The Stroke Penumbra is a Translational Target

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Therapies for acute stroke have yielded very limited success in clinical trials. The current target of acute stroke therapy is to salvage the ischemic penumbra. The ischemic penumbra is a region surrounding the ischemic core that maintains some blood flow supplied by collateral circulation, and therefore survives the initial perfusion deficit. Regrettably, the penumbra often progresses to infarction over time with irreversible damage advancing from the region of the most severe blood flow reduction to the peripheral regions with less disturbed perfusion. This progression of damage is characterized by a complex cascade of electrophysiological, molecular, metabolic and perfusion disturbances. Although reduced local cerebral blood flow (LCBF) is a major factor responsible for necrotic injury, other events, including lipid peroxidation, inflammatory responses and brain edema, may contribute to either the severity or progression of penumbral injury. Thus, ischemia in the penumbra causes dysfunctions, but not severe enough ones to result immediately in irreversible damage. Prompt restoration of adequate perfusion in the penumbra by injection of thrombolytic agents may slow down the onset of irreversible damage in this area, thus limiting neurological deficit.

The window of opportunity for salvaging the penumbra is very short. Restoration of the blood supply can reduce more extensive brain tissue injury by salvaging reversibly damaged penumbral tissue. One therapeutic modality that has shown efficacy is thrombolysis using either intravenous or intra-arterial infusion of tissue plasminogen activator (r-tPA). This mechanism provides a rationale for clinical trials, which have demonstrated that reperfusion after thrombolysis improves clinical outcome in selected patients with acute stroke. Neuroprotection strategies are novel experimental therapies that aim to diminish blood–brain barrier (BBB)

breakdown and polymorphonuclear (PMN) activation in the parenchyma, accelerate inflammatory resolution, and downregulate apoptotic cell death. In animal models, intravenously infused docosahexaenoic acid (DHA) provides an expanded time window of penumbra protection with neurological recovery after middle cerebral artery occlusion (MCAO) (Belayev et al., 2011).

Imaging the penumbra is a new strategy for detecting tissue at risk. It has been reported that roughly half of all acute ischemic patients still have penumbral tissue 18 hours after stroke on magnetic resonance imaging (MRI), and as such these areas are potentially salvageable. Yet, due to comorbid conditions and contraindications, only 8% of all ischemic stroke patients are eligible for treatment with r-tPA. The remaining patients have potentially salvageable tissue with no medical means to increase the chance of survival. The penumbra has traditionally been studied by positron emission tomography (PET) and single photon emission computed tomography (SPECT), but recently magnetic resonance imaging (MRI) techniques have also allowed us to gain insight into the mechanisms underlying ischemia. Cerebral blood flow techniques such as PET and SPECT have been shown to correlate with clinical outcome and have been used with success for clinical trials. More recently, the hypoxic ligand ^{18}F-fluoromisonidazole (FMISO) and the neuronal receptor ligand ^{11}C-flumazenil (FMZ) have been used to refine the capability of PET to identify the penumbra. The use of ^{18}F-FMISO PET with quantitative three-dimensional mapping of the penumbra in acute ischemic stroke patients, grouped by time since stroke onset, demonstrates a central to peripheral evolution of infarction with eventual loss of the penumbra. CT perfusion has great promise as a diagnostic tool due to its ability to deliver reliable perfusion maps accurately. The passage of the contrast agent through the brain can be recorded, and parametric maps of cerebral blood volume and flow, as well as

contrast mean transit time, can be generated. Using these imaging modalities to identify the ischemic penumbra is an important next step in extending the therapeutic time window beyond five hours and providing acute stroke therapy to those patients most likely to respond (see figure below).

Panel A: Drawing showing ischemic core and penumbra. Blood flow reduction causes metabolic disturbances at certain blood flow thresholds. The ischemic core has depleted ATP levels while the penumbra has a gradient reduction of ATP between normal/oligemic tissue and the ischemic core. **Panel B:** Diffusion-weighted image (DWI), T2-1weighted image (T2-WI), apparent diffusion coefficient (ADC) and fluid-attenuated inversion recovery (FLAIR) showing a hyperintense lesion and edema (bright regions; yellow arrows) 18 hours after stroke (Courtesy of Karen A. Tong, M.D., Loma Linda University, CA).