



National  
Multiple Sclerosis  
Society

**MS Learn Online**  
**Feature Presentation**  
*To Repair and Protect: The Future of MS Treatments*  
*Part Three*

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**Tom>>** Welcome to MS Learn Online. I'm Tom Kimball.

**Tracey>>** And I'm Tracey Kimball. I'm glad to be back as we get ready to watch the third and final part of "To Repair and Protect: The Future of MS Treatments".

**Tom>>** So far we've spent some time on the protection and repair of the damage to the nervous system caused by MS. We also looked at how cell biology is advancing the research into finding treatments for MS

**Tracey>** In this episode, we'll hear from researchers who are trying to better understand the types of damage caused by MS. Let's watch.

**>>EJ Levy** I'M AT THE CENTER FOR NEUROSCIENCE AND REGENERATION RESEARCH, WHICH IS LOCATED AT THE VA HOSPITAL AT YALE UNIVERSITY. TODAY I'M GOING TO BE ABLE TO TALK WITH DR. JEFFREY KOCSIS AND DR. STEPHEN WAXMAN.

DR. JEFFREY KOCSIS, THANK YOU SO MUCH FOR SPEAKING WITH US THIS MORNING.

**>> Dr. Kocsis** IT'S MY PLEASURE.

>>EJ Levy SO I UNDERSTAND YOUR RESEARCH IN REPAIRING THE DAMAGE IN MS IS FOCUSED ON CELL TRANSPLANTATION. CAN YOU TELL ME A LITTLE BIT ABOUT THAT?

>> Dr. Kocsis YEAH, WE'VE, FOR SOME YEARS NOW, BEEN VERY INTERESTED IN THE PROSPECT OF BEING ABLE TO HARVEST CELLS, INITIALLY PRIMARILY TO FORM MYELIN, WHICH OF COURSE IS RELEVANT TO MS. BUT I THINK THROUGH THE YEARS, OUR CONCEPTS HAVE EXPANDED IN THAT, ONE CAN USE CELLS THAT CAN PROTECT AXONS FROM DYING, CAN PROTECT NERVE CELLS FROM DYING, CAN ENCOURAGE AXONS TO REGENERATE AS WELL AS REPLACE MYELIN. AND IN OUR WORK THERE'S ACTUALLY THREE PRIMARY CELL TYPES THAT WE UTILIZE AT THE MOMENT. ONE IS A SCHWANN CELL; THAT'S THE CELL THAT NORMALLY MAKES MYELIN IN THE PERIPHERAL NERVOUS SYSTEM. AND ANOTHER CELL IS CALLED THE OLFATORY ENSHEATHING CELL, WHICH IS SIMILAR TO A SCHWANN CELL, BUT IT HAS SOME UNIQUE PROPERTIES. AND FINALLY WE HARVEST FROM ADULT BONE MARROW, FROM HUMANS, A MESENCHYMAL STEM CELL THAT ONE COULD, IN PRINCIPLE, REMOVE FROM A PATIENT, HARVEST THEM, AND UTILIZE THEM FOR CELL THERAPY APPROACHES.

>>EJ Levy SO ARE THERE SOME BENEFITS TO BEING ABLE TO HARVEST A CELL FROM THE PATIENT THAT'S GOING TO ACTUALLY RECEIVE THE TRANSPLANT?

>> **Dr. Kocsis**      TREMENDOUS BENEFIT, THAT IN PRINCIPLE ONE SHOULD BE ABLE TO HARVEST THESE CELLS AND THE BODY WOULD NOT REJECT THEM, AND IF WE CAN TEACH THEM AND INSTRUCT THEM HOW TO REPAIR, IT'S VERY EXCITING.

>> **EJ Levy**            SO YOU MENTIONED A LITTLE EARLIER ABOUT THE OLFACTORY ENSHEATHING CELLS FUNCTION IN A UNIQUE MANNER. HOW IS THAT?

>> **Dr. Kocsis**      WE HAVE TO TALK ABOUT A LITTLE BASIC NEUROBIOLOGY IN ORDER TO SEE WHY THEY BECAME OF INTEREST FOR POSSIBLE CLINICAL USE. IN OUR OLFACTORY SYSTEM, WE HAVE AN AREA WITHIN OUR NOSES, IT'S MUCOSA, AND THERE'S A NEUROEPITHELIUM. AND HERE WE HAVE NERVE CELLS THAT ACTUALLY DIVIDE THROUGHOUT LIFE, AND WHEN THE CELLS DIVIDE, THEY'RE REPLACING CELLS THAT HAVE DIED, AND AXONS WILL GROW NERVE FIBERS BACK THROUGH TUNNELS OF THESE OLFACTORY ENSHEATHING CELLS, ENTER THE CENTRAL NERVOUS SYSTEM AND MAKE NEW CONTACTS. SO WE HAVE A NEUROGENIC ZONE, AND THE OLFACTORY ENSHEATHING CELLS, WHICH ARE GLIAL CELLS, ARE SPECIALIZED SO THEY ALLOW FIBERS TO GROW BACK INTO THE CENTRAL NERVOUS SYSTEM. THIS IS UNIQUE; THIS DOESN'T OCCUR ANYWHERE ELSE IN THE BODY, AND THE THINKING AND THE RATIONALE WAS THAT MAYBE IF WE COULD HARVEST THESE CELLS, PULL THEM OUT, AND TRANSPLANT THEM INTO SITES OF AXON INJURY, THAT WE MIGHT BE ABLE TO ENCOURAGE REGENERATION, AND AS WE AND OTHER GROUPS,

SUCH AS ROBIN FRANKLIN'S GROUP IN CAMBRIDGE HAVE SHOWN, THEY CAN FORM MYELIN. SO WE'RE KIND OF GETTING DOUBLE BANG FOR OUR BUCK. THEY CAN PROTECT AND ENCOURAGE AXONS TO REGENERATE, BUT THEY CAN ALSO FORM MYELIN. SCHWANN CELLS HAVE MANY PROPERTIES OF THE OECs, BUT AGAIN, THEY HAVE THIS UNIQUE PROPERTY TO BE ABLE TO MIGRATE WITHIN THE CENTRAL NERVOUS SYSTEM THAT'S GOING TO BE CRITICAL FOR CELL THERAPIES. IT'S VERY DIFFICULT IF ONE HAS AN MS PLAQUE WHERE YOU HAVE GLIOSIS, SCARRING, TO GET CELLS TO SURVIVE AND MIGRATE IN THAT ENVIRONMENT, AND THE OECs OFFER SOME OPPORTUNITY THAT WE MAY BE ABLE TO ENHANCE THEIR ABILITY TO MIGRATE AND HAVE A GREATER AREA OF REPAIR.

>>EJ Levy

NOW YOU'RE OBVIOUSLY JUST WORKING WITH THE ANIMAL MODEL; WHAT ARE SOME OF THE CHALLENGES OR OBSTACLES THAT YOUR TEAM IS FACING THAT YOU KIND OF NEED TO ADDRESS BEFORE YOU MOVE ON TO HUMAN CLINICAL TRIALS?

>> Dr. Kocsis

WELL, THERE ARE SEVERAL, AND THE FIRST ONE, WHICH IS VERY BASIC, IS WE NEED TO FIND THE RIGHT TYPE OF CELL TO HAVE THE RIGHT TYPE OF REPAIR, AND IN THE CASE OF MS, YOU KNOW, WE TALK ABOUT REPAIR, BUT I THINK WE AS A COMMUNITY ARE STARTING TO REALIZE THAT SIMPLY REMYELINATING AXONS IS NOT GOING TO BE THE FULL ANSWER. SIMPLY PROTECTING AXONS IS NOT GOING TO BE THE FULL ANSWER. THAT HAVING CELLULAR APPROACHES THAT MIGHT IMMUNOMODULATE THE SYSTEM TO PREVENT PROGRESSION OF THE INFLAMMATORY RESPONSE IS VERY EXCITING. SO IT'S GOING TO BE A

COMBINATION OF THESE THREE EVENTS. I'LL MENTION A GROUP AT THE SAN RAFFAELE HOSPITAL IN MILAN, ITALY. THEY'VE PUBLISHED SEVERAL VERY EXCITING PAPERS OVER THE LAST FEW YEARS SHOWING THAT SYSTEMIC OR INTRAVENOUS DELIVERY OF A NEUROPRECURSOR CELL INTO ANIMALS THAT HAVE AN MS-LIKE DISEASE, EAE -- EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS -- THAT THEY CAN STOP PROGRESSION OF DISEASE, AND THESE ANIMALS ACTUALLY LIVE CONSIDERABLY LONGER. AND THE UPSHOT OF THE WORK, TO PUT IT SIMPLY, IS THAT THEY HAVE AN IMMUNOMODULATORY EFFECT FROM THESE CELLS, SO COUPLING THAT WITH CELLULAR THERAPIES THAT COULD ACTUALLY REMYELINATE OR PROTECT AXONS FROM DYING IS GOING TO BE A VERY EXCITING PROSPECT. AND FOR ME, PART OF THE EXCITEMENT OF CELLULAR THERAPIES IS THAT CELLS ARE VERY PLASTIC AND WE MAY HAVE CELLS THAT CAN CARRY OUT MULTIPLE FUNCTIONS AT MULTIPLE PERIODS OF TIME IN MULTIPLE DISEASE STATES. SO ONE COULD HAVE A CELL THAT COULD MODULATE THE IMMUNE SYSTEM, BUT IF IT COULD ALSO ENTER THE LESION SITE AND CONTRIBUTE TO INDUCING REPAIR, IT'D BE VERY EXCITING. AND THERE'S EVIDENCE THAT THESE KINDS OF PLASTIC EVENTS FROM CELLS CAN INDEED OCCUR IN ANIMAL MODELS. SO THAT'S ONE OBSTACLE.

>> **EJ Levy**

ARE THERE SAFETY ISSUES THAT NEED TO BE ADDRESSED?

>> **Dr. Kocsis**

TONS OF SAFETY ISSUES. I MEAN, THE ULTIMATE SAFETY ISSUE, OF COURSE, IS TUMOR FORMATION. IF WE HAVE A CELL THAT IS PLASTIC, THAT IS PLURIPOTENT, IS VERY DIVERSE, THE LAST THING

WE WANT TO HAVE IS A TUMOR FORM IN A PATIENT. WE HAVE ANOTHER -- IT'S A LITTLE MORE ARCANE, BUT WE HAVE ANOTHER POTENTIAL POSSIBILITY. WHAT IF WE PUT CELLS INTO A PATIENT OR AN ANIMAL MODEL, AND THEY CAUSE REGENERATION, AND THEY ELICIT SPROUTING OF AXONS AND NEW CONNECTIONS ARE MADE? WHAT IF THOSE CONNECTIONS ARE MALADAPTIVE? BY THAT I MEAN, WHAT IF THEY NOW SIGNAL INAPPROPRIATE SENSATIONS OR MOVEMENTS? IT'S PRETTY WELL ESTABLISHED THAT AFTER CERTAIN INJURIES, THAT A PERIPHERAL NERVE, THAT ONE CAN HAVE CHANGES IN THE WIRING OF THE SPINAL CORD, SUCH THAT, IF YOU TOUCH SKIN, WHERE YOU WOULD NORMALLY FEEL SENSATION, YOU NOW REWIRE TO FEEL PAIN. SO THE LAST THING WE WOULD WANT TO DO IS HAVE CELLS ELICIT INAPPROPRIATE CONNECTIONS THAT ARE GOING TO LEAD TO NEUROLOGIC OR PATHOLOGIC EVENTS. THAT'S THE DOWNSIDE. THE GOOD SIDE IS VERY FEW STUDIES SUGGEST THAT IT OCCURS AFTER THE MULTIPLE TYPES OF CELLS THAT WE'VE TRANSPLANTED. IT DOESN'T SAY THAT IT DOESN'T, BUT THESE ARE NEGATIVE ELEMENTS THAT WE'RE ALL ON GUARD AGAINST IN THE ANIMAL STUDIES TO MINIMIZE THAT PROSPECT OCCURRING IN A CLINICAL STUDY.

>>EJ Levy

I'M SO EXCITED TO BE HERE AT THE VA HOSPITAL AT YALE TO TALK TO YOU TODAY, DR. STEPHEN WAXMAN.

>>Dr. Waxman

I'M REALLY INTERESTED IN RESTORATION OF FUNCTION IN DISEASES OF THE BRAIN AND SPINAL CORD, AND SO TO RESTORE FUNCTION, YOU

NEED TO UNDERSTAND FUNCTION, AND TO DO THAT, YOU NEED TO UNDERSTAND HOW NERVE FIBERS WORK. THAT TURNS OUT TO BE A WONDERFUL STORY IN TERMS OF THE BIOPHYSICS OF MOLECULES THAT MAKE NERVE CELLS MAKE NERVE FIBERS SPECIAL, AND WE'VE SPENT A LOT OF TIME STUDYING A FAMILY OF MOLECULES CALLED SODIUM CHANNELS. SODIUM CHANNELS ACT AS TINY MOLECULAR BATTERIES, AND THEY'RE PRESENT IN NERVE CELLS AND IN MUSCLE CELLS AND THESE MOLECULAR BATTERIES, THE SODIUM CHANNELS, ALLOW NERVE FIBERS TO GENERATE NERVE IMPULSES.

SO THAT'S BEEN A MAJOR THEME OF OUR WORK -- HOW DO NERVE FIBERS WITHIN THE BRAIN AND SPINAL CORD NORMALLY WORK; WHAT HAPPENS TO THOSE NERVE FIBERS IN DISEASES LIKE MS; WHY DO WE SEE REMISSIONS? WHY DO WE SEE THIS STRIKING RESTORATION FUNCTION IN SOME PEOPLE WITH MS? WHAT'S GOING ON TO SEE THIS REMARKABLE RECOVERY OF FUNCTION THAT WE DON'T SEE IN OTHER NEUROLOGICAL DISORDERS? CAN WE UNDERSTAND WHAT'S GOING ON, AND CAN WE THINK ABOUT INDUCING REMISSIONS? THOSE ARE OUR MAJOR MOTIFS IN OUR RESEARCH.

>>EJ Levy

SO WHAT DOES HAPPEN IN MS WITH LOSS OF FUNCTION TO THESE TINY MOLECULAR BATTERIES?

>>Dr. Waxman

WELL, THAT GOES BACK TO A FUNDAMENTAL QUESTION ABOUT THE ARCHITECTURE OF NERVE FIBERS WITHIN THE BRAIN AND SPINAL CORD. AS YOU KNOW, THEY'RE INSULATED BY A SUBSTANCE CALLED MYELIN. AN ELECTRICAL ENGINEER WOULD

SAY THAT MYELIN HAS A HIGH ELECTRICAL RESISTANCE, A LOW CAPACITANCE. WHAT THAT MEANS IS IT ACTS AS AN INSULATOR, AND THE MYELIN IS MISSING AT SMALL LITTLE GAPS, A MILLIMETER OR SO FROM EACH OTHER ALONG THE NERVE FIBER. THESE ARE CALLED NODES OF RANVIER AND TRADITIONALLY IN WHAT I CALL THE PREMOLECULAR ERA, MS WAS THOUGHT OF AS PURELY A PASSIVE DISEASE; THE MYELIN INSULATION IS DAMAGED, THERE'S A SHORT CIRCUIT AND THAT'S THE END OF THE STORY. AND IT WASN'T UNTIL THE DEVELOPMENT OF MODERN MOLECULAR TECHNIQUES THAT IT BECAME POSSIBLE TO SAY, WELL, WHAT'S GOING ON IN THE AXON, THE NERVE FIBER? AND THE FIRST QUESTION WAS HOW IS IT BUILT? WHERE ARE THE SODIUM CHANNELS, HOW DO THEY FUNCTION? AND THE FIRST SURPRISE IS THAT THE SODIUM CHANNELS IN MYELINATED NERVE FIBERS ARE NOT DISTRIBUTED ALONG THE ENTIRE LENGTH OF THE NERVE FIBER. THEY'RE CLUSTERED, THEY'RE FOCUSED JUST WHERE THEY'RE NEEDED, AT THE SMALL NODES OF RANVIER, WHERE THERE'S NO MYELIN. AND FROM AN ARCHITECTURE POINT OF VIEW, THIS IS REALLY ELEGANT ARCHITECTURE. EVERY MOLECULE IS IN ITS PLACE. THESE ARE BEAUTIFULLY DESIGNED DEVICES, NERVE FIBERS, BUT IT DOESN'T WORK SO WELL WHEN THE MYELIN IS DAMAGED, BECAUSE NOW ONE NOT ONLY HAS A SHORT CIRCUIT, BUT THERE ARE VERY FEW SODIUM CHANNELS UNDER THE MYELIN. SO WHEN THE MYELIN IS GONE, NOT ONLY IS THE INSULATION DESTROYED, BUT THE PART OF THE NERVE FIBER UNDER THE MYELIN IS ELECTRICALLY DEAD. IT'S INCAPABLE OF GENERATING ELECTRICAL IMPULSES, AND THAT WAS

THE FIRST HINT THAT THE AXON IS A MAJOR PLAYER AS WELL AS THE MYELIN IN DISEASES LIKE MS, AND THE SURPRISE THERE WAS THAT NERVE FIBERS CAN REBUILD THEMSELVES -- SOME NERVE FIBERS. AFTER LOSS OF MYELIN, THEY CAN PLUG IN ADDITIONAL SODIUM CHANNELS IN AREAS THAT USED TO LACK SODIUM CHANNELS. THEY USED TO BE COVERED BY MYELIN; NOW THERE'S NO MYELIN THERE AND THE NERVE FIBER IN SOME WAY PLUGS SODIUM CHANNELS IN MOLECULAR BATTERIES INTO THE AREAS WHERE THEY'RE NEEDED, AND NOW IS ABLE TO CONDUCT IMPULSES WHICH CREEP SLOWLY BUT SECURELY ALONG THE NERVE FIBER, CARRYING INFORMATION. SO THIS IS A REMARKABLE FORM OF WHAT I CALL MOLECULAR REMODELING, AND IT'S WHAT HAPPENS WHEN VISION IS RESTORED, ABILITY TO WALK IS RESTORED, IN PEOPLE WITH MS.

>>EJ Levy

SO IF WE KNOW IF THAT'S KIND OF NATURAL REPAIR, I'M ASSUMING THAT SOME OF YOUR RESEARCH IS INTERESTED IN HOW WE CAN MAKE THAT -- STIMULATE THAT TYPE OF REPAIR WHEN IT'S NOT NATURALLY HAPPENING.

>>Dr. Waxman

THAT'S ABSOLUTELY RIGHT, AND SO A NEXT STEP, NOW THAT WE KNOW WHAT IS HAPPENING, IS TO DISSECT THE PROCESS AND GET CONTROL OF IT. OUR GOAL IS TO BE ABLE TO INDUCE RESTORATION OF IMPULSE CONDUCTION IN CHRONICALLY DEMYELINATED AXONS. TO DO THAT, WE HAVE TO UNDERSTAND HOW THE GENES ARE CONTROLLED THAT PRODUCE THINGS LIKE SODIUM CHANNELS -- HOW THE GENES ARE TURNED ON, HOW THEY'RE TURNED ON IN THE RIGHT CELLS, HOW ARE THEY THEN TURNED OFF, AND THAT'S A MAJOR THRUST OF OUR RESEARCH RIGHT NOW.

>>EJ Levy

I'M LOOKING AT MS DIFFERENTLY NOW THAN I EVER HAVE, AND I'M SO THANKFUL TO EVERYONE AT THE MS SOCIETY THAT GOT ME INVOLVED IN THIS PROJECT, AND THAT I GOT TO ACTUALLY GO IN AND THANK THE DOCTORS AND THANK THE LAB TECHNICIANS THAT GO TO WORK EVERY DAY TO TRY TO MAKE MY LIFE BETTER AND YOUR LIFE BETTER, AND WHEN YOU SEE ALL THOSE PEOPLE HARD AT WORK, YOU JUST KNOW THAT WE WILL FIND A CURE SOMETIME SOON.

**Tracey** >> We've certainly learned a lot over the past three segments of "To Repair and Protect: The Future of MS Treatments".

**Tom** >> Yes we have,. And if you want to learn more, click on the Resources button below. Thanks for joining us on MS Learn Online.