MS CLINIC NEWSLETTER

London Health Sciences Centre - University Hospital

www.lhsc.on.ca/programs/msclinic Winter 2009

In this issue...

Stem Cell Research

INTRODUCTION

We have all heard about the extraordinary promise that stem cell research holds for the treatment of a wide range of diseases and conditions, including MS. However, there is a lot of work still needed to take this research and turn it into safe and effective treatments.

Available MS therapies—steroids, interferons, glatiramer acetate, natalizumab, and mitoxantrone—are effective mostly for the relapsing type of MS. However, as with other autoimmune diseases, some patients do not respond to these drugs and other more aggressive options must be considered. Intense immunosuppression followed by experimental stem cell transplantation has been investigated in the past 20 years for a few selected very severe MS patients around the world, including Canada. In these early stages, they may not work, and there may be downsides. There is growing concern that unapproved stem cell therapies are being sold even before they have been proven safe and effective. Make sure you understand what to look out for before considering a stem cell therapy. Remember, most medical discoveries are based on long years of research first in laboratory studies and then in large clinical trials performed at well known universities and reputable companies,

and study results end up published in well respected international medical journals for information dissemination (not just a paid webpage, newscast or TV spot!). Like any new drug, stem cell therapies must be assessed and meet certain standards before receiving approval from national regulatory bodies to be used to treat people.

WHAT ARE STEM CELLS?

Stem (also known as pluripotent) cells can 'self-renew' by dividing and giving rise to more stem cells of the same kind, and they can also mature or 'differentiate' into specialized cells that carry out a specific function, such as in the skin, brain, muscle, or blood. There are many different types of stem cells, including "embryonic" stem cells, that exist only at the earliest stages of development; and various types of 'tissue-specific' stem cells (sometimes referred to as 'adult' or 'somatic' stem cells) that are found in various tissues in our bodies.

STEM CELLS AS A TREATMENT

There are two kinds of stem cell transplantation: autologous (a graft of the patient's own stem cells from the blood or bone marrow that have been purified of immune cells) and allogeneic (stem cells from a donor). Proven treatments based on stem cells are still extremely limited. Fatal disorders of the blood and immune system (i.e. leukemia) can, in some cases, be treated effectively with blood stem cell transplantation. Doctors have been transferring blood stem cells by bone marrow transplant for more than 50 years, and advanced techniques for collecting blood stem cells are now used clinically. Umbilical cord blood, like bone marrow, is often collected as a source of blood stem cells and is being used experimentally as an alternative to bone marrow in transplantation. Other tissue-specific stem cells may also play a role in tissue transplants that have been performed for several years. For tissues and organs such as skin and cornea, stem cells contained in these tissues contribute to long-term regeneration. **Other stem cell treatments (including MS) are still highly *experimental***. This means that it has not yet been shown that this treatment is safe or that it will work at all.

HOW CAN STEM CELLS HELP IN MS?

There are ongoing clinical trials worldwide and also in Canada using autologous transplantation to treat MS by completely destroying the patient's immune system through chemotherapy and then reintroducing stem cells taken from the patient's own bone marrow or blood, so the immune system can be reconstituted. When transplanted, the stem cells can differentiate into all of the different types of blood cells, but hopefully they will not carry the "immunologic memory" that previously triggered MS. Highly specialized care is required for patients undergoing the high doses of chemotherapy and transplantation because of the serious complications that could develop. To the degree that MS does not progress (new lesions are not created), this may help to prove the principle that MS is due to a learned immune response to an unknown environmental agent rather than to only a genetic predisposition.

Although this therapy may well arrest inflammation and prevent new lesions in clinical trials, it does not appear to have stemmed the progressive neurodegenerative aspects of MS that were already underway. In order to address the question of whether myelin that has already been destroyed by MS can be repaired, cell biologists are trying

to determine how and why immune cells create and perpetuate the autoimmune response and by what mechanism the demyelination occurs. MS not only destroys myelin but it damages or kills the cells that make myelin (oligodentrocytes) and nerve cells (neurons). We are hoping to crack the cell signaling codes and interrupt the pathways that orchestrate destruction of the myelin sheath. This will help us understand under what conditions remyelination (regeneration of myelin) might occur, and the possible role of drug therapy, or stem cell therapy.

CONCLUSION: Regenerating lost brain tissue is the next frontier in MS - to add repair to what we can already do to fight inflammation. Whether the transplanted stem cells are responsible for the functional improvement seen in some MS patients, or whether stopping inflammation may allow the brain to repair itself is unclear, but understanding these mechanisms might lead to treatments to enhance and encourage remyelination and healing. While our ultimate objective is to find a cure, in the meantime stem cell research is providing vital clues and making it possible in the foreseeable future to induce and prolong remission, or even alter the course of the disease.

For more information on stem cell research go to:
http://www.isscr.org/clinical_trans/pdfs/ISSCRPatientHandbook.pdf
For information on stem cell research occurring in Canada, go to:
http://www.cihr-irsc.gc.ca/e/15255.html

For more information on stem cell research for MS go to:
http://www.mssociety.ca/en/research/stemcell.htm or call your local MS Society chapter or division

Dr. Marcelo Kremenchutzky
Neurologist

New Treatments Under Investigation at the MS Clinic

The Freedom Study

Oral Fingolimod (also known as FTY 720) is another potential MS drug with promising immunomodulatory effects, already in Phase III trials. Fingolimod seems to be very powerful but has some side-effects that need to be worked out. Presently, these include nausea, inflammation of the nasal passages, breathing difficulties, and/or reduction in heart rate. Recruitment for this study is complete and the trial is going forward to phase IV open label for the patients who have now completed the Phase III study.

The Allegro Study

Another new investigational oral medication taken once daily called Laquinimod has shown promising immunomodulatory effects and good tolerance. It is being tested over 24

months with monthly evaluations for safety and efficacy and four MRI scans through the study.

The CONFIRM Study

BG-12 is an oral fumarate also known as dimethyl fumarate or Fumaderm ®. This older oral drug has been approved for psoriasis and immune system disorders in Europe for years. Due to immune similarities with MS, these pills are now being further tested for efficacy and safety in people with relapsing type of MS. This two year study is still open, and also a "head to head" comparative trial of the BG-12 versus placebo and also versus an approved MS treatment (Copaxone®/ glatiramer acetate).

The Minocycline Study

Minocycline is used to treat bacterial infection including acne; pneumonia and other respiratory tract infections; and infection of skin, genital and urinary systems. Minocycline is in a class of medications called tetracycline antibiotics. It works by preventing the growth and spread of bacteria. It comes in pill format. Recent studies have demonstrated its anti-inflammatory properties, a key factor for MS researchers to look closely at the drug.

No, this is not a cure for MS and wouldn't necessarily replace current therapies but if the research hypotheses are confirmed, minocycline may prove to be an orally effective treatment that when used at the time of the very first symptoms (even before a diagnosis of MS is given to you) can delay the full onset of MS. Every drug has side effects, however early studies have shown a reduction in activity of MS on brain MRI, meaning this treatment has the potential to slow the disease down significantly.

Minocycline is generally available as a prescription medication for acne and other bacterial infections but until it is proven to be safe and beneficial it is NOT recommended for treatment of MS. In fact, at this time, study sites will enroll people within 90 days of their first attack of "MS like" symptoms. People who currently have MS or suspected MS are NOT eligible for this study.

The UCB Study

The drug in this study is called CDP323, classed as a integrin (same class as natalizumab). CDP323, via intrgrin inhibition may reduce the ability of leukocytes to participate in the inflammatory response and may be effective at reducing tissue inflammation seen in diseases such as MS. CDP323 offers an oral route of administration and will as a small molecule not lead to the occurrence of neutralizing antibodies or injection site reactions.

The TERIFLUNOMIDE Studies

Immunomodulatory drugs are agents that may help immune cells, which drive the immune attack in MS, 're-learn' and 're-direct' their actions. Teriflunomide has shown some promising immunomodulatory effects in other immune based disorders such as rheumatoid arthritis. The studies completed to date have shown encouraging effect on MRI activity and suppression of clinical flares of the disease. The side effects of this medication have been tolerable. Additionally this treatment is in pill form and

administered orally which is good news for patients!

Phase 2 studies being conducted, which have evaluated the safety and tolerability of teriflunomide when added to interferon or copaxone, are just concluding. Teriflunomide appears to be well tolerated and safe when used in conjunction with interferon therapy or copaxone.

Currently a trial with Teriflunomide for patients with first symptoms suggestive of demyelination and 'at risk' of developing MS is being conducted. The purpose of this trial is to investigate if this oral medication can delay the time to a second attack and prevent the confirmation of a definite diagnosis of MS.

In the near future a trial comparing Teriflunomide to injectable interferon treatment will be conducted. This study will compare the effectiveness and safety of teriflunomide verses interferon.

The ALEMTUZUMAB Study

Alemtuzumab is another immunomodulatory medication that has shown promising immunomodulatory effects in previous trials. This medication is administered by intravenous over the several days approximately one time per year. The advantage to this medication is that, although the initial infusion would be over 3 to 5 days, this treatment could potentially have lasting benefits over a long period of time. The aim for this study is to examine if this medication will help to prevent the accumulation of disability by reducing relapse rate and by preventing the progression to an advanced stage of MS.

Currently this study is being conducted and will compare the safety and efficacy of 2 annual treatments of alemtuzumab to 3 times weekly subcutaneous injections of Rebif.

The NERISPIRDINE Study

Nerispirdine is currently in clinical development for the symptomatic treatment of MS and soon a study with this medication will be launched. This medication is thought to potentially improve neuromuscular function measured by walking ability in patients with MS. Nerisperdine is a potassium and sodium blocker and early studies indicate that MS patients have been responsive to this type of medication.

Shelly Cosma
Anne Howley
Clinical Research Coordinators

From the Research Bench

What is the CCPGSMS Study?

The CCPGSMS study is a cross-Canada study involving 15 Multiple Sclerosis (MS) clinics and potentially more than 20,000 MS patients and their family members. The primary goal of the study is to direct it's efforts to pinpoint the gene or genes involved in the onset and development of MS, while also intending to determine what non-genetic

factors play a role, if any, in the development of MS.

Participation in the study is entirely voluntary. Participants can decide to take part, or not, at any time. Patients with a confirmed diagnosis of MS are asked if they would like to participate within the scope of the study. A clinical research staff member interviews those patients that decide to participate. Questions regarding the patient's family composition, birthplace, medical history, etc; are asked to determine the degree to which further information may be requested. The patient's mother, spouse, mother-in-law and extended family members may be asked to participate as well to provide a more detailed genetic profile.

Those patients whom have more than one family member in addition to themselves affected with MS, or whom have living grandparents may be asked to participate in the genetic portion of the study. This may include the request to collect blood samples from the patient and from the patient's immediate family members and/or grandparents (e.g. parents, siblings etc). Blood samples can be collected from anywhere in Canada and the US. The cost of collecting the samples is covered by the study.

To date we have completed Phase 4 of the CCPGSMS. Below are the findings:

- A familial susceptibility was identified
- Incidence of the disease was increasing
- There is a definite gender difference
- A correlation between genes and environment was seen.

In Phase 5, we will be expanding on the findings from Phase 4 and will be looking at the following:

1. When and on whom does the environment act?
2. What are the familial trends seen previously?
3. What is the increase in incidence of MS in Canada?
4. Identifying the susceptibility to offspring born from the mating between susceptible and resistant populations.

Currently we are contacting patients born in 1975 or later and not already participating in the CCPGSMS. We are also interested in hearing from any families who have more than one family member affected with MS and have not already participated in the CCPGSMS.

If you would like to participate or have any questions regarding the CCPGSMS please contact Ashley Bowering at 519-685-8500 ext 34706 or Ashley.Bowering@lhsc.on.ca

Ashley Bowering
Site Coordinator CCPGSMS

Vitamin D and MS

There has recently been a lot of discussion around vitamin D. Why is vitamin D important in MS and why has vitamin D deficiency been linked with MS?

Vitamin D is a fat-soluble essential vitamin that is produced in the skin as a result of exposure to ultraviolet B (UVB) rays from

sunlight. It is naturally present in very few foods. Some foods are fortified with vitamin D, and some people take vitamin D supplements, but the main source of vitamin D in most people is exposure of the skin to UVB. The vitamin D that is produced from sun exposure, or obtained from food and supplements is inactive. It is activated in the body, first in the liver, and then mainly in the kidneys to the active vitamin D, also known as calcitriol.

We know that vitamin D is necessary for calcium absorption from the gut, which is essential for maintenance of healthy teeth and bones. However, vitamin D has other roles in human health, including a role in immune function. Vitamin D acts in the body by binding to its receptor, which is seen in many cells. It has also been shown to have a role in the formation of some cells of the nervous system. Vitamin D deficiency is believed to have a role in a number of autoimmune diseases including insulin dependent diabetes mellitus, rheumatoid arthritis and inflammatory bowel disease

The causes of MS are really unknown, but we know that both environmental and genetic factors play a role. It has been known for decades that as we move further away both North and South from the Equator, there are more people with MS. For example, MS is more common in Canada and the Northern US than the Southern states. The effect of latitude has also been seen in the UK, where MS is seen more frequently in Scotland than in England, in France, and in Australia. It has also been shown that migration to an area with lower levels of sunshine during early childhood increases the risk of developing MS. This geographical distribution suggests that the risk of developing MS may be somehow related to sunlight exposure. As latitude increases, the amount of UVB reaching the surface of the Earth decreases, because it is travelling a longer distance through the Earth's atmosphere. What can best account for the effect of sunlight on MS risk, is vitamin D, which is produced in the skin as a result of exposure to UVB.

It is also very interesting that MS risk is extremely low in certain populations that live in extreme northern latitudes: some Scandinavians and the Inuit who eat oily fish, and the Sami who consume reindeer meat on a daily basis. Oily fish and reindeer meat are among the rare foods that contain naturally high levels of vitamin D, and in these populations, the main source of vitamin D comes from their diet.

Results of several studies in large populations suggest that patients with MS have lower vitamin D levels, and that high levels of vitamin D are associated with a lower risk of MS. But 'association' does not mean 'causation'. Other studies have shown differences in vitamin D metabolism in males and females. A study of vitamin D supplementation in an animal model of MS, found that vitamin D protected against the disease in female mice, but not in the males. In another study, higher levels of vitmin D were associated with a lower incidence of MS only in women. These findings may help us understand why MS is more common in females, and also why MS is increasing, especially among women, but more research is needed to explain the association between vitamin D and MS.

A very recently published study has suggested that vitamin D deficiency before birth and during early childhood may have a direct influence on genetic factors associated with MS. This study looked at the effect of

vitamin D on a specific gene called HLA-DRB1*1501. Our immune system produces T cells, a sort of 'defence cells' that recognize bacteria and viruses, and then attack and destroy them. There are many different T cells, and sometimes they might incorrectly identify particles of our own body as invaders and attack them by mistake. Ordinarily, these T cells are removed by the immune system. The researchers found that vitamin D affects the ability of this gene to do its normal job. They believe that in people with this gene variant, a lack of vitamin D during early life impairs the ability of our immune system in getting rid of T cells that will later go on to attack the myelin covering the nerve fibres, thus causing MS.

In Canada, long winters and lack of exposure to the sun causes lower levels of vitamin D among Canadians in late winter and early spring. Currently, Health Canada recommends that daily intake of vitamin D in healthy adults should not exceed 2000 IU/day from all sources of vitamin D, including milk and over the counter supplements. Some researchers are concerned that the currently recommended levels of daily vitamin D may be too low for adequate levels in the body. However, too much vitamin D is associated with some health risks, especially in people with kidney disease, hypercalcemia, sarcoidosis, or hypoparathyroidism. Furthermore, vitamin D may interfere with some medications. There is also a small increase in the risk of kidney stones. Therefore, it is always necessary to consult with your family physician or health care professional prior to taking vitamin D or other supplements.

Dr. K. Alikhani
Clinical Fellow in Neurology

Bowel Management

Bowel problems are common in MS. Constipation occurs more often but involuntary bowel movements can also happen and be very upsetting.
Constipation in MS can be due to a number of causes such as: (1) neurological impairment that slows the motility of the bowel, (2) decreased physical activity from fatigue or reduced mobility, (3) medications used to treat MS symptoms of pain, depression or bladder urgency. Involuntary bowel movements or fecal incontinence can occur because of impaired anal sphincter control, reduced rectal sensation or puborectalis muscle weakness. As well, over distention of the bowel when constipated may cause sudden involuntary loss of stool.

The best way to manage any problem is to identify the cause. You may not be able to change the neurological impairment but be aware of how this may impact on bowel function. Interventions can be used to improve function.

Constipation:

1. Identify ways to exercise, going for regular walks, use a stationary bicycle, or assisted range of motion.
2. Ensure adequate fluid intake 6 to 8 cups per day
3. Increase fiber intake 20 to 30 grams per day (see list of high fiber foods)
4. Establish a bowel routine (20-30 minutes after same meal daily or every other day)
5. Maintain a meal schedule (Breakfast is the most important meal of the day)

6. Use stool softeners or suppositories when needed

Involuntary Bowel Movement:

1. Maintain a regular bowel routine to prevent bowel distention
2. Bulk up the stools with increased fiber intake
3. Identify dietary intolerances such as lactose
4. Avoid bowel irritants (caffeine, fatty and spicy foods, smoking)
5. Do pelvic floor exercises
6. Use suppository or enema to ensure complete evacuation of the bowel

Foods High in Dietary Fiber
-Whole grain breads and cereals
-Apples, raspberries, blackberries
-Peas, beans, broccoli
-Dried fruits, figs, prunes, raisins
-Nuts

*Important to increase your fluid intake when you increase your fiber.

Lynn McEwan
Advanced Practice Nurse (APN)

CLINIC NOTES:

- ✓ When you receive a questionnaire notifying you of an upcoming clinic appointment, please complete it and return it to us promptly. This allows us to plan your visit. Additional appointments with team members may then be booked around your clinic appointment time if required.
- ✓ Please call to confirm your appointment and your attendance at least two weeks prior to your appointment date. Confirmation of your attendance is mandatory. Failure to confirm your attendance will result in cancellation of your appointment.
- ✓ Please allow yourself enough time for travel and parking. Report to Patient Registration only if your personal information (address, last name, or family physician) has changed, or if your health card number has been replaced or changed since your last visit to the hospital.
- ✓ Please bring your blue hospital card and your health card to each visit.
- ✓ If you are traveling by ambulance you will need to be accompanied by a relative or health care professional.
- ✓ We require at least 48 hours notice of appointment cancellations.
- ✓ For prescription renewals, have your pharmacy fax the renewal request to 519-663-3744 at least two weeks before your prescription is needed. Remember to check with your pharmacy about when your prescription can be picked up or delivered.
- ✓ Please keep us informed of any changes to your personal information (address, telephone number, family physician, health card number, etc.).
- ✓ Since clinic time is limited, please prepare for your clinic appointment by bringing with you a list of your current

medications and any specific MS-related questions or concerns you with to address.

- ✓ If you wish to be seen in the clinic and have not received an appointment within one year of your last appointment, contact the MS Clinic office at (519) 663-3697. If you have not been seen in the clinic in over a year, we will require a referral note from you family physician.

THE MS CLINIC WHO'S WHO:

Director
Dr. Marcelo Kremenchutzky

Neurologists
Dr. Chris Hyson
Dr. Katayoun Alikhani

Coordinator
Cathy-Lee Benbow

Nurse Practitioner/Clinical Nurse Specialist
Lynn McEwan

Occupational Therapist
Betty Dietrich

Dietician
Sue Ward

Physiotherapist
Anu Sawant

Clinical Research Coordinators
Shelley Cosma
Anne Howley

Research Assistants
Deborah Armitage
Teresa Field

Clinic Secretaries
Cheryl Johnson
Doris Bucciarelli

Senior Lab Technician
Holly Armstrong

Lab Technicians
Beverley Scott
Danielle Guetter

Site Coordinator CCPGSMS
Ashley Bowering

Remember to visit us at out website:

www.lhsc.on.ca/programs/msclinic