

The effect of modulating the dystrophic skeletal muscle environment on donor stem cell engraftment.

Supervisors: Jennifer Morgan and Silvia Torelli

Aims:

Satellite cells are the principal skeletal muscle stem cell [1]. Satellite cells derived from normal donors are able to contribute to muscle regeneration and restore dystrophin expression when transplanted into muscles of the mdx mouse (a model of Duchenne muscular dystrophy (DMD))[2, 3]. Our aim is to modulate the host satellite cell niche to improve either endogenous muscle repair or regeneration, or donor stem cell-derived reconstitution of dystrophic muscle.

Project background and methods:

Satellite cells contribute to robust muscle regeneration on transplantation into dystrophic host muscles that have been pre-treated by high doses of radiation [4, 5]. We intend to investigate the mechanism by which radiation of host muscle affects donor satellite cells. First, we will determine which cells within skeletal muscle are responsible for mediating the radiation-induced effect. Next, we will investigate radiation-induced alterations in candidate effectors, including microRNAs that might promote skeletal muscle regeneration and/or satellite cell function. We will then up-or down-regulate those that are significantly altered by irradiation within non-irradiated host muscles and determine the effect on donor satellite cell engraftment. Elucidating the mechanism of the radiation-mediated effect and finding other means (e.g. pharmacological) of inducing this effect would be invaluable in translating stem cell therapies for DMD into the clinic.

References:

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- [3] Montarras D, Morgan J, Collins C, Relaix F, Zaffran S, Cumano A, et al. Direct isolation of satellite cells for skeletal muscle regeneration. *Science (New York, NY)*. 2005;309:2064-7.
- [4] Boldrin L, Zammit PS, Muntoni F, Morgan JE. Mature adult dystrophic mouse muscle environment does not impede efficient engrafted satellite cell regeneration and self-renewal. *Stem Cells (Dayton, Ohio)*. 2009;27:2478-87.
- [5] Boldrin L, Neal A, Zammit PS, Muntoni F, Morgan JE. Donor Satellite Cell Engraftment is Significantly Augmented When the Host Niche is Preserved and Endogenous Satellite Cells are Incapacitated. *Stem Cells*. 2012.

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