Ischemic Stroke: New Targets from a Clinically Relevant Primate Model

Monash University researchers have developed a non-human primate (NHP) model that accurately replicates the stages of disease progression in human ischemic stroke. Using this model, the team has identified new receptor tyrosine kinase based targets that distinguish the differential responses of human and infant brains to ischemic injury. These targets modulate reactive astrocyte activity and their stimulation could ameliorate functional recovery in the weeks following ischemic insult in the adult to provide a paradigm shift in the treatment of this indication.

Summary of Opportunity:

- Novel and clinically relevant NHP model for developing ischemic stroke drugs.
- Identified targets and agents for modulating reactive astrocyte activity in adult brain to prevent glial cell scar formation in the days and weeks post ischemic event.
- Potential for a differentiated MoA and administration route/timing; and
- Potential for ‘first in class’ and ‘best in class’ stroke drugs suitable for all ischemic stroke patients.

Background

Ischemic stroke and other cardiovascular diseases are the world’s second leading cause of mortality, after ischemic heart disease. Stroke survivors often suffer permanent, irrecoverable functional impairments including motor or sensory loss, speech impediments as well as other cognitive impairments including memory loss.

In 2012, the total economic burden of stroke was estimated at $50 billion. However, despite the overwhelming incidence and socioeconomic burdens, only one treatment option is used to any effect in the clinic.

Tissue plasminogen activator (tPA) is a thrombolytic that is only administered to around 7-10% of stroke victims to remove/reduce the blockage. Strict criteria govern the use of tPA due to the risk of intracranial haemorrhages, therefore, not all patients qualify for treatment such as those suspected of having hypertension and related CV indications. Given the ischemic nature of the disease, this immediately rules out many patients.

More importantly, the effective time window for tPA treatment is within the first three hours after the initial stroke onset. These criteria limit the effectiveness and long-term feasibility of tPA as a treatment standard. Especially since tPA treatment becomes ineffective after the initial acute time window has closed. As such, there is only a 35% success rate—suggesting that only 3% of all ischemic patients receive any benefit from tPA treatment.

As such there is a great need to discover new medicaments that can treat stroke via more sophisticated mechanisms in all patients over the hours, days and weeks post a cerebral ischemic event.

The opportunity

The major factor limiting functional recovery in adult stroke patient is the formation of scar tissue in the brain in the sub-acute period. This glial scarring is formed by reactive astrocytes and exaggerated around 2-4 weeks post injury. The result is a scar that is refractory towards regeneration, leading to permanent functional impairments.

However, it has been observed that infants retain greater capacity for functional recovery after brain injury compared to adults. The Monash team therefore studied if this capacity is related to differences in glial scar formation. Using a proprietary NHP model which bears excellent translatability to the human disease, Monash University researchers have shown that the infant brain undergoes less extensive reactive astrocyte activity compared to adults after stroke. This correlates to the establishment of a smaller glial scar in infants that is, presumably, more permissible to functional recovery.

Further, the team was able to identify pathways and molecules that regulate astrocyte activity after injury in the infant and, using the compositions that stimulate the ‘infant pathway’, show a strong inhibition of astrocyte reactivity in adult cell models in vitro.

This finding is significant because the reduction in astrocyte reactivity could minimize scar formation in the adult brain, especially during the sub-acute period where regeneration is halted by glial scarring, and drive functional recovery. PoC experiments to test this theory are being initiated in the NHP model. The team has also compared the mouse and human models of stroke and detected fundamental differences in the timing of astrocyte reactivity. These data suggest that rodent models are likely to be unsuitable for the discovery of stroke drugs and could explain why drugs that inhibit this mechanism have never been previously discovered—and why previous drugs failed to show utility in the clinic.

Monash is seeking partners to find and develop new ischemic stroke targets and medicaments using its NHP model.


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