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A Therapy for Duchenne Dystrophy Based Upon Inhibition of Mechanically Sensitive Ion Channels

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The dystrophin lattice serves as a mechanical reinforcing network for the lipid bilayer. Any break in the dystrophin sequence prevents it from bearing stress. A loss of intact dystrophin transfers stress to the fragile bilayer causing mechanosensitive ion channels to open. These channels are cation selective creating a local influx of Na^+ and more significantly, Ca^{2+}. Eccentric contractions of MD muscles cause a calcium influx that has been correlated opening of mechanosensitive channels and calpain activation. A drug to inhibit open mechanosensitive channels promises to be a phenotypic therapy for MD.

Our studies of mechanosensitive channels led us to a 34AA ICK peptide that selectively inhibits open mechanosensitive channels (GsMTx4, US patent). It remains the only known specific inhibitor for this class of channels. GsMTx4 has a distinctive pharmacology where the D and L enantiomers are equally efficacious, yet GsMTx4 is highly specific for mechanosensitive channels. Administered chronically to *mdx* mice at <100nM, L-GsMTx4 improves behavioral performance in a concentration dependent manner with no sign of toxicity in behavior or histology. GsMTx4 does not affect the mechanotransduction channels in differentiated mechanosensors such as the cochlea or muscle spindle. It also has no effect on the electrophysiology or ionotropy of normal cardiac tissue (human, mouse, rabbit, etc) although it inhibits stretch-induced arrhythmias, clearly relevant to late stage dystrophy. The D form of the peptide is indigestible and hence may be delivered orally, and in view of the unique specificity of GsMTx4, it could be used in combination with other therapies.

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