Title: Endoxifen: A Potential Novel Therapy for Duchenne Carrier Associated Pathologies

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Co-authors' details: The foundational paper for this presentation is: *A Hypothesized Therapeutic Role of (Z)-Endoxifen in Duchenne Muscular Dystrophy (DMD).* ***Degener Neurol Neuromuscul Dis.*** **2025;15:1-15; https://doi.org/10.2147/DNND.S496904.** The co-authors are: Sandra S Hammer[1]; Laurence A Neff[2,3]; Olivier M Dorchies[2–4]; Leonardo Scapozza[2,3]; Dirk Fischer[5]; Steven C Quay[1].

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Abstract:

Duchenne Muscular Dystrophy (DMD) is an inherited, X-linked disorder that is progressive, debilitating, and ultimately fatal. Symptomatic (manifesting) DMD carriers have also been reported with various DMD carrier associated pathologies (D-CAPs). Estimates indicate that approximately 2.5–19% of DMD carriers have skeletal muscle symptoms and 7.3–16.7% develop dilated cardiomyopathy. Research on this population is extremely limited, in part because of difficulties in diagnosis of carrier status. Foundational work with the estrogen receptor modulator tamoxifen suggests the potential of a unique spectrum of therapeutic benefit from endoxifen, an active metabolite of tamoxifen in this population. Analyses of the mechanisms of action of endoxifen support this potential. For example, the PKC family of proteins has been implicated in DMD pathogenesis indicating PKC's essential role in muscle physiology and pathophysiology. PKC-θ is of particular interest as it is thought to be involved in skeletal muscle regulation and chronic inflammatory responses. In mdx mice, genetic ablation of Prkcq (the PKC-θ gene) resulted in reduced inflammation and improved muscle healing, which was paired with reductions in pro-inflammatory genes and pro-fibrotic markers, including a reduction in NF-κB activation. Studies using a PKC-θ inhibitor led to reduced inflammatory pathway activation and immune cell infiltration, which was associated with a significant reduction in muscle damage. Inhibition of PKC-θ also resulted in maintained muscle generation, preserved muscle integrity, and improvements in muscle activity recovery performance. Inhibition of PKC-θ has also been found to reduce dystrophic heart inflammation and improve the dystrophic heart phenotype and function of DMD cardiomyopathy in mdx mice. PKC-β, another PKC family member, and known target of endoxifen, is also known to be involved in

NF-κB activation, although its effect on DMD pathogenesis, if any, is unknown. Several studies have shown that activation of PKC-β leads to muscle damage in DMD by promoting inflammatory processes, increasing oxidative stress and modifying calcium signaling within muscle fibers. Thus, it is hypothesized that inhibition of PKC-β signaling has the potential to reduce inflammation cytokine production and consequently reduce immune cell infiltration into damaged muscle tissue. Together these data indicate that targeting PKC-θ or PKC-β, or both, may be a potential therapeutic approach for treatment of D-CAPs patients. There is preliminary evidence that some of the other downstream pathological mechanisms born by DMD carriers are therapeutic targets for D-CAPs that are potentially modulated or effected by endoxifen's multiple mechanisms of action, in a manner that would be beneficial to patients. This evidence is both in vitro and in vivo. There is now a substantial body of clinical evidence developed in indications other than DMD that supports the safety profile of endoxifen as a therapeutic agent. Endoxifen may provide a material mitigation of symptoms for D-CAPs patients without causing adverse effects. Mitigation of symptoms in and of itself would have a positive effect on D-CAPs patients, which should as well benefit DMD patients themselves.

Biography:

Dr. H Lawrence Remmel currently is a doctoral candidate in the Graduate School of Life Sciences of the University of Utrecht, in the Department of Clinical and Translational Oncology, with a thesis project in novel diagnostics and therapies in early-stage hormonal positive breast cancer. He received his Juris Doctor from the Washington & Lee University School of Law in 1979 and his B.A. from Princeton University in 1975. He is a Visiting Graduate Assistant in Pediatrics, in the Laboratory of David Lyden, at Weill Cornell Medical College, Cornell University.