# Gregg B Fields

*Florida Atlantic University, USA*
*The Scripps Research Institute, USA*

## Structure-guided design of selective matrix metalloproteinase (MMP) inhibitors and their application in animal models of multiple sclerosis, sepsis, and osteoarthritis

Analysis of matrix metalloproteinase (MMP) expression profiles in various pathologies correlated their presence in promoting disease progression. Drugs were designed to inhibit MMPs by chelating the active site zinc ion. This approach did not distinguish between the MMP family members and had devastating consequences during clinical trials. Subsequent knockout mouse studies showed that some MMPs were beneficial in regulating tumor growth and metastasis and stimulating indirectly the immune system. The broad-spectrum inhibitor approach was rethought in order to increase the specificity, taking into account the non-conserved secondary binding sites (exosites) within MMPs. Structural evaluation of the collagenolytic mechanisms of MMP-1 and MT1-MMP revealed differences in exosites, facilitating the development of triple-helical peptide inhibitors (THPIs). THPIs achieved selectivity within the MMP family and showed efficacy in *in vivo* models of multiple sclerosis and sepsis, where MMP-9 and MMP-8, respectively, were targeted. MMP-13 has been identified to be mainly responsible for the cleavage of type II collagen in osteoarthritis, which leads to the destruction of articular cartilage. The development of an allosteric MMP-13 inhibitor began with a lead compound identified as part of a high throughput screening campaign. Subsequent biochemical experiments and X-ray crystallographic structure determination revealed that our hit bound to the S1' subsite, which is surrounded by a long loop that differs significantly among MMPs. Comparative structural analysis and molecular modeling enabled the design and synthesis of small molecules three orders of magnitude more potent (IC50≤5 nM) than the original hit. Further optimization has led to highly potent and selective inhibitors of MMP-13 with favorable PK properties. The recent technological advances that allow us to better understand the function and structure of MMPs are aiding in the development of selective inhibitors.

### Biography

Gregg B Fields is the Director at the Center for Molecular Biology & Biotechnology in Florida Atlantic University, USA. He did his PhD in the year 1988 from Florida State University. He has been an elected President of American Peptide Society and Full Member at University of Minnesota Comprehensive Cancer Research Center. He also received BIT Life Sciences Lifetime Membership Award and Texas Higher Education Science and Technology Acquisition and Retention (STAR) Plus Award. He performs research focusing on collagen-mediated diseases. Cancer, arthritis and neurodegenerative diseases (such as multiple sclerosis) which are commonly treated as distinct maladies. However, each of these diseases has overlapping factors that contribute to disease progression. Amongst these factors are proteases that enhance the breakdown of collagen. The progression of cancer, arthritis and neurodegenerative diseases involve similar or even identical proteases. His current researches are to evaluate the link between inflammation and cancer, arthritis and neurodegenerative diseases and developing new drugs that block the action of proteases common to all of these disease states.

fieldsg@fau.edu

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