Neuroprotective strategy

Experienced neurosurgeon and innovative bench investigator Professor Ludmila Belayev is studying neuroprotection in brain ischaemia and trauma. Her goal is to improve existing therapies, ultimately enhancing care for an ageing population.

What are ischaemic and haemorrhagic stroke, and what are their neurological implications?

A stroke is the sudden death of brain cells in a localised area due to inadequate blood flow. About 85 per cent of strokes are ischaemic – usually as a result of a blocked artery, which is often caused by a blood clot or embolus. Thus brain cells are deprived of their blood supply and do not receive enough oxygen and glucose, which are carried by blood.

The other 15 per cent of strokes – haemorrhagic – are due to bleeding in or around the brain. In this type of stroke, a blood vessel ruptures, interfering with normal blood flow and allowing blood to leak into brain tissue or around the brain. Depending on the region of the brain affected, a stroke may cause paralysis, speech impairment, loss of memory and reasoning ability, coma, or death.

Are there drawbacks associated with current treatments for these conditions?

Ischaemic stroke therapy is aimed at removing the blockage by breaking down a localised area of tissue (thrombolysis) or by removing it mechanically (thrombectomy). The only Food and Drug Administration (FDA)-approved treatment for ischaemic strokes is tissue plasminogen activator (tPA). Unfortunately, use of tPA is restricted by a narrow therapeutic window of up to four and a half hours after stroke onset and has multiple absolute contraindications, especially for individuals with any increased bleeding risk. As a result, only 3-5 per cent of patients qualify for this therapy.

Therapies for haemorrhagic stroke are limited and depend upon the cause of bleeding. The types of surgery used include aneurysm clipping, coil embolisation, and arteriovenous malformation repair. A potential treatment for haemorrhagic stroke is surgical evacuation of the haematoma. However, the role of surgical treatment for supratentorial intracranial hemorrhage remains controversial. Endovascular therapy using coil embolisation, as an alternative to surgical clipping, has been increasingly employed with great success, although controversy still exists over which treatment is ultimately superior.

Can you explain how you are improving existing therapies?

The pathology of stroke is incredibly complex, and treatment of its devastating effects is a continuing medical challenge. One complicating factor in the development of neuroprotective strategies is the dual nature of many of the processes that occur in the brain during stroke. The activity of microglia and other inflammatory cells, for example, can be either damaging or protective depending on the extent of injury, location, and timing of their effects. Even mechanisms of cell death can be beneficial in the right circumstances. The development of prospective neuroprotective agents, therefore, must take both the positive and negative aspects of the stroke response into consideration, to ensure that they are administered under the conditions that are most appropriate and will produce the greatest benefit.

Does collaboration play an important role in these efforts?

The field of translational research requires extensive interaction among academic, clinical and translational researchers and industrial developers. These collaborations are needed to help steer research in the right direction, and can only be addressed by a multidisciplinary, multi-institutional approach.

You tested a docosahexaenoic acid (DHA)-albumin (Alb) combination as a potential treatment for ischaemic and haemorrhagic stroke. What did you find?

Treatment with this DHA-Alb complex, in an experimental stroke model, resulted in improved neurological outcomes, reduced infarct volumes and greater cell survival compared to that obtained with native Alb alone and at considerably lower Alb doses (0.63 g kg⁻¹). The DHA-Alb complex also provides neuroprotection against haemorrhagic stroke in rats by improving behavioural score and reducing haematoma volume, compared to the corresponding Alb groups.

How have you overcome potential challenges during this work?

The preclinical evaluation of neuroprotective drugs for stroke has almost totally relied on the use of young animals, despite the effects of ageing on cerebrovascular disease development in humans. In addition, difficulties in establishing a reproducible stroke model in aged animals, and lack of attention to the penumbra and to several risk factors that heavily affect stroke outcomes (including hypertension and diabetes), might partly explain the failure of the clinical studies attempting to translate findings from neuroprotective drug studies in animals to humans. We employed several features in our experimental design that are commonly overlooked in preclinical stroke studies, including the use of aged rats with long-term follow up and attention to diabetes and hypertension, major factors known to exacerbate stroke outcomes.

What do you expect the impact will be?

The knowledge generated from our project will have a significant direct impact on translation of this therapy for ischaemic and haemorrhagic stroke to the clinic, and will be highly relevant to improving care for an ageing population.
On average, a stroke occurs every 40 seconds in the US, where it is the fourth leading cause of death and the principal cause of significant, long-term disability. Age is one of a number of risk factors for the disease, with nearly 75 per cent of all strokes occurring in people aged 65 or over. The most common kind, ischaemic stroke, occurs when a blood vessel carrying blood to the brain is obstructed by a blood clot, preventing the transportation of oxygen and nutrients and causing brain cells to die. Haemorrhagic stroke, which accounts for 15 per cent of cases, is caused by a ruptured brain aneurysm or a weakened blood vessel leak. This results in blood spilling into the brain, which damages cells and tissue due to swelling and pressure.

The need to act fast to limit damage caused by this life-threatening condition is well documented and treatment consists of administration of antiplatelet medicine – chiefly tissue plasminogen activator (tPA) – or surgery, including aneurism clipping or coil embolisation. tPA is an enzyme that occurs naturally in the body and dissolves clots. Recombinant DNA technology has allowed large amounts of this natural substance to be produced, which can be administered to the site of the blockage, enabling high concentrations of the protein to build up and dissolve the clot. However, a notable shortcoming of this line of defence is its limited window: to be effective tPA must be administered within four and a half hours of the start of the stroke.

Firm Foundations

Professor Ludmila Belayev, an expert in neurosurgery, neurology and neuroscience, is based in Louisiana State University Health Sciences Center (LSUHSC)’s Department of Neurosurgery and the Neuroscience Center of Excellence. Her aims are aligned with those of the Center; conducting research of the highest calibre that advances understanding of brain function and diseases that affect the nervous system, as well as mentoring the next generation of neuroscientists. An accomplished bench investigator, Professor Belayev is recognised both nationally and internationally for her innovative studies on the pathophysiology and treatment of ischaemic and haemorrhagic stroke, and since joining LSUHSC she has begun a pioneering programme in stroke research.

In a bid to develop a therapy without the limitations associated with tPA, Professor Belayev is engaged in multidisciplinary research on the pathophysiology and treatment of stroke. She has developed a comprehensive series of experimental studies demonstrating the neuroprotective properties of high doses of the most common protein found in the blood, albumin [Alb]. This work led to clinical trials supported by the National Institutes of Health (NIH) and has formed a solid foundation for continuing studies.

A Novel Combination

In response to a lack of preclinical studies that translate into clinical trials Professor Belayev ensured the careful design of her investigations. “The Stroke Therapy Academic...
Having demonstrated the potential clinical feasibility of administering DHA-Alb therapy to patients with acute ischaemic stroke, looking ahead, the focus of Professor Belayev and her team will be on further defining the effects of this treatment using their elderly experimental stroke model.