Mr Larry Glass: Absolutely. For acute CNS injuries, I think that neuroprotective agents (as well as hypothermia) are probably the only therapies (other than potentially stem cells) that offer any reasonable hope of preventing secondary brain injury. For chronic neurodegenerative diseases, neuroprotection is the most promising strategy for developing disease-modifying therapeutics. A product which can slow or even reverse loss of neurons or neuronal function – as opposed to only controlling symptoms – would clearly achieve market penetration quickly (and probably at premium with respect to reimbursement).

Visiongain: What other important points ought to be made about neuroprotective agents R&D that the above questions don’t take into account?

Mr Larry Glass: As we learn more about the underlying molecular and cellular phenomena that cause loss of neurons and/or neuronal function, it is becoming apparent that many of these processes are common to multiple CNS diseases and conditions. In particular, over-expression of inflammatory cytokines (neuroinflammation) can activate microglia, up-regulate pro-apoptotic genes and down-regulate anti-apoptotic genes, inhibit neurogenesis, cause EEG abnormalities, impair synaptic plasticity, etc. These effects are involved in a wide range of diseases and conditions from TBI, stroke and SCI to Alzheimer’s, Parkinson’s, Huntington’s, depression and even autism spectrum disorders (particularly Rett Syndrome and Fragile X).

Agents that can effectively attenuate neuroinflammation could potentially be applicable to a surprisingly diverse number of indications. As an example, microglial activation, which can be induced by as well as contribute to neuroinflammation, has been implicated in the progression of TBI, AD, PD, Huntington’s, multiple sclerosis, Rett Syndrome and others. Effective inhibition of microglial activation has been demonstrated by a number of compounds and compound classes – NNZ-2566, cannabinoid receptor agonists, selective serotonin reuptake inhibitors (paroxetine, fluoxetine, sertraline), COX-2 inhibitors and even minocycline and tetracycline.

The bottom line is that I think it’s time to break down the indication- and mechanism-specific silos.

8.2 Interview with Winston Ko, CEO, Genervon Biopharmaceuticals
(March 2012)
Visiongain interviewed Mr Winston Ko (CEO, Genervon Biopharmaceuticals) in March 2012. We are grateful for his time and views.
8.2.1 Lack of Approved Neuroprotective Agents

Visiongain: To my knowledge so far, not a single agent has been approved exclusively for neuroprotection. The drugs that are currently used as neuroprotectants are actually approved for another indication. What do you have to say about this situation?

Mr Winston Ko: True. As one authority recently said, “114 cell-based drug treatments had been advanced into the clinical arena by 2007; these have uniformly failed…clinical trials targeting single mechanisms continue to fall short.” Of note, AZ and GSK continued the exodus of big pharma from the central nervous system (CNS) arena after the Targacept failure in trials. Big pharma covets a disease-modifying biologic CNS drug, but they simply cannot afford to continue paying for their in-house CNS R&D and hope for a different outcome by repeating the same mistakes.

Drug development for both chemical and biologic drugs is still dominated by the paradigm of trying to find a highly selective drug aimed at a single target and hoping to show that changing that target changes the outcome. Genervon hypothesized back in the 1990s -- and recent genomic, proteomic, and systems biology studies have confirmed -- that CNS disorders and diseases involve the interplay of a highly complex, multi-factorial process of many non-dominant effectors in an interwoven dynamic network. This complexity reduces the probability that any single-action drug will demonstrate efficacy in CNS diseases because, at best, it could interrupt only a part of the pathological process.

8.2.2 Sub-classes of Neuroprotective Agent

Visiongain: I’ve read that neuroprotective agents work by a number of mechanisms. For example, as glutamate antagonists, free radical scavengers, anti-apoptotic agents, monoamine oxidase inhibitors, neurotrophic agents, etc. Which of these many sub-classes of neuroprotective agents do you think are most promising and why?

Mr Winston Ko: It is correct that neuroprotective agents work by a number of mechanisms. However, because that is true, targeting any one of the mechanisms you mentioned (or any other) is a failing strategy for developing drugs for CNS diseases and disorders. That may seem like a very radical statement, but it is not if you look at all the evidence. No single mechanism is the most important or promising.

All the mechanisms have to work in sync because CNS disorders and diseases (and thus ischemic and neurodegenerative brain damage) involve the interplay of a highly complex, multi-factorial process of many non-dominant effectors in an interwoven dynamic network. One cannot deal with the CNS diseases/disorders through a single action. Moreover, not only are the biological
processes complex, but they are also networked, interwoven, and dynamic. For example, anti-inflammatory mechanisms are highly activated at the beginning of ischemia, but at a certain stage, inflammation has to calm down to the right level at the right time to allow for remodelling.

Due to the dynamic nature of the interwoven network of biologic systems, scientists and doctors cannot figure out when, what, or how much to activate or deactivate any of the many pathways and genes dynamically over time. It is highly unlikely that “master control panels” will ever be devised to allow doctors to push the right buttons at the right times.

8.2.3 Agent GM6

Visiongain: I know that Genervon is in the process of developing GM6 as a neuroprotective agent for a variety of indications, including Parkinson’s, Stroke, multiple sclerosis, spinal cord injuries, etc. Can you please talk about how GM6 was discovered and developed as a CNS drug candidate?

Mr Winston Ko: Genervon thinks differently. It has the courage to break from the classical way of thinking. Genervon has stayed focused on finding the master regulators that, in embryonic development, are responsible for the development of the human nervous system and other systems. Genervon has also created the technology platform to find the small active sites of protein/peptides in order to penetrate the blood-brain barrier (BBB) to effectively deliver the drug into the brain for CNS diseases.

Throughout the embryonic development process, there are crucial master regulatory pathways that oversee cell proliferation/apoptosis, differentiation, repair, inflammation/anti-inflammatory, and overall developmental balance. Embryonic development is incredibly intricate and yet is accurately repeated with remarkable consistency.

There are many levels of master regulators. In the foetal developmental stage, the regulators are at the highest level, controlling the most pathways. Genervon set out to find the specific master regulators that participate in regulating embryonic stage nervous system development by tracking the function in all our assays. We hypothesized and confirmed that the foetal master regulators are able to correct inadvertent errors in foetal development and thus be life sustaining and potentially therapeutic in adults.

Genervon spent years in drug discovery before selecting GM6. Instead of using high throughput screening to search for molecules to target diseases from human genomes, genomes of microbes,
etc, Genervon developed two proprietary scientific platforms in order to discover and develop new classes of novel biologic drugs that were endogeneous master regulators.

The first platform allows us to discover novel endogenous foetus stage master regulators that modulate multiple pathways of gene expressions that are useful to treat disorders and diseases in the CNS and the vascular system. One of Genervon’s discoveries is a novel motoneuronotrophic factor (MNTF), a master regulator responsible for the development, protection, and correction of the CNS.

The second platform Genervon developed is an in silico analysis platform that can identify active sites of proteins and peptides. Analog GM6, an active site peptide drug candidate of MNTF, penetrates the BBB and has multiple functions, including neuro-protection and neuro-regeneration. These two platforms led to the discovery of GM6, which has been approved for Phase II CNS human clinical trials.

Visiongain: Can you please provide more details about GM6 and its mechanism of action?

Mr Winston Ko: Genervon used DNA micro-array and PCR array analysis tools and found that GM6 modulated thousands of significant genes through multiple pathways involving 22 specific biological processes, including neurogenesis, neural development, neuronal signalling, etc.

Specific receptors activated by GM6 respond to distress signals from anywhere in the nervous system. GM6 thus activates appropriate genes through multiple pathways to induce the expression of proteins that are anti-inflammatory, anti-apoptosis, anti-oxidant, regenerative and re-innervative, etc in response to the nature of the distress signals and as the distress signals changes over time.

Visiongain: What is GM6 current status including the expected timeline of filing for approval?

Mr Winston Ko: Genervon’s Phase I clinical trial of GM6 was completed in the first quarter of 2010 and showed that GM6 is very safe at high and multiple doses (5mg/kg). FDA approved Phase II clinical trials of GM6 for ischemic stroke (third quarter of 2010) and Parkinson’s disease (fourth quarter 2010) indications. We hope to finish recruiting stroke patients before the end of 2012 and PD patients by middle of 2013. We also hope to initiate two more Phase II trials for GM6 by the end of 2012 and two more by the middle of 2013.

Visiongain: Are there any other neuroprotective agents under development by Genervon?
Mr Winston Ko: Genervon has discovered other master regulators and is currently evaluating their potential application to other diseases and indications, such as cardiovascular, oncological, haematological [disorders], and other conditions. The results of these evaluations are proprietary at this time.

Visiongain: What are the characteristics of GM6, a biologic peptide master regulator?

Mr Winston Ko: Normally peptides are very large in size, thus causing all the disadvantages of peptide[s] listed below:

**Peptide Advantages:**
- High activity
- High specificity
- Little unspecific binding to molecular structures other than desired target.

GM6, however, has no unspecific binding. With our in silico analysis platform, we ran through millions of matches until we identified GM6. Every one of the atoms of the GM6 peptide structure docks perfectly into the hundreds of atoms of the receptor molecular structure.

- Minimization of drug-drug interactions
- Less accumulation in tissues
- Lower toxicity
- Often very potent
- Biological & chemical diversity.

**Peptide Disadvantages:**
- Low oral bioavailability
- Injection required
- Less stable
- Difficult delivery: challenge to transport across membranes
- Challenging & costly synthesis
- Solubility challenges
- Risk of immunogenic effects
- Cleared from body quickly.

We created the in silico analysis platform to identify the smallest active sites of MNTF. GM6 was identified and confirmed that it mitigated the critical negatives.
GM6 is very stable in the form of lyophilized powder, stored at -20°C and has no delivery difficulty and easily passes through the BBB. Moreover, GM6 has no solubility challenges, as it is easily reconstituted with saline and it does not cause immunogenicity or mutagenicity.

Our Phase I trial indicated that GM6 is cleared very quickly from the body and therefore is very safe and has low toxicity. Because GM6 is safe and tolerable at 5mg/kg in humans, large amounts of GM6 can be delivered by bolus IV injection, allowing GM6 to bind to specific receptors inside and outside of the brain within minutes. Thus, GM6 is very fast-acting.

8.2.4 Promising Neuroprotective Agents

Visiongain: What do you think are some of the most promising neuroprotective agents that will have a huge impact on the market in the next 5-10 years, if they get approved?

Mr Winston Ko: We think that GM6 may be the first significant "master regulator" neuroprotective agent but that other master regulators will be developed as well. We believe that, over the next ten years, there will be major shift in the industry’s R&D paradigm, biological drugs will finally show their promise, and, hopefully, many unmet medical needs will be met.

8.2.5 Potential of Neuroprotective Agents

Visiongain: Do you think neuroprotective agents have the potential to replace (in the next 5-10 years) some of the currently used therapies for the treatment of neurodegenerative diseases? Please explain. Are there any technologies or developments that are particularly interesting?

Mr Winston Ko: Yes, most definitely. Symptomatic drugs are stopgap measures because there is no better option. But with the advance of biologic master regulator drugs such as GM6, we believe the pharmaceutical industry will be very different within 10 years. The “Biotech Century” (a term popular back in the 1990s) will yet live up to its claim.

Drugs with the ability to broadly regulate multiple pathways are still very alien to the vast majority of scientists. But with recent advances in genomic and proteomic research, we have notice a slight shift in sentiment by a few scientists and firms. We are hopeful.

Visiongain: What other important points ought to be made about neuroprotective agents R&D that the above questions don’t take into account?
Mr Winston Ko: For real efficacy, a drug has to modify the course of a disease significantly, not just marginally. We have to appreciate the complexity of our human biologic systems and we will do well to work with nature in that regard. Foetal stage master regulators issue all of the instructions to signal pathways to maintain the health of the biologic systems dynamically. Our data from years of animal studies suggest that the effects of GM6 on disease modification are potent, comprehensive, and broad.