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2008 : July 2008 - Fast Moving Fronts : Tiziana Borsello

FAST MOVING FRONTS - 2008

July 2008



Tiziana Borsello talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Neurosciences & Behavior. The author has also sent along images of their work.


Article: A peptide inhibitor of c-Jun N-terminal kinase protects against excitotoxicity and cerebral ischemia

Authors: Borsello, T;Clarke, PGH;Hirt, L;Vercelli, A;Repici, M;

Schorderet, DF;Bogouslavsky, J;Bonny, C

Journal: NATURE MED, 9 (9): 1180-1186 SEP 2003

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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

We believe that this paper is of general interest in the field of neuroscience since it illustrates the death of neurons during stroke and a possible way to prevent death. This is a hot field. Stroke is one of the leading causes of death and long-term disability and despite intensive research efforts there are currently no effective treatments.

We believe that the results presented in this paper open new frontiers against ischemia. In fact, the neuroprotectant used in this work, D-JNK11, prevents the activation of the JNK enzyme, involved in death signalling pathways, and powerfully protects against stroke in experimental models.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Yes, we proved for the first time that it is possible to prevent the death of neurons after stroke by using a new methodology.

The discovery: By preventing JNK action it is possible to avoid neuronal death after stroke. The compound used, D-JNK11, prevented 90% of the lesion (generated by the ischemia) in the brain. More importantly, targeting the JNK cascade in a very specific way (see methodology), provides a promising therapeutic approach for ischemia. This is because the injection of the neuroprotectant within 6-12 hours after the brain injury still resulted in a powerful protection and we still obtained a reduction of the



Co-author
Mariaelena
Repici

infarcted zone of 50-90%. This is considered a useful temporal window for treating human patients after ischemia.

The methodology: We described the possibility of targeting protein complexes and enzymes involved in intracellular death signalling pathways by means of cell permeable peptide (CPP). The CPP represents a novel, versatile, and extremely powerful way of blocking the propagation of intracellular processes, with an unprecedented specificity allowing for reduction of side effects.

SW: Would you summarize the significance of your paper in layman's terms?

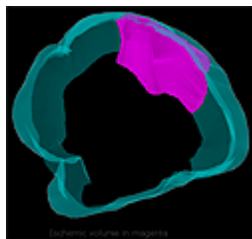
Despite a considerable worldwide research effort, current therapies for stroke are of limited efficacy. In cerebral ischemic stroke, which is the most common kind, the occlusion of a blood vessel inside the skull deprives brain tissue of oxygen and nutrients, leading to the death of many neurons.

The brain insult (stroke) triggers biochemical intracellular cascades activation (chains of reactions) inside neurons that ultimately kill them.

This sequence of events has been studied for almost 20 years, and scientists were quick to develop drugs to prevent it, by studying different neuroprotective agents. All these studies raised hopes for a clinical breakthrough, because when given to rats and mice at the time of brain-artery occlusion, the neuroprotective agents prevented much of the brain damage. But, when used in the incidence of human stroke, they were a dismal failure, partly because they protected the brain only when given at the time of ischemia or within the next 2-3 hours, whereas few stroke patients reach the hospital that quickly.

Our results, as published in this paper, offer new hope for stroke treatment. We showed for the first time that a novel drug can strongly protect the brains of adult mice and baby rats even when given 6-12 hours after the ischemia. Such late treatment had always been a theoretical possibility, because most of the neuronal death occurs relatively late (within 6-24 hours) after ischemia. This is the first drug to actually achieve such a strong protection during such late administration.

Figure 1: [+ details](#)

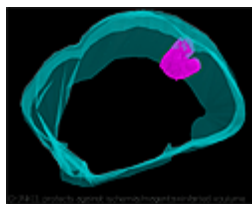


These studies really offer a possible basis for stroke therapy. In fact, Xigen S. A., a Swiss biopharmaceutical company that concentrates on research and development of novel peptide therapeutics, is now developing the clinical trial of this compound in Lausanne, Switzerland.

SW: How did you become involved in this research and were there any particular problems encountered along the way?

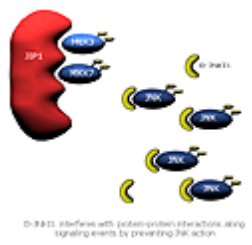
Neuronal death plays a critical role in most of the important neural pathologies, including stroke, epilepsy, Parkinson's disease, Alzheimer's disease, and multiple sclerosis. This is why an understanding of the mechanisms of neuronal death is our main challenge. To identify some death pathways is in fact very important and to achieve neuroprotection is one of the primary interests for the neuroscientist. An understanding of the control mechanisms of neuronal death allows the development of new tools to prevent it. In 2000, I was studying neuronal death *in vitro*. The overall goal of my studies was to establish the molecular details of signal transduction pathways that are initiated by environmental stress (in this case: excitotoxicity *in vitro*) and lead to the regulation of the neuronal death machinery.

Figure 2:



In particular, I was studying the JNK cascade role in neuronal death and I was aware of the inhibitor peptide D-JNK11 because I was working near Dr. Christophe Bonny's lab and he designed this inhibitor for preventing the cell death of pancreatic cells in the field of diabetes research. He agreed to work with me and we began our collaboration.

Figure 3:



I was the first to utilize the peptide in the central nervous system, and to characterize its distribution inside cells and its neuroprotective functions in neurons. I first tested D-JNK11 in the *in vitro* model to prevent neuronal death and, since it worked so well, I immediately decided to move to *in vivo* models. I finished two collaborations in order to verify if the powerful neuroprotection found *in vitro* was also maintained *in vivo* model, which it was.

found *in vitro* was also maintained *in vivo* model, which it was.

We had many difficulties due to the long-term of these studies and also due to the intrinsic difficulties you find while working with other laboratories. But we succeeded and discovered the powerful neuroprotective capabilities of this compound. We understood the enormous implications this would

have in acute diseases and in fact, our study is still going on in this field, but now we are also focusing on the possibility of its application in different brain insult models and in chronic diseases (my ongoing studies at the Mario Negri Institute in Milano, Italy). In the meantime, other authors discovered many different paradigms in which D-JNK11 protects against neuronal death in the central nervous system. Seeing the wide range of applications for our discovery is for us the greatest pleasure.

SW: Where do you see your research leading in the future?

The research of my laboratory is heading in three main directions.

First, in our view, the most significant challenge in this area is developing CPPs to treat chronic diseases. We are performing the first CPP treatment in a chronic *in vivo* model of neurodegenerative disease and we've now received very encouraging results. However, we still have plenty of additional work to do in this direction.

Secondly, we are now looking for new important key modulators of neuronal death pathways, with the aim of determining if they can be targeted for therapeutic intervention. This is because neurons may decide to die in many different ways and clearly distinct pathways are involved in their death processes.

Third, this is a methodology improvement. One of the limitations of the CPPs methodology is the poor control of the delivery, in fact these CPP compounds diffuse over all the tissues in the body. We are currently at work on having a spatio-temporal control of CPP delivery: this will reduce possible side effects and will enhance the efficacy.

SW: Do you foresee any social or political implications for your research?

The costs of stroke are enormous. In Europe and the USA, 2-6% of all health care costs—on average 0.27% of the GDP—are spent on direct stroke care, inclusive of the costs of hospital and nursing home care, the services of physicians and other medical professionals, drugs, appliances, and rehabilitation. (See: Evers S, *et al.*, "International Comparison of Stroke Cost Studies," *Stroke* 35:1209-15, 2004.)

Indirect costs, defined as production losses, further increase the burden of the disease. In Europe, direct costs are in the range of 3,000-16,000 euros per patient during the first year, whereas the lifetime direct cost may reach 30,000 euros. Taken together, direct and indirect costs may be as high as 20,000-26,000 euros per patient in the first year. In Europe, 22 billion euros are spent on stroke annually (See: Truelsen T, *et al.*, "Cost of stroke in Europe," *Eur. J. Neuro.* 12, Suppl 1:78-84, 2005).

The growing number of subjects with stroke is likely to increasingly burden health and social systems in the future. The situation may be worsened by the estimated decrease in the European population, shifting the dependency ratio, with fewer young people supporting an increasing proportion of elderly people. In addition to stroke, the overall health impact of chronic neurodegenerative diseases is certainly more than merely obvious.

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Keywords: cerebral ischemic stroke, neurons, ischemia, neuronal death, D-JNK11, JNK enzyme, cell permeable peptide (CPP), costs of stroke, euros per patient, chronic neurodegenerative diseases.



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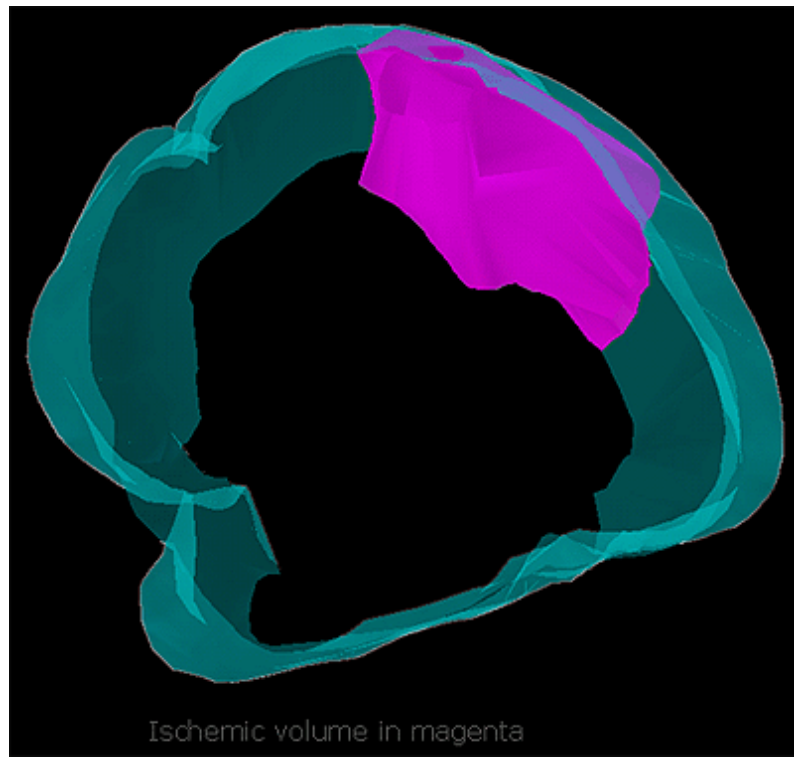


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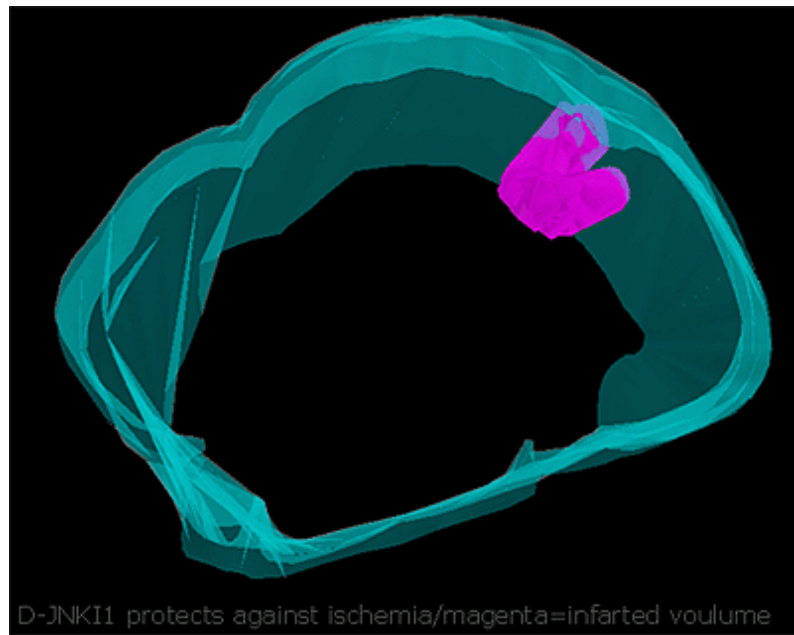
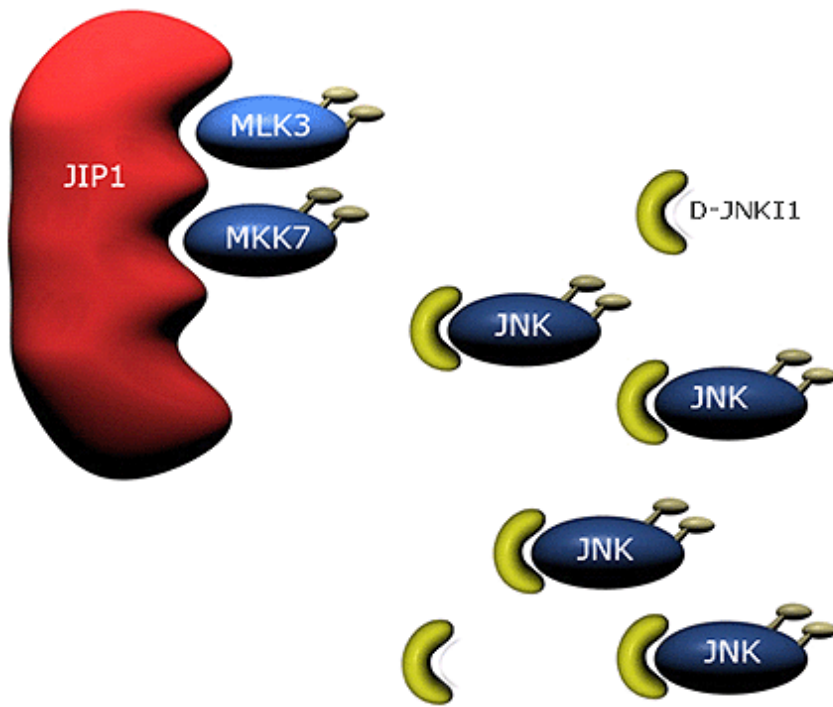


Figure 3:



D-JNKI1 interferes with protein-protein interactions along signaling events by preventing JNK action

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