

PROPOSITIONS

Engineering Human iPSC-derived Skeletal Muscle to Model Pompe Disease Towards novel gene and regenerative therapies

1. iPSCs are amenable to gene-editing, allowing the generation of genetically-matched disease models to diminish the genetic variation when studying lines from multiple individuals. (This thesis)
2. iPSC-derived skeletal muscle cells show greater expansion potential *in vitro* than primary muscle cell lines, representing more suitable cell sources for large drug screenings and potential cell transplantation therapies for muscle disorders. (This thesis)
3. By testing the strategies to damage skeletal muscle that are currently used *in vivo* in mice using *in vitro* human muscle models, we can evaluate complex physiological responses in humans, which was impossible to investigate otherwise so far. (This thesis)
4. Shortening the intron 1 of the *GAA* gene in Pompe disease patients carrying the *IVS1* variant could potentially lead to novel gene-editing interventions to restore *GAA* enzyme activity levels for these patients. (Adapted from this thesis)
5. *Ex vivo* gene-editing requires efficient cell engraftment of modified cells in host tissues which remains challenging for skeletal muscle. (This thesis)
6. While AAV-based gene therapies cannot be used for prolonged gene expression, precision gene-editing strategies allow for the correction of defective genes at the genome level and thus restore gene expression that could last a lifetime.
7. Cell therapies, particularly personalized ones, are notoriously expensive. “Off-the-shelf” therapies will save patients time and money while enabling manufacturers to carefully engineer the cells. (Adapted from Diana Crow, *Cell*, 2019)
8. Using disease-specific iPSCs to generate 3D disease models enable the examination of spatiotemporal cellular interactions that could reveal more physiologically relevant disease parameters, thus providing an unprecedented drug-screening platform and offering a new option for tissue-replacement therapy. (Adapted from Yanhong Shi *et al.*, *Nat Rev Drug Discovery*, 2017)
9. “The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of starstuff.” (Carl Sagan, *Cosmos*)
10. “La ciencia siempre vale la pena porque sus descubrimientos, tarde o temprano, siempre se aplican”. “Science is always worth it because its discoveries, sooner or later, are always applied.” (Severo Ochoa)
11. “If a man never contradicts himself, the reason must be that he virtually never says anything at all.” (Erwin Schrödinger, *What is Life? With Mind and Matter and Autobiographical Sketches*)