Weill Cornell Medicine

Small Molecule Activators of p38-β for Improved Bone Healing

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Background & Unmet Need

- Bone fractures are the most common impact injury that require medical attention
- About 6 million fractures occur in the US and 5 -10% of these do not heal properly
- About 10 million people in the US have osteoporosis and another 44 million people are at increased risk of developing osteoporosis due to having low bone density
- Individuals with osteoporosis are at increased risk of having a bone fracture
- Recombinant bone morphogenic proteins (BMPs) are approved to treat bone fracture healing, however, this treatment has challenges due to adverse side effects and manufacturing costs
- **Unmet Need:** Pharmacologically acceptable compounds to aid in bone regeneration and healing

Technology Overview

- **The Technology:** Small molecule inhibitors that activate osteoblast differentiation
- **The Discovery:** A high-throughput screen for activators of osteogenesis markers led to the identification of DIPQUO
- DIPQUO drives osteoblast differentiation by activating the β isoform of P38, leading to MAPK signaling and subsequent inhibition of GSK3-β
- **PoC Data:** DIPQUO treatment accelerated the differentiation of mouse myoblasts and bone-marrow derived human mesenchymal stem cells into mature osteoblasts
- DIPQUO increased the number of osteoblast cells in the caudal fins of zebrafish larvae and increased the mineralization of vertebrae in zebrafish regeneration models
- In addition to the P38 mechanism of action, DIPQUO synergized with other GSK3-β inhibitors to promote osteoblast differentiation

Inventors:
Todd Evans
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Patents:
US Patent 11,478,466

Publications:
Cook et al. *Cell Chem Biol.* 2019.
Cook et al. *JBC*. 2021.

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Cornell Reference:
D-8431, D-9712

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DIPQUO: 6,8-dimethyl-3-(4-phenyl-1H-imidazol-5-yl)quinolin-2(1H)-one
GSK3-β: Glycogen Synthase Kinase 3-Beta

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Technology Applications

- Therapy to stimulate healing of bone fractures
- Treatment of osteoporosis and other aging-related chronic disorders associated with bone healing dysfunction
- Therapeutic for hypophosphatasia, a rare bone disease
- DIPQUO may also have therapeutic relevancy in cognitive disorders associated with GSK3-β signaling, such as Alzheimer's Disease

Technology Advantages

- DIPQUO is more effective at stimulating bone deposition in comparison to BMPs
- DIPQUO is a stable small molecule that is less costly to produce at a larger scale than BMPS, which are produced as recombinant proteins
- DIPQUO accelerates bone deposition without inhibiting bone remodeling

Supporting Data / Figures

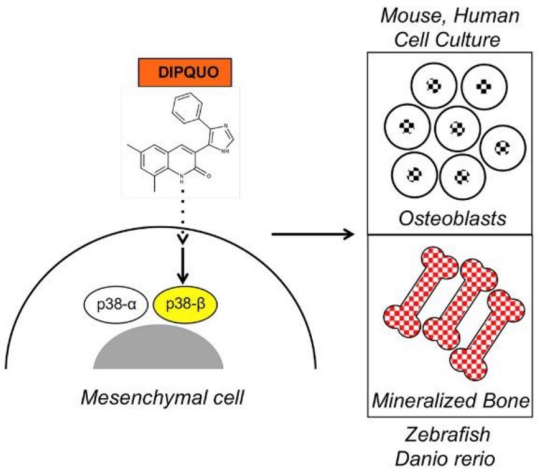

Figure 1: DIPQUO activates p38-β MAPK signaling, which leads to differentiation of mouse myoblasts and human bone-derived stem cells into mature osteoblasts. DIPQUO also increases bone mineralization in zebrafish.

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BMP: Bone Morphogenic Proteins

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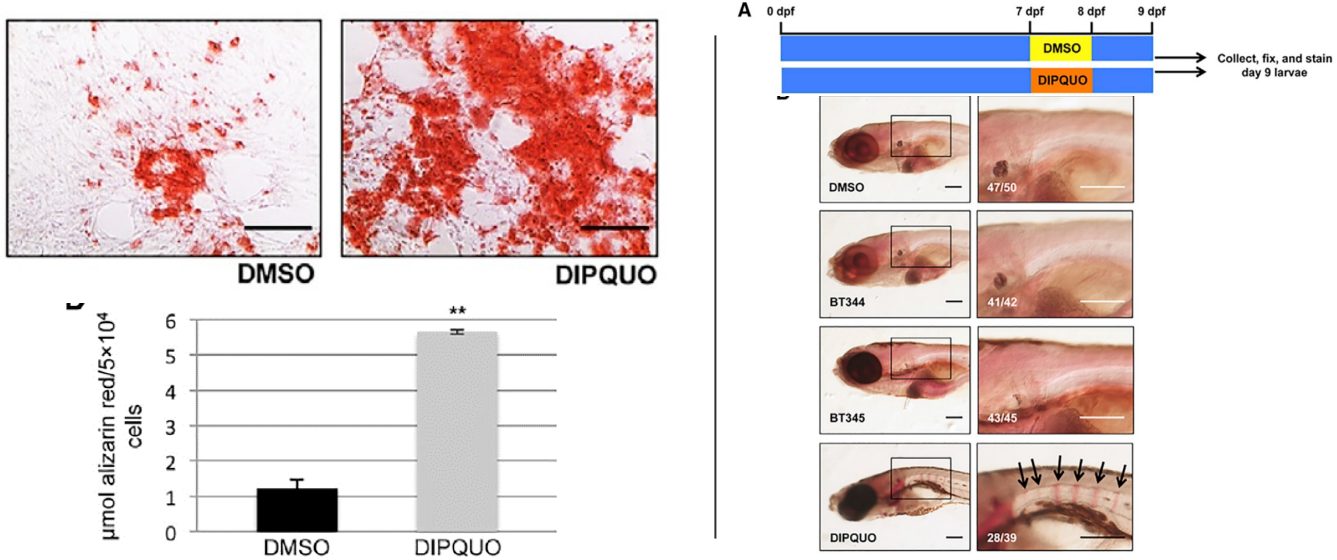

Figure 2: Left: Human Mesenchymal Stem Cells demonstrate increased calcium deposits (stained in red) following treatment with DIPQUO ($p<0.01$)
Right: Zebrafish larvae treated with DIPQUO demonstrate increased bone formation (indicated in red) compared to inert analogs.

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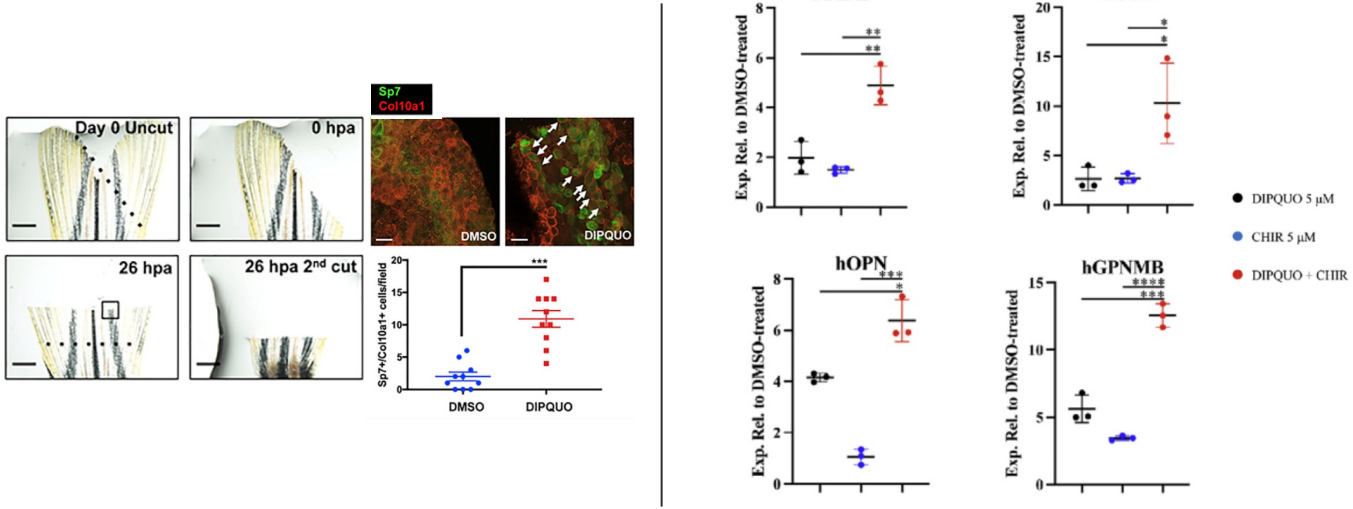

Figure 3: Left: DIPQUO increases osteoblast differentiation, indicated by SP7+/Col10a1+ cells (white arrows), in regenerative zebrafish models. **Right:** DIPQUO acts synergistically with GSK3-β inhibitor CHIR to increase expression of osteoblast marker genes in human skeletal muscle satellite cells.

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