NRC Institute for Biological Sciences (NRC-IBS)

Business Opportunity:

Anti-Apoptotic Antibodies

The Business Opportunity

Stroke is an acute neurologic injury whereby the blood supply to a part of the brain is interrupted, either by a clot in the artery or if the artery bursts. The result is that the part of the brain perfused by that artery no longer can receive oxygen carried by the blood and dies (becomes necrotic), causing the cessation of function from that part of the brain. Initial treatment for ischemic stroke involves the use of Tissue plasminogen activator (tPA) as a medication to break up blood clots and restore blood flow when administered within 3 hours of the event. However, oxidative stress-induced apoptosis leads to tissue and neurological damage as a consequence of the ischemic event and loss of some basic brain functions.

Approximately 50,000 Canadians and 750,000 Americans suffer stroke incidents each year – with annual incidence rates rising to greater than 1.5% for Americans over 65. Due to the narrow time window for delivery, it is estimated that tPA is given to only 4% of stroke patients, the most popular being Activase by Genentech/Roche with sales over $500M per year. A successful anti-apoptotic antibody or small molecule, with a much larger window of delivery, should expect a larger market.

NRC-IBS, with a University of Windsor collaborator, has developed several antibodies and isolated two small molecular weight compounds capable of inhibiting oxidative stress-induced apoptosis, thus offering protection against neurological damage during an ischemic event.

The Technology

Inappropriate induction of apoptosis has been shown to be involved in the development of neurodegenerative diseases and neurological damage due to ischemic stroke. Since Bax and Caspase 3 are key intracellular components in the apoptosis pathway, single-domain intracellular antibodies (‘intrabodies’) with inhibitory action against Bax and Caspase 3 would have potential for the therapy of neurodegenerative disorders and stroke. The efficacy of intrabodies critically depends on their stability. Since in the reducing environment of the cytoplasm intrabodies cannot form their stabilizing disulfide linkage(s), only those that are of sufficient stability can tolerate the absence of the disulfide linkage and be expressed in functional form.

Traditionally, single chain Fvs (scFv; a molecule consisting of an antibody heavy chain variable domain, VH, and a light chain variable domain, VL, joined together by a linker) have been used as intrabodies. More recently, the feasibility of three types of single-domain antibodies (sdAbs), VLs, VHs and VHHs (VHs derived from camelid heavy chain antibodies), as intrabodies has also been demonstrated. While offering a comparable affinity, sdAbs have higher stability, solubility and expression level than scFvs and thus, are more efficacious as intrabodies.

Several Bax- and Caspase 3-specific VHH single-domain intrabodies have been developed. These intrabodies are nontoxic to their mammalian host cells and rendered them highly resistant to oxidative-stress-induced apoptosis and, thus, are promising drugs in the context of gene therapy.
Additionally, using one of the aforementioned VHH intrabodies in competition assays, NRC-IBS identified, from a pharmacore library, two small molecular weight (MW) compound (VHH mimetics) which are capable of inhibiting Bax activity as well as apoptosis induced by oxidative stress in human neuroblastoma and differentiated neuronal cells. These small MW compounds protect various neuronal cells against oxidative-stress-induced apoptosis and apoptosis following hypoxia/hypoglycemia. The compound has also been shown to be non toxic in vivo, and has the added advantage over VHH-based intrabody therapeutics in that it can conveniently penetrate into cells, reaching its site of action.

**Patent Position**
- Patent applications are pending. NRC patent case 11749.
NRC-IBS has the lead for patent protection and commercialization of this technology.

**Key Publications**


**The Market**
In the US, the total costs of stroke are estimated to be $43 billion per year, over half of which are the direct costs of medical care and therapy. In Canada, total costs are estimated at $2.7 billion annually.

**Technology Transfer Possibilities**
- A commercial exploitation license for the technology.

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