For Years, neurologist Petra Kaufmann, M.D., has been working to improve the lives of her young patients who have spinal muscular atrophy. The rare genetic condition causes extreme weakness and deterioration of the arm and leg muscles in infants and children, preventing them from walking, standing, sitting, or moving.

Due to a mutation in a gene that codes for a protein vital to spinal neurons that control movement, babies with the most severe form of spinal muscular atrophy, type I, have breathing and swallowing problems and cannot sit without support. Type II patients have milder symptoms but never walk. Type III is the least severe: Individuals can live until adulthood but have muscle weakness.

A range of health care professionals treat SMA patients by addressing their nutritional, respiratory, and rehabilitation needs, explains Dr. Kaufmann, assistant professor of neurology. Some children develop bone and spine deformities that require surgery. Others need ventilatory support to help them breathe. Most people with SMA require physical therapy.

Since joining Columbia in 2000, Dr. Kaufmann has treated dozens of patients and conducted clinical research, including trials to test new drugs. Throughout, she also has helped her patients to be functionally more independent. “These are smart kids,” she says. “Their cognitive abilities are fine but they often are limited by arm weakness. It is very important for a child to interact with the environment and for the brain’s nerve cells to develop and understand space.”

One day, in the late spring of 2007, Dr. Kaufmann had an epiphany. She called Elisa Konofagou, Ph.D., assistant professor of imaging science and director of the Biomedical Optics Program at the College of Engineering.

Spurring the Change: The Irving Institute for Clinical and Translational Research
A study of collaboration patterns among Columbia obesity researchers resulted in figures that show collaborations across seven departments (top) and collaborations between one department and a hospital partner through only one bridge (center and left). Nodes in the figures represent obesity experts and edges signify collaborations. Departments are indicated by colors. Figures courtesy of Chunhua Weng, Ph.D.

professor of biomedical engineering, to discuss designing a device that would enable her SMA patients to use their arms. She had seen pulley systems some children used at home to move their arms to read a book or work on a computer. These devices, however, were not widely available.

It never occurred to Dr. Kaufmann to reach outside her discipline to find a collaborator to build an apparatus to help children with SMA until she saw an announcement for an interdisciplinary pilot grant funded by the Irving Institute for Clinical and Translational Research. It inspired her to expand her scientific outlook.

**What is the Irving Institute?**

Getting Columbia scientists to find novel ways to do collaborative and interdisciplinary research to accelerate the development of new diagnostics, treatments, and disease prevention approaches for human health is the goal of the Irving Institute for Clinical and Translational Research. Formerly the Irving Center for Clinical Research, the program evolved into the Irving Institute in October 2006 as one of the first 12 clinical and translational science centers funded by the National Institutes of Health.

The Irving Institute has become a transformative agent for research innovation at Columbia and for the national consortium of 37 other CTSA — Clinical and Translational Science Award — recipients nationwide, including those that have joined the original 12. NIH aims to fund 60 centers. The Irving Institute, with 40 members and affiliated faculty, also receives substantial support from Herbert and Florence Irving.

In 2003, NIH director Elias Zerhouni, M.D., decided that revamping clinical research was a key component of his Roadmap for Medical Research, his blueprint for transforming research in the United States. The goal of the clinical research overhaul, he wrote in the New England Journal of Medicine in 2005, is to more quickly move findings from basic science laboratories into the clinic, in what is called translational research, and to hasten clinical research applications. To do so, he said, young clinical investigators need more support to do patient-oriented research and institutions need to revise their education of the next generation of clinical investigators. To spur the revolution, he said, institutions should develop new information and biomedical technologies, employ interdisciplinary approaches to answer clinical questions, and solicit public input in the process. He also called attention to the importance of research about how clinical research progresses.

Columbia was an inaugural recipient of a five-year, $51 million CTSA grant because of the accomplishments of its clinical research program under the leadership of Henry Ginsberg, M.D., the Herbert and Florence Irving Professor of Medicine and Irving Institute director. The strength of Columbia’s basic research laboratories, the collaboration that exists among the medical, nursing, public health and dental schools, its renowned biomedical informatics program, and its strong connection to the surrounding Washington Heights community were other factors in Columbia’s favor.

“The goal of CTSA is to find ways to move from preclinical to clinical applications and develop therapies for patients at a faster rate,” Dr. Ginsberg says. “But to be able to make the transformation, the culture of science has to change, from its training of young researchers and clinical investigators to the development of new technologies that foster change.”

Today, the Irving Institute has 10 resources that support clinical and collaborative research. The education initiative, for example, is called TRANSFORM, (Training and Nurturing Scientists for Research that is Multidisciplinary), led by Melissa Begg, Sc.D., professor of biostatistics and co-director of the Irving Institute, and Karina Davidson, Ph.D., the Irving Associate Professor of Medicine and Psychiatry. TRANSFORM offers a master’s degree in patient-oriented research for postdoctoral fellows and junior faculty, a certificate in clinical/translational research for predoctoral students, an NIH-supported grant program, called K12, for young investigators, and other short-term courses and career development opportunities in clinical research.

The Irving Institute affects many other aspects of clinical and translational research at Columbia: It has web-based services to help researchers design and execute a clinical research project. It offers expert advice about research subject protection, Institutional Review Board requirements, ethical considerations, and statistical and data analysis. It has mentoring programs for young investigators writing clinical and collaborative grants. Its clinical research center is expanding clinical research throughout the medical center. Its biomedici-
cal informatics resource helps scientists use computer-based information technologies to facilitate clinical research and performs original research about the nature of research and how information technology can improve the translational research enterprise. Its competitive pilot grants program, such as the one to which Dr. Kaufmann and Dr. Konofagou applied, provides different levels of funding for clinical and collaborative research. Its community resource engages Washington Heights’ residents in research projects. Its core facilities offer scientists an array of biochemical assays and imaging technologies for research purposes. A self-evaluative program measures the success of the CTSA, in terms of resulting grants, publications, and collaborations, and recommends strategies to push improvements further. Institute leadership also engages with the CTSA consortium members to share challenges and achievements in transforming the clinical research nationwide.

Reaching outside of one’s discipline

Dr. Kaufmann was primed to contact Dr. Konofagou because the two had attended meetings the Irving Institute convened to foster cross-disciplinary clinical research. Both are members of the Institute’s Development of Novel Clinical/Translational Methodologies Resource and are Irving Fellows, faculty ambassadors for the Institute’s mission. They met, wrote a proposal, and their team was one of the four winners of the first stage of CTSA’s interdisciplinary pilot grant: $25,000 for six months beginning in September 2007 to plan their project. The second phase awards $125,000 each to two of the four first-phase winners.

During their “planning phase,” Drs. Kaufmann and Konofagou and Jessica O’Hagen, formerly clinical coordinator and clinical evaluator in physical therapy of Columbia’s SMA Clinical Research Center, and other collaborators created a prototype. Dr. Konofagou engaged seniors in Columbia’s engineering department on the Morningside campus to participate during the design class of their senior year.

Their starting point was a wooden pulley system devised by physical therapist Linda Tomkow who had built one for Dr. Kaufmann’s patient. “These kids do not have the strength to lift their arms because they cannot overcome the force of gravity,” Dr. Konofagou explains. “By suspending their arms in a frame they are able to move their arms sideways so they don’t have to fight gravity.”

The team members and engineering students, who met with family members at Columbia and at patients’ homes and schools, soon realized a wooden frame was not flexible enough. A plastic version allowed adaptability for individuals of different ages and with varying mobilities.

The group also came up with a way to objectively evaluate the extent of movement of the arms of a person in the device. They could measure the distance a person’s arms moved using two accelerometers, one on each arm. A sensor in each accelerometer communicates with the other to calculate distance. A video camera in a laptop also could record motion. “The accelerometer has to be sensitive to catch small movements,” Dr. Kaufmann says. “These people are not strong, but if the device works, then we have the beginnings of a measure of success for reimbursement by health insurers or for monitoring the effectiveness of future device treatments or drug treatments.”

Supporting young clinical investigators

Besides cultivating Drs. Kaufmann and Konofagou and other junior faculty members to do collaborative and clinical research with pilot grants, the Irving Institute nurtures young faculty as they pursue a clinical research career. David Lederer, M.D., assistant professor of clinical medicine, says he would not have been able to do clinical research if not for the Irving Institute.

Dr. Lederer, who received his medical degree in 1999 from State University of New York, Downstate, was a pulmonary fellow at NewYork-Presbyterian Hospital/Columbia from 2003 to 2005 and research fellow from 2005 to 2006. Between 2005 and 2007, he enrolled in a program
to earn a master’s degree in patient-oriented research, jointly run by the Mailman School of Public Health and the Irving Institute. For his master’s project, Dr. Lederer was interested in studying racial disparities in survival rates of people with pulmonary fibrosis, a condition characterized by lung tissue scarring. The lung damage can cause severe breathing problems and in severe cases patients need lung transplants.

“No one had looked at race as a predictor of outcome for people with pulmonary fibrosis before,” says Dr. Lederer, who had discussed researching health disparities in advanced lung disease patients with Olveen Carrasquillo, M.D., at Columbia’s Center for the Health of Urban Minorities. “In our clinic, we had observed and reported that Hispanics and blacks had more advanced disease and declined more rapidly than whites.” In a subsequent study of 2,500 pulmonary fibrosis patients waiting for lung transplants, Dr. Lederer validated that Hispanics and blacks also fared more poorly in a larger, nationwide population.

At the end of 2006, Dr. Lederer applied for a K12 grant administered by the Irving Institute to expand his research into understanding the risk factors responsible for the racial disparities. The CTSA provides funds for 10 to 12 K12 positions at CUMC. He received the K12 intramural grant in January 2007 and then applied extramurally to the NIH’s National Heart, Lung and Blood Institute for the more prestigious K23 grant, which he received in April 2008, replacing his K12. He also applied for and received a physician scholar award from the Robert Wood Johnson Foundation to study racial disparities in pulmonary fibrosis.

“A doctor who sees patients nine to 10 hours a day and is involved in clinical responsibilities does not have time to write grants or have free time to think and write papers,” Dr. Lederer says. “The Irving Institute K12 grant gave me a salary and protected time to develop as a clinical investigator and to obtain subsequent grants to support my research.”

His next step will be to obtain an NIH R01 independent investigator grant, for which he can apply in his K23’s last two years. The Irving Institute will, no doubt, help him as they have helped other young faculty members with K grants writing their first R01 grants. Institute staff review the applications and mentor researchers through the bureaucratic process.

Expanding where clinical research occurs, too

Expanding clinical research at the medical center is another key goal of the Irving Institute. Fulfilling that mandate is Karen Marder, M.D., clinical research center resource leader and the Sally Kerlin Professor of Neurology (in psychiatry, the Gertrude H. Sergievsky Center, psychiatry, and the Taub Institute on Alzheimer’s Disease and the Aging Brain).

“The GCRC used to be discrete units with adult and pediatric inpatient and outpatient capabilities in the Presbyterian and Vanderbilt Clinic buildings,” Dr. Marder explains. “Now clinical research with the help of the Irving Institute-funded staff members is occurring throughout the hospital in the intensive care units, the emergency departments as well as at our original sites.”

Soon after Columbia received the CTSA award, Dr. Marder met the directors of the various ICUs and the emergency departments to ask them what they needed to do research. “These places are so busy doing clinical work, they often don’t have time to develop protocols and administer a research project,” she says.

To help, the CTSA eventually provided coordinators for the adult neurological and neurosurgical ICUs, surgical ICU, coronary care unit, pediatric ICU, and neonatal ICU. Coordinators were also provided to the adult and pediatric emergency departments. The coordinators submit Institutional Review Board applications for approval to perform human research, recruit participants, collect data, and educate participants and staff about ongoing research.

As of June 2008, Dr. Marder’s team was working with 40 new investigators managing 73 new protocols. More
than half are projects in the ICUs or emergency departments. Research topics range from anesthesia use in the surgical ICU to the effects of temperature in serious brain injury patients.

“Ultimately, we would like to go to inpatient floors to work more closely with nursing, physician assistants, and residents as they conduct research,” Dr. Marder says. “The more people who understand research, the better able they are to perform it.”

**How does research that benefits patients actually succeed?**

Although the NIH’s vision for CTSA is to transform clinical research, how to do it most effectively is not completely understood. A significant focus of the Irving Institute is to study the clinical research process with the goal of enhancing it.

Understanding and facilitating collaboration are goals supported by WorkWeb, an online software system under development for investigators engaged in clinical and translational research. “This project is itself a collaborative research project among the faculty in the Biomedical Informatics Resource within the Irving Institute,” says Stephen Johnson, Ph.D., director of the biomedical informatics resource and associate professor of clinical biomedical informatics. When fully functional the system will connect investigators to experts, mentors, collaborators, service providers, and other campus resources that will enable them to carry out their research.

“We envision that WorkWeb can help address some of the information processing needs of the clinical and translational research enterprise, both at the organizational level (by modeling networks and their activities directly) and by providing tools to conduct daily tasks required by the research.”

Similar to a social network but with important distinctions, WorkWeb will connect individuals through their relationships within departments, grants, publications, trials, and other entities. Each investigator will be a “node” within the network with links to other entities, and each entity, such as a grant or publication, will be modeled as a set of links to individuals, such as staff working on the grant or co-authors of the paper. Users of the system will navigate the social network to access their own information to update or track status of requests or to find others in the network to obtain advice on an experimental design or to collaborate on developing a grant proposal. Areas of the social network can be restricted to protect information when appropriate.

“The WorkWeb model is simple but very powerful,” says Dr. Johnson. “It will be used not only to model people and activities in clinical and translational research within Columbia University, but also in the Clinical Trials Network, a network of community practices in the tri-state area. Our current network contains nodes of 3,500 Columbia investigators, 230 departments that engage in some kind of clinical or translational research, 300 centers, 900 grants, and the publications of all the investigators involved in these organizations and activities.”

WorkWeb also may be used as a tool to support daily tasks of clinical research by combining elements of a Wiki (web pages that can be edited) with those for project management and protocol tracking. “The Wiki platform allows users to collaboratively author and edit web pages and documents and to participate in online discussion forums,” says Dr. Johnson. The system also includes features for scheduling visits in clinical trials and managing to-do lists to track research activities. “For example, a clinical research coordinator will be able to track future and completed patient visits, populate the calendar, and generate quarterly reports.”

Irving Fellow Chunhua Weng, Ph.D., assistant professor of biomedical informatics, studies collaboration patterns among obesity researchers across the organizational and disciplinary boundaries at Columbia University to see how they might be improved. “We chose obesity research for a variety of reasons,” Dr. Weng explains. “It is a major societal health issue; we thought we could tackle the problem by leveraging the resources of the CTSA throughout Columbia; we didn’t know how many Columbia obesity researchers there were; and we hoped ultimately with our findings we might facilitate new ways of bringing together people to work on the topic.”
Today, the Irving Institute has 10 resources that support clinical and collaborative research.

By searching the PubMed medical literature database and Google, and choosing a wide range of obesity research-related search terms, Dr. Weng found 113 individuals engaged in obesity research in 17 academic departments, 53 research divisions, and 20 centers throughout Columbia, including Teachers College and the urban planning department. She also found that these investigators published in 136 peer-reviewed journals, a finding, she says, that implies a need for more interdisciplinary journals that more multidisciplinary researchers would share, read, and publish in.

Once the obesity researchers were identified, she surveyed them about their collaborators at Columbia. Using social network analysis computer software to map linkages from her survey results, she investigated how the collaboration patterns were correlated with factors such as academic ranks, shared organizational affiliations, and shared research topics among obesity researchers. Example research questions: “Do collaborations occur more often between peers than between a senior and junior investigator?” and “Do collaborations occur more often among those who share the same MeSH terms in their published manuscripts?” Her analysis led to the discovery of weak ties between communities in obesity research. Based on the survey data, for example, Dr. Weng found only one bridge that links the Department of Surgery and the Institute of Nutrition. This result suggests that the ties between surgery and nutrition could be expanded and researchers forming the bridge are key research brokers across the two communities. “If there were more relationships and collaborations, there might be more benefits for patients,” Dr. Weng says.

She is now surveying the 113 experts to ask about the factors associated with sustained collaboration within Columbia, challenges for identifying collaborators and initiating the first contact, and areas where researchers would benefit from tools such as WorkWeb to identify collaborators or sustain collaboration. She hypothesizes that some researchers may connect via a colleague, while others may establish connections through meetings. Some may collaborate with peers, while others might prefer to strengthen collaboration with mentees. Each finding may suggest ways to improve future collaborations. Mentor/mentee success stories, for example, may become role models for the training of the next generation of clinical investigator.

Wiki for Collaboration

Dr. Kaufmann and Dr. Konofagou’s team also recorded a narrative of their collaboration as a requirement of the pilot grant program, intended to help others learn from their experience. They built a wiki, a collection of web pages that allows team members to contribute files, images, and continuing commentary about the project.

Now, the spinal muscular atrophy device team will have a chance to push their project further. The group won one of the two second-phase pilot grant awards in May 2008. With the new resources and more engineering undergraduate and graduate students, its team of approximately 20 hopes to build five prototypes to be tested by patients in their homes. The accelerometer data and other outcome measurements will allow a Mailman School of Public Health consultant to develop a cost/benefit analysis of the device, which a potential manufacturer would use to justify making the device and a health insurer would use for possible reimbursement. Columbia holds patent rights to the devices, which it would license to interested firms. The team also plans to apply for federal funding to expand the project. Related devices may assist others with disabilities, such as the elderly and disabled veterans.

“The key to this project was the interdisciplinary approach,” Dr. Kaufmann says. “A university is a unique environment that allows for the collaboration of a large number of excellent people in different departments, but they need ways in which to work together. Without the Irving Institute, this project never would have materialized.”

Dr. Konofagou echoes Dr. Kaufmann’s assessment. “Before, I only worked in cardiac and cancer imaging,” she says. “I never came across the engineering problems raised by patients with spinal muscular atrophy. This project pushed me outside my comfort zone, which was great. It also was a great experience for the engineering students. Hopefully, we’ll soon know whether our efforts will help people with spinal muscular atrophy.”