

Stem Cells & MS:

What the investigators see

BY MARTHA KING

illustrations by Jill K. Gregory

Last month, the National MS Society hosted an international meeting in San Francisco, which allowed 30 cutting-edge investigators to present new findings, share insights, and debate some issues emerging from this frontier in MS research. After lengthy discussions, they forged preliminary agreements about the best ways for the MS research community to move ahead. They grappled with these questions:

- What are the prospects for stem-cell-based treatments for people with MS?
- What are the prospects for stem cell systems to speed drug development by identifying promising compounds?
- How can stem cells help scientists understand the cause of MS?
- What technologies need to be developed or applied to get results in these three areas in the shortest possible time?
- What are the major roadblocks?

Prospects for “endogenous” stem cells

In San Francisco, Dr. Anne Baron-van Evercooren led a discussion with colleagues from the U.K. and the University of Rochester in New York on the potential and current limitations for “endogenous” stem cell therapies. These cells reside in the individual’s central nervous system. In her laboratory in Paris, she and her colleagues have shown that tissues damaged by MS attacks send distress signals. These signals appear to trigger endogenous stem cells to begin differentiating into immature myelin-making cells, a first step in the body’s natural repair process. These stem cells are therefore candidates of great interest in the

quest to enhance myelin repair. Her studies also show that they migrate into areas of MS damage in very limited numbers. “We need to find ways to enhance migration and recruitment by the MS lesions,” she said. Her group is deep in work with laboratory animals to learn more about how this might be done.

Prospects for adult stem cells

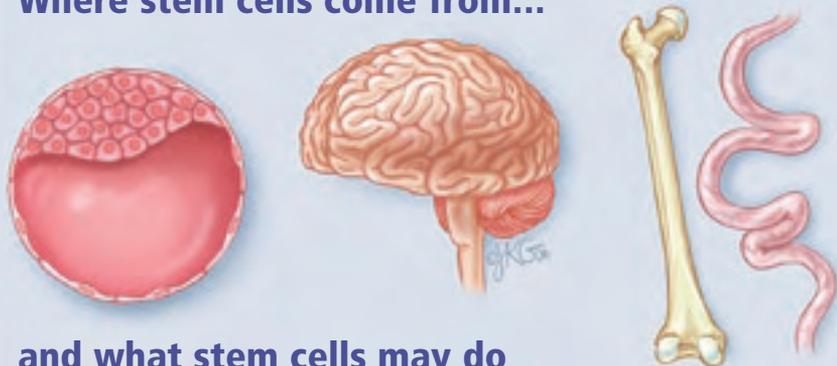
Dr. Jeffrey Kocsis and his team at Yale have been analyzing the potential of stem cells from the human nose, called olfactory ensheathing cells (or OECs); of cells that produce myelin for the nerves outside the central nervous system (called Schwann cells); and of stem cells found in bone marrow.

The Yale team is finding that OECs have a remarkable ability to heal and protect. Surgically transplanted OECs supported regrowth of broken axons (or nerve fibers), protected damaged axons, and promoted remyelination of stripped axons in lab animals. Moreover, the remyelinated axons showed no sign of abnormalities that could spell poor nerve conduction or pain.

The team is also injecting gene-modified stem cells into lab animals with brain injuries and seeing reductions in lesions and improved function.

Dr. Kocsis and his group expect to learn a great

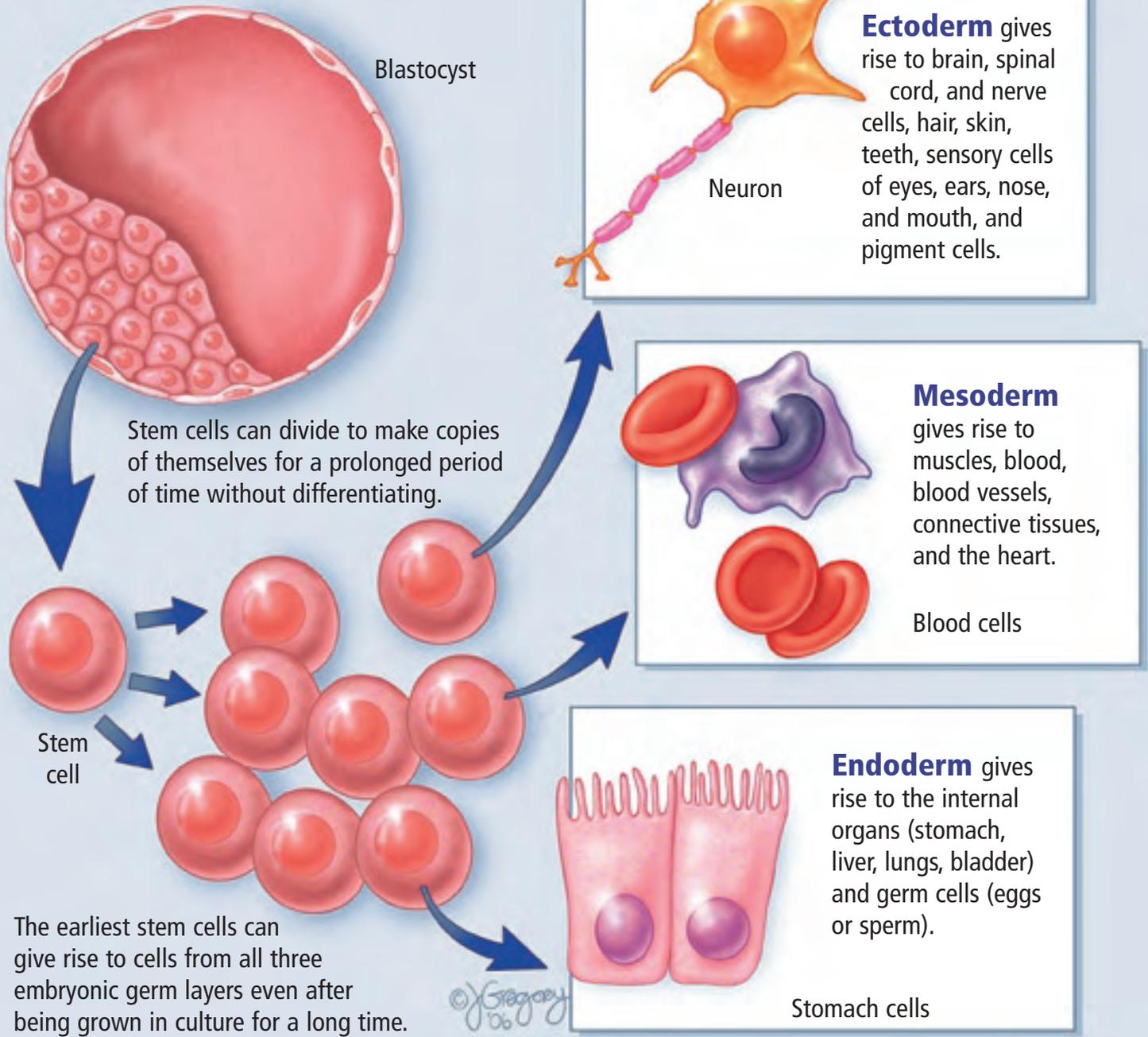
Where stem cells come from...



and what stem cells may do

Stem cells derived from **blastocysts** (left), **neural tissue** (center) and **bone marrow** or **cord blood** (right) have different properties. Some might be transplanted directly to differentiate into myelin-making cells or nerve cells or to prompt regrowth of these cells. Some can spark growth of a new immune system to replace one that continually attacks an individual’s myelin. Still others might be genetically modified before being transplanted to make them stimulate development of cells that produce nerve-protecting molecules. And finally, drugs could be developed that recruit a person’s own—or endogenous—stem cells to a specific area in the body. Once in an injured area, these cells can promote repair and limit additional injury.

“Differentiation”—basic to life



deal more about the potential of bone marrow-derived stem cells to repair MS damage from studies of spinal cord injury repair now going on at Tulane University Medical Center. Cross-disciplinary collaboration like this is becoming a norm in this rapidly developing field.

Prospects for the youngest of the adult cells

The healing potential of stem cells derived from umbilical cord blood is of interest to researchers in spinal cord injury and a long list of neurologic diseases including MS. These cells have less potential for differentiation than embry-

onic cells but far more than do adult stem cells from fully developed individuals. Moreover, blood in an infant's umbilical cord can be readily and harmlessly retrieved right after birth.

Researchers from Australia to Michigan discussed cord blood studies and listened intently to an update from Dr. Joanne Kurtzberg of Duke University, a world-renowned expert in this area. She described successes in cord blood-derived transplants for children with neurologic diseases. These experiences may translate into workable strategies for people with MS.

Something completely different

There are a number of researchers who believe that one potential of embryonic stem cells lies in their ability to help scientists identify effective treatments. An enhanced ability to measure safety and effectiveness means, quite simply, speeding the movement of new findings out of the lab to something useful for people with MS. Picking up the turtle-pace of new drug development should also help reduce the expense.

Dr. Wendy Macklin of the Cleveland Clinic Foundation is working with mouse embryonic stem cells. Her group is using them to screen thousands of chemical compounds looking for any that can prompt immature precursors to develop into mature myelin-making cells. Compounds that do this in the animal cell cultures will be tested in human embryonic stem cell cultures. If they prove safe and effective there, trials of the compounds in people with MS can

be planned. This new and very rapid I.D. method allows Dr. Macklin's group to assess an array of substances that might never have been tested for possible MS therapy by conventional methods.

Go slow to go fast

"There is a real and achievable prospect that stem cells will enable us to repair damaged tissue in MS," said Dr. Robin Franklin, of the Cambridge (England) Centre for Brain Repair, which is taking part in the Society's multicenter Repair and Protection Initiative. "That said, we are still in the very early days," he said, cautioning people to keep their hopes in perspective. "The prospects are too precious to damage them by rushing ahead too fast."

"We are fully committed to pursuing any research avenues with promise for getting us to a world free of MS," said Dr. Aaron Miller, chief medical officer and chairman of the Society's Medical Advisory Board. "Presentations at this conference illustrated that stem cells may have many uses: for tissue culture systems, for drug and gene discovery, for understanding and modeling MS, for delivery of growth or stimulating factors, and for directly repairing or protecting brain tissue."

However, Dr. Miller continued, "we still don't know which type of stem cell will be most valuable, which approach will be safest, or which strategy will produce results soonest. Thus, we support policies that promote research using all stem cell types." ■

Martha King is the editor of **InsideMS**.

Stem Cells and MS: Some basic definitions

The world of stem cell research swirls with unfamiliar terms as well as voices of profound objection by some and unrealistically optimistic expectation by others. Here's a review of the basics, as a service to all those who hope to clarify these issues for themselves.

“Differentiation”

When an ordinary cell divides, whether skin cell, red blood cell, or a cell lining internal organs, the product is two cells that are copies of the original. But a stem cell can divide into two cells that become something different. This differentiation is a basic life process, and, thanks to the tools of molecular biology, differentiation offers enormous possibilities for human health. Stem cells of various types may be a source of replacements for sick or injured tissues anywhere in the body.

In recent years, adult human stem cell transplants, derived from bone marrow, have slowed or stopped MS progression in a limited number of people with very rapidly worsening disease that didn't respond to anything else.

In a groundbreaking animal study, immature neural stem cells, found in adult mice, were injected into mice

with an MS-like disease. The cells were able to travel to the area of damage, stimulate tissue repair, **and** suppress damaging immune attacks. These findings suggest that neural stem cells residing in the adult brain may not only foster tissue repair, but may, in some circumstances, protect the brain from inflammatory attacks.

In other studies, new glial cells (the glial family includes the cells that make myelin) have been grown from animal stem cells in culture. And finally, living nerve tissue has been grown from stem cells, although robust normal nerve function has not yet been achieved.

The diagram on page 45 helps explain what scientists mean when they use the term “stem cell.”

The earliest stage

Embryonic stem cells, or ESCs, taken from a human blastocyst are capable of the greatest range of differentiation and are the object of the most intense ethical concern. These stem cells are obtained from a blastocyst, a human egg that has been fertilized—typically from a fertility clinic storage facility. (Clinics store fertilized eggs that are left over after in vitro fertilization procedures; the couple may opt to donate them.)

Alternatively, ESCs are obtained from an unfertilized human egg, from

For the official Society position on stem cell research, go to nationalmssociety.org/StemCell, or call your chapter.



A researcher at the University of Illinois at Chicago probes the possibilities that stem cells may offer for curing difficult diseases.

which all of the mother's DNA was extracted. The egg is then induced to grow using artificial hormones and DNA from a body cell given by the person for whom this therapy is being tailored. This method, called SCNT or "somatic cell nuclear transfer," offers a promise of producing cells and tissues that will not be rejected as foreign by the recipient's body.

Should an egg like this ever be implanted and survive to term, the infant would be a clone of the DNA donor, an exact genetic copy of just one person. Both law and science agree that this must not happen. Instead, stem cells are removed from the center of the blastocyst between day 4 and 6, to be cultured in laboratory dishes.

While SCNT-based therapy promises to avoid immune-system rejection, the great Catch-22 of transplantation, SCNT therapy would work only for the donor whose cell provided the DNA. In short, this therapy would be engineered one by one, for just one person—a painstaking process, by no means guaranteed of success every time.

The later stages

Since stem cell research began in earnest, scientists have learned that

adult humans have many later-stage stem cells in various parts of their bodies with various potentials for differentiation. Research laboratories have isolated stem cells from bone marrow, skin, and nasal linings, as well as somewhat less accessible parts of the body, such as the retina. They have also identified later-stage cells, called progenitor or precursor cells, that differentiate into mature cells of a specific type if they are exposed to biological prompters.

As scientists learn more about cell development and differentiation pathways, they are more and more encouraged about eventually being able to tap their potential for healing MS damage or stopping MS injury. ■