# Advances in Translational Medicine 2012

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Translational stroke research moves ahead in spite of a few more failures of clinical trials in 2012. Several factors are thought to contribute to explain the failure in translating experimental studies in stroke to the clinics, e.g. experimental stroke models might be too different to human stroke, there might be biases in some experimental findings, and the pathophysiology of acute brain damage caused by stroke might be different in humans and animals. The current criticism is forcing to improve the quality of experimental studies and to increase the requisites and filters that any molecule has to overcome before going into clinical research. In this short overview we will describe some translational stroke research that has taken place in 2012.

Currently, a candidate drug for successful translation is the PSD-95 inhibitor NA-1 that uncouples postsynaptic density protein PSD-95 from neurotoxic signaling pathways.[1] PSD-95 binds NMDAR GluN2 subunits and the neuronal nitric oxide synthase.[2] Disrupting this complex with PSD-95 inhibitor administered after stroke onset in rodents and non-human primate models reduced infarct volume, and ameliorated the neurological deficit.[1] Investigation on this therapeutic strategy has followed a process that illustrates bench to bed translation on the basis of the pre-clinical evidence of beneficial effects of this drug. Results of the ENACT phase II trial evaluating safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair showed lower stroke incidence in patients of the NA-1 group,[3] but larger trials are needed to demonstrate efficacy.

Several concepts arising in part from experimental findings are now being tested in humans. The notion that co-administration of certain drugs could augment the value of thrombolytic therapy is attractive but needs validation in the clinic. Several stroke trials combining hypothermia with intravenous thrombolysis are currently underway (e.g.

ICTuS2/3, EuroHYP-1). The benefits of hypothermia are supported by very robust results in experimental research,[4] but its translation to the clinics is methodologically extremely challenging.[5] Other ongoing trials test the hypothesis that damping oxidative stress will synergistically benefit tPA treatment. For instance, a phase III trial is testing the administration of the natural antioxidant uric acid in thrombolysed patients in view of the improved outcome and smaller infarctions in rodents treated with this combination.[6] Neurons are rapidly lost after stroke leading to the concept 'time is brain'.[7] Accordingly, neuroprotection is more frequently found in animal models when drugs are administered shortly after stroke onset. This urgency led to designing strategies for emergency treatment starting before the patient reached the hospital, before distinction between ischemic and hemorrhagic stroke can be made. Completion is waiting for the large phase III FAST-MAG stroke trial in which magnesium sulfate, a compound with antagonistic actions at the NMDA receptor, is administered at the ambulance.

Following experimental results showing anti-inflammatory actions of minocycline,[8] the outcome of a phase I stroke clinical trial aiming to test the efficacy of this drug in reducing neurological sequelae is awaited. Increasing experimental evidence supports that stroke induced-inflammation is accompanied by immune responses that affect the outcome.[9-11] The deleterious role of complement activation has been shown in experimental stroke models,[12-14] and complement-induced neuronal cell death after brain ischemia was prevented by intravenous immunoglobulin (IVIG).[15] Now a clinical trial (IVIG/AIS) will test whether immunoglobulin can affect the rate of progression of brain ischemia by scavenging complement fragments. Neuroinflammation and immune responses are tightly related to abnormal function of the blood-brain barrier (BBB) after brain ischemia, and the involvement of matrix metalloproteinases has been extensively documented.[16,17] Loss of BBB integrity is associated to hemorrhagic transformation,

which is a frequent complication of thrombolysis. Therefore, strategies aimed to prevent BBB leakage deserve future clinical investigation.

Compared to ischemic stroke, there have been less experimental investigations on intracranial hemorrhage,[18] and the molecular and cellular mechanisms underlying hemorrhagic brain damage remain poorly understood.[19] Secondary vasospasm after subarachnoid hemorrhage has been the main target in clinical trials, but failure of anti-vasospastic drugs to improve the outcome again points to the need of better understanding early and delayed brain injury after hemorrhage.[20]

Finally, cell therapies, particularly stem cell transplantation, remain an attractive research target.[21,22] Exciting recent experimental findings showed that adult human somatic cells that have been reprogrammed to become induced pluripotent stem cells form functional neurons and improve recovery after grafting in stroke-damaged rodent brain.[23] A number of clinical trials administering various types of stem cells to stroke patients are currently ongoing in China, North America, and Europe. Plasticity mechanisms supporting recovery after stroke have been demonstrated in animals after different interventions,[24, 25] and non-invasive imaging techniques are invaluable tools to monitor some of these responses.[26] However, translating restorative therapies from the laboratory to the clinic is still facing tremendous challenges.[27]

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