IMPRS Abstract

MAK122: A Novel Drug Utilizing Innovative Fracture Site Targeting Technology to Improve Bone Healing

Nicholas Hux[1], Jeffery Nielson[3,4], Caio de Andrade Staut[1], Vincent Alentado[2], Abduallah Elsayed[1], Christopher Dalloul[1], Samuel Zike[1], Nikhil Tewari[1], Murad Nazzal[1], Hanisha Battina[1], Alex Brinker[1], Mustafah Shaikh[1], Sarah Myers[1], Rachel Blosser[1], Ushashi Dadwal[1], Jiliang Li[6], Stewart Low[3,5], Philip Low[4,5], Melissa Kacena[1,7]

Departments of [1]Orthopaedic Surgery and [2]Neurological Surgery, Indiana University School of Medicine, Indianapolis, IN; [3]Novosteo Inc., West Lafayette, IN; Departments of [4]Chemistry and [5]Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN; Department of [6]Biology, Indiana University Purdue University, Indianapolis, Indianapolis, IN; [7]Richard L. Roudebush VA Medical Center, Indianapolis, IN

Megakaryocytes play a pivotal role in the bone fracture healing process through enhancing osteoblast proliferation, osteoclastogenesis, and angiogenesis. Current fracture repair therapies require direct implantation during surgery (BMP-2, grafts etc.), which has limitations. In order to address this, a novel drug, compound MAK122, was created with targeting technology that directs its actions to the fracture site without needing to be implanted during surgery, limiting undesirable offsite effects, increasing the quantity of drug at the fracture site, and allowing for non-invasive treatment following assessment of the natural healing process. Therefore, this study examined the ability of MAK122 to stimulate megakaryocytes and subsequent bone healing. To accomplish this, male mice on a C57BL/6 background underwent a surgically induced femoral fracture. Following surgery, the mice were injected daily for the first 7 days with either saline (vehicle) or MAK122. Mice were then euthanized 2, 3 and 4 weeks post-

surgery. Fracture healing was assessed by standard and novel methodologies. Biweekly X-rays were evaluated and bone union was scored showing that MAK122 accelerated bone healing compared to controls. Ex vivo μCT analysis demonstrated that MAK122 increased callus volume and the percentage of mineralized callus tissue compared to vehicle treatment. Biomechanical testing showed that MAK122 treatment resulted in stronger repairs as compared to vehicle treated controls with nearly a 2-fold increase in twist to failure and toughness parameters. Additionally, histological assessment demonstrated accelerated remodeling in MAK122 treated femurs compared to those treated with saline. Taken together, these pre-clinical data suggest that MAK122 is capable of promoting an environment in which megakaryocytes can favorably influence bone remodeling mechanisms, expediting fracture repair in murine models. Though further pharmacokinetic, pharmacodynamic, and toxicology studies are required, MAK122 displays potential to serve as a state-of-the-art therapy for improving fracture healing in humans.