A sirtuin inhibitor enters a phase 1a clinical trial in Europe

Siena Biotech has begun testing a Sirt1 inhibitor in multiple doses in 96 healthy male and female volunteers in Europe. The randomized, double-blind and placebo-controlled study will assess safety, tolerability and pharmacokinetics preparatory to initiating clinical trials in Huntington's Disease patients.

The name sirtuin comes from the Silent Information Regulator gene 2 (Sir2), a gene which is associated with aging in yeast and invertebrates. The equivalent gene in mammals is called Sirt1.

In a series of preclinical studies, researchers at Siena Biotech have demonstrated the neuroprotective properties of the sirtuin inhibitor (SEN0014196 or EX-527) in a series of *in vitro* systems as well as its capacity to increase survival and ameliorate psychomotor and histological phenotypes in a widely employed *in vivo* preclinical model of Huntington's Disease, indicative of a disease-modifying activity. Additionally, the product exhibits a biopharmaceutical and preclinical safety profile compatible with chronic treatment of Huntington's Disease.

The sirtuin inhibitor was granted orphan drug status from the European Medicines Agency (EMEA) in October and from the FDA in December, 2009. These designations provide regulatory and financial incentives to develop drugs for diseases which affect a relatively small number of people.

"The Orphan Drug Designations obtained by this molecule brought into clinical trials by Siena Biotech, reaffirms the commitment of our company and its reference shareholder, the Monte dei Paschi di Siena Foundation, to fight diseases still without a cure", stated Marco Parlangeli, Managing Director of the Monte dei Paschi di Siena Foundation and President of Siena Biotech. "We are excited to bring forward SEN0014196 into the clinic as it has the potential to be the first use of this class of molecules in this devastating disease".

Siena licensed the inhibitor from Elixir Pharmaceuticals. Elixir was founded by Cynthia Kenyon and Lawrence Guarante, following their groundbreaking work on lifespan extension in the c.elegans worm and in yeast, respectively. Increasing the expression of Sirt2 in yeast and worms increases lifespan. Accordingly, initial interest in modifying the expression of Sirt1 as a treatment for Huntington's Disease focused on enhancing rather than inhibiting it since the onset of neurodegenerative diseases appears to be associated with the aging process, as the defense mechanisms of cells become less efficient. However, the Sirt1 protein is also a deacetylase. Inhibiting it appears to modify the acetylation of the HD protein causing the enhancement of the clearance of the HD protein but not the normal version. It is this function which appears to produce the positive effects in cell and animal models of Huntington's.

"This is a major accomplishment for Elixir and its partner, Siena Biotech," said Peter DiStefano, CSO of Elixir. "This represents the first sirtuin inhibitor to enter clinical trials and validates the work of our drug discovery and design program focused on the sirtuin family of enzymes, specifically, our selective SIRT1 inhibitor program. Based on *in vivo*

preclinical and mechanistic studies, EX-527/SEN0014196 offers the potential for novel and effective therapy for Huntington's Disease, a debilitating and ultimately fatal neurodegenerative disease."

References:

Elixir Pharmaceuticals Press Release
Siena Biotech Press Release

Leonard Guarente and Cynthia Kenyon. "Genetic pathways that regulate ageing in model organisms." *Nature* 408(6809), 255-262 (2000).

Marsha L. Miller, Ph.D., *January 21, 2010*