Highlighting the importance of upper motor neurons

Dr Hande Özdinler is a neurobiologist whose research into upper motor neuron biology has unearthed many significant findings. She discusses her motivations and vision for her own research and that of young women scientists.

Could you begin by explaining what amyotrophic lateral sclerosis (ALS) is and how it affects motor neurons in the spinal cord?

ALS is one of the most complex neurodegenerative diseases, where the motor neurons in the spinal cord, brainstem and the brain deteriorate. Because it is the motor neurons that are primarily affected, the patient cannot move, but can remember and still have cognitive function. The neurons in the brain and spinal cord that are important for movement die, which results in paralysis and, eventually, death. However, other neurons remain relatively healthy in the patient.

Why did you become interested in studying ALS? What made it particularly important for you to focus your research on corticospinal motor neurons (CSMN)?

The reason has a personal touch behind it. I lost my brother to a thalamic stroke at the age of 23 and, at the time, knew nothing about the brain. I changed my topic and programme, and earned a PhD in the fields of cell biology, anatomy and neuroscience at Louisiana State University Health Sciences Center. After that, I went to the Harvard Medical School Neurosurgery Department for postdoctoral studies.

I focused on corticospinal motor neurons during my studies and these are the neurons that die in ALS patients’ brains. I immediately developed a personal bond with the patients, their caregivers and loved ones.

You were the first person to label, isolate and culture CSMN. What did you discover about these upper motor neurons’ requirements for survival and growth?

We found many cellular pathways and events that are crucial for the function and health of CSMN. When these cellular events are perturbed, or become dysfunctional, CSMN begin to show signs of vulnerability and early degeneration. One example is the endoplasmic reticulum (ER) stress; when there is increased ER stress, other neurons manage to cope with it, but CSMN cannot do so as effectively as other neurons.

Your team received a Northwestern University Translational Innovation Award for creating an effective method for selectively targeting CSMN without affecting other neuron populations. How does this retrograde transduction approach work?

Transducing just the neurons of interest is extremely important for developing long-term and effective treatment strategies. The cerebral cortex is complex, with billions of neurons that are different in type, function, size and shape, and all interconnected with each other. However, in diseases, not all neurons show initial vulnerability; for reasons still unknown, only a select set of neuron populations show primary vulnerability and undergo degeneration. When we better understand the causes that underlie these diseases, we will want to deliver the therapies directly to these neurons, without affecting other neurons in the brain so that we do not perturb their balance.

How did you come to generate and characterise a reporter line that made upper motor neurons visible in the brain?

We searched thousands of genes that showed high levels of expression in CSMN and are longlasting and stable. UCHL1 gene is expressed in almost all neurons to varying degrees, but CSMN express high levels, with expression present even at very old ages. We therefore chose to generate using a BAC construct that expresses the eGFP gene under the control of UCHL1 promoter.

Finally, how important is it for women to be fostered in science and technology to help drive innovation forward?

I think women have the potential to lead the way in innovation because they have a different way of leading – with understanding, compassion and desire. Innovation stems from our ability to see what others do not, and is fuelled by our will to make a difference in the world. In my opinion, women have an intrinsic ability to be innovative and creative. When given an equal chance, women always do well and exceed any expectations. Thus, in addition to being a scientist, I am a keen supporter of women in science.

I am one of the Women in STEM faculty members and am on the board of the Turkish American Women Scholar Fund (TAWSF), which funds the college education of young women who are accepted to universities but have socioeconomic limitations. So far, we have helped over 125 female students to graduate and we will continue to offer assistance.
Researchers at the Northwestern University Feinberg School of Medicine, USA, have made several important findings in their research on a neurodegenerative disorder that renders patients paralysed. In facilitating analysis of specific neurons, there is hope of a cure in the future.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a disorder that leads to the deterioration of neurons in the spinal cord, brainstem and brain. As many of these neurons control voluntary movement, patients are often rendered paralysed by the condition. The disorder is known also as Lou Gehrig’s disease, named after the former American baseball player whose career – and life – was tragically cut short as a result of this disease. Currently, there is no known cure for the condition, which affects two in every 100,000 people.

Attempts to understand the underlying causes of neurodegenerative diseases such as ALS are challenging for various reasons. Not only is the brain one of the most complex organs known to science, it is made up of billions upon billions of neurons and non-neuronal cells. These vast numbers make it extremely difficult to pinpoint the specific neuron populations affected by ALS, thereby hindering development of effective treatment strategies.

Indeed, in addition to the thousands of different types of neurons and non-neuronal cells, ALS is known to only affect some neurons and, even then, does not affect them to the same degree. While some neurons might show vulnerability from the outset of the disease, others appear to be intact. The complexity of the brain makes isolating those affected neurons from their unaffected counterparts particularly difficult, but is a necessary step in understanding why they become vulnerable and degenerate in patients.

SPOTLIGHTING SPECIFIC NEURONS Over the past few years, researchers at the Northwestern University Feinberg School of Medicine have given cause for hope in successfully treating this extremely debilitating condition. Led by Dr Hande Özdinler, the team has developed innovative approaches to studying the biology of motor neurons in the brain that become vulnerable as a result of ALS. Indeed, Özdinler became the first person to label, isolate and culture the corticospinal motor neurons (CSMN), in an effort to understand their requirements for survival.

CSMN are extremely complex neurons and control voluntary motor function. They are therefore of particular interest to researchers investigating ALS. Özdinler’s research now enables direct investigation of CSMN by employing novel cellular and molecular approaches. “Being able to see the neurons that become vulnerable in the disease has been very important, because for the first time we were able to see and identify them within the complex and heterogeneous structure of the brain,” explains Özdinler. “This allowed their isolation as a pure neuron population and determined why they become vulnerable in the disease while others remain healthy.”

ENABLING APPLICATION DEVELOPMENT Finding a means of accessing the information directly from the neurons affected by ALS is
BRINGING LIGHT TO THE UPPER MOTOR NEURONS IN AMYOTROPHIC LATERAL SCLEROSIS

OBJECTIVES
• To further understanding of the causes of amyotrophic lateral sclerosis (ALS) through using innovative approaches to study corticospinal motor neurons (CSMN)
• To emphasise the crucial role that upper motor neurons play in the development of ALS to help find a cure

PARTNERS
Cognitive Neurology and Alzheimer’s Disease Center, USA
Robert H Lurie Comprehensive Cancer Research Center at Northwestern University, USA

FUNDING
Les Turner ALS Foundation
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HANDÈ ÖZDİNLER is trained in the fields of molecular biology, genetics, cell biology, anatomy and neuroscience. Her research focuses on CSMN and she is Founding Director of the second Les Turner ALS Laboratory at Northwestern University, USA. She received awards from Harvard and Northwestern University for her ability to study these neuron populations in detail.

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FUNDING SUCCESS

To continue research on amyotrophic lateral sclerosis (ALS), Özdinler was awarded over US $2.5 million in new grants from the US National Institutes of Health (NIH) and the ALS Association – a record amount for a single young investigator to receive at one time. Visit:


of extreme importance and enables analysis of those of specific interest without affecting other neurons. Previous research endeavours have used cell lines that are not related to the disease, or differentiated neurons that are forced to become one neuron type, despite carrying many different variations. Özdinler’s research is exciting because it moves away from former practices, uncovering many of the mysteries associated with ALS. “We are at the doorstep of many important discoveries,” she says. “Our research will reveal the mystery of why these neurons die, while others remain healthy.”

Finding a means to analyse the neurons involved in the paralysis associated with ALS – without unduly affecting other neurons – is crucial to the development of successful therapeutic applications. Finding an effective treatment for the condition is one thing, but unless that treatment can be delivered to the cells responsible, any treatment will remain ineffective. As their studies continue, so too does the impact of their findings, with other studies revealing potential detection markers for the diseases in which CSMN are affected, including hereditary spastic paraplegia, primary lateral sclerosis as well as ALS.

PULLING IN THE SAME DIRECTION

Özdinler’s research is funded and supported by the US National Institutes of Health (NIH), the ALS Association and, most significantly, by the Les Turner ALS Foundation, which Özdinler readily acknowledges: “Foundations are the engines of innovation. They are founded by people who want to implement change and have

the energy and desire to make that happen. They generate a momentum that no one can resist. If there were no active foundations for causes that are important, we would not be able to move the field forward at such a speed”.

The ALS Association is the largest in the US, and the Les Turner ALS Foundation is one of the first foundations in the world to promote a better life for patients affected by ALS, and encourages and facilitates research into understanding the biology of the disease and finding an effective cure.

ALS associations and foundations have embraced initiatives like the ‘ice bucket challenge’ to provide people with a voice to communicate their desire to stop the disease. It is important that researchers such as Özdinler take up the challenge laid before them to make a real difference to people’s lives. “Now the ball is in our court,” says Özdinler. “We have to be as ambitious as the patients and caregivers to find a cure. It’s not really about papers, grants and promotions – it is about getting together to work towards a solution.”

Özdinler’s research has highlighted the important role that upper motor neurons play in motor neuron diseases where movement is impaired, thereby encouraging other researchers around the world to focus their energies on these particular neurons to develop a cure. Emphasising this importance could signal positive change for ALS patients, which is certainly something to be celebrated.

DIRECT CORTICAL INJECTION

CORTICOSPINAL TRACT INJECTION

AAV-GFP serotypes
Red fluorescent microspheres

AAV-GFP serotypes
Red fluorescent microspheres

AAV-GFP serotypes
Red fluorescent microspheres

AAV-GFP serotypes
Red fluorescent microspheres


INTERNATIONAL INNOVATION