

Blocking expression of the *DUX4* gene using small molecules.

Losmapimod is an FDA-approved p38 inhibitor in clinical trial with Fulcrum Therapeutics.

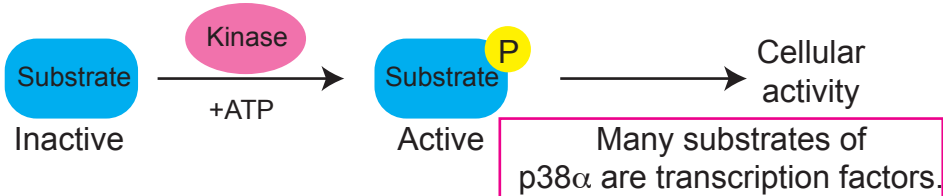
Disclosure: Dr. P. Jones, President of MyFSHD, was a scientific consultant for Fulcrum Therapeutics. He is not involved in the losmapimod clinical trial.

The term p38 refers to p38-alpha MAPK (Mitogen-activated protein kinase). It has a 38kDa mass. There are four isoforms of p38 MAPK (α , β , δ , and γ). The α , β , and γ isoforms are expressed in skeletal muscle, however p38 α is the most highly expressed.

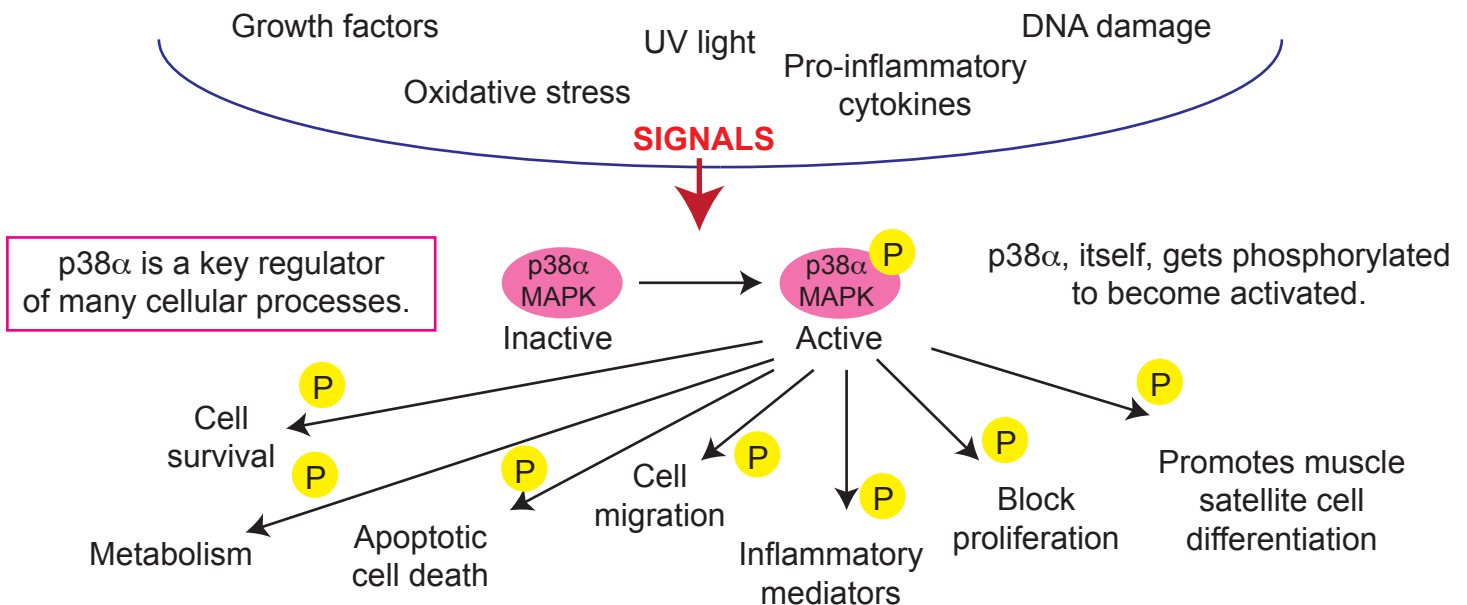
What is a protein kinase?

Protein kinases are enzymes that phosphorylate (add a phosphate to) proteins. This phosphorylation can affect the substrate protein's function and/or cellular localization.

Example



p38 MAPK is activated by many cellular signaling pathways and, in turn, can have many effects on the cell.



p38 α regulates a large number of genes during muscle differentiation and is critical for ensuring the correct temporal order of events from muscle satellite cell to myotube.



FSHD Therapeutic Approaches: Losmapimod

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Key studies showing inhibition of p38 α significantly reduced expression of *DUX4* in FSHD-derived muscle cells *in vitro* and in a xenograft mouse model.

The Journal of Pharmacology and Experimental Therapeutics (2019) 370:219-230.
Clinically Advanced p38 Inhibitors Suppress *DUX4* Expression in Cellular and Animal Models of Facioscapulohumeral Muscular Dystrophy^[S]

Jonathan Oliva, Scott Galasinski, Amelia Richey, Amy E. Campbell, Marvin J. Meyers, Neal Modi, Jun Wen Zhong, Rabi Tawil, Stephen J. Tapscott, and Francis M. Sverdrup

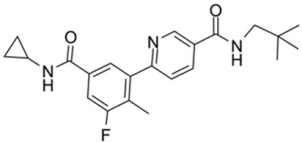
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The Journal of Pharmacology and Experimental Therapeutics (2020) 374:489-498.
p38 α Regulates Expression of *DUX4* in a Model of Facioscapulohumeral Muscular Dystrophy^[S]

L. Alejandro Rojas, Erin Valentine, Anthony Accorsi, Joseph Maglio, Ning Shen, Alan Robertson, Steven Kazmirski, Peter Rahl, Rabi Tawil, Diego Cadavid, Lorin A. Thompson, Lucienne Ronco, Aaron N. Chang, Angela M. Cacace, and Owen Wallace

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Losmapimod



Losmapimod, a selective and potent inhibitor of p38 α and β , was developed by GlaxoSmithKline for multiple conditions including post-myocardial infarction, COPD, and major depressive disorder. None of the clinical trials were successful; however, losmapimod was found to be well tolerated in trial subjects and deemed safe.

Model for action against FSHD. Results of Fulcrum Phase IIb trial pending in spring 2021.

