anecdotally in perfumists. The fact that these highly trained and sensitive "noses" are unable to overcome this deficiency in smelling musks suggests it cannot be learned, and may reflect an underlying genetic variation.

In fact, work from Doron Lancet's group in Israel has recently shown that people differ considerably in the genetic basis of the sense of smell. We detect odors through genes called odorant receptors. Animals possess hundreds or thousands of different odorant receptors, each of which is capable of binding to a subset of all the odors we can smell. These receptors are present in smell neurons in the nose. By binding to the odorant receptors, the odors then trigger electrical activity that signals to the brain what is being smelled.

These odorant receptors are encoded by the largest gene family in mammalian genomes, and are undergoing rapid evolutionary change. Dogs and rats, which have a very keen sense of smell, have many more odorant receptors than humans. At about the same time in evolution that primates acquired trichromatic color vision, the olfactory repertoire degenerated rapidly. For instance, in humans, approximately 60% of the more than 1,000 odorant receptor genes are pseudogenes that are incapable of making a functional odorant receptor. The number of pseudogenes is highly variable, with each person potentially having a different set of odorant receptor genes. In the Laboratory of Neurogenetics and Behavior, we propose to examine whether these genetic differences cause us to perceive smells differently.

Our study is aimed at finding people with specific anosmias and correlating these to genetic polymorphisms in odorant receptor genes. Since we don't know to which odorants the polymorphic odorant receptors respond, we will ask our volunteers to sample a large number of different smells. Subjects will be invited to The Rockefeller University Hospital Outpatient Research Center, where they will sniff a wide variety of odorants, from the pleasant scent of vanilla to the sweaty odor of butyric acid. We will assess the lowest concentrations at which odors can be detected and have the subjects describe the quality and intensity of odorants at different concentrations. To make sure the profile is accurate, we plan to repeat the whole procedure at a later date for each subject, since there are many factors that influence olfactory acuity on any given day (such as a cold or allergy, spicy food or cigarettes, etc.). We plan to screen several hundred subjects.

Ultimately, we will need to relate olfactory perceptions to genes, and to do this we will be collecting small blood samples from each subject. We will analyze the DNA sequence of the odorant receptor genes in each person and relate their genes back to their odor perceptions. Our hope is to find an association between peculiarities in the olfactory profiles and specific odorant receptor genes. In follow-up studies, we plan to test family members of subjects with interesting olfactory profiles and sequence their odorant receptor repertoire.

For all of these activities, we are highly dependent on the help of The Rockefeller University Hospital staff for designing and performing the experiments as well as for evaluating the data. We look forward to interesting months ahead as we investigate these essential questions in odor perception.

Bionutrition Department:
Key Asset in High Fat vs. High Carb Study

Janet Maturi
Bionutrition Research Director

Which is more effective for weight loss – a diet that is high in fat and protein, or a diet that is high in carbohydrates? This is just one of the many interesting questions that the Bionutrition Research Department is helping investigators to study. This particular research project was initiated by Dr. Jan Breslow, and serves to illustrate many of the capabilities of the Bionutrition Department.

Everyone is aware of the controversy and media publicity surrounding this question. Almost two years ago, the *New York Times* featured an article suggesting that a high-fat diet, shunned for years by the majority of the American medical community, may actually be an effective tool for weight loss. Dr. Breslow and his "nutrition brain trust" took on the challenge of designing a rigorous scientific protocol to assess for the first time the metabolic impact of these two diets.

Janet Maturi, Bionutrition Research Director, and Diane Meehan, Research Bionutritionist, worked closely with Dr. Breslow and his research team from the inception of this important project. The protocol was designed to be a 16-week inpatient study. Once the nutrition parameters were established, it was time to create diets using real food to meet the protocol requirements. We not only had to control for macronutrients, but several micronutrients as well.

Janet Maturi

Beside the obvious requirement of meeting the nutrition specifications of the protocol, there were many other factors that we needed to consider when we developed complex diets for this metabolic feeding study. For example, we needed to consider our ability to procure and store foods, establish the staffing requirements to produce the food, ensure that lunch foods were "packable" so that participants could go to work or school, and most importantly make sure the food was palatable. The high-fat/protein diet (65% fat, 25% protein, 10% carbohydrate) and the high-carbohydrate diet (20% fat, 15% protein, and 65% carbohydrate) were designed with the help of a sophisticated software program unique to nutrition research. We designed a three-day rotating diet for each arm of the study. Once we had the menus outlined on paper, it was time to produce the foods and show the team. The research team wholeheartedly approved, photos of the meals were taken, and we proceeded to the next step.

After the diets have been produced, tasted, and approved, we will homogenize each days food separately, and then send the samples to an external lab to verify the nutrient content. Once we have these results, we will put the diets into production. Our involvement with the study does not end here, however. We see all potential participants during the screening process to review the nutrition aspects of the protocol in detail. This is where the photos of the meals come into play. Every food on every diet has to be reviewed with participants to determine whether they will be able to adhere to the diet throughout the study. Once a metabolic diet is created, it cannot be changed, and it is not possible to accommodate individual preferences.

If a participant successfully completes the screening process, we can plan for admission. For this particular study, all of the participants are first stabilized on a weight maintenance diet for three weeks. The weight maintenance diet is the metabolic diet that we created for one of Dr. Breslow's previous studies. After the maintenance period, participants are randomized to either the high-fat/protein or high-carbohydrate diet for the weight-loss period.

We calculate the participant's calorie requirements for weight stabilization and create production sheets for the Bionutrition Staff to begin weighing foods. (Every food item is weighed to a tenth of a gram!) Once the subject's weight has been stabilized, we know which diet he or she will be randomized to, and we go through the process of determining the calorie level for weight loss (a 40% reduction) and creating production sheets again. At the end of the weight-loss period, we go through this process a third time to add back calories to keep the participant at the 10-week weight-loss level for the last three weeks of stabilization.

Education for each participant is extensive and ongoing for the duration of the study. We see participants on a daily basis to offer encouragement and support and to assess compliance. We also provide anthropometric assessment at several time points during the study. We utilize a Bod Pod to track changes in body fat and lean body mass.

The first participant in this project has just begun, and it will be very exciting to see how the study progresses. In the not too distant future, we may be able to answer the question: Which is more effective for weight loss – a diet that is high in fat and protein, or one that is high in carbohydrates?

Martha Vasquez prepares patient trays for the High Fat vs. High Carb study

Hospital Employee Barbeque

On July 29th, the hospital held its first employee appreciation barbecue in the scholar's garden. We enjoyed a beautiful afternoon relaxing with our friends and co-workers. We captured guests having fun with a Polaroid camera and gave them the photos in a souvenir frame. Those with an artistic flare contributed to a communal mural painting – now on display in the recreation department. We also had assorted lawn games and a piñata for the children. All in all, everyone had a great time and we have had many requests to make this an annual event.

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presentation provided a full description of our clinical services; provision of medical care; safeguards of patient safety, privacy, and rights; the broad role and high quality of Bionutrition; initiatives in information technology; and the training programs provided for physicians, nurses, dietary interns, and medical students.

For the remainder of the morning, the site visit team heard three 15-minute scientific presentations from Drs. Krueger, Mary Jeanne Kreek, and Madhav Dhodapkar, with each one followed by a 15-minute question-and-answer period. (See sidebar below.)

Concurrent with the morning scientific presentations, a 90-minute Administrative Review focused on budgetary issues, equipment requests, and Nursing and Bionutrition operations. The site visit team's administrative reviewer, Garrett Sanders, MPA, Director of the Office of Sponsored Research at Albany's Ordway Research Institute, conducted this in-depth discussion with Susan Richer, the hospital's Administrative Director; Kelly McClary, Director of Nursing and Patient Care Services; and Janet Maturi, Director of Bionutrition. Marta Torruella, The Rockefeller University's Assistant Director of Sponsored Programs, also participated in the administrative review, regarding grants management topics.

Lunch was provided in the Cohn Library for the site visit team, the presenters, key GCRC staff, and several Clinical Scholars, offering an opportunity to talk one-on-one with the review team members in an informal setting. Following lunch, Dr. Krueger led the visitors on a tour of the Hospital.

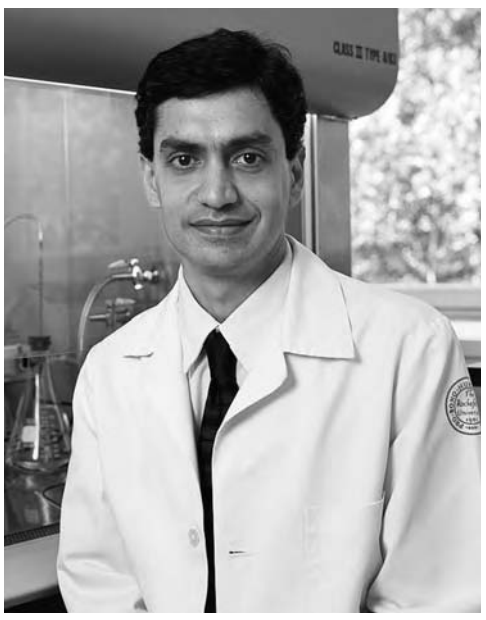
The team reconvened in room 110B of the Nurses' Residence, where four other scientific programs were presented by Drs. Jan Breslow, Jeffrey Friedman, David Ho, and Bob Darnell. (See sidebar below and on page 9.)

The review team evaluated the hospital's scientific programs (including the seven major presentations), as well as the organizational structure, budget, and physical facility. The overall objective of the site visit was to confirm that NIH funds support the highest quality science.

The study section that reviews the site visit reports of GCRCs met on June 10th and gave The Rockefeller University Hospital a very favorable score, ensuring that we will obtain continued funding for the five-year period beginning December 1, 2004. The hospital first successfully competed for GCRC grant support in 1963; this latest five-year award provides 45 years of continuous NIH funding for the hospital.

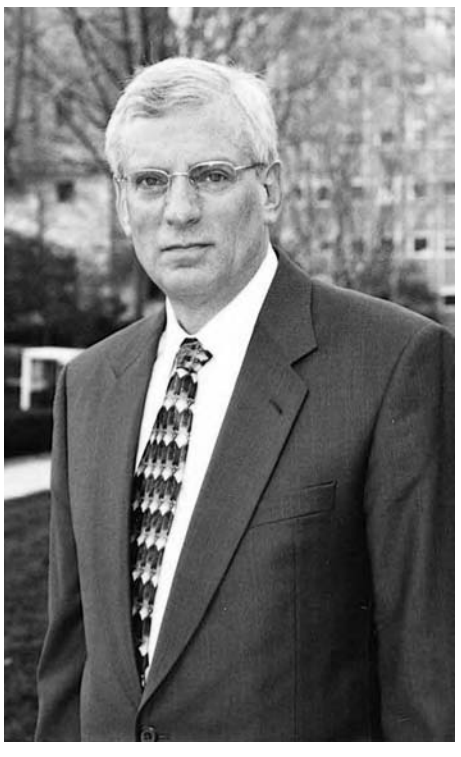
Scientific presentations made at the May 11th NIH site visit to the GCRC included the following:

Dr. Jim Krueger described his work in psoriasis: *Dissecting Cellular and Genomic Pathways of "Autoimmune" Inflammation in Psoriasis Vulgaris Using Efalizumab as a T-cell Targeted Disease Modifier*. While psoriasis is similar in many ways to other human organ-specific autoimmune diseases, it is the most accessible to study of cellular and molecular inflammatory pathways. Dr. Krueger described a general approach to the cellular and genomic inflammatory pathways in psoriasis that will lead to a better understanding of pathogenic disease mechanisms and the pharmacologic actions of targeted immune drugs in patients. Dr. Krueger and his colleagues will study patients treated with efalizumab, a humanized monoclonal antibody. They will dissect efalizumab's therapeutic mechanisms and refine general methods, including new statistical tools, that will aid in selecting the most important pathogenic elements from a complex array of disease-defining cellular and genomic alterations. Later they will use this approach to test antagonists to even more selective immune pathways. Their efforts will allow them to test alternative hypotheses of pathogenic immunity in psoriasis vulgaris, and allow them to ascertain *in vivo* contributions of specific molecular pathways to this disease.



Dr. Madhav Dhodapkar presented a study called *Pilot/Phase I Trial of Autologous Mature Dendritic Cells Pulsed with α-Galactosyl Ceramide*, which evaluates the tolerability of intravenous injection of autologous monocyte-derived mature dendritic cells (DCs) – both unpulsed and after *ex vivo* pulsing with α-galactosyl ceramide (a synthetic glycolipid ligand) – in patients with advanced cancer. In prior studies, Dr. Dhodapkar has shown that injection of antigen-bearing DCs in humans can lead to both antigen-specific enhancement and suppression of T-cell responses *in vivo*. His studies have also shown that DCs are efficient at presenting α-galactosyl ceramide to stimulate natural killer T cells, both *in vitro* in human cells and *in vivo* in mice. The proposed studies will provide insights about the recruitment of innate effectors using DCs to boost host defense against pathogens and tumors.

Dr. Mary Jeanne Kreek presented an overview of her laboratory's scientific program: *Neurobiology Of Addictions: Roles Of Stress Responsivity and the Endogenous Opioid and Dopaminergic Systems in Specific Addictive Diseases*. Heroin, cocaine, and alcohol addictions, alone and in combination – along with their medical complications – remain major medical problems. Effective treatments must be based on a fundamental understanding of the biological basis of each addictive disease, including the effects of exposure to drugs of abuse. This project will continue to explore atypical stress responsivity of the hypothalamic-pituitary-adrenal (HPA) axis seen in specific addictive diseases. Contributions of opioid and dopaminergic pathophysiological mechanisms will also be investigated. The roles of the endogenous opioid system in affecting the HPA axis and the roles of mu- and kappa-opioid receptors on tuberoinfundibular dopamine will be studied. Genetic association studies and functional studies of specific genetic polymorphisms will be conducted in normal volunteers and in subjects with specific addictive diseases. This work will complement rodent and non-human primate studies conducted in Dr. Kreek's NIH-NIDA P60 Center.



Dr. Jan Breslow described his research, *Comparison of Weight Loss Diets in Obesity Treatment*, an inpatient metabolic study in 40 obese or overweight subjects randomized to either a high-fat/protein or high-carbohydrate weight-loss diet. This includes 3 weeks of stabilization on a typical American diet, 10 weeks on either a high-fat/protein or high-carbohydrate diet with 40% fewer calories than on the stabilization diet, and 3 weeks of weight maintenance by adding back calories of a similar type to each of the diets. The proposed study is unique, and will provide answers to many of the important questions pertaining to which type of weight-loss diet is more effective without compromising overall health. This information will be very valuable to the medical community and the dieting public.

Dr. Jeff Friedman's presentation, *Studies of the Metabolic, Immune and Endocrine Sequelae of Weight Loss With and Without Leptin*, addressed a comprehensive analysis of the biologic response to weight loss after a very low calorie diet (VLCD), with or without leptin. Leptin is an adipocyte hormone, discovered by Dr. Friedman, that functions as an afferent signal in a feedback loop regulating body weight. When a normal adult reduces his or her caloric intake, leptin levels fall. In animals and humans, decreased leptin levels activate a biologic response similar to that observed after a VLCD. To study the biological response to a VLCD and leptin's possible effects in this setting, an extensive evaluation (including metabolic, endocrine, and immune studies) will be performed at baseline, after 10% and 20% weight loss have been achieved, and after the reduced weight is stabilized. This study is already under way, with 14 patients having completed the study.

Dr. David Ho presented *Developing an Effective Clade C HIV-1 Vaccine Employing DNA Containing HIV-1 Env, Gag, Pol and Nef/Tat as a Prime and Boosting with a Recombinant Multivalent Modified Vaccinia Ankara Expressing Env, Gag, Pol, Nef and Tat*. He and his colleagues at the Aaron Diamond AIDS Research Center have designed this DNA vaccine prime, to be followed by an modified vaccinia Ankara (MVA) boost. Encoded HIV-1 gene sequences are derived from a clade C strain – the Circulating Recombinant Form 007, a dominant subtype found in the southern regions of China. The first of two plasmid DNA vaccines, termed ADVAX e/g, encodes both full-length envelope and gag sequences, while the second plasmid, termed ADVAX p/n-t, encodes a modified pol and a nef-tat fusion gene. Separate promoters in the plasmid control the expression of each gene. The pVAX1© plasmid is used as the backbone, with subsequent addition of the hEfF1_ promoter and insertion of HIV-1 genes into the cloning sites. The full complement of these five HIV-1 genes has also been introduced into an MVA vector for further development as the corresponding booster immunization. Dr. Ho and his colleagues propose a phase I study of ADVAX e/g and p/n-t, and plan for further clinical development in the U.S. and China.

Dr. Robert Darnell's project, *Tumor Immunity in Paraneoplastic Neurologic Disease and Its Application to the General Population of Cancer Patients*, is a bedside-to-bench and back-to-bedside approach to exploiting naturally occurring effective tumor immunity in cancer patients. Paraneoplastic neurologic degenerations (PNDs) provide rare but important instances of naturally occurring tumor immunity associated with autoimmune neuronal degeneration. Dr. Darnell proposed to take the principles learned from the study of PND tumor immunity and apply them to the general population of cancer patients. In these proof-of-principle studies, Dr. Darnell and his colleagues will immunize prostate cancer patients with a vaccine prepared *ex vivo*: apoptotic tumor cells that have been captured by autologous dendritic cells. The safety and immunogenicity of this vaccine will be monitored as primary endpoints, with clinical responses monitored as secondary endpoints.

Nursing Assistants: Vital Members of the Clinical Research Team

Brian Whitefield and Peggy Hempstead

Nursing Assistants at The Rockefeller University Hospital provide essential services in patient care and management of the research environment to help meet our mission and goals. Their professional and caring attitude is vital to the conduct of clinical research in both the Outpatient and Inpatient Units.

In the Outpatient Research Center, Nursing Assistants are often the first members of the research team to meet patients and introduce them to the hospital and its procedures. Nursing Assistants are responsible for taking vital signs and EKGs, performing phlebotomies, collecting and processing specimens, and assisting with biopsies and other procedures. Much of this work is performed independently, as part of a daily routine.

On the Inpatient Unit, Nursing Assistants help prepare and assist with a variety of procedures, maintain and sterilize equipment, and monitor oxygen levels in the Procedure Suite. They help monitor patients' physical conditions by taking vital signs and performing EKGs. Nursing Assistants also provide invaluable comfort by taking care of the various details that make up each patient's hospital experience, while always managing to create a relaxed living and working environment with their good humor and positive demeanor.

All Nursing Assistants are trained to be part of the Campus Medical Emergency Response Team, and are among the first to arrive at any medical emergency. Nursing Assistants from both units are officers and members of the Nursing Department Environment of Care Committee. Their participation in these meetings as well as in preparing daily reports is essential to maintaining a safe environment of care.

Members of the hospital staff use the Nursing Assistants as a resource for everything from medical equipment to University Policy. Members of the Nursing Assistant staff are responsible for Fire Safety Training, management of materials and equipment, and maintenance of facilities and safety quality control. Nursing Assistants often provide instruction on topics varying from specimen processing and collection to safety procedures. Clinical research at The Rockefeller University Hospital is greatly enhanced by this competent, knowledgeable, diverse and good-natured group of individuals.

Olga Ford

Lorna Harper-Green

Eswin Hercules

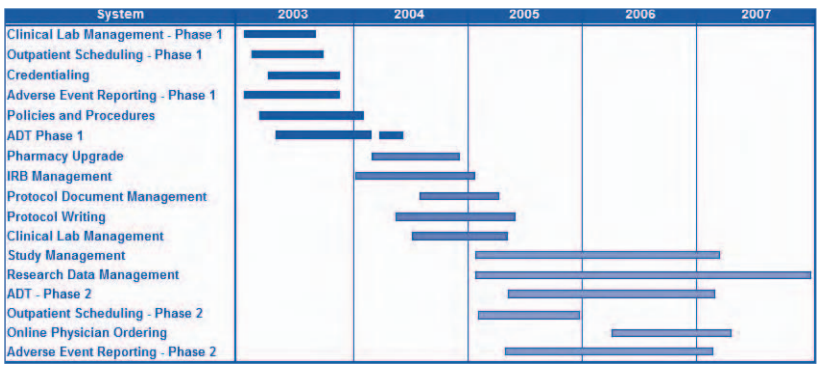
Strategic Information Technology Update

Jean Jenkins

Significant progress has been made in implementing The Rockefeller University Hospital Strategic Information Technology (IT) plan. In early 2004, we completed the first release of the new Admission Discharge and Transfer system (ADT), created a new Clinical Desktop, and started developing our new Institutional Review Board (IRB) Management System. We created a detailed project plan that defines the schedule for each component in the plan (see chart below). This plan will guide us to completion of the Strategic IT plan sometime in the latter half of 2007.

Jean Jenkins

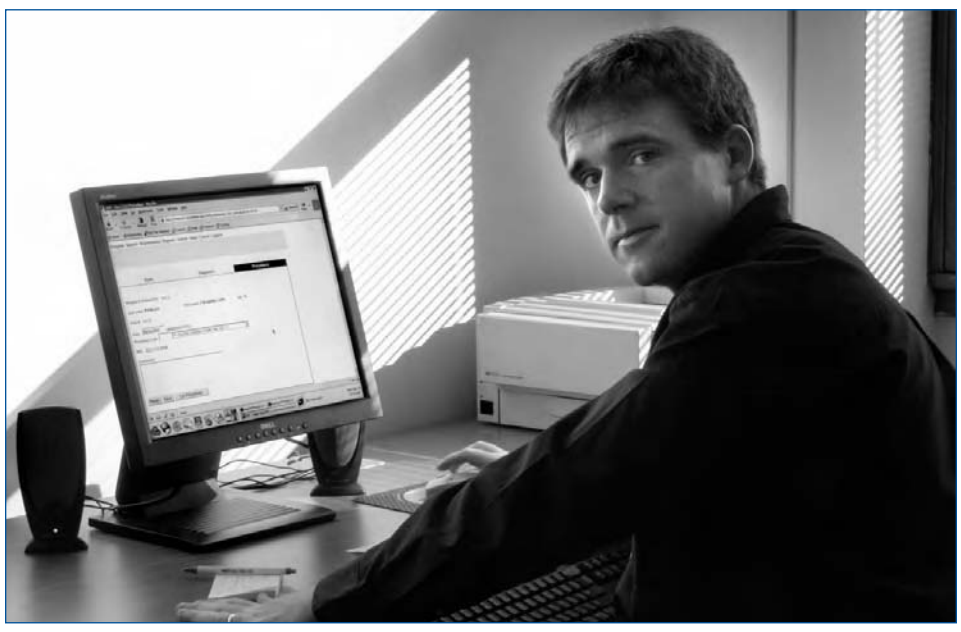
Strategic Information Technology Timeline



We are currently focusing on the design and development of the Protocol Writing system, the IRB Management system, and Protocol Document Management system. Our goal is to release the first versions of these systems within the coming year. These systems will provide the base for the Study Management system and the Research Data Management system, which are scheduled to begin design in 2005.

ADT

The new ADT system was initially developed by Robert Ju, Applications Programmer in IT, and handed over to Eamonn O'Donnell, Scientific Programmer, to complete the development and support the system. The new system is accessible via a Web browser, and offers significant improvements. For example, users now have the ability to display medical record information by patient identification number, admission identification number, principle

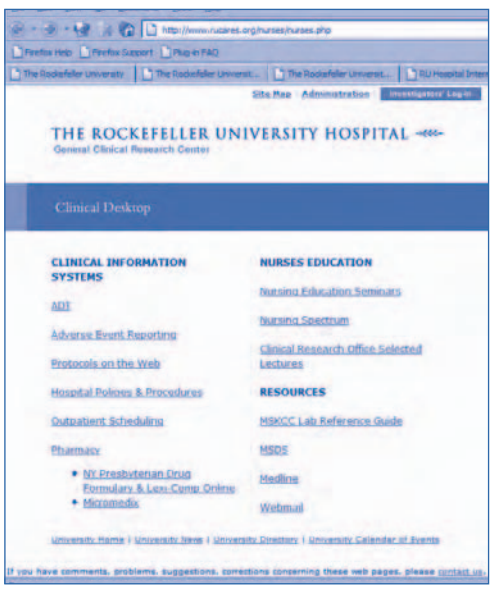


Eamonn O'Donnell

investigator (PI), or protocol name. The system also includes a real-time interface to our Credentialing system for retrieving investigator license information, thus saving the time it would take to look up this information on another system.

Oneida Ortiz, Rockefeller University Hospital Admissions Officer, commenting on the new link between outpatient scheduling and ADT, said, "The new version of ADT saves me time. The outpatient visits are now saved to the ADT program from the outpatient scheduling system, and I no longer have to re-enter the visits for each patient seen in the clinic. The list is saved on a daily basis, making the information readily available."

Clinical Home Page



Working closely with the nursing staff and Gale Kremer in the IT Web Development department, we designed the new Clinical Home Web page pictured here and deployed it on all clinic desktops in March of this year. The new home page contains links to ADT, Outpatient Scheduling, Adverse Event Reporting, Protocols on the Web and the Policies and Procedures systems, as well as links to educational and external information resources frequently used by clinical staff. Kelly McClary, Director of Nursing and Patient Care Services, noted, "The new Clinical Desktop has saved the nursing staff time by making their clinical systems easily available on one page, and it has encouraged them to make use of the additional resources available to them." The Clinical Desktop is a work in progress designed to meet the needs of investigators, nurses, and other staff. Please contact me (jean@rockefeller.edu) with suggestions about links that are helpful to you.

IRB Management

The IRB Management system will replace the current paper-based protocol submission and review processes. Our mission is to make the protocol submission process less cumbersome for PIs and to streamline the review process. Highlights of the new system include:

- The ability for PIs to upload protocols and supporting documents via a well-designed Web page that will guide the PI through the submission process.
- The ability for PIs, IRB administrators, and IRB reviewers to access submitted protocols online.
- System security that will provide PIs with access to their protocols.
- The ability for IRB administrators to check and report on the status of submitted protocols at any time throughout the process.
- A streamlined collaboration process between the IRB and PIs for incorporating recommendations and stipulations.
- Faster turnaround time for protocol approval notification.
- Automated transfer of approved protocols, informed consent forms, and delegation of authority forms to a new Protocol Document Management system for retrieval by the clinical staff during the study.

The IRB Management design team consists of Alex Peshansky, Eamonn O'Donnell, Dr. Emil Gotschlich, Dr. Rhonda Kost, Pat Macklin, Dale Miller, Jennifer Spada, and Jean Jenkins. The group meets regularly to define the requirements and scope of the system, and to review progress and offer solutions. Most of the development for the system is planned for this summer, and will be done by Eamonn O'Donnell, Scientific Programmer. User testing is planned for the last quarter of the year, and will include PIs from the research community. We plan to roll out the first release of the IRB Management system during the winter of 2004/2005.

Strategic Plan For Rockefeller University Clinical Studies

Barry S. Coller

As part of President Nurse's strategic planning process, a broadly representative group of individuals knowledgeable about clinical studies at The Rockefeller University has drafted a comprehensive Strategic Plan. Chaired by Dr. Barry Coller, the group met initially with President Nurse on January 14, 2004, and then broke into three subgroups devoted to Physical Plant and Equipment (chaired by Dr. Emil Gotschlich), Infrastructure to Support Clinical Investigation and Partnering with Other Institutions (chaired by Dr. Robert Darnell), and Education (chaired by Dr. Barry Coller). In addition, all members of the committee were invited to offer ideas on a broad range of topics related to the overall clinical studies scientific mission and recruitment via an online questionnaire that allowed the participants to view all of the responses. After the committee reports were completed, they were distributed to the members of the committee for review, and then a final meeting of the entire committee was held on June 23. The committee's recommendations, along with the supporting documents, were then submitted to the University's Core Strategic Planning Group for review. The summary, reports, and questionnaires can be accessed online via The Rockefeller University Home Page.

Highlights of recommendations made by the group include:

1. Further strengthen and expand the Clinical Scholars program by enhancing mentoring, extending the appointments to three years, and formalizing the review process after 18 months. In addition, Scholars will be given the new title of Instructor in Clinical Investigation.
2. Begin planning for the renovation of the remaining areas of the hospital.
3. Complete the implementation of the Information Technology Strategic Plan, with emphasis on support of investigators to facilitate protocol development, regulatory compliance, Institutional Review Board review, study management, and data management and analysis.
4. Provide additional personnel to help investigators develop data collection and reporting systems that comply with good clinical practice (GCP) guidelines, and to help investigators interact with regulatory agencies, such as the U.S. Food and Drug Administration.
5. Consider developing a rigorous course on Translational Research, focusing on both the scientific basis of translational research in select areas and the elements involved in preparing a protocol and conducting clinical investigation.
6. Provide through cooperative agreements and/or by establishing on campus advanced MRI, PET, and CT imaging, cell preparation facilities, advanced genotyping, stable isotope detection instrumentation, and a New York State-certified genetic testing laboratory.
7. Provide enhanced educational opportunities to promote excellence in research nursing, under the leadership of Kelly McClary, Director of Nursing and Patient Care Services.
8. Expand biostatistical support to investigators.
9. Strengthen the Seminars in Clinical Research Series by encouraging broad participation in selecting speakers and attending the seminars.

In summary, the committee identified a number of crucial elements necessary for The Rockefeller University to maintain and enhance its status as a premier site for clinical investigation. Many of the recommendations have already been implemented or will be implemented shortly, while those that require major new resources will be reviewed as components of the University Strategic Plan. As strategic planning remains an ongoing process, I welcome your comments on the recommendations and any new ideas you have to improve our scientific productivity.

Progress Report: Online Clinical Research Teaching Modules

Rhonda Kost

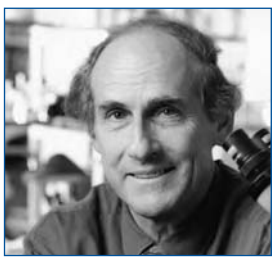
In November 2003, the Clinical Research Office announced a new educational initiative to develop a series of novel online modules to train the research community in the safe and ethical conduct of clinical research. The modules address the six standards detailed in the Clinical Center's Guidelines and Standards for Clinical Investigative Research at the National Institutes of Health: clinical informatics and data support; biostatistics support; quality control and quality assessment; protocol review; human resources and physical plant; and training and education. The latter encompasses history, standards, ethics, Institutional Review Board procedures, protocol design and writing, and informed consent.

In January, Andrea Scott joined the Clinical Research Office as our Clinical Research Education Staff member. Andrea brings to the task her extensive experience teaching, creating online materials, and leading writing workshops, as well as her sense of humor and personal warmth. Previously she has helped to create other teaching materials related to the Protection of Human Subjects, such as the Inpatient and Outpatient Patient Information Brochure, the Clinical Research Office Brochure, and the training materials for universal Human Subjects Protection Training at The Rockefeller University. She has made great progress in drafting the modules for the current initiative, drawing from a wide variety of resources. The next steps are 1) working with focus groups of Rockefeller coordinators, clinical scholars, investigators, and housestaff at the collaborating hospitals to refine the content, look, and feel of the modules to meets users' needs; 2) working with Information Technology to customize the online application that will support each module; and 3) helping Dr. Rhonda Kost to develop the research component of the educational initiative. The latter is perhaps the most exciting component of the project.

Rhonda Kost

As there are many existing resources that convey a traditional introduction to clinical research, we have elected to focus first on Informed Consent as an area in which more advanced training will be especially valuable to research team members. The emphasis of the Informed Consent I and II modules will be to train research team members and staff in how to conduct a valid and thorough Informed Consent process practically, including how to recognize and overcome common obstacles to comprehension. A novel research protocol is being designed to assess the impact of the Informed Consent training modules on the behavior of investigators as they interact with research volunteers. This will be undertaken collaboratively with the Morchand Center at the Mount Sinai School of Medicine, and involves the use of actors performing in standardized informed consent scenarios. Look for more details in upcoming issues as this research project evolves, and consider signing up for a focus group as the educational initiative proceeds so when the modules are complete and offered to you and your colleagues, they will meet your needs as well.

GOOD NEWS



Dr. Ralph Steinman

Faculty Honors and Awards

Dr. Ralph Steinman received the Novartis prize in Basic Immunology at the 12th International Congress for Immunology in Montreal in July.

Dr. Mary Jeanne Kreek received the Columbia University College of Physicians & Surgeons Alumni Association Gold Medal for Distinguished Achievements in Academic Medicine in May.

Dr. Kavita Dhodapkar

Clinical Scholars Honors and Awards

Dr. Kavita Dhodapkar has received an NIH K08 award for her grant proposal, entitled *Immune resistance to glioma via dendritic cells*.

Dr. Christine Hogan, who was a Clinical Scholar in the Ho lab from July 2001 to June 2003, was appointed Instructor in Medicine in the Division of Infectious Diseases, Department of Medicine, Columbia University College of Physicians & Surgeons. She will continue to conduct clinical investigation in HIV/AIDS and will collaborate with investigators at the Aaron Diamond AIDS Research Center.

Dr. Anita Shet

Dr. Anita Shet delivered an oral presentation entitled *Prevalence of Transmitted Antiretroviral Resistance in Antiretroviral-Naïve Patients with HIV-1 Primary Infection in 2003* at the Second International Workshop on Acute HIV Infection in Bethesda, Maryland in May.

Dr. Saurabh Mehandru

Dr. Saurabh Mehandru gave a Gastroenterology Grand Rounds presentation at New York University on July 6 on the topic *Characterizing the Role of Gut-Associated Lymphoid Tissue in Acute and Early HIV-1 Infection*.

THE ROCKEFELLER UNIVERSITY HOSPITAL

UPDATE

The *Update* newsletter is produced by the Rockefeller University Hospital and the New Media and Design Resource Center

Editor:
Barry Coller, M.D.

Design:
John Haubrich
New Media and Design

Contributing Editor:
Rosie Foster

Photographers:
Lubosh Stepanek, Marie Kotschedoff, New Media and Design

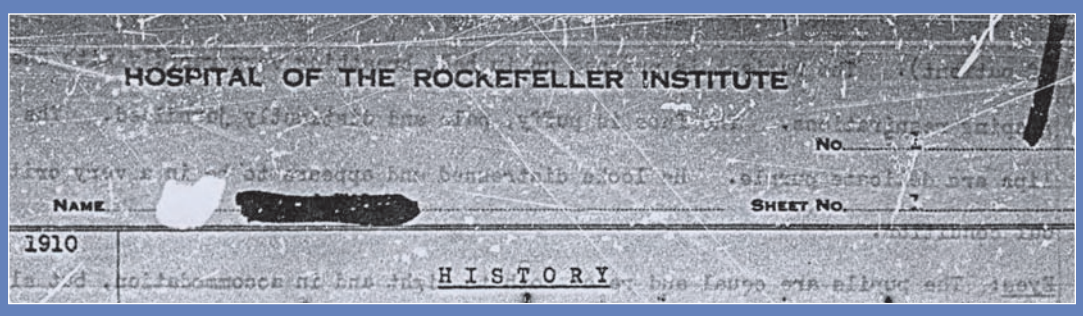
Zach Veilleux, The Office of Communications and Public Affairs

Karen Zaremba-Soto, The Rockefeller University Hospital

Production Manager:
Lynn Kolibaba

Archiving Patient Research for More Than 94 Years

Terri Collins, Hospital Information Systems


HOSPITAL OF THE ROCKEFELLER INSTITUTE

No.

NAME

SHEET NO.

1910

HISTORY

On October 28, 1910, The Rockefeller University Hospital (then called the Hospital of The Rockefeller Institute for Medical Research) admitted its first patient (see above). Ninety-four years, seven months, and nine days later, the Rockefeller University Hospital reached a historic milestone by admitting its 50,000th patient.

Fastidiously maintaining such vital data is the responsibility of The Rockefeller University Hospital Information System (HIS) department.

The University's commitment to its extraordinary archive of patient research is absolute. HIS has every medical record on every patient ever seen at the hospital, saved on microfiche, microfilm, or in original hard copy. HIS also maintains a number of registers and hospital-specific statistics – including admissions, discharges and diagnoses – organized by time periods, treating physicians, and laboratories. A separate log of U.S. Naval and Coast Guard personnel treated here between 1942 and 1943 is also maintained.

HIS continues to capture vital statistics today, but now does so electronically, reporting the results to local, state, and federal agencies. HIS has long anticipated the upgrade from paper to electronics. Earlier this year, the Web-based automated information system, ADT, was developed, enabling HIS to capture, maintain, and generate the various registers, indexes, and hospital statistics electronically. The migration from paper to electronic medium continues in the chart retrieval and release function. Implementation of a chart-tracking system using bar code technology will allow HIS to locate charts electronically, rapidly and efficiently.

Lastly, the HIS department is exploring the rapidly evolving technology of speech recognition-directed transcription. Upgrading to a speech recognition system will allow investigators to generate self-transcribed reports, thus providing access to patient data in a more efficient and rapid manner. The pace of change in the requirements for medical documents and the technology to generate them is truly staggering, making HIS an exciting place to work.