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Modulators of FGF-FGFR-Heparan sulfate complex: identifications of allosteric antagonists and oligosaccharide agonists as potential novel therapeutics

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Abstract

The fibroblast growth factor (FGF) / fibroblast growth factor receptor (FGFR) signaling network plays an important role in cell growth, survival, differentiation and angiogenesis. FGFR activation requires also the presence of heparan sulphate chains functioning as a template to favor dimerization and ultimately signaling when ligand binding. In the search of antagonists of FGFR signaling, we have identified after a lead optimization phase , SSR128129E (SSR), which binds to the extracellular part of the receptor. SSR does not compete with FGF for binding to FGFR but inhibits FGF-induced signaling linked to FGFR internalization in an allosteric manner as shown by crystallographic and NMR studies, Fourier transformed infrared spectroscopy, molecular dynamics simulations, free energy calculations, structure-activity relationship (SAR) analysis and FGFR mutagenesis. SSR is the first reported small molecule allosteric inhibitor of FGF/FGFR signaling, acting via binding to the extracellular part of the FGFR.

Conversely, in the search of agonists of these ternary complexes, we have investigated fragments of heparan sulphate. Through rational design, we have identified a series of oligosaccharides optimized in terms of lengths, O-sulfation pattern, N-sulfate optimization and substituents at the reducing end. Apparent incoherent results between biological angiogenic responses and X-Ray structures of ternary complexes, led us to use a panel a biophysical techniques to investigate the dynamics of such complexes leading to a novel reunified model. The potential of these optimized oligosaccharides as therapeutics agents will be discussed.

Biography

Gilbert Lassalle has completed his PhD from Rennes University (France) with Dr R Grée and postdoctoral studies from Ohio State University with Prof. L.A. Paquette. He is the section leader of medicinal chemistry of the “Early to Candidate” (E2C) therapeutic strategic unit (TSU) in Toulouse since 2007, a discovery entity from Sanofi R&D. He is co-author of more than 40 patents and 10 research articles. Moreover, he has contributed to the identification of 2 clinical and 6 preclinical candidates in the cardiovascular/ thrombosis and cancer fields.