

AVENUES

THE NEWSLETTER OF THE PINE STREET FOUNDATION



17

SPRING 2007



Welcome to the spring issue of *Avenues!* 2007 is already off to an amazing start and this coming year promises to be our best yet, with new research projects and educational initiatives.

EVENT: HEALTHY AT 100

On Saturday, March 17th, the Pine Street Foundation has invited John Robbins to speak about his new book, *Healthy at 100*. As author of the hugely influential *Diet for a New America* and *The Food Revolution*, Robbins is one of the most eloquent speakers on how diet, health, and the environment are inextricably linked. See page 7 for more.

BECOMING YOUR OWN ADVOCATE

In 2005, as part of our continuing *Becoming Your Own Advocate* series of articles, we addressed the issue of chemotherapy-related cognitive decline, sometimes called “chemo brain” or “chemo fog.” Since then, there have been some important new studies that provide more evidence of this problem, which we discuss and summarize in an article starting on the opposite page.

READER SURVEY

WE NEED TO HEAR FROM YOU!

When applying for foundation and government grants, we're often asked to provide information about the people we reach through our research and educational programs (such as the *Avenues* newsletter). By completing a brief survey, you'll help us better justify our need for funding. It's also an opportunity for you to share your thoughts about the Pine Street Foundation and how we can improve our programs and services.

Please visit:

www.PSFoundation.org/survey

THANK YOU

We would like to acknowledge all the individuals, foundations, and companies who so generously supported the Pine Street Foundation during 2006. Your generosity is integral to the success of our mission and we hope you'll continue to support our work during the coming year. See page 8 for more.

Best wishes,

Michael Broffman, LAc

Michael McCulloch, LAc, MPH

Your Mind & Cancer Treatment

THE LATEST RESEARCH ON CHEMOTHERAPY-RELATED COGNITIVE DECLINE

INTRODUCTION

In the Winter 2005 issue of *Avenues*, we discussed the important issue of how the mind can be negatively impacted by various conventional cancer treatments. Commonly referred to as “chemo brain” or “chemo fog,” patients often experience adverse effects in cognitive function. The original article, which provides general information on this topic, is available on our website.

In this follow-up article, we discuss and summarize some of the latest research that has been published since 2005. We also identify recent research on vitamin, herbal, and dietary compounds that are known to help support brain cells, which may possibly provide protection from chemotherapy. This research on these “neuroprotective” compounds may point the way towards practical steps patients can take, in collaboration with their health-care providers, to help reduce or minimize the negative effects chemotherapy treatment can have on the mind.

EVIDENCE OF THE PROBLEM

Earlier data suggested that among breast cancer patients receiving standard-dose chemotherapy, 18% showed cognitive deficits on post-treatment evaluations two years after treatment.¹ Among patients treated with high-dose chemotherapy, that proportion rose to 30%. However, these numbers may be conservative as a recent longitudinal study involving breast cancer patients showed that high-dose chemotherapy caused changes in the brain’s white matter in up to 70% of individuals, usually with a delayed onset of several months after treatment.

JOURNAL OF BIOLOGY

In the November 2006 issue of the *Journal of Biology*, researchers report that chemotherapy drugs – specifically carmustine, cisplatin, and cytosine arabinoside – were associated with increased cell damage and death in the brains of mice; this effect was seen for weeks after the drugs were administered.²

Researchers also found that neural progenitor cells (sometimes called “neural stem cells” since they have the ability to restore function in damaged nerve tissues) and oligodendrocytes (a type of cell found in the brain and spinal cord that helps improve the speed and reliability of impulse conduction, allowing faster information processing and better motor control) are exceptionally vulnerable to the action of chemotherapeutic drugs; this is the first study to show definitive evidence of chemotherapy’s damaging effects on the physical structure of the brain.

What is particularly interesting about this study is that this damage was found both *in vitro* (cells cultured or tested in the laboratory) and *in vivo* (in live animals). This is important because it means that researchers could potentially test the effects a drug may have on brain cells in the lab before testing it on human subjects. Similarly, researchers could also lab test the effectiveness of treatments to help minimize the cognitive side effects of chemotherapy before involving actual patients.

In the same issue of the *Journal of Biology*, another author notes that it had been previously believed that irradiation was the key culprit to cognitive decline but now there is growing evidence that confirms that chemotherapy itself – even when used without radiotherapy – is indeed toxic to the central nervous system.³

JOURNAL OF THE AMERICAN CANCER SOCIETY

In a study published in the November 2006 issue of *Cancer*, the journal of the American Cancer Society, researchers used high-resolution brain MRIs of breast cancer patients and controls and observed the differences. They found that breast cancer patients had smaller grey and white matter in the prefrontal cortex, parahippocampal gyrus, cingulate gyrus, and precuneus one year after chemotherapy treatment. These areas of the brain are responsible for attention, concentration, and visual memory.

Encouragingly, no difference between breast cancer patients and controls was observed at three years after treatment, suggesting that such damage is not necessarily permanent.

BREAST CANCER RESEARCH & TREATMENT

While the study in the journal *Cancer* used MRI images to determine the effect of chemotherapy on the brain, a study published in the August 2006 issue of *Breast Cancer Research & Treatment* used PET scans to monitor blood flow in specific regions of the frontal cortex and cerebellum. They found that blood flow was significantly altered in patients who had received chemotherapy and that this was associated with patients' ability to perform short-term memory tasks.⁴

Researchers also found that for patients who received tamoxifen along with their chemotherapy, the metabolism of the basal ganglia (a part of the brain responsible for motor movement) was significantly decreased when compared with patients receiving chemotherapy alone and compared to a control group.

In contrast to the findings of the other studies discussed in this article, these researchers found that changes in blood flow were found five to ten years after completion of chemotherapy, suggesting chemotherapy can have very long-term detrimental effects on brain cells and cognitive function.

PRACTICAL STEPS

While there is increasingly compelling evidence suggesting that chemotherapy does indeed have negative effects on the brain and central nervous system, there is relatively little research providing guidance for what patients can do to prevent or minimize these effects.

Neuroprotective Vitamin and Plant-derived Compounds

While generally not specific to patients undergoing chemotherapy, a considerable amount of work has been done investigating readily available, over the counter herbal medicines and dietary supplements that may have neuroprotective benefits. It is important to note that most of this work has been done using cell cultures in the laboratory or on animals; relatively few research studies have been completed that recruited human subjects.

Many of these herbal medicines and dietary supplements have long been used by practitioners of Chinese medicine or have been studied and used for health benefits unrelated to neuroprotection in humans. Additionally, for most of these compounds, safe doses have been established for human consumption.

The research that still remains to be done is on what specific herbal medicines or dietary supplements would help protect brain cells from damage due to chemotherapy, and at what specific dosage levels. Therefore, we encourage people considering using the information presented here to review this material with their healthcare providers prior to proceeding with treatment. Important information to discuss in consultation include the individual suitability of specific compounds, appropriate dosage levels, and whether they may interact with other treatments, such

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ON THE COVER
Detail of silk brocade on *thangka* painted and blessed by
His Eminence Kalu Rinpoche (1905-1989). India, circa 1971.

ABOUT *AVENUES*
Avenues are choices. When managing disease, there are many different possibilities to consider. Through this newsletter, the Pine Street Foundation seeks to illuminate some of these choices through evidence-based research in the hopes that by having more options, patients and health care providers will be able to make better, more informed treatment decisions.

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www.PineStreetFoundation.org

as chemotherapy. An excellent resource for clinicians detailing herb-drug or vitamin-drug interactions is the Natural Medicines Comprehensive Database, www.NaturalDatabase.com.

Ginsenoside Rg1

Ginsenoside Rg1 is an active ingredient isolated from ginseng and is most abundant in both Chinese and Korean ginseng. Ginseng is one of the most widely known herbal medicines in the world, commonly used for its immunostimulating and anti-tumor properties.⁵ Specific to its potential neuroprotective effects, ginsenoside has been shown to enhance survival rate of neural stem cells in vitro in a study using rat stem cell cultures.⁶ Commonly used dosage levels of ginseng extract range between 200 and 1000mg.⁵

Ren Shen Yang Rong Tang

Ren Shen Yang Rong Tang is a Chinese herbal formula first published in a Song Dynasty Chinese medical text in 990 AD. This combination of herbs, which includes ginseng, has been shown to improve the capability of rat oligodendrocyte precursor cells to grow and differentiate four to five fold.⁷

Acupuncture

Acupuncture is a technique used in Chinese medicine for many different health concerns. A review paper has discussed the possibility that acupuncture can promote proliferation of neural stem cells in the hippocampus (a part of the brain used for memory and spacial navigation). Acupuncture has been used to help Alzheimer's patients in this way.⁸

Antioxidants

Progenitor cells and immature oligodendrocytes are affected by oxidative stress (damage to cells by oxidation).^{5,6} When oxidative stress is lower, the body promotes self-renewal of progenitor cells and when oxidative stress is higher, the body promotes the growth of fully matured neural cells.⁷

Oxidative stress has not yet been identified as a cause of progenitor cell death due to chemotherapy. However, many chemotherapy agents cause oxidative stress throughout the body, which contributes to both the desired therapeutic effects – and the undesired side effects – of chemotherapy.¹²⁻¹⁵ As explained above, the growth and survival of neural stem cells and their precursor cells (progenitor cells and oligodendrocytes) is in part regulated by the level of oxidation, so decreasing oxidative stress may help to protect them.

Antioxidants (whether they are produced by the body, taken as a supplement, or eaten in foods) can combat oxidative stress and promote better survival and increased proliferation of neural stem cells. Below are various antioxidant compounds that have been shown in animal or laboratory studies to promote growth or survival of neural stem cells, progenitor cells, and oligodendrocytes. (Work is already underway for a future report in *Avenues* reviewing the evidence for how various antioxidants interact with

chemotherapy – including whether they increase or decrease chemotherapy effectiveness – and their impact on chemotherapy side effects.)

Melatonin

Melatonin is a hormone released from the pineal gland in the evening, and secretion diminishes significantly with age. It is known to help maintain cell health and many people take it to improve sleep. Melatonin has also been shown to slow down neural cell death through its antioxidative effects. Melatonin receptors in neural and glial progenitor cells have been detected and play a role in neuroprotective strategies for Alzheimer's patients.^{16,17} Melatonin also has neuroprotective effects on both axons and myelin sheaths of white matter after spinal cord injury, which helps improve recovery.^{18,19} (Melatonin's neuroprotective benefits are akin or better to the steroid medication methylprednisolone, which is also used after spinal cord injury.)²⁰ Melatonin has also been demonstrated to protect nerve fibers from damage due to lack of blood flow.²¹ Melatonin is typically used in doses ranging from 1 to 10mg per capsule. Research studies on its anti-tumor effects have reported on its use at up to 20mg per day.⁵

Epigallocatechin-gallate (EGCG)

EGCG is an active compound found in green tea leaves. It is an antioxidant that is 25 to 100 times more potent than vitamins C and E.²² According to an animal study, EGCG may promote neural stem cell survival or differentiation.²³ This compound also inhibits the proliferation of many cancer cell lines.⁵ Research studies on its anti-tumor effects have employed a dosage range between 460 to 550mg per day.⁵

Alpha-lipoic Acid

Alpha-lipoic acid is an important antioxidant that can regenerate other essential antioxidants, such as vitamins C and E, coenzyme Q10, and glutathione. It is also a co-factor for some of the key enzymes (alpha-keto acid dehydrogenases) involved in generating energy. In animal research that investigated the aging process in rats and mice, alpha-lipoic acid has been shown to slow down the development of age-related cognitive dysfunction and brain cell deterioration.²⁴ According to a laboratory study, alpha-lipoic acid protects oligodendrocytes against oxidative damage.²⁵ Alpha-lipoic acid is typically used in a dosage range between 200 and 600mg per day.⁵

Coenzyme Q10

Coenzyme Q10 (CoQ10) is produced by the human body and is necessary for the basic functioning of cells. It is a vitamin-like substance that can also act as an antioxidant. Among other functions, it is incorporated into the mitochondria of cells throughout the body and facilitates and regulates the transformation of fats and sugars into energy. Patients with heart problems often use CoQ10. According to laboratory studies, the oxidative damage to oligodendrocytes can be prevented using coenzyme Q10.²⁵ It

may also protect oligodendrocytes during the terminal stages of maturation.²⁶ Coenzyme Q10 is typically used in a dosage range between 30 and 200mg per day.

Quercetin

Quercetin is the most abundant of the plant-derived flavonoid molecules and is a very active antioxidant. In laboratory studies, quercetin has been demonstrated to prevent oxidative damage in oligodendrocytes.²⁷ Quercetin is typically used in a dosage between 500 and 1500mg. Studies have been published on its use as an anti-tumor treatment at doses up to 3.8g per day.⁵

Glutathione

Glutathione is a molecule synthesized in the body from three amino acids: L-glutamic acid, L-cysteine, and glycine. Glutathione is one of the body's most important and powerful antioxidants and a depletion of glutathione can be damaging to oligodendrocyte progenitor cells.²⁸ Glutathione is typically used in a dosage range between 250 and 500mg per day.

N-acetyl Cysteine

N-acetyl cysteine is an efficiently absorbed and used form of the amino acid, L-cysteine. In laboratory studies, N-acetyl cysteine has demonstrated protective properties in the process of oligodendrocyte maturation.²⁶ It is typically used in dosages ranging between 600 and 1800mg per day.


Folic Acid

Folic acid has been shown in laboratory studies to help stem cells proliferate.²⁹ Folic acid is a member of the B vitamin family and is typically used in dosages ranging between 50 and 400µg.

Vitamin K1 and K2

Vitamin K has been shown in laboratory studies to help in preventing oxidative injury to developing oligodendrocytes and neurons.³⁰

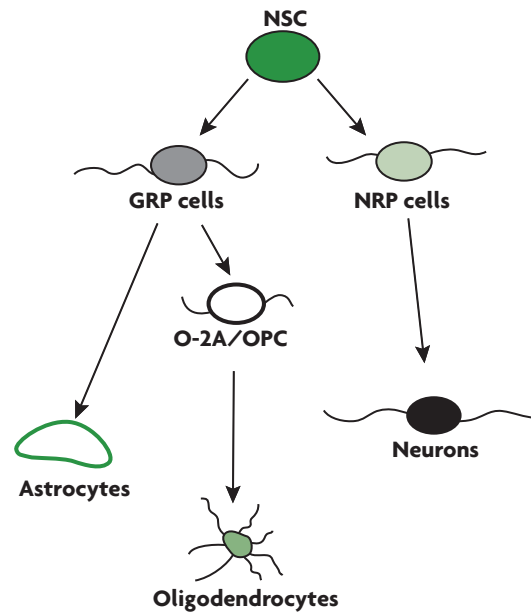
SUMMARY

Since chemotherapy is currently an important element in many treatment protocols, future research must focus on developing strategies to help shield the brain from the toxic effects of chemotherapy as well as on the development of more selective and targeted cancer drugs with a lower side-effect profile. We believe that some of the work cited above can suggest potentially non-toxic vitamin or plant-derived compounds worthy of testing for their neuroprotective potential before, during, or after chemotherapy treatment. 

MORE ONLINE

For more information and complete references, visit:
www.PineStreetFoundation.org

FROM STEM CELLS TO NEURONS



Step One - Neural Stem Cells

Neural stem cells (NSC) are cells that can mature into any type of cell and can continually renew themselves.

Step Two - Progenitor Cells

Progenitor cells do not themselves perform active neurological functions but are “reserve” cells that become activated when mature nerve tissue is damaged. When there is injury, the progenitor cells then develop into mature active cells in order to repair or replace the damaged tissue. Progenitor cells include:

- GRP: Glial-Restricted Precursors
- NRP: Neuron Restricted Precursors
- O-2A/OPC: Oligodendrocyte-Type-2 Astrocytes

Step Three - Mature Nerve Cells

Astrocytes are cells in the central nervous system that, while they are not themselves nerve cells, provide several functions: (1) they provide a framework of structural support in the brain for nerve cells, (2) they provide metabolic support, assisting neurons to obtain nutrients, such as glucose, and (3) they are part of the blood-brain barrier which protects the brain.

Neurons are the primary nerve cells in the nervous system that process and transmit information via electrical signals.

Oligodendrocytes are cells in the central nervous system that, while they are not nerve cells themselves, provide support and nutrition to nerve cells, help form the myelin coating of nerve cells, and participate in signal transmission in the nervous system.

Adapted from Dietrich J, Han R, Yang Y, Mayer-Proschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J Biol. Nov 30 2006;5(7):22., Page 3, Figure 1.

HEALTHY AT 100

An Afternoon with John Robbins

AUTHOR OF *DIET FOR A NEW AMERICA* & *THE FOOD REVOLUTION*

SATURDAY, MARCH 17TH, 2007 · 3:00 PM

The Pine Street Foundation is pleased to welcome John Robbins to Marin County to speak about his new book, *Healthy at 100*. Through the example of four very different cultures that have the distinction of producing some of the world's healthiest, oldest people, Robbins reveals the secrets for living an extended and fulfilling life in which our later years become a period of wisdom, vitality, and happiness. From Abkhasia on the eastern coast of the Black Sea, where age is beauty, and Vilcabamba in the Andes of South America, where laughter is the greatest medicine, to Hunza in Central Asia, where dance is ageless, and finally the southern Japanese islands of Okinawa, where people regularly live beyond a century, Robbins examines how the unique lifestyles of these peoples can influence and improve our own.

ABOUT JOHN ROBBINS

Widely considered to be one of the world's leading experts on the dietary link with the environment and health, Robbins' work has been the subject of cover stories and feature articles in the *San Francisco Chronicle*, *Los Angeles Times*, *Chicago Life*, *Washington Post*, *New York Times*, *Philadelphia Inquirer*, and many of the nation's other major newspapers and magazines. His life and work have also been featured in an hour long PBS special titled *Diet for a New America*.

The only son of the founder of the Baskin-Robbins ice cream empire, Robbins was groomed to follow in his father's footsteps, but chose to walk away from Baskin-Robbins and the immense wealth it represented to "...pursue the deeper American Dream... the dream of a society at peace with its conscience because it respects and lives in harmony with all life forms. A dream of a society that is truly healthy, practicing a wise and compassionate stewardship of a balanced ecosystem."

EVENT DETAILS

What:

An afternoon with John Robbins, author of *Diet for a New America*, *The Food Revolution*, and *Healthy at 100*.

When:

Saturday, March 17th, 2007 at 3pm. Please arrive early to allow time to find parking and seats.

Where:

Osher Marin Jewish Community Center.
200 North San Pedro Road in San Rafael.

Tickets:

\$20 suggested donation. Tickets will be available at the door the day of the event. No reservations necessary.

Please visit our website for more information: www.PSFoundation.org/events

Thank You

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SAVE THE DATE

An Afternoon with John Robbins

*Author of *Diet for a New America**

March 17th, 2007 · 3:00 pm

See page 7 for details.

