

## **Computational Design of Small Molecular Inhibitors to Promote Induction of Bone Growth by BMPs**

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Many Americans are afflicted with low back pain, degenerative spinal disease or bone fractures. Orthopedic surgical treatment of these problems frequently requires bone grafting to promote healing. Over 500,000 bone grafting procedures are performed each year in the United States. Over 50% of these are related to some type of spine fusion. Using small molecular inhibitors of different interacting partners in the BMP mediated pathway have potential to promote osteoblast differentiation and there by quick healing of the surgical treatments. We present the three approaches we have adapted to design the small molecular antagonists to Noggin, Smurf1 and Ski proteins: (i) To design inhibitors that may block BMP2/Noggin interaction with the goal of lowering the dose of BMP-2 required in clinical applications. (ii) To design inhibitors that may block Smad-WW2/Smurf1 interaction with the goal to reduce the ubiquitination of Smads there by promoting BMP induced cascade of events. (iii) To design inhibitors to the Smad binding nuclear protein Ski to promote Smad mediated gene expression.