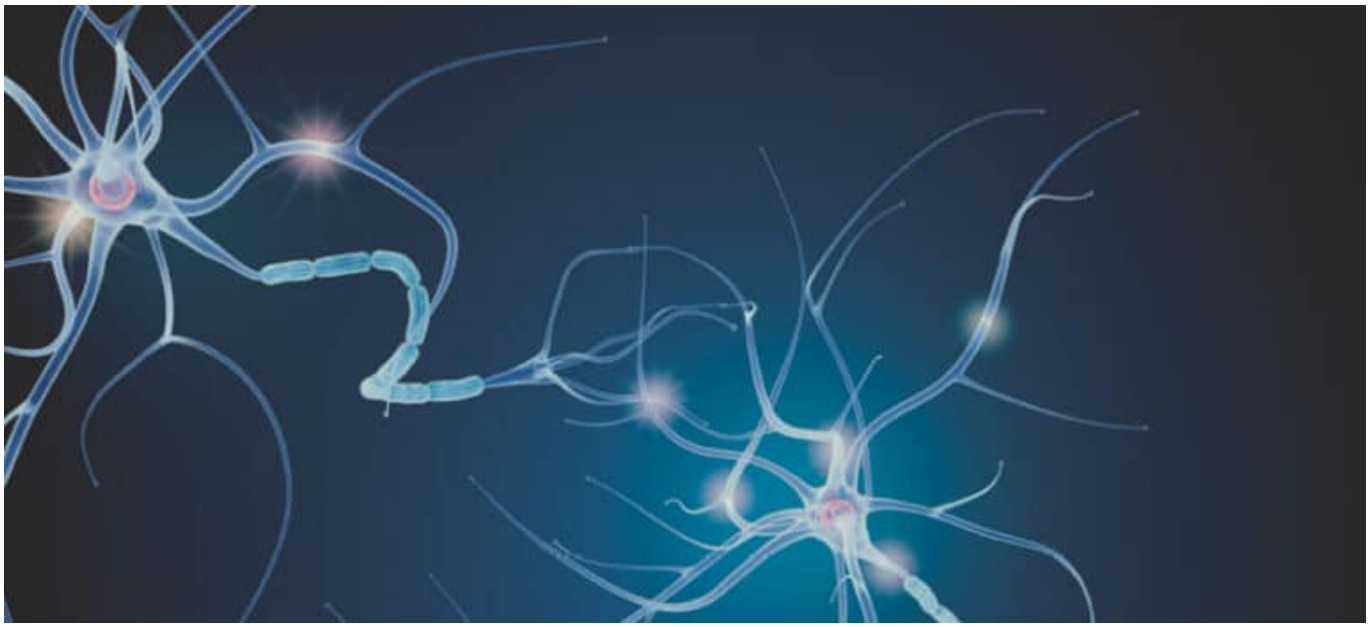
Repair work



Dystel prize winner focuses on myelin.

by Vicky Uhland

Many people yearn for a cure for multiple sclerosis. It’s the focus for hundreds of scientists and millions of dollars in research funding. However, what if it were possible to develop a treatment that improves function and eradicates the symptoms of MS? For the nearly 1 million people living with the disease in the U.S., that may be just as relevant as a cure.

Ian Duncan, PhD, led a team that researched how human stem cells could repair myelin loss and reduce MS symptoms. Photo courtesy of Ian Duncan, PhD

Clinical trials of drugs that potentially promote myelin repair have already been carried out thanks to the pioneering research of Ian Duncan, PhD. For decades, Duncan has investigated how to repair myelin, the insulating and protective coating of nerve fibers in the central nervous system. MS attacks and erodes myelin, leading to the symptoms associated with the disease. Duncan has been awarded the 2020 John Dystel Prize for Multiple Sclerosis Research for his groundbreaking work on remyelination.

The annual prize, which is awarded by the National Multiple Sclerosis Society and the American Academy of Neurology, recognizes an outstanding researcher who is helping to advance the understanding, treatment or prevention of MS. The late Society National Board member Oscar Dystel and his late wife, Marion, established the prize in 1994 in honor of their son John Jay, an attorney whose promising career was cut short by progressive disability from MS. John died of complications of the disease in June 2003.

“Dr. Duncan was one of the earliest investigators to tackle central nervous system repair in demyelinating disease and to uncover leads as to how to best achieve this,” wrote Stanford University professor Lawrence Steinman, MD, in a letter nominating Duncan for the Dystel Prize. “This work began before we had any approved treatments for MS and considerably before relative stabilization of the disease was achieved with our current armamentarium of therapies, which have subsequently provided the cornerstone for the now-more-accepted belief that central nervous system repair is an important next step to achieve.”

Like previous Dystel Prize winners, Duncan has devoted his professional life to research on MS and other myelin disorders. But Duncan has taken a different route than many of his peers.

From horses to humans

Duncan grew up in Scotland and graduated from Glasgow University’s School of Veterinary Medicine in 1971. Four years later, he earned his PhD with a thesis on experimental neuropathology in horses.

Until his third year as an undergraduate, Duncan intended to be a practicing veterinarian. However, after spending a summer in a lab he realized that he was more interested in neuroscience and exploring mechanisms of disease, and so he opted for a research career.

Shortly after Duncan earned his PhD, he became a postdoctoral fellow in the Department of Neurology at McGill University in Montreal, Quebec, Canada. With Albert Aguayo, MD, and

Garth Bray, MD, Duncan conducted research into experimental cellular interactions in the central nervous system, supported by the MS Society of Canada.

Animals don't get MS, so it may seem like Duncan made quite a leap from veterinary school to his research into remyelination. But it's not as unusual as it sounds.

"The field of remyelination has been significantly represented by people with veterinary training," Duncan says. "I think it's because research on remyelination often involves animals, and of course we have the right background to work with animal models."

Remyelination revelations

At McGill University, Duncan discovered that myelinating cells could be taken from the peripheral nervous system of mice and transplanted into their central nervous systems where they made small areas of myelin. That gave him the idea that maybe those cells could be used clinically in demyelinating disorders, if larger areas could be remyelinated.

In 1982, Duncan moved to the University of Wisconsin to research this idea further. "That was the time when I really became totally enamored with all things myelin —both the development of myelin and how to repair the myelin sheath," he says. "My lab became immersed in how to restore myelin in genetic myelin disorders and MS."

Duncan and his team of researchers were the first to show that transplanting cells into a canine model that lacked myelin throughout the central nervous system could result in myelination of areas close in size to some MS plaques.

But the challenge was to discover how a similar transplantation approach could be carried out in people. One of Duncan's focuses was to determine which developmental stage of oligodendrocytes — the cells in the human body that produce the myelin sheath — would be best for transplanting into the central nervous system and rebuilding missing myelin.

It took several phases of research to accomplish this. Duncan and Joe Hammang, PhD, and Su-Chun Zhang, PhD, were the first to demonstrate that transplanting animal neural stem cells into the central nervous system could generate oligodendrocytes and initiate remyelination. Then with Oliver Brustle, PhD, they showed that human embryonic stem cells could also give rise to neural stem cells. This paved the way for research into using human stem cells in MS that could potentially repair focal myelin loss and reduce or even eradicate MS symptoms.

'Functional recovery' in MS

Duncan moved away from cell transplantation and switched his attention to studying remyelination by enhancing the resident cells of the nervous system as the source of new myelin following demyelination. Using an enigmatic model in the cat, he has re-examined fundamental questions relating to myelin repair. In this model, cats fed irradiated food develop profound demyelination that results in a progressive neurologic disease. Return to a

normal diet leads to remyelination and neurologic recovery.

While it had been proposed that remyelination in MS and animal models results in neurologic recovery, definitive proof had been lacking until Duncan's demonstration in the feline model. He and colleagues then showed that surviving adult oligodendrocytes could participate in remyelination; this had previously been thought unlikely and identified this cell as an additional target for future remyelinating drugs.

"In a complex war, the more diversified soldiers you have, the better chance you have for winning, if I can make that analogy," Duncan says. "The final cure in MS will probably not be a single treatment, but rather a multi-treatment solution."

While current disease-modifying treatments are effective in many patients in reducing relapses and severity of disease, none of these drugs has been proven to promote myelin restoration.

"People with MS are looking for a number of things. They want to stop ongoing disease, that's for sure," Duncan says. "But almost equally, they'd like to have some improvement. They would like to be less tired, they'd like to be more mobile, have better balance and see normally. So we can't just stop the disease. We need to actually improve people's function."

Drug trials underway

There have been two recent clinical trials on remyelinating drugs. One trial was unsuccessful and one had mild success, though measuring their effect and clinical benefit was difficult. But Duncan's recent work with cats has revealed a better way to measure if a drug is actually doing its remyelinating job — and potentially stopping MS symptoms.

"The field is challenged by the lack of primary outcome measures that reliably identify remyelination," wrote Bruce D. Trapp, PhD, chairman of the Cleveland Clinic's Department of Neurosciences, in his letter nominating Duncan for the Dystel Prize. "[Duncan's] studies have important implications for future clinical trials of remyelinating therapies in multiple sclerosis patients."

Evaluating drug-induced remyelination by MRI has proven difficult. However, Duncan's research found that a type of test called visual evoked potentials can measure whether the optic nerve in a cat has become demyelinated, and then whether a drug or other treatment has actually remyelinated the nerve.

Duncan says there is currently a human clinical trial planned in the United Kingdom for a drug that promotes remyelination that will use the visual evoked potential as an outcome measure, and it is likely that this test will be included in future trials of remyelinating drugs.

Outside the lab, Duncan contributes to MS as a Bike MS fundraiser. Photo courtesy of Ian Duncan, PhD

A fundraising prizewinner

The scientists who nominated Duncan for the Dystel Prize noted that his dedication to MS research extends outside the laboratory.

Duncan has participated in Bike MS fundraisers and has also raised money for the Society through the American Birkebeiner cross-country ski race. His efforts have been so successful that he's been elected to the Society's Volunteer Hall of Fame in both the Professional and Outstanding Fundraiser categories.

Duncan also co-produced a PBS documentary with Steinar Hybertsen, "Multiple Sclerosis, The Vikings and Nordic Skiing," that discusses the value of active lifestyles for people with MS. And he's even had a Hollywood moment, as a character in the movie "Lorenzo's Oil," which deals with healing myelin damage in a young boy with a genetic myelin disorder.

Trapp also notes that "Dr. Duncan has had a stellar career as an academic educator and mentor of young scientists." Duncan is a frequent lecturer at medical and research institutes around the world and has served on many study and advisory boards in the U.S., Canada and Norway.

The future

With the identification of a model to test new remyelinating drugs, Duncan plans to collaborate with a biotech company to test a new molecule and determine whether it correlates with myelin repair. He also plans to explore the reasons irradiation of food results in demyelination in cat models.

Vicky Uhland is a writer and editor in Lafayette, Colorado.

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