IS01-3 **Discovery of the First Sphingosine 1-Phosphate Receptor Modulator, Fingolimod Hydrochloride (FTY720) as an Oral Drug for the Treatment of Multiple Sclerosis**

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Fingolimod hydrochloride (FTY720) is a first-in-class, orally active sphingosine 1-phosphate (S1P) receptor modulator and has been used as an oral drug for multiple sclerosis (MS) in more than 80 countries. FTY720 was designed and synthesized in the early 1990s starting from an immunosuppressive natural product, ISP-I (myriocin) isolated from the culture broth of *Isaria sinclairii*, a type of vegetative wasp that was an 'eternal youth' nostrum in traditional Chinese medicine. ISP-I is a rather complex amino acid having three successive asymmetric centers and some functionalities. We optimized the structure based on phenotypic drug discovery (PDD) strategy using in vivo assays as the main screens (e.g. rat skin allograft rejection test) and discovered FTY720. During the course of the optimization process, we encountered an unexpected dramatic change of the mechanism of action (MOA). FTY720 does not inhibit serine palmitoyltransferase, the target enzyme of ISP-I, while FTY720 is phosphorylated to FTY720-phosphate (FTY720-P) by sphingosine kinases and FTY720-P acts as a potent agonist of four of the five G protein coupled receptors for S1P: S1P1, S1P3, S1P4 and S1P5. FTY720-P down-regulates S1P responsiveness of lymphocytes by internalization and degradation of the receptors, acts as a functional antagonist at S1P1, and inhibits S1P-S1P1 axis-mediated lymphocyte egress from the secondary lymphoid organs. The FTY720 story provides an example showing that PDD is still a powerful and promising strategy that can lead to the discovery of first-in-class drugs with novel and unique MOAs.