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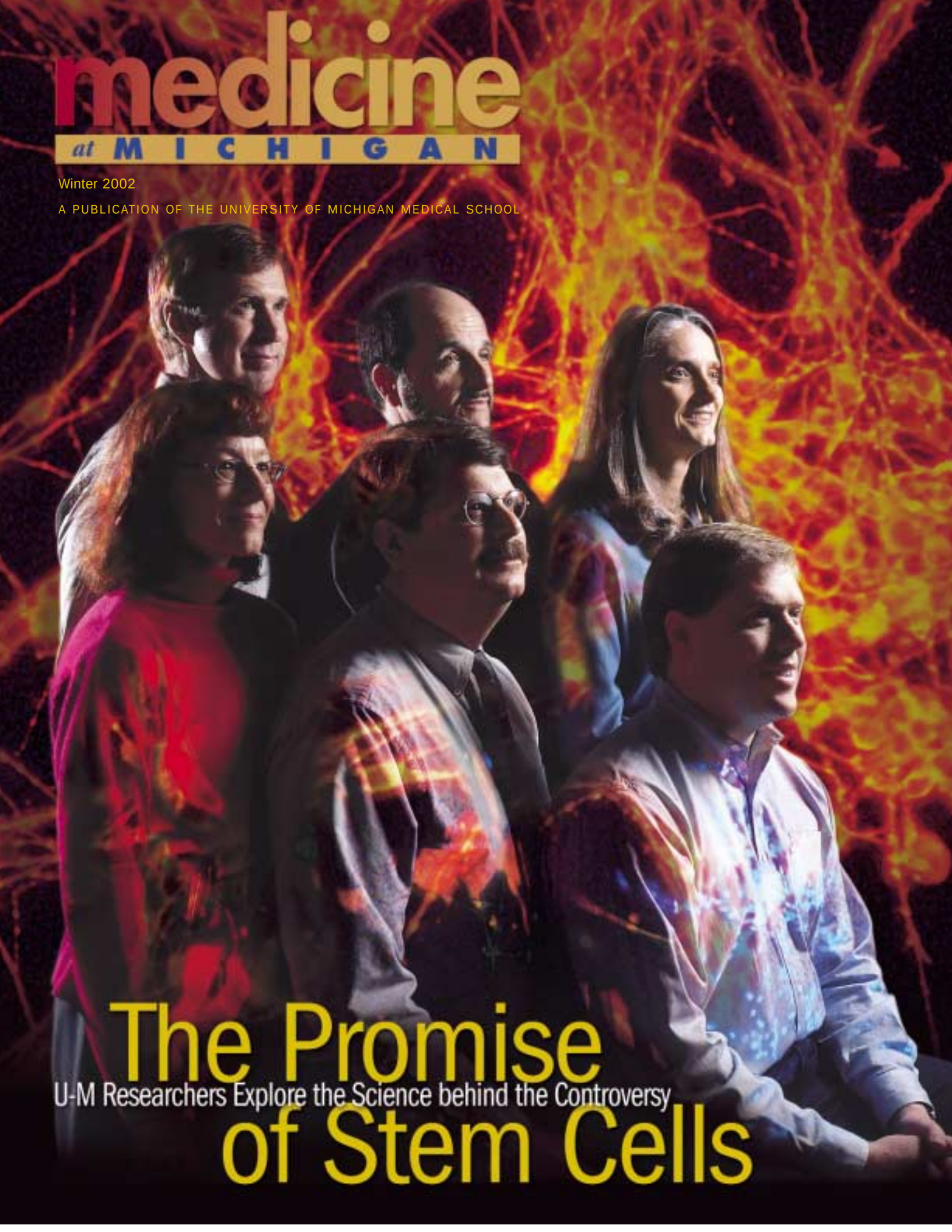
Winter 2002

A PUBLICATION OF THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL



The Promise of Stem Cells

U-M Researchers Explore the Science behind the Controversy

1 blastocyst = infinite

RECIPE FOR A HUMAN

- 35,000 GENES
- 100 TRILLION CELLS
- 5 QUARTS OF BLOOD
- 115 LBS OF MUSCLE & BONE
- 2 SQUARE YARDS OF SKIN
- ONE HEART WITH VEINS AND ARTERIES
- 5 SENSORY SYSTEMS
- ONE 3 LB BRAIN WITH 600 MILES OF NEURONS

35,000

100 000 000 000

5.0

BIND TOGETHER WITH CARTILAGE & CONNECTIVE TISSUE

SEASON WITH ENVIRONMENT, UPBRINGING & THE RANDOM CHANCE OF LIFE.

Amidst intense public hope, media hype and ethical debate, U-M scientists study the incredible potential of stem cells — and voice caution about the work ahead

The Stem Cell Debate

by Sally Pobojewski

The potential for all human complexity is locked inside 30 to 35 cells nestled within a five-day-old embryo called a blastocyst — the product of a union between one egg and one sperm. All 100 trillion cells in the human body are descended from these original cells. When removed from an embryo and grown in a culture dish under the right conditions, they continue to divide indefinitely. Scientists call them embryonic stem cells.

Stem cells are the black box of biomedical research. Scientists know what goes in and what comes out, but what happens in between — how we develop from a blastocyst small enough to fit on the point of a pin to a living, breathing, thinking human being — remains one of life's most profound mysteries.

The mystery becomes even more intriguing when you consider that other stem cells, which scientists call somatic or adult stem cells, remain in many types of tissue throughout life. While embryonic stem cells are generalists, adult stem cells are specialists. They can make copies of themselves — a process called self-renewal — in addition to producing specialized cells, such as heart, skin or muscle cells. But unlike embryonic stem cells, adult stem cells usually have limits on what types of cells they can become.

Scientists at the University of Michigan Medical School are searching for answers to the many questions about adult and embryonic stem cells. These researchers come from different disciplines, have different goals and study different types of stem cells, but all have devoted their careers to the detailed, painstaking process of unlocking the stem cells' secrets one by one. Research underway in U-M laboratories today could help answer fundamental questions about the development of life itself and lead to major advances in the future of medicine.

"Stem cells are the key to everything," says Michael Clarke, M.D., associate professor of internal medicine and one of the Medical School's stem cell experts. "Their potential is huge, but an incredible amount of work remains to be done before we can begin to tap that potential."

EMBRYONIC STEM CELLS AND DEVELOPMENT

In the beginning is the stem cell...

Scientists say that embryonic stem cells are pluripotent, meaning they have the remarkable ability to become any of the more than 200 distinct cell types in the human body. But their unlimited potential doesn't last for long.

Fourteen to 16 days after fertilization, stem cells in the human embryo begin to separate into three layers called the endoderm, mesoderm and ectoderm. Each layer must develop in a precise location within the embryo. Scientists call this complex process gastrulation and it is fundamental to all later development. If gastrulation doesn't proceed normally, the embryo will die.

During the next few months of human development, a process of increasing specialization takes place. "Every step in the formation of each organ requires a precise orchestration of a number of processes to form the tissue, grow the tissue and differentiate the many different kinds of cells within the tissue," says Deborah Gumucio, Ph.D., associate professor of cell and developmental biology and co-director of the U-M Center for Organogenesis.

"What tells stem cells to differentiate into the various organs? How do the organs, blood vessels and connective tissues become situated in the correct places? Once organs form, how do they know when to stop growing?" asks Gumucio. "We are beginning to learn tiny bits of information about individual signaling pathways, and some of these discoveries could translate into major medical advances. However, we are decades away from a complete understanding of these processes."

STEM CELLS IN THE ECTODERM OR OUTER LAYER BECOME

Skin • Neurons in Brain & Spinal Cord • Peripheral Nervous System
Pituitary & Part of Adrenal Glands • Eyes & Ears

STEM CELLS IN THE MESODERM OR MIDDLE LAYER BECOME

Bone Marrow & Blood • Cartilage & Fat • Cardiac, Skeletal & Smooth Muscle
Heart & Blood Vessels • Connective Tissue • Kidneys • Lymphatic System
Reproductive Organs

STEM CELLS IN THE ENDODERM OR INNER LAYER BECOME

Thyroid Gland • Lungs & Respiratory System • Bladder & Urethra
Liver & Pancreas • Stomach & Intestinal Lining

Nothing in the embryo develops in isolation. Stem cells need a supportive matrix or scaffold to grow into a heart. The primitive heart sends molecular signals required for liver development. Organs can't form without help from other stem cells, especially endothelial cells that form the walls of blood vessels and are active signaling and induction centers.

During early development, the embryo is a biochemical version of the Internet. Interactive messages fly back and forth, signaling genes to turn on or turn off and telling cells when to grow, when to change and when to die. The process is so complicated that it involves half of the 35,000 genes in the human genome.

ADULT STEM CELLS AND TISSUE RENEWAL

Mending broken hearts and shattered spines

Adult stem cells appear to have fewer options than their embryonic counterparts. Instead of being pluripotent, scientists say they are multipotent — meaning their potential for development is limited to a few specific types of cells.

Adult stem cell development is a gradual transition, which begins with production of intermediate cells called precursor or progenitor cells. Precursor cells then morph into a series of increasingly more specialized cells. Scientists used to believe a precursor cell could become just one specific kind of cell. Now they're not so sure.

True adult stem cells are rare and separating them from the more-common precursor cells is not easy. In 1988, Irving Weissman, M.D., and his Stanford University research team became the first scientists to isolate adult stem cells. They were hematopoietic or blood-forming stem cells found in mouse bone marrow at a ratio of one stem cell for every 10,000 bone marrow cells.

U-M stem cell researcher Sean Morrison, Ph.D., who was a graduate student in Weissman's laboratory during the mid-1990s, refined the techniques scientists use to find mouse hematopoietic stem cells in different types of tissue and at different periods of development. Morrison is now an assistant professor of internal medicine and of cell and developmental biology in the U-M Medical School, and a Howard Hughes Medical Institute assistant investigator.

MICHAEL F. CLARKE M.D.

QUESTION HE'D MOST LIKE TO ANSWER:

» WHAT DRIVES A CANCER STEM CELL AND HOW DO WE STOP IT?

If Michael Clarke is right, it may not be necessary to destroy every malignant cell to cure cancer. Killing just five percent of cells in the tumor may be sufficient. The trick, of course, is finding the right five percent.

Working with U-M scientist Sean Morrison and Max Wicha, M.D., director of the U-M Comprehensive Cancer Center and a professor of internal medicine in the Medical School, Clarke recently discovered that, just like every organ in the human body, the growth of cancerous tumors is regulated by stem cells. "One population of stem cells in cancer is responsible for its uncontrolled growth," he says. "Current cancer therapies are only minimally effective, because the stem cells just keep making more tumor."

Photo: Marcia Ledford

Muhammad Al-Hajj

Muhammad Al-Hajj, Ph.D., a post-doctoral research fellow in Clarke's laboratory, spent the last two years sifting through hundreds of protein markers on the surface of cells from human breast tumors. "When we found cells with a marker that was common to tumors from most patients," Al-Hajj says, "we isolated those cells and injected them into mice. Up to five percent of cells from human tumors also produced tumors in mice. These cells are capable of unlimited proliferation; the others divide up to a point and then die."

Clarke and Al-Hajj now are completing DNA analysis on breast tumor cells to identify which genes are active in cancer stem cells, but inactive in other cells from the same tumor.

The University of Michigan has filed a patent on Clarke's discovery of stem cells in cancer. Clarke, Morrison and Wicha have established a new company called Cancer Stem Cell Genomics (CSCG) to develop and test new therapies to destroy or disable cancer stem cells.

In related work, Clarke identified recently a key gene involved in self-renewal of hematopoietic stem cells. Morrison is analyzing the neural crest stem cells he studies to see if the same gene is responsible for their ability to make copies of themselves. Since uncontrolled growth is the essence of cancer, Clarke hopes his work with hematopoietic stem cells may help identify genes and proteins that would be good targets for future cancer therapies.

"I'm optimistic, because before this we couldn't see the cancer cells we were trying to kill," Clarke says. "Now we can at least identify the cells and see the target. It gives us a much better shot at a cure than we've ever had before." ■

Photo: D.C. Goings

SEAN J. MORRISON PH.D.

QUESTION HE'D MOST LIKE TO ANSWER:

» HOW IS SELF-RENEWAL REGULATED IN STEM CELLS?

Most scientists find it difficult enough to study just one type of stem cell. Sean Morrison works with two. He studies neural crest stem cells — which develop into the peripheral nervous system, connective tissue and other types of cells — as well as hematopoietic stem cells, which form the blood and immune systems.

"The interdisciplinary focus in my lab is fundamentally important to what we're trying to accomplish," says Morrison. "We want to test our hypotheses by integrating data from two stem cell systems. We use hematopoietic and neural crest stem cells, because scientists know the most about them and have developed powerful tools to study them."

By examining similarities and differences between stem cells, Morrison hopes to answer some of the most basic questions in stem cell biology. Questions like: how do stem cells reproduce themselves in a process called self-renewal? Do all stem cells have a master regulatory gene or are there many different genes involved? Can adult stem cells be reprogrammed or induced to change from one type of cell to another?

Unlike his U-M colleagues, Morrison isn't interested in working with human embryonic stem cells, although he agrees they have great potential for use in medicine. "The scientific questions that interest me can best be answered with somatic or adult stem cells from mice and rats," he says.

In recent research, Morrison discovered that undifferentiated neural crest stem cells can be found in sciatic nerves of rats for several days after birth — long after the formation of the nervous system is complete. The discovery that stem cells remain in animals much longer than scientists previously believed supports the intriguing possibility that adult stem cells could be harvested and reprogrammed for use in another organ system.

While he recognizes the importance of clinical applications for stem cell research, Morrison is still most intrigued by basic science. "People who have the biggest impact clinically are people who learn fundamentally important new things at a basic scientific level," Morrison says. "The most exciting thing for me is to discover things no one has ever seen before and link them together to understand how nature works. A scientist is like a storyteller. It's exciting to discover a good story and be able to tell people about it." ■

Photo: D.C. Goings

Photo: D.C. Goings

(above): Mark Kiel, from Grand Rapids, has spent a year working as a research assistant in Sean Morrison's laboratory to see if he wants to devote his career to biomedical research. In this photo, he's using a technology called Fluorescent Activated Cell Sorting, or FACS, to separate stem cells quickly and efficiently from millions of other cells in a cell sample.

When Kiel sorts cell samples with FACS, he relies on years of work by other scientists who have already identified the unique pattern of receptor proteins on the stem cell's surface. Since each type of cell has its own combination of receptor proteins, Kiel can program the computer to sort for the surface receptor patterns of stem cells he wants to study. Before he begins the FACS procedure, Kiel treats the cell sample with a special technique that attaches a fluorescent molecule or "tag" to the specific surface receptors he's looking for.

Like a half-million-dollar vacuum cleaner, FACS then sucks the cells in Kiel's sample one at a time through a narrow high-pressure nozzle and a laser beam. When the laser strikes a cell with a fluorescent tag, it becomes negatively charged. Cells without the fluorescent tag are positively charged. An electric field inside the device pulls all the negatively charged cells into a separate sample.

Kiel studies the role of hematopoietic stem cells during early embryo development in mice. He has applied to the M.D./Ph.D. program in the U-M Medical School and hopes to begin work on his dual degrees in the fall.

Since he joined the U-M faculty in 1999, Morrison has found stem cells in the peripheral nervous system of rats. Other scientists have identified adult stem cells in several areas of the brain and spinal cord, skeletal muscle, bone marrow, liver and skin of rats, mice and humans.

Scientists have known for 50 years that hematopoietic stem cells found in bone marrow, liver and the spleen can reconstitute every cell in the blood and immune systems. Cancer patients often receive transplants of these cells following intense radiation or chemotherapy. Injected into the bloodstream, they somehow home directly to bone marrow and begin differentiating, replacing the red and white blood cells killed during treatment. Even though hematopoietic stem cells grow rapidly inside the body, scientists have yet to find a way to grow them outside the body in cultures where they can be studied.

WHILE EMBRYONIC STEM CELLS ARE GENERALISTS, ADULT STEM CELLS ARE SPECIALISTS. THEY CAN MAKE COPIES OF THEMSELVES — A PROCESS CALLED SELF-RENEWAL — IN ADDITION TO PRODUCING SPECIALIZED CELLS, SUCH AS HEART, SKIN OR MUSCLE CELLS. BUT UNLIKE EMBRYONIC STEM CELLS, ADULT STEM CELLS USUALLY HAVE LIMITS ON WHAT TYPES OF CELLS THEY CAN BECOME.

Identified more recently than blood-forming stem cells, neural stem cells currently are under intense study, because some scientists believe they could replace dead or damaged neurons after spinal cord injuries or in Parkinson's and Alzheimer's disease. Scientists have shown that neural stem cells produce three different kinds of specialized cells in the central nervous systems of mice, rats and humans. Neural crest stem cells, which develop into the peripheral nervous system, also have been isolated in rats.

The discovery that stem cells exist in many types of tissue has led to new research on stem cell plasticity — the ability of adult stem cells or precursor cells to shift gears, change their differentiation pathway and become a completely different type of cell. Under certain conditions, scientists can force a developmental shift by treating cultured stem cells with specific proteins called growth factors or by inserting genes into their DNA.

"Growth factors can trigger a series of changes inside the cell that cause differentiation," says Michael Long, Ph.D., professor of pediatrics and another of the Medical School's stem cell scientists. "But ultimately,

genetics is everything. If you don't have the right genes turned on or turned off, all the external factors in the world won't make any difference."

Photo: Bill Wood

Deborah Gumucio

Scientists are interested in plasticity's potential for regenerative medicine — growing new organs or tissues from stem cells to replace those damaged by accident or disease. "When I was in school, I learned that bone marrow, gut, blood and skin were the only tissues capable of regeneration," Long says. "But recent experiments in mice show that bone marrow stem cells can regenerate the liver. Liver cells can develop into pancreas cells. Muscle cells can give rise to many types of tissue. Someday, we may be able to transplant bone marrow cells and treat diseases in ways we never thought possible before."

Many obstacles remain before scientists can tap the full potential of adult stem cells, however. For one thing, most of the successful plasticity studies so far have involved stem cells from mice and rats. Scientists are all too familiar with the fact that just because something works in mice doesn't mean it will work in people.

FOLLOWING THE BUSH DECISION, SCIENTISTS WERE FLOODED WITH CALLS FROM REPORTERS WANTING TO KNOW WHEN THE PUBLIC COULD EXPECT CURES FOR DIABETES, PARKINSON'S DISEASE OR CANCER. U-M RESEARCHERS STRESS THAT WE ARE A LONG WAY FROM KNOWING WHETHER STEM CELL RESEARCH WILL LEAD TO CURES OR EVEN MORE EFFECTIVE TREATMENTS FOR THESE AND OTHER DISEASES.

"There is limited evidence that adult stem cells may have broader potential than previously thought," Morrison cautions, "but much of that evidence is still controversial and inconclusive."

CELL DEATH AND STEM CELLS

Live and let die

Even in the earliest stages of an embryo's development, death is part of life. Some cells must die to make it possible for organs to grow into the proper size and shape. Scientists are intrigued by the role stem cells play in programmed cell death — a process they call apoptosis — because the ability of stem cells to regulate the balance between cell proliferation and cell death is directly relevant to cancer.

"Tissues like skin, blood and intestine have stem cells that proliferate constantly," explains Deborah Gumucio. "For example, the entire lining of the gut is renewed every three to four days. A process of programmed cell death must accompany this proliferation to prevent the accumulation of too many cells. Cancer in these tissues is, in many cases, simply a mismanagement of this balance — too much proliferation, too little cell death, or both."

U-M stem cell scientist Michael Clarke has been intrigued by the relationship between stem cells and cancer since — during his medical residency at the Indiana University Medical School — he had to watch helplessly as one of his patients, the girlfriend of basketball legend Larry Bird, died from leukemia. "I realized then that if we understood stem cells, we'd have a better chance at a cure," Clarke says.

Now he studies self-renewal of adult hematopoietic stem cells and recently discovered an important gene involved in the process. "Self-renewal is a tightly regulated process under strict genetic control," Clarke explains. "Only an absolute or fixed number of hematopoietic stem cells are allowed to exist in bone marrow. Otherwise every stem cell would be like a cancer."

Michael D. Long, Ph.D.

QUESTION HE'D MOST LIKE TO ANSWER:

» HOW DO YOU MAKE A FUNCTIONAL ORGAN FROM STEM CELLS?

When it's time to make bone, Michael Long knows that stem cells need intimate contact with their own kind. In a study published in the September 2000 issue of *Nature Biotechnology*, he reported that osteogenic or bone-producing stem cells from human bone marrow merge into

Photo: Martin Vloet

Jennifer Fuller

three-dimensional spheres to produce bits of crystallized bone. Long is the first scientist to grow small amounts of human bone in culture from an isolated cell population containing osteogenic stem cells.

"Engineering the growth of human bone is a complex process," says Long. "It requires a precise combination of regulatory signals, growth factors, supporting matrix, cell architecture and density. Everything has to occur in a specific order and timing is critical."

Most of Long's research focuses on understanding the cellular and molecular signals involved in producing bone and its connective tissue from osteogenic and other types of stem cells in human bone marrow. Next year he hopes to begin animal testing of a new stem cell therapy for osteoporosis — the progressive, aging-related bone loss that leads to fracture, disability or death for 75 million people worldwide.

Long wants to transfer his research on how stem cells build bone to the private sector. He has started an Ann Arbor-based biotechnology company called Osteomics. The company finds new therapeutic targets for bone diseases and works with bio-pharmaceutical firms searching for new and more effective treatments for osteoporosis and other bone diseases.

"Current therapies can stop or delay bone loss, but they can't stimulate new bone growth," he says. "We focus on therapies that stimulate bone formation. If we could transplant osteogenic stem cells from bone marrow into areas with damaged bone or around a hip implant, it might be possible to induce growth of new bone cells."

One big problem is finding the right cells to transplant. Four different varieties of stem cells have osteogenic capacity, according to Long. Some become bone and cartilage; some are destined to be blood cells; some develop into connective tissues. Much more research is needed to determine how these various types of stem cells are related and what stage of development would transplant best.

What really intrigues Long these days is a new phenomenon, discovered within the last 18 months, called stem cell plasticity. What if you could harvest stem cells from human bone marrow, which predominantly grow up to become blood cells, and manipulate them to become cardiac, liver or neural cells instead? Recent evidence indicates it's possible, but the clinical significance remains unclear.

Jennifer Fuller, a graduate student in the Long laboratory, and Theresa Gratsch, a research investigator in Sue O'Shea's laboratory, recently found one way to make stem cell plasticity work in cultures of bone marrow cells from adult mice.

"We found that exposing cells to powerful embryonic growth factors called *noggin* and *chordin* caused them to stop differentiating into bone cells called osteoblasts and become neural cells instead," Fuller says. "We used to think that only embryonic stem cells had the potential to differentiate into neurons, but now we know that adult stem cells also have this capacity." ■

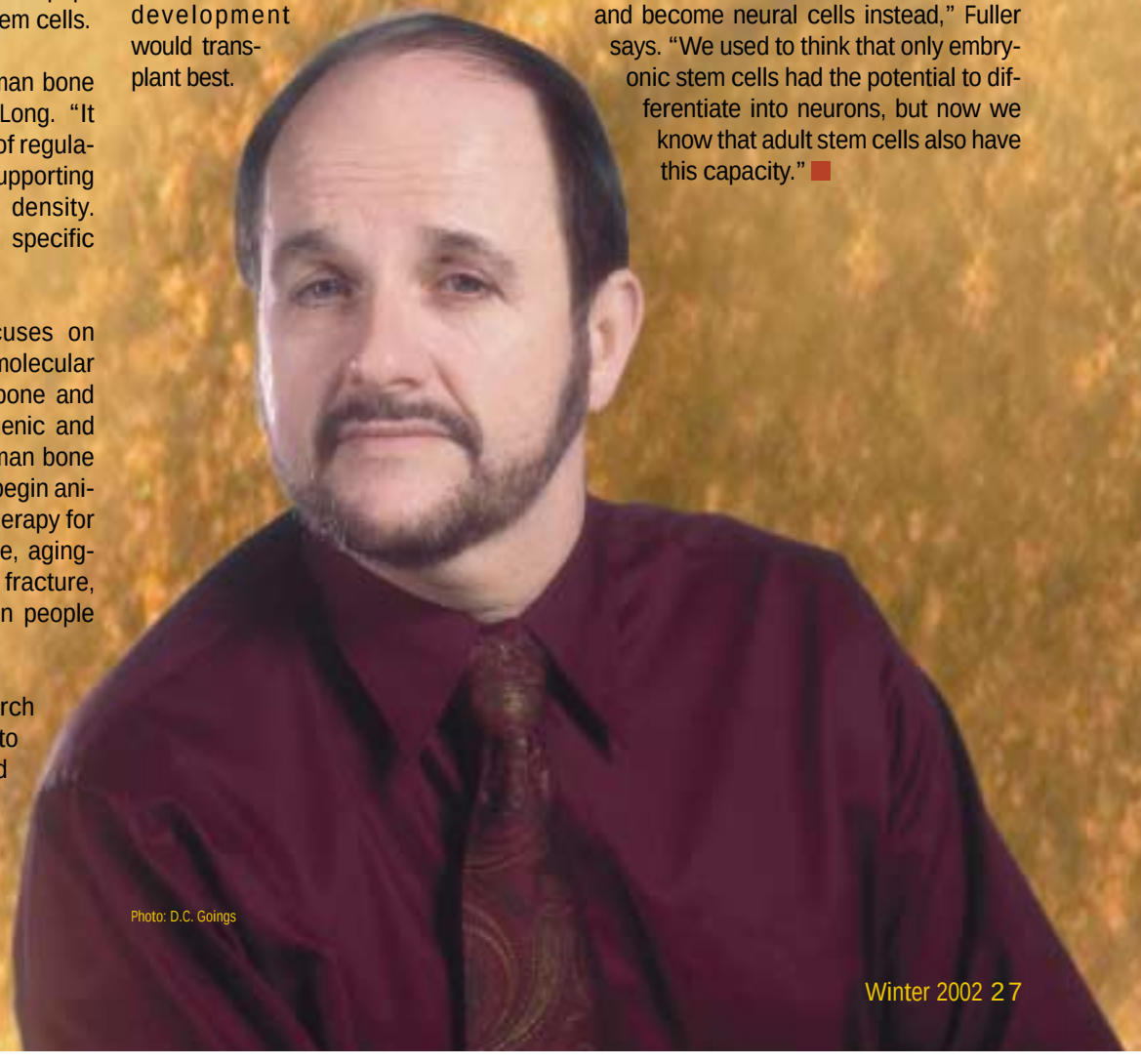


Photo: D.C. Goings

MARIE CSETE, MD, PhD

QUESTION SHE'D MOST LIKE TO ANSWER:

» DO ALL STEM CELLS DIRECT DEVELOPMENT OF THEIR OWN BLOOD SUPPLY?

Photo: Gregory Fox

Nicole Slawny

OXYGEN may be good for you, but it's not so great for your stem cells — says Marie Csete, a cell biologist and anesthesiologist in the U-M Medical School. She maintains that too much oxygen can kill stem cells, slow growth and even trigger an alternate developmental pathway that converts pre-muscle stem cells into fat cells.

Csete began her career as an anesthesiology professor at the University of California-Los Angeles Medical School, where she taught medical students the critical importance of maintaining the correct amount of oxygen in body tissues during surgery. So when she took a sabbatical in 1996 at the California Institute of Technology to study molecular biology, it made sense to Csete that the proper amount of oxygen was just as important to stem cells as it was to her former patients.

"The more primitive the stem cell, the more sensitive it is to oxygen," says Csete, who joined the U-M Medical School faculty in 2000. "The skeletal muscle satellite cells we study grow faster, live longer and develop into muscle cells more consistently when cultured with the amount of oxygen — between two percent and six percent — found in their natural environment inside the body," she says. "In the body, stem cells never are exposed to the 20 percent levels of oxygen they encounter in a typical biomedical laboratory."

During the five years she has been studying the effects of oxygen and other gases on stem cells, Csete has encountered more than her share of skeptics. "It was difficult initially to get people to even consider the idea that oxygen matters, because scientists have been culturing cells the same way for decades," she says.

To control the oxygen exposure of her stem cell cultures, Csete works with them inside a large, custom-designed plastic box with an entry hatch. She programs the device to monitor and maintain a specific mixture of oxygen and other gases within the box.

Nicole Slawny, a graduate student in Csete's laboratory, handles cell cultures using long gloves that fit through sealed entry holes in the side of the box — much like scientists working with radioactive isotopes. Slawny admits it's a bit clumsy and time-consuming, but says the results are worth it. "When you see the differ-

Photo: D.C. Goings

ence in stem cells grown with low oxygen, you can't deny it. Cultures that took one week to grow in the lab, grow here in two days. I'm a 100 percent believer now."

In a recently published study, Csete showed that gene expression patterns changed significantly when stem cells were exposed to varying amounts of oxygen, and that these changes altered the basic biologic function of the cells.

Csete's study focused on adult stem cells from mouse muscle tissue, which develop into muscle cells — providing a continuous source of new cells to replace those damaged during daily wear-and-tear. Under abnormal oxygen conditions, however, Csete discovered they can morph into fat precursor cells called adipocytes instead.

Csete suspects the abnormal behavior of stem cells grown with too much oxygen may mimic the reaction of aging cells exposed to free radicals and oxidative stress. The toxic effects of oxygen may not be limited to just one type of stem cell. In related experiments with Sean Morrison, Csete found that neural crest stem cells from adult mice have similar reactions to too much oxygen.

In the future, Csete hopes to tackle a new area of research — how stem cells regulate what she suspects is a feedback loop between a developing organ's stem cells and its network of blood vessels. "This is the one area of developmental biology where people are aware of the importance of gases," she says. "Vascular biologists know that blood vessels grow faster when oxygen levels are low, in order to increase the supply of blood and oxygen to cells in the developing organ system.

"No one has studied this before, because the stem-cell-to-organ developmental process is already so complicated, no one wants to tackle how the vascular system develops at the same time," she says. "But some day, if I have enough time, I'd really like to know how it works." ■

TO CLONE OR NOT TO CLONE

The stem cell controversy

In a nationally televised address last August, President George W. Bush announced new regulations for scientists conducting federally funded research with human embryonic stem cells. The new rules restricted research to stem cell lines already in existence that were derived from "leftover" or excess human embryos created at fertility clinics. Since then, the National Institutes of Health have listed 72 cell lines worldwide that meet the approved criteria.

Intense media attention and public interest followed the President's announcement — much of it focused on important ethical and religious questions about the morality of using human embryos for research. Most scientists appreciate that, for many, this is a controversial issue. But somewhere in the process, they say — between national opinion polls, opposing newspaper editorials, dueling expert television coverage and Congressional politics — facts about the science of stem cells are being lost, misrepresented or ignored.

Following the Bush decision on human embryonic stem cell research, scientists were flooded with calls from reporters wanting to know when the public could expect cures for diabetes, Parkinson's disease or cancer. U-M researchers stress that we are a long way from knowing whether stem cell research will lead to cures or even more effective treatments for these and other diseases.

"The fundamentals of stem cell biology have been skipped in the excitement these cells generate," says Marie Csete, M.D., Ph.D., assistant professor of cell and developmental biology, associate professor of anesthesiology, and one of several stem cell biologists in the U-M Medical School who emphasize the need for more basic research. "We are all likely to be sorry about skipping these ABCs down the road."

Then there's the fact that stem cell research often is portrayed as leading to cloning — or creating a genetically identical copy of an organism, especially a human being. "Stem cell research and cloning are two different things," Morrison says. "The public needs much more education about the different types of stem cells and different types of cloning."

"There's a big difference between reproductive cloning — the technology used to create Dolly the sheep — and therapeutic cloning," says U-M stem

cell scientist Sue O'Shea, associate professor of cell and developmental biology. "No reputable scientist is interested in reproductive cloning of human beings and, clearly, it should be banned. But therapeutic cloning has great potential to help people who need to replace damaged or diseased tissue and organs.

MOST SCIENTISTS APPRECIATE THAT, FOR MANY, STEM CELLS ARE A CONTROVERSIAL ISSUE. BUT SOMEWHERE IN THE PROCESS, THEY SAY — BETWEEN NATIONAL OPINION POLLS, OPPOSING NEWSPAPER EDITORIALS, DUELING EXPERT TELEVISION COVERAGE AND CONGRESSIONAL POLITICS — FACTS ABOUT THE SCIENCE OF STEM CELLS ARE BEING LOST, MISREPRESENTED OR IGNORED.

"In therapeutic cloning, physicians take a small sample of your tissue and transplant the nucleus from some of these cells into a line of human embryonic stem cells," O'Shea explains. "Under the right culture conditions, scientists could grow neurons with your specific antigens. Because they are genetically identical to you, there should be no immune transplant reaction."

While O'Shea, Clarke, Csete, Long, Morrison and Richard Mortensen, M.D., Ph.D., the newest stem cell scientist to join the Medical School, have chosen to focus their research on these cells, there are many U-M scientists using stem cells in other scientific or clinical research initiatives. For example:

In a series of recent animal studies, U-M neurologist Jack M. Parent, M.D., has shown that neural progenitor cells in the brain respond to acute brain injury by moving to damaged areas and producing new neurons. Understanding this self-repair mechanism could help physicians limit brain damage from strokes or neurodegenerative diseases.

U-M pediatricians John E. Levine, M.D., and Gregory A. Yanik, M.D., recently performed the U-M's first cord blood stem cell transplant for sickle cell anemia using stem cells from the umbilical cord of the patient's infant sister.

James Ferrara, M.D., professor of pediatrics and internal medicine, hopes to learn how to prevent an immune reaction called graft-versus-host disease in cancer patients following bone marrow stem cell transplants. In recent studies with laboratory mice, Ferrara discovered that giving mice additional interleukin-18 during the procedure helped prevent this serious complication.

"We can see stem cells' potential for developing new cell therapies for diabetes, cancer and neurodegenerative diseases," says Mortensen, associate professor of internal medicine and physiology. "We have the expertise and the commitment. Working together, we hope to begin to tap that potential."

To learn more about stem cells, visit:

WWW.NIH.GOV/NEWS/STEMCELL
WWW.NATURE.COM/NATURE/INSIGHTS/6859.HTML
WWW.NYTIMES.COM/SCIENCE
WWW.WHYFILES.ORG/127STEM_CELL/INDEX.HTML

A STEM CELL GLOSSARY

BLASTOCYST
A mammalian embryo before it implants in the uterus. An outer ring of cells surrounds the inner cell mass, which contains undifferentiated embryonic cells.

DIFFERENTIATION
The process of transition from stem cell to specialized cell, such as a blood, heart or bone cell.

DNA
Deoxyribonucleic acid. A complex molecule containing genetic instructions for making everything the body needs.

EMBRYONIC GERM CELLS
Undifferentiated stem cells that become sperm or eggs.

EMBRYONIC STEM CELLS
Self-renewing, undifferentiated stem cells removed from the inner cell mass of a blastocyst and grown in culture.

FACS
Fluorescence-activated cell sorting. A technique scientists use to separate different types of cells based on surface protein markers.

FREE RADICALS
Chemically unstable atoms that can damage cells. Free radicals are toxic by-products produced when cells convert food to energy.

GASTRULATION
An early stage of mammalian embryonic development in which stem cells divide into three layers called the endoderm, mesoderm and ectotoderm.

GROWTH FACTOR
A substance that stimulates cells to grow or inhibits their growth.

HEMATOPOIETIC
Type of stem cells that produce all the red and white blood cells in the body's blood and immune systems.

MULTIPOTENT
A stem cell with the ability to develop into a limited number of cell types.

OSTEOGENIC
Type of stem cells that develop into bone and its connective tissue.

OXIDATION
A chemical reaction inside cells which uses oxygen to convert food to energy.

PLASTICITY
The ability of adult stem cells to change their normal developmental pathway and produce a different type of specialized cell.

PLURIPOTENT
A stem cell capable of developing into every type of cell derived from the endoderm, mesoderm and ectoderm of the early embryo.

PROGENITOR OR PRECURSOR CELL
A partially differentiated cell midway between a stem cell and a specialized cell.

REPROGRAMMING
Manipulating stem cells in a way that changes their developmental pathway from one type of cell to another.

SOMATIC (OR ADULT) STEM CELLS
Stem cells found in tissue other than the egg, sperm, or pre-gastrulation embryo.

STEM CELL
A cell capable of self-renewal and development of specialized cells.

Q. SUE O'SHEA PH.D.

QUESTION SHE'D MOST LIKE TO ANSWER:

» WHAT ARE THE INHIBITORS OF STEM CELL DIFFERENTIATION?

SUE O'Shea is an outspoken advocate for the importance of embryonic stem cells in research. She works with colonies of mouse embryonic stem cells, which she has maintained in culture since the early 1990s when she was a graduate student at Cambridge University in the United Kingdom. Recently she became the U-M's first scientist to work with one of the human embryonic stem cell lines approved by the Bush Administration for use in federally funded research.

"Embryonic stem cells are difficult to handle," O'Shea acknowledges. "They're picky and caring for them is an art. Cell lines have to be divided or fed specific growth factors every day, including holidays and weekends, to keep them from differentiating."

But O'Shea maintains that embryonic stem cells have many advantages over adult stem cells, which makes them worth the extra time and trouble. "If you want to learn about how an embryo develops or how cells differentiate, you have to use embryonic stem cells. Adult cells develop too late in the process. Adult stem cells have some plasticity, or the ability to change into other types of cells, but we don't know how far it goes. Plus, embryonic stem cells grow much faster in culture and we need to grow large numbers of them, so we can learn how they work."

Photo: Bill Wood

Theresa Gratsch

As a child, O'Shea loved to dissect the fish her father caught, so she could examine the brain. Now graduate students in O'Shea's laboratory are using mouse and human embryonic stem cells to model early neural system development. "The nervous system is clearly the most interesting aspect of development," she says.

One of her goals is to develop a library of "designer neuron" human stem cell lines for transplantation after spinal cord injuries or in neurodegenerative disease. By inserting genes called *noggin* and *chordin* into embryonic stem cell DNA, O'Shea has triggered embryonic stem cells to begin differentiating into primitive neurons. "It has just not been possible to study an equivalent early stage of neural development in humans before," O'Shea says.

It took Theresa Gratsch, a research investigator in the O'Shea lab, nearly one full year to find the best way to get the *noggin* gene into stem cell DNA. "We have learned that *noggin* is a powerful neural inducer," Gratsch says. "Ninety percent of stem cells transfected with *noggin* begin differentiating into primitive neurons as early as one day after treatment."

Photo: D. C. Goings

Richard A. Mortensen, M.D., Ph.D.

QUESTION HE'D MOST LIKE TO ANSWER:
» HOW ARE DIFFERENTIATED CELLS FORMED FROM STEM CELLS?

Richard Mortensen has nothing against mice — the traditional workhorse of biomedical research. It's just that stem cells provide a faster, cheaper and more efficient way to identify the effect of one particular gene on a living organism.

Mortensen specializes in developing knock-out lines of embryonic stem cells. By carefully removing or "knocking-out" a gene from mouse DNA and then culturing the genetically altered stem cells, he sees the effect in days, instead of the months it takes to breed mice and see results in their offspring.

The newest stem cell scientist in the Medical School, Mortensen left Harvard Medical School in June 2000 to join the faculty at U-M. He brought with him embryonic stem cell lines with inactivated genes, which can be differentiated into cardiomyocytes in culture. Cardiomyocytes are partially differentiated cells midway on the developmental pathway between stem cells and specialized cardiac cells in heart tissue. Mortensen uses these cell lines in research to define gene targets for treatment of cardiovascular disease.

"No one has found a cardiac stem cell and we know very little about the mechanisms that drive development of cardiac cells from cardiocytes," says Mortensen, as he prepares to view the stem cells — beating spontaneously in their culture dish — under a microscope. "We can maintain these cell colonies for several weeks, but hope to find ways to extend them long enough to see them differentiate into adult-like atrial and ventricular cells."

Photo: Martin Vloet

Matt Merrins

With U-M colleagues Sue O'Shea and Edward Stuenkel, Ph.D., associate professor of physiology, Mortensen hopes to begin a new research study. Their goal will be to identify all the different factors regulating insulin secretion by specialized cells in the pancreas called beta cells. Mortensen plans to use human embryonic stem cells to develop new cell lines of insulin-secreting beta cells and then knock out specific genes to determine their impact on insulin production. Knowing all the signaling molecules and proteins that control how beta cells react to glucose and understanding how they work could one day lead to a new cell therapy for diabetes.

Matthew Merrins, a first-year U-M graduate student in physiology, will be helping Mortensen create the new line of beta islet cells — the fist such cell line to be developed at the U-M Medical School. "I'll be the one developing the selection and purification scheme for the embryonic stem cells," Merrins says. "Just as the stem cells begin to differentiate, we want to select out only those cells differentiating along a specific neuronal lineage pathway. Then we will use hormones and other techniques to get the cells to switch from neural lineage to beta islet development." ■

Photo: D.C. Goings