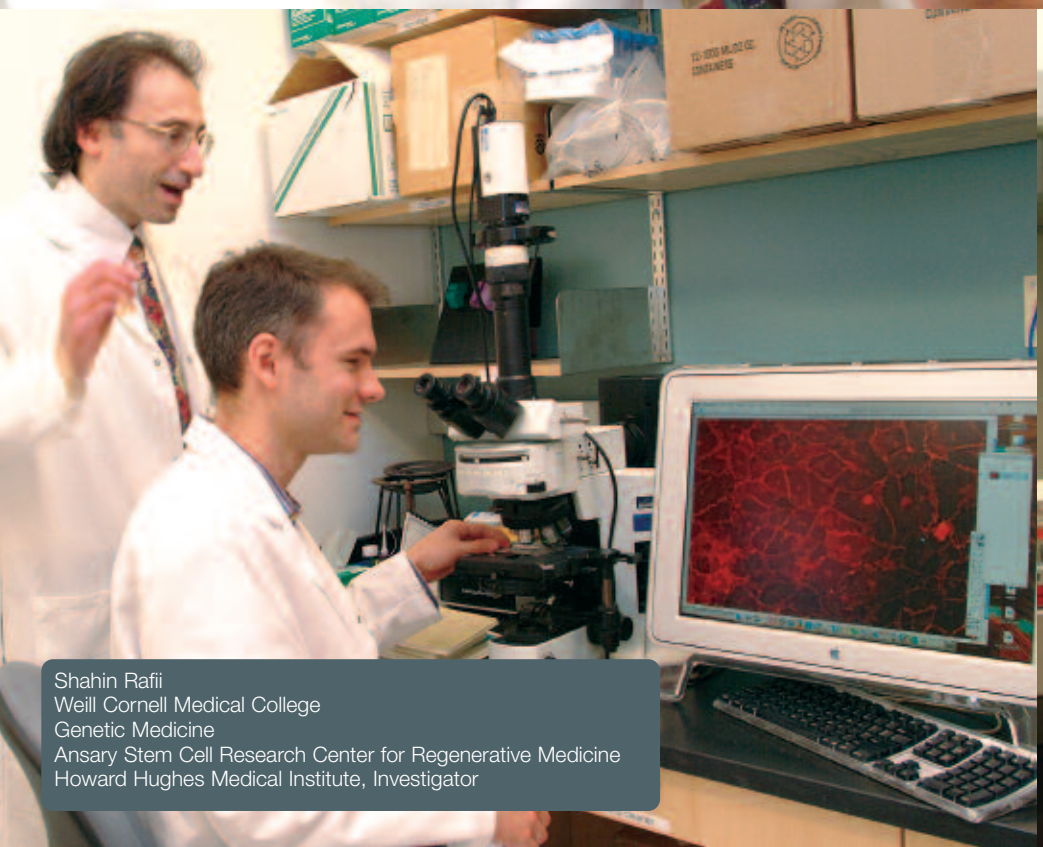
Patricia Kuharic



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STEM CELLS: THE GOOD, THE BAD, THE UGLY

Identifying the Problem

As a physician-scientist, most of my scientific approach to solving problems is derived from health-related problems, such as cancer, heart disease, stroke, and neurological disorders. We identify the patients' problems—the diseases they have—and we go back to the lab to try to solve them. I'm a hematologist-oncologist and vascular biologist, so I take care of cancer patients and patients with blood and cardiovascular disorders. The problem is obvious: 540,000 people die from cancer every year in the United States and twice as many are diagnosed with cancer. The same number of people also succumbs to cardiovascular disease. We can cure only a very small percentage of patients with cancer or heart disorders. So the problem is tremendous, and the solutions are difficult.

Twenty years ago researchers thought of finding one cure—a mechanism that we could use to target all cancers. We have found, however, that each cancer is unique: lung, colon, and breast cancers and leukemias. They are driven by specific types of mutations. Now we must focus on specific types of cancer. My lab, for example, studies leukemia. In adults only 30 percent are cured. When young people come in with leukemia, we give them prolonged and aggressive treatment, but only a small percentage of patients achieves a long-term cure. Breast cancer is the same; in advanced disease, very few people are cured. Although there is a huge body of knowledge from basic biology that we can apply to finding new treatments for these cancers, translating this knowledge to a clinical setting is a daunting task.

When I graduated from Cornell in 1982, very little was known about how cancer spreads to other organs. Oncogenes were just being discovered, and during the last 20 years most of the focus has been on the cancer cell itself—how to target it. Now the habitat also known as the "tumor microenvironment" of cancer is the major issue in cancer biology. How cancer grows depends on interaction with its surrounding environment. It is now believed that the tumor microenvironment is altered and, as such, provides a fertile ground for tumor growth. Therefore, targeting the supporting cells around tumor tissue provides a novel strategy for targeting cancer cells, with the hope of slowing their growth.

One of the most exciting topics in cancer biology relates to the identification of cancer stem cells. Researchers had thought

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that tumor tissue is composed primarily of a homogenous population of cancer cells, but it turns out that each cancer cell is unique and that there may be a cancer stem cell, which may be the primary cell driving tumor growth. If we kill 99 percent of the cancer cells, but not the cancer stem cells, we haven't solved the problem. The problem is the cancer stem cells, which can survive chemotherapy or treatment and come back, or metastasize and spread. We have a cancer problem, we have a cancer stem cell problem, and we have a cancer microenvironment problem.

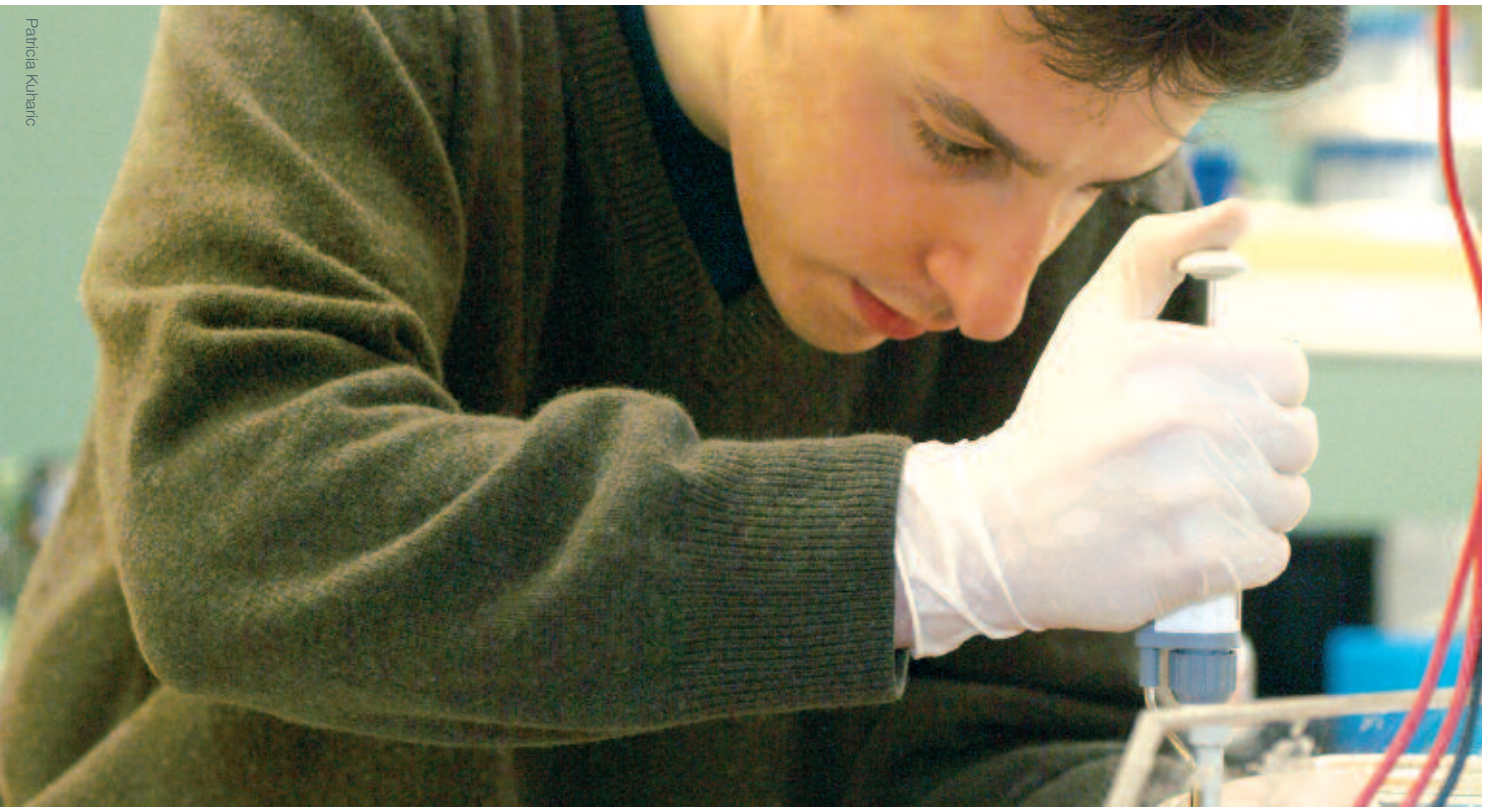
Stem cells can regenerate themselves and save lives when injected into the body to regenerate organs, or they can be wild and crazy "dysregulated" cancer cells. It's like the proverb: the good, the bad, and the ugly. The good is a normal stem cell that regenerates organs. The bad is the stem cell that expands irregularly and causes organ dysfunction. When stem cells become cancerous, such as leukemias, they're ugly. These are the issues that we are dedicated to solving.

Solving the Problem

It's amazing how the molecular biology field has advanced so much that we can take the research in molecular biology related to how to silence genes and apply it to cancer. Researchers have found the mechanism to quiet oncogenes by using advances in molecular biology. Applying this technology to cancer biology, we can identify a target cancer gene and silence it. Initially we could go on a fishing expedition and look at all the genes from the patient's cancer. These genes are "dysregulated." We identify them, block them, and see if this blocks cancer growth. This is a patient-oriented hypothesis. We now know that targeting one gene is not enough. We have to target many cancer-specific genes to cure cancer. We can take breast cancer from a patient, bring it to the lab, identify what is wrong genetically about these cancer cells, identify those genes, and target them. This is patient-oriented biology.

Physician, Researcher, Teacher, and Patient Caretaker

One advantage of Cornell's medical college, and academic institutions in general, is access to grants that enable physicians to become basic scientists. I did my training in medical school; after medical school, I did an internship and a residency in



Patricia Kuharic


Patricia Kuharic

medicine, treating patients with a wide variety of disorders. Subsequently, I specialized in hematology (blood disorders) and oncology (cancer). Then I began postdoctoral research in cancer biology and stem cell biology. This was four years of medical school, three years of internship and residency, three years of fellowship, and then postdoctoral training in research. After that, I did some work to understand basic molecular biology and cellular biology.

During these years, as I was doing Ph.D.-like training, I was seeing patients. To be a successful physician-scientist—taking care of patients and doing very good research—is tough. Gradually the research started to work out, and I was less involved with patient care. Although taking care of patients is very difficult and time-consuming, it is extremely rewarding. My lab has many clinical research fellows who see patients and are also engaged in basic research. Research fellows get training to bridge the gap between basic and clinical medicine—the so-called bench to bedside approach. Supervising clinical research fellows is a rewarding experience and keeps me close to clinical medicine. Currently I teach medical students, research fellows, and graduate students, and I see patients for about one month per year in conjunction with other physicians. Ninety percent of my work is pure basic science. It is molecular biology research attempting to decipher the complex mysteries of stem and cancer cells.

Now the habitat also known as the "tumor microenvironment" of cancer is the major issue in cancer biology. How cancer grows depends on interaction with its surrounding environment.

The Evolution of Ideas

Many researchers might say that Friday afternoon, when they're relaxing in some way, ideas begin to flow. In my case, many ideas come when I'm taking care of patients. Every patient is unique. When they present us with a type of cancer, we treat them. When the treatment no longer works or when patients present us with specific clinical dilemmas, this somehow sparks an idea. We link point A to point B, because the patient told us how to get from point A to point B. In many situations, the patients and their clinical courses tell us the secrets of the disease.

Talking to colleagues and teaching are important to the flow of ideas. When we talk to colleagues and brainstorm, we may connect a few lines—the A and B of a concept—and a new concept is born. This is why an academic center is where most ideas evolve. It's fascinating how a conversation between a postdoc and a principal investigator suddenly sparks a new hypothesis leading to a scientific breakthrough. This may ultimately result in a new treatment. Sometimes the naive question that a student asks makes the connection. I've given many talks where students ask the most incredibly unsophisticated, simple questions, and I think, "Aha, that's the answer!"

A lot of serendipity happens—serendipity, but with watchful eyes. As Louis Pasteur said, the power of observation is the key. There are many situations in which something happens, but if our minds are not set for that idea, we may miss the concept.

IT TURNS OUT THAT EACH CANCER CELL IS UNIQUE AND THAT THERE MAY BE A CANCER STEM CELL, WHICH MAY BE THE PRIMARY CELL DRIVING TUMOR GROWTH. IF WE KILL 99 PERCENT OF THE CANCER CELLS, BUT NOT THE CANCER STEM CELLS, WE HAVEN'T SOLVED THE PROBLEM.

Cancer Biology versus Normal Physiology

Our lab concentrates on cancer biology and normal physiology. They are 100 percent connected. A cancer and a fetus both grow in and invade the body. In the mother's uterus, a fetus grows in and invades the body of the mother in a highly controlled and regulated manner. A cancer grows like a fetus, but a cancer does not grow normally. It becomes a tumor, grows, and invades the body without following a specific set of rules or road maps. We think of a cancer patient as having a fetus that grows irregularly and kills because it doesn't grow normally. If we tame a cancer cell to behave like a fetal cell, so that it grows normally, we can perhaps tame a cancer. So we study, compare, and contrast the molecular and cellular pathways that regulate the growth of both fetus and cancer.

Stem Cell Research Realizing Its Potential

One of the potentials of stem cells is that they can self-renew and generate identical progeny. We are all here because our stem cells reproduce in an organized manner. At this time, we have no clue how stem cells reproduce. If we can identify the complex pathways involved in stem cell self-renewal, then we will have solved one of the most fundamental problems of biology. To discover the mechanism by which stem cells reproduce themselves will be as significant as Einstein's discovery of relativity.

Influential Events Shape a Career

I have been privileged to be mentored by two of the most accomplished physician-scientists: Dr. Judah Folkman and Dr.


Patricia Kuharic

Ralph Nachman, who are internationally known leaders in vascular and cancer biology. Folkman and Nachman encouraged me to pursue a career in medical research and showed me the essential elements of conducting experiments: formulating simple hypotheses, designing focused simple experiments, and spending a great deal of time analyzing data.

Our discovery that stem cells within the bone marrow could contribute to the formation of blood vessels was a highlight. Many of our ideas were challenged, but our findings were validated in the clinical arena. This suggested to us that indeed our findings might have major clinical relevance.

The first leukemia cancer patient that I treated was a very significant highlight of my career. This cancer patient was amazing. Despite treatment with very potent chemotherapeutic agents, her leukemia persisted and relapsed like a wildfire. She was told that she had three months to live. This was in 1995. At the same time a drug from China was just making its way to the clinical trials at the National Cancer Institute. The drug was a retinoic acid analogue. This drug exerts its anti-leukemic effect by differentiating leukemic cells into mature cells. It had been shown to be effective in blocking the growth of the type of leukemia from which my patient was suffering. Encouraged by published data, I contacted the National Cancer Institute and got the drug for her. At that time, she was so sick that her family was told that she would not survive beyond one week. She was bleeding from every organ, and she couldn't swallow. She was kept alive through artificial ventilation. This drug came as a pill. I called the National Cancer Institute and asked how we were going to give this to her. They told me to go to our cafeteria and get olive oil, a fat solvent, dissolve the drug in the olive oil, and administer it orally to the patient. To this end, we put a tube in her stomach. We mixed the drug with olive oil and injected it into her stomach. Within 48 hours, the leukemia cells started to differentiate. This patient had been treated with thousands of dollars worth of advanced technology, but olive oil and a newly discovered drug saved her life. She went into remission and is still leukemia-free 15 years later. She is happy, married twice, and she's doing very well!

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Using the drug, retinoic acid analogue, we tamed the rapid growth of the cancer cells and allowed the patient's own cells to grow back and her own immune system to take over again. This shows how a simple breakthrough can save lives. In 1995, we didn't know we could give this drug to leukemia patients. It was very experimental. And nobody would have believed that this patient would respond, because she had a unique type of leukemia. Now the drug has been used extensively. Not all leukemias can respond to it; however, if the drug had not been available, many of my patients would have died of the disease. This is a big highlight because I realize I made a difference. This shows that as a physician-scientist, I can make translational connections—bench to bedside.

But if our minds are not set for that idea, we may miss the concept.

Preventing the Progression of Leukemic Stem Cells

My lab has discovered other factors that slow down the progression of leukemias by depriving them of circulating growth factors produced by the blood vessels. One of these discoveries will soon be tested in human subjects at Cornell. We believe that some of the factors we discovered are expressed by the leukemia stem cells. Our drug targets the leukemia stem cells, deprives the leukemia of the potential of expanding within the bone marrow, and destroys the habitat. We don't cure leukemia, but we prevent its progression.


Patricia Kuharic

Let Discovery Meet Humanity

Most of the experiments we do now are done with mouse embryonic stem cells. Research might progress more quickly if we could work with cells or tissue that is derived from human embryonic stem cells. The more we can tap the potential of human embryonic stem cells for tissue regeneration, the faster we will be able to gain the knowledge we need to regenerate heart and brain, and other applications for restoring organ regeneration. For example, if we could use human embryonic stem cells to regenerate heart muscle, we could help the 560,000 people who die from heart attacks because we cannot restore function.

Millions of people have Alzheimer's disease. We could make a huge impact, saving many lives from this disease, as well as from Parkinson's disease, diabetes, and cancer. Schizophrenia is another example: a synaptic dysfunction takes place, and as a result a person displays schizophrenic behavior. Let's say that, in schizophrenia, a set of neurons is misfiring. We have to

Patricia Kuharic

(l. to r.) Seated: Lauren Young, Koji Shido, Shahin Rafii. Standing: Adam Intrator, Isabelle Petet, Fan Zhang, Pui Ki Siu-Lau, Carlos Ramos, Sergey Shmelkov, Jia Ruan, George Lam, Hans-Georg Kopp, Krstian Jansen, Andrea Hooper, Scott Avecilla, Loic Vincent, Matthias Karajannis.

Our discovery that stem cells within the bone marrow could contribute to the formation of blood vessels was a highlight.

replace them. We take the patient's own stem cells, differentiate them to that particular normal neuron, and put it back in the brain—rewire the dysregulated brain. Tremendous! I predict that there is no type of disorder that we can't target with stem cells. To produce a safe technology that will take advantage of the regenerative potential of human embryonic stem cells for regenerating human organs and targeting tumors will be an incredible feat for human diseases!

The Public's Understanding

As people talk about ethical issues of research, we must first eliminate misinformation. For example, we need to help educate the public about the basics of stem cell research and its benefit—how differentiated cells can save lives. Here's an example. Whenever I take a taxi, the driver wants to know what I do. When I explain my research, many are anti–stem cell research, until I explain the benefits of conducting stem cell research. Most taxi drivers completely change their opinion. By the time I get to my destination, most become friendlier and won't take money for the ride. The key is in explaining how the cells are still living to make a heart muscle pump—educating people about the process. I also remind them of the pictures of the war, with injured or dying soldiers. Stem cells can be used to help soldiers who lose their limbs to regenerate them or can regenerate the eyesight of soldiers whose eyes have been hit by shrapnel.

On one occasion, I brought a visitor into the lab and showed the person some of the human embryonic stem cells and how we could differentiate them into viable beating heart muscle. This person underwent a change in belief about stem cell research. I said, "If I take you to the intensive care unit, and you see young people dying, you will understand." But our inability to use newly derived human embryonic stem cells has really slowed down the progress of this research. It's difficult to expand.

THE MORE WE CAN TAP THE POTENTIAL OF HUMAN EMBRYONIC STEM CELLS FOR TISSUE REGENERATION, THE FASTER WE WILL BE ABLE TO GAIN THE KNOWLEDGE TO REGENERATE HEART AND BRAIN, AND OTHER APPLICATIONS FOR RESTORING ORGAN REGENERATION.

Let's Trade Cards

As an oncologist, I see patients from age 18 on who may die from cancer. However, many colon cancers are cured; other cancers are also cured. Lance Armstrong is a perfect example. People don't realize that this has come about because of medical research and that medical research has made a huge impact on society. Take polio for example. If I ask an average kid right now: What do you know about polio? Who discovered the polio vaccine? They don't know. If I ask what are the batting averages of the Mets baseball players, they know all the batting averages. But they don't know that,

before the discovery of the polio vaccine, thousands of kids were paralyzed. Instead of baseball cards, we should have science and philosophy cards or cards of people who have won Nobel Prizes and contributed to humanity throughout the years. Make science part of this popular cult.

INSTEAD OF BASEBALL CARDS, WE SHOULD HAVE SCIENCE AND PHILOSOPHY CARDS OR CARDS OF PEOPLE WHO HAVE WON NOBEL PRIZES AND CONTRIBUTED TO HUMANITY THROUGHOUT THE YEARS.

A Visionary Funding Strategy Needed

I feel that almost two-thirds of my life—perhaps nearly two-thirds of any productive scientist's time—is used on competing for research funding. Calculate this: there are 1,000 scientists, and two-thirds of their time is used to write grant proposals. Only 10 to 20 percent of the proposals get funded! This amounts to millions of potentially productive hours that could be used to find a cure for cancer or heart disease. If a strategy to fund more research—to fund a greater percentage of grant proposals—could be achieved, this could benefit millions of people.

Patricia Kuharic

Enduring the Passage of Time

To pioneer a field is exciting, and at the same time, it's daunting. Why? Because we always have to make sure that whatever we have discovered is true, and it's going to be applicable to the treatment of human diseases without causing any harm. When we are pioneers of new treatment, we want to make sure that the ideas we're going to disseminate are valid. No matter how careful we are, we worry that perhaps we made a mistake, or we were inaccurate, or we were not careful enough. We worry that some of the ideas we put forth might make too much of the interpretation of the results. Even when we're careful, we can exaggerate the results. What is daunting for me, or the most important thing as a pioneer, is to make sure that a new idea that I generate will endure the passage of time, be validated and corroborated by other scientists. Enduring the passage of time is key.

More Time for Research

As a Howard Hughes Medical Institute (HHMI) Investigator, I can spend less time writing grant proposals. HHMI provides money and intellectual support to do some of the critical research that is tough with other sources of funding. So this is a huge advantage. When I was at the HHMI initiation meeting in Washington, I was amazed at how progressive the institute is. The institute's main goal is to identify new strategies to cure human disease and promote human well-being.

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I'm very happy to be a part of this visionary institute, because it allows us to tap into high risk–high yield avenues of research. When I applied for the HHMI program, my proposal was based on conducting stem cell research. The HHMI provides support for, at minimum, five to seven years, so that we can push our research forward. This makes life a little easier. We are funded based on our creativity and conduct of new areas of research that will benefit humanity. I hope HHMI becomes a model for other altruistic organizations to support research that could not be funded by other means.

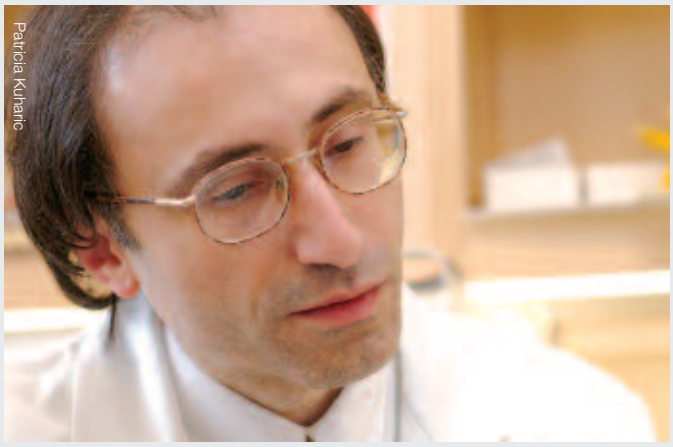
Translation Is the Key

Given that we have one of the best medical schools and academic hospitals with which to partner, my goal is to exploit the potential for human stem cells and to use the Ansary endowment to translate the stem cell research to the clinical area. In five years, I want to see the cell regenerated in my lab injected into a patient as a cure for damaged heart tissue or to target tumor tissue. The mission of the Ansary Stem Cell Center is to bridge the gap between bench and bedside.

The center allows for enormous collaboration among scientists. We can bring all the different disciplines together: surgeons, bioengineers, bioethics professionals, people who work in clinics, people who work in labs and the mouse-human clinics. To translate the research to clinics is a very difficult task, because we want to make sure we do no harm. The Ansary Center makes it possible to recruit the best clinical physician-scientists to translate the knowledge to clinical settings.

I'm usually explaining what I do in this way: I say, "If you have a heart disease or if you have coronary artery disease because you have high cholesterol, we can take your own cells and generate new heart tissue for you using stem cell technology. We put your own cells back into your heart."

The best motivator of passion for the physician-scientist is to see patients, especially young people, die from cancer. Just looking at the patients and knowing the plight of their families is very disturbing.



Patricia Kuharic

Heart and Cancer Patients on the Street

I answer questions about our research all the time, because our work is so broad. I'm usually explaining what I do in this way: I say, "If you have a heart disease or if you have coronary artery disease because you have high cholesterol, we can take your own cells and generate new heart tissue for you using stem cell technology. We put your own cells back into your heart. If you have a family member with cancer, whatever cancer the patient has, that cancer has a stem cell. We want to target that stem cell."

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Patricia Kuharic

To talk with senators about accelerating funding for cancer stem cell research is an advantage to the patient, because that patient is going to benefit faster. Let's say the person was a breast cancer patient—had cancer a few years ago, but it came back, or in five or six years it will come back. By then we may have the technology to help that patient. A good example is HIV. The government, National Institute of Health (NIH), and private foundations put substantial money in it, and we found a solution. We discovered how to slow the proliferation of the HIV virus. HIV patients live much longer now. Look at Magic Johnson. He's doing TV commentary 22 years later. Nobody talks about this, but it's a major breakthrough in medical research. We can do the same for cancer with more funding for the research. The public must understand that, if they want to prevent cancer and heart diseases, they must talk with their congresspeople and senators about an increase in funding for the research—at least 20 times more.

WHENEVER I TAKE A TAXI, THE DRIVER WANTS TO KNOW WHAT I DO.... MANY ARE ANTI–STEM CELL RESEARCH, UNTIL I EXPLAIN BENEFITS OF CONDUCTING STEM CELL RESEARCH. MOST TAXI DRIVERS COMPLETELY CHANGE THEIR OPINION. BY THE TIME I GET TO MY DESTINATION, MOST BECOME FRIENDLIER AND WON'T TAKE MONEY FOR THE RIDE.

More About Rafii

Rafii was chosen by the Howard Hughes Medical Institute as one of 43 new HHMI investigators, the most promising and gifted biomedical scientists. Rafii is the first Weill Cornell Medical College physician-scientist to be named for this honor.

Rafii pioneered the concept that tumors and regenerating or damaged organs rely on circulating stem cells to build new blood vessels and to regenerate. He has identified the key molecular pathways involved in stem cell recruitment, facilitating the cells' differentiation into vascularized and blood tissues.

For more information:

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