

Developing Novel Oral Drugs that Reduce Inflammation and Prevent Neurodegeneration

Paratek's Evolving Co-Development Collaboration with Serono.

TEXT

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Paratek was founded in 1996 as a company specializing in the development of products to overcome bacterial resistance to antibiotics. One of the company's key proprietary platform technologies is the chemical synthesis of novel tetracycline analogues. As an integral part of its strategy, Paratek pursues licensing, research and development agreements with larger pharmaceutical companies for certain internal programs stemming from its technology platforms. Paratek's lead tetracycline compound, MK-2764, is a novel orally available broad-spectrum tetracycline derivative that overcomes bacterial resistance and may be used in hospital infections and in increasingly serious community-based infections. Currently, the company is participating in the clinical development

of MK-2764 in partnership with Merck & Company, Inc. In addition, Paratek has formed a research and licensing collaboration with Serono to develop a non-antibacterial tetracycline derivative for treatment of MS. Like all successful partnerships, these collaborations have entailed a great deal of hard work by researchers, a little luck and the spirit of teamwork and cooperation to achieve mutually beneficial outcomes.

Targeting multiple sclerosis

The tetracycline class of drugs was introduced more than 50 ago and all commercially available tetracyclines were designed as broad-spectrum antibiotics. However, tetracycline derivatives such as minocycline have been described as having neuroprotective and anti-inflammatory activity.

The class is increasingly seeing use in diseases such as acne and rheumatoid arthritis as a result of its non-antibacterial properties despite the limited clinical data to support this use. This situation changed when Luanne Metz, M.D., Professor of Clinical Neurosciences, University of

Calgary, presented a study in 2003, in which the oral form of minocycline, a generically available antibiotic tetracycline, benefited patients with active relapsing-remitting multiple sclerosis (RRMS).

The Metz study had only a modest number of patients, but it showed dramatic and statistically significant reductions in lesions and substantially fewer relapses in active RRMS patients with safe and approved doses of oral minocycline. These results coupled with other reports dating back to 1997 were sufficient proof-of-concept that an improved tetracycline, with the antibiotic activity removed, could hold promise as a treatment for RRMS.

Paratek researchers envisioned that a superior orally available tetracycline derivative could be designed that was non-antibacterial as well as possess improved potency/activity in reducing inflammation and preventing neurodegeneration. Simply removing antibacterial activity would eliminate some of the poorly tolerated effects seen with long-term use of broad spectrum tetracyclines like minocycline and avoid causing antibiotic resistance. Further, a more potent, specific and better drug could avoid significant side effects seen with longer-term use, as sometimes seen in acne patients taking minocycline. Within 6 months of initiating its program, Paratek had successfully adopted an Experimental Allergic Encephalomyelitis (EAE) mouse model, which mimics multiple sclerosis (MS), and was able to show that novel patented tetracycline derivatives were similarly active to minocycline in

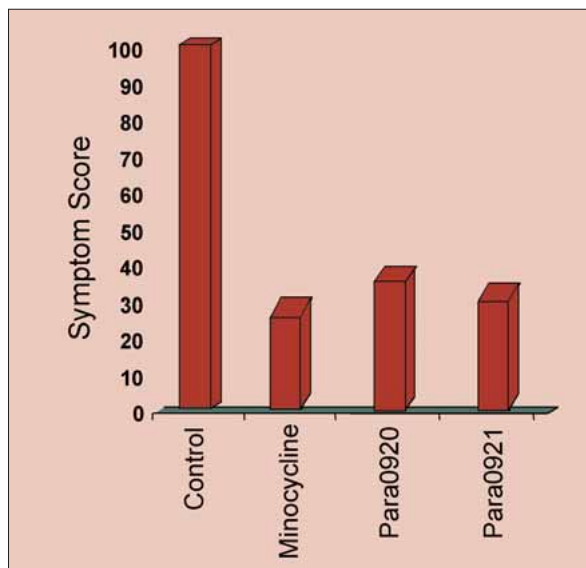


Figure 1: First *in vivo* demonstration that novel non-antibacterial Paratek tetracycline derivatives are active at reducing neurological disability scores (extent of paralysis) in mouse EAE model (all test compounds dosed at 50mg/kg).

the model (Figure 1) and were non-antibacterial as demonstrated by Minimum Inhibitory Concentrations, also known as «MICs» (Table 1).

The collaboration

As a new entrant to the field of inflammation and neurological diseases, Paratek sought a partner that could provide guidance and support for its efforts in RRMS. In October 2004, the company signed a Collaborative Research and License Agreement with Serono to discover, develop and commercialize orally-available novel disease modifying tetracycline derivatives for MS. The data demonstrating that novel non-antibacterial tetracyclines were active in

colony and initial toxicology. In parallel, Serono researchers sought to validate an *in vitro* assay that would simplify the primary screening process. One assay utilized primary neuronal cells to assess the neuroprotective attributes of the compounds (Figure 2).

Six months later, the partners identified the first promising series of non-antibacterial tetracycline derivatives that had strong activity in the EAE model. Paratek continued to evaluate preliminary toxicology, while Serono began metabolism and acute toxicity studies in its laboratories on the best compounds.

This summer (2006), the Collaboration achieved a goal, designating the

Compound	Gram-negative Activity (MIC µg/mL)	Gram-positive Activity (MIC µg/mL)
Minocycline	0.3	0.1
Para0920	>64	32
Para0921	>64	>64

Minocycline shows potent, broad-spectrum antibacterial activity against tetracycline sensitive strains of *E. coli* (Gram negative) and *S. aureus* (Gram-positive), while novel Paratek tetracycline derivatives are non-antibacterial.

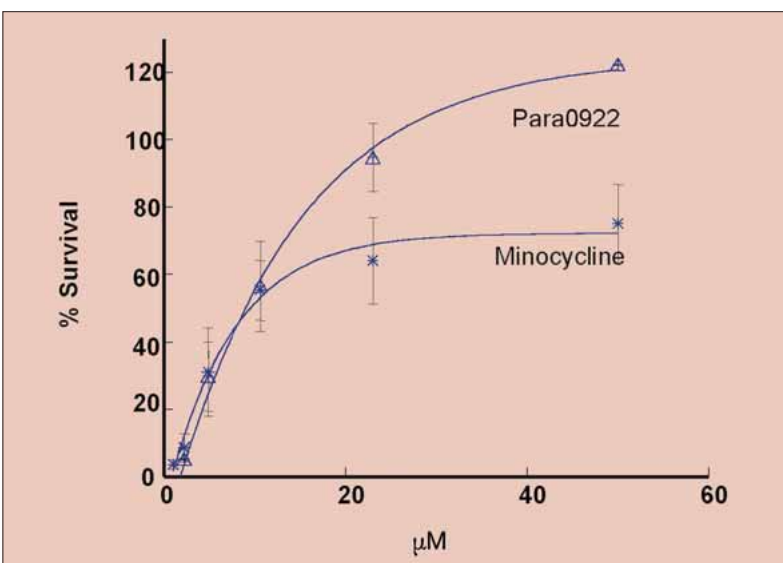


Figure 2: Protection from Glutamate Excitotoxicity. Minocycline and novel Paratek compounds possess neuroprotective activity, shown as survival of neuronal cells to external toxicity (glutamate).

EAE helped to close the deal. During the initial phase of the collaboration, Paratek and Serono worked collectively to identify new tetracycline derivatives from non-antibiotic compounds discovered and synthesized by Paratek chemists. Researchers from both companies began seeking to identify the mechanism of action for tetracyclines in diseases like MS, meanwhile continuing the primary screening method for new compounds with the mouse EAE model. The company increased its internal effort, running multiple studies each month and assessing promising compounds for pharma-

first lead compound. This lead has improved activity at lower doses than minocycline in the EAE model and is more active after oral administration than minocycline in a Collagen Induced Arthritis (CIA) model. In addition, several potential back-up compounds have been identified, all in just over 18 months from the start of the collaboration.

The future

As the collaboration moves into the clinical development phase, Serono will be conducting the lion's share of work, including preclinical studies and all clinical and regulatory func-

tions. Paratek will continue to support manufacturing into development, providing supplies for GLP studies and leading manufacturing process development in the near-term. Geneva, Switzerland-based Serono would exclusively market any Multiple Sclerosis products approved for sale around the world, while Boston, USA-based Paratek will receive milestone payments and royalties.

Beyond MS, Paratek has been exploring the development of additional non-antibacterial or narrow-spectrum antibacterial tetracyclines for use in the treatment of other inflammation associated or neurodegenerative conditions. Specifically, the company has begun *in vivo* testing of its novel non-antibacterial derivatives in Stroke and other cardiovascular disorders, Arthritis, Spinal Muscular Atrophy, and Acute Respiratory Distress Syndrome (ARDS). Paratek is also developing narrow-spectrum tetracyclines with improved anti-inflammatory activity as new agents for Acne and Rosacea. Paratek plans to license development and commercial rights to partners who are experts in these other fields, just as Serono is in Multiple Sclerosis. □

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