

Development of “second-generation” forms of FGF-1 for therapeutic application

Michael Blaber

Florida State University College of Medicine, USA

Fibroblast growth factor-1 (FGF-1) is a candidate growth factor for the treatment of chronic diabetic ulcers and other ischemic diseases. However, the relatively low thermal stability of FGF-1 makes it a poor candidate as a pharmaceutical compound. Formulation with soluble heparin substantially increases the thermo stability of FGF-1; however, while this approach to stabilizing FGF-1 improves the aggregation, storage and reconstitution properties it adds a number of undesirable cost and safety issues associated with heparin. Mutations that either stabilize FGF-1 or eliminate buried reactive thiols improve the *in vitro* functional half-life, protease resistance, and mitogenic activity in the absence of heparin. Pharmacokinetic (PK) studies of such mutants identify an additional undesirable consequence of heparin additive in the formulation; namely, it increases the endocrine-like properties of IV bolus FGF-1, and therefore also increases the probability of mitogenic activity at a distance from the site of delivery. Mutant FGF-1 with a diminished heparin binding site shows that heparan sulfate proteoglycan (HSPG) is the major effectors of the peripheral compartment in the pharmacokinetics of FGF-1; consequently, mutations that can enhance HSPG affinity can increase the mean residence time. Mutant FGF-1 proteins that do not require heparin in their formulation can therefore provide a number of important benefits for human therapeutic application.

Biography

Michael Blaber received his Ph.D. in 1990 from the University of California at Irvine College of Medicine and was an NIH funded postdoctoral fellow at the Institute of Molecular Biology at the University of Oregon. He has published more than 100 peer-reviewed articles, reviews and book chapters in areas of protein chemistry and biophysics, and is a current or past editorial board member for seven notable journals.

michael.blaber@med.fsu.edu