



## TROPHOS AND TRO19622: FAQs

### WHO IS TROPHOS?

Trophos is a biopharmaceutical company founded in 1999 to discover and develop new drugs to treat neurodegenerative disorders [www.trophos.com]. Today, Trophos focuses its expertise on two motor neuron diseases, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease) and spinal muscular atrophy (SMA), as well as Huntington's disease (HD). Trophos has also developed expertise and offers screening services for targets implicated in Alzheimer's disease.

Trophos has 37 full-time employees; 25 are scientists and half of these have doctorate degrees. The Trophos management team has decades of previous experience in drug discovery and development, having come from major pharmaceutical companies.

### WHAT IS TRO19622, HOW WAS IT DISCOVERED, WHAT IS ITS DEVELOPMENT STATUS?

TRO19622 is a new chemical entity derived from the Trophos compound collection. The molecule has a cholesterol-like structure and displays remarkable neuroprotective properties both *in vitro* and *in vivo*. It was discovered thanks to the original high-throughput screening platform using primary motor neurons that Trophos developed to support its drug discovery strategy. TRO19622 is as effective as a cocktail of three neurotrophic factors in keeping motor neurons alive in culture. TRO19622 also improves survival of striatal neurons in a cell-based model of Huntington's disease and displays anti-apoptotic properties for other types of primary neurons. *In vivo*, TRO19622 is active in several preclinical models of neurodegenerative disease.

TRO19622 has satisfactorily completed preclinical evaluation involving cardiovascular, CNS, respiratory and immune system safety studies. It also shows no mutagenic potential and is not toxic *in vivo* at drug concentrations >50 times the expected therapeutic level for four weeks. An oral formulation has been developed for clinical trials.

TRO19622 has successfully completed Phase I clinical trials. These were conducted in France and involved single and multiple dose studies on healthy adult subjects. TRO19622 was demonstrated to: i) be well tolerated; ii) have achieved the predicted effective clinical dose via the oral route and, iii) have an excellent safety profile.

TRO19622 is now in Phase Ib clinical trials. These studies will insure there is no interaction between TRO19622 and riluzole, the only approved drug for the treatment of ALS, and evaluate the pharmacokinetics and tolerance for one month in ALS patients. These trials pave the way to start an 18 month pivotal Phase II/III clinical trial of TRO19622 as an add-on to

riluzole in ALS patients in Q4 2006. The trial will be conducted in the USA and Europe. A Phase Ib study in juvenile SMA patients is also anticipated to start by the end of 2006, with support from the AFM.

## HOW DOES TROPHOS BENEFIT FROM ORPHAN DRUG STATUS?

TRO19622 has been granted orphan drug designation status for the treatment of ALS in the USA, and for the treatment of SMA in the EU. This status allows Trophos the opportunity to benefit from the advice of regulatory authorities in order to design the clinical trials, and thereafter seek 'fast track' review by both the FDA and the EMEA.

## HOW DOES TRO19622 WORK?

By a process of reverse engineering, Trophos scientists have found that TRO19622 interacts with a physiologically relevant target: the mitochondrial permeability transition pore (mPTP). Mitochondria are central mediators of cell death and are implicated in most if not all neurodegenerative diseases regardless of the initiating factor: genetic mutations, excitotoxicity, reactive oxygen species, ischemia, chemical toxicity, etc. Mitochondria play diverse roles in all cells.

In neurons, especially near synaptic sites, mitochondria are essential calcium-buffering organelles in areas where membrane excitability leads to large influx of calcium through calcium channels. Mitochondria also produce the ATP necessary for microtubule-based axoplasmic transport and maintaining the activity of ion and nutrient transporters. If a neuron fails to establish or maintain its functional role, mitochondria are responsible for eliminating it by releasing apoptotic factors.

TRO19622, by interacting with protein components of the mPTP, prevents the release of these apoptotic factors and therefore protects the neuron. This mechanism of action may lead to a general neuroprotective activity with utility in other therapeutic indications.

## WHAT WILL BE POTENTIAL BENEFIT OF TRO19622 TO PATIENTS?

In patients suffering from a neurodegenerative disease, specific classes of neurons become dysfunctional, progressively lose their capacity to maintain their synapses and axons, and finally undergo cell death. The stresses that trigger this slow degenerative process are multiple, and differ from disease to disease.

For the patient suffering from a motor neuron disease, ALS or SMA, TRO19622 is expected to preserve existing neuronal function, by delaying or even stopping further progression of the disease. Furthermore, by improving neuronal survival and promoting regeneration (as observed in preclinical models), TRO19622 may even lead to some recovery in function.



## WHEN WILL TRO19622 BE AVAILABLE TO PATIENTS?

Trophos is actively developing TRO19622 to treat patients with the motor neuron diseases ALS and SMA. TRO19622 has successfully completed Phase I clinical studies and is currently being evaluated for its tolerance and safety in Phase Ib studies involving ALS patients. These studies pave the way for the initiation of a pivotal Phase II/III clinical trial in ALS patients in Q4, 2006. In the meantime, Trophos is working with paediatric neurologists and the AFM to develop protocols for clinical trials in juvenile SMA patients.

Assuming the continued success of the ALS and SMA clinical trials, and regulatory approvals, TRO19622 may be available by 2010.

## WHAT HAS BEEN THE ROLE OF THE AFM?

The Association Française contre les Myopathies - AFM - is a French Foundation that supports research into the cause and cures of neuromuscular disorders. Their annual Telethon attracts wide public support. The AFM has funded the Trophos motor neuron program since the beginning, supporting the development of Trophos' original, neuron-based screening strategy, the optimization of the hits and leads coming from this screening platform, the development of *in vivo* models to test compounds for proof of potential clinical efficacy and now, the preclinical and clinical development of Trophos' drug candidates.

It is important to note the critical role that foundations like the AFM are playing in drug discovery initiatives for orphan diseases like ALS & SMA. The AFM is actively supporting the Phase Ib clinical studies in SMA planned by Trophos.

## WHAT IS THE DRUG DISCOVERY STRATEGY AT TROPHOS?

We consider the neuron as a cellular test tube filled with the diverse products of the 30,000 genes expressed by the cell under the conditions that are as close to the physiological environment as possible. We reproduce neuronal death in the test tube and screen collections of small molecules to select those which improve the neuronal survival or block neuron's death. This phenotypic screening approach using "sick neurons" attempts to mimic the clinical situation in the culture dish. Assays are developed using the class of neurons affected in each neurodegenerative disease: motor neurons for ALS or SMA, striatal neurons for Huntington's disease and cortical neurons for Alzheimer's disease.

Trophos has favoured the idea that focusing on the desired endpoint - neuronal survival - is a "fast track" to the identification of neuroprotective compounds in a relevant pathophysiological context that can be considered "validated leads". Because these assays require the compounds to be stable, non-toxic and cross the cell membrane to get to their target and keep neurons alive, they already meet a number of criteria to be considered drug candidates and can be rapidly developed for clinical evaluation.



## HOW IS THIS DIFFERENT FROM TRADITIONAL DRUG DISCOVERY APPROACHES?

The standard drug discovery approach is based on validated molecular targets: enzymes, receptors, ion channels, etc. In neurodegenerative disorders, there are no validated targets or clearly understood mechanisms. Despite the identification of specific genes and proteins that are associated with neurodegenerative disorders, the role of these proteins or how the mutations cause neurodegeneration are largely unknown.

Trophos' cell-based functional assays are a "black box" approach containing multiple potential targets. This approach presents a challenge to chemists who need structure-activity relationships to optimize drug candidates. Indeed, the conventional approach often uses recombinant protein or cell lines expressing selected drug targets enabling rapid screening of millions of compounds; these assays do not reproduce the pathophysiological context of a sick neuron.

Enormous efforts have gone into developing the genomic and proteomic tools to identify all human genes and their protein products, their tissue distribution and the changes associated with diseases or injury. Yet, validating these potential drug targets is a long and laborious process and there are many surprising differences between man and model organisms. For a target to be truly validated clinical evidence is required and with this limitation, drug discovery based on validated targets is forced to focus on "me-too" molecules.

Our approach, while more labour intensive, skips the target identification steps of the conventional methods and any lead obtained is already validated to be active *in vivo* so the subsequent development is faster and the attrition rate is reduced.

## HAS THIS APPROACH PAID OFF?

Trophos has successfully applied this approach to screen its own 45,000 compounds chemical library on several models of neurodegeneration: three models based on motor neurons, an original model of Huntington's disease using primary striatal neurons and other models are currently being screened or under development. TRO19622, which was discovered in a screen for small molecules that rescue motor neurons from death due to trophic factor deprivation, went from "hit" to Phase 1 clinical trials in only two years.

The molecule identified a physiologically relevant target in the mitochondrion and this information has allowed us to optimize the molecule and identify a backup, which is in preclinical development. We expect to develop drug candidates from the other screening hits in a similar fashion. We already have brought several leads into optimization.



Using the skill of chemists willing to formulate structure-activity relationships without a fixed molecular target, Trophos is bringing innovative new drugs to the clinic the way most drugs were discovered in the pre-genomic era.

## ABOUT TROPHOS

Trophos is a biopharmaceutical company committed to the discovery and development of novel therapeutic compounds for the treatment of neurodegenerative disorders.

Trophos has a fully integrated preclinical and clinical capability. The company has developed specific know-how and is focused on recreating neuronal degeneration in the test tube and screening small molecules. Compounds that improve neuron survival in that context are rapidly developed to drug candidate stage, thus giving Trophos a competitive advantage. The company has proprietary compounds in pre-clinical and clinical development for the treatment of motor neuron diseases, Huntington's disease and neuroprotection in general.

Trophos, founded in 1999, is based in Marseilles, France. The company has 37 employees.

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