GENERAL AUDIENCE SUMMARY

APPLICANT NAME	DATE SUBMITTED
Quattrocelli, Mattia	7/15/2016 4:06:59 PM

TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

Glucocorticoids in fiber repair and regeneration of dystrophic muscles.

This General Audience Summary will become public information; therefore, do not include proprietary/confidential information.

Muscular dystrophies are characterized by chronic disruption of muscles, with consequent wasting of muscle. Normally, in response to muscle injury that disrupts the membrane around muscle, there is a repair complex that seals the damage. In dystrophic muscle, however, this process is impaired and in addition, dystrophic muscle do not regenerate as well as normal muscles. At present, glucorticoid steroids are the only pharmacological treatment for Duchenne Muscular Dystrophy. However, the side effects are prominent and the role of glucorticoids on the actual fiber repair process is still unknown. Moreover, the effects of glucorticoids on the stem cells in muscle are not well studied. With this project, we aim to define the effects of glucorticoids on muscle membrane repair and regeneration in dystrophic muscles using newly developed methods. We will first test the effects of pulsed and chronic administration of glucorticoids on fiber repair and resident stem cells of dystrophic muscles. We will then examine how glucocorticoids counteract the negative effects of the TGFß molecular pathway on muscle repair and regeneration. Finally, we will study how glucocorticoids and the novel genetic modifier Jagged converge towards beneficial effects on dystrophic muscles.

SCIENTIFIC ABSTRACT

APPLICANT NAME	DATE SUBMITTED
Quattrocelli, Mattia	7/15/2016 4:06:59 PM

TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

Glucocorticoids in fiber repair and regeneration of dystrophic muscles.

This Scientific Abstract will become public information; therefore, do not include proprietary/confidential information.

Muscular dystrophies are characterized by chronic disruption leading to muscle wasting. Normally, in response to injury that disrupts the myofiber membrane, there is a repair complex that seals the membrane, mitigating muscle damage. The repair complex involves many proteins, including annexins. In dystrophic muscles, however, this process is impaired and, in addition, dystrophic muscles do not regenerate as well as normal muscles. At present, glucocorticoid steroids are the only pharmacological treatment for Duchenne muscular dystrophy (DMD). However, the side effects are prominent and the mechanism by which glucorticoids impact the myofiber repair process is not well known. Importantly, while being beneficial for DMD, glucocorticoids appeared detrimental for other forms of muscular dystrophy like (LGMD) type 2B due to dysferlin mutations. Moreover, the effect of glucorticoids on muscle stem cell function is not well studied. Our preliminary data show that a glucocorticoid pulse increases annexin levels and improves sarcolemmal repair efficiency. Moreover, these data show that glucocorticoid pulse also enhances endogenous stem cell potential and differentiation ability. Furthermore, molecular analysis of the glucocorticoid response implicates specific pathways that trigger fiber repair. Therefore, with this project, we aim to define the clinical effects of glucocorticoids and their downstream molecular pathways on muscle membrane repair and regeneration in dystrophic muscles. We will tackle this problem using high-resolution confocal microscopy, stem cell characterization and pathophysiological studies. In the first aim, I will test the effects of pulsed versus chronic administration of glucorticoids on myofiber repair and regeneration in dystrophic imuscles, using the mdx model for DMD and Sgcg-null model of LGMD. In the second aim, I will examine how glucocorticoids counteract the hyper-TGF?eta molecular pathways that undermine repair and regeneration, using deleterious Ltbp4 allele and soluble TGF?eta modulators. In the third aim, I will evaluate the role of Jag1-dependent Notch signaling in sarcolemmal repair, and how Jag1- and glucocorticoid-elicited pathways converge to positively modulate myofiber repair and regeneration. These data will provide mechanistic pathways to explain the effects of glucorticoids on the reparative and regenerative aspects of muscle in the muscular dystrophies with the goal of improving the safety profile of steroid use.