CLOSER LOOK

MEMORANDUM

JDRF announces new partnership with Stanford and UCSF to create Center of Excellence focused on stem cell type 1 cures - September 4, 2019

This Cure Accelerator aims to develop cell replacement cures without immunosuppression

JDRF just announced a new partnership with Stanford and UCSF to create the JDRF Northern California Center of Excellence with the goal of developing cell replacement cures for type 1 diabetes that do not require immunosuppression. A high-impact collaboration among three powerhouse organizations, the partnership will focus its research on better understanding and targeting interactions between the immune system and the beta cell to eventually generate stem cell-based cures without the need for chronic immunosuppression. Check out the press release here.

The Center will build upon two key advancements pioneered by Stanford and UCSF: (i) Stanford's protocol for kidney transplantation without immunosuppression; and (ii) UCSF's method for deriving insulin-producing beta cells from stem cells. Insights from both of these advancements (more details below) will drive forward stem cell cures that do not require immunosuppression.

The Center's funding model will expedite project approval and reduce administrative load for researchers at Stanford and UCSF, thereby accelerating and streamlining this highly collaborative research process. It will also provide key flexibility to be nimble in response to new findings from projects or as new science emerges - JDRF is central to this and a unique element of what is sure to be an impactful partnership.

Leadership for the Center will include Drs. Matthias Hebrok (UCSF), Seung Kim (Stanford), Aaron Kowalski (JDRF President and CEO), Andrew Rakeman (JDRF AVP of Research), and Jeffrey Bluestone (UCSF). JDRF is currently spearheading funding efforts for the Center and is committed to providing annual funding for the first five years of operation with funding beyond year three confirmed after a review and evaluation. Notably, Dr. Hebrok was in the news earlier today as a key scientific advisory board member to Semma, which was just purchased for just under a billion dollars in cash from powerhouse biotech Vertex.

The Center brings together experts in the fields of stem cells, T1D immunology, gene editing, transplant immunology, and technology. Notably, many of the scientists have received JDRF early-career grants that prompted them to make T1D research the focus of their life's work; it goes without saying that the leadership of Dr. Aaron Kowalski at JDRF reinforces the movement needed to drive this forward.

- **Stanford's novel immunosuppression technique relies on a combination of (i) targeted lymphoid irradiation, specifically of the patient's lymph nodes, spleen, and thymus; and (ii) infusion of hematopoietic stem cells (HSCs; stem cells that give rise to the blood system) from the kidney donor.** This one-two punch temporarily weakens the patient's immune system, allowing donor HSCs to better integrate, after which, the HSCs can differentiate into immune cells that mix with the patient's native immune system. Big picture, this technique has the potential to significantly reduce long-term costs of islet transplantation, which typically requires the lifelong use of immunosuppressant drugs. Looking ahead, the Center aims to translate this novel technique to the islet cell transplant field, as well as to stem-cell derived beta cells. Excitingly, Dr. Judith Shizuru, one of the authors on the original *NEJM* letter published on the technique, will be a member of the Center's scientific team at Stanford.
- **Amongst the vast spread of beta cell advances from UCSF, a recent publication in *Nature Cell Biology* from Dr. Hebrok's lab detailed the generation of insulin-producing cells from human embryonic stem cells.** While a hefty number of published protocols have successfully produced "beta-like cells" from pluripotent stem cells, none have made fully mature cells that can adequately respond to glucose and secrete insulin. Specifically, *in vitro* recapitulation of beta cell development remains one of the last challenges to loom over the field. The

Hebrok lab protocol focused on the clustering of endocrine cells as a novel key step in beta cell generation. Immature beta-like cells were isolated and reaggregated to form islet-sized beta cell clusters, closely mimicking events during standard islet organogenesis. The mature beta cells (i) rapidly and robustly released C-peptide; (ii) elevated calcium signaling upon glucose stimulation; (iii) had highly sensitive K^+-ATP channels that could reversibly open and close; and (iv) had mature mitochondrial metabolism. These findings are the first of their kind, and while human embryonic stem cells are not a source for patient treatment, shed considerable light on *in vitro* recapitulation and the field at large.

- **In the broader industry landscape, several companies are pursuing stem cell based cures as well, albeit with a focus on encapsulated systems**. Sernova recently announced positive preliminary results in a first human patient for its Cell Pouch system, and Semma also recently revealed positive pre-clinical data for its stem cell islet infusion and immunoprotective device (presumably the MAILPAN macroencapsulation system). Semma should certainly have less risk now, and even larger resources at Vertex. Further along in the landscape is ViaCyte, with its phase 1/2 PEC-Encap/VC-01 and PEC-Direct/VC-02 programs underway. Crucially, both Stanford's immunosuppression protocol and encapsulation technology are meant to tackle the same problem of transplant rejection, using vastly differently approaches. This distinction uniquely positions the Center to develop a protocol that does not rely on encapsulation (that will presumably need periodic replacing) like the majority of commercial players in the market or potentially create a protocol that complements with the technology. See our full competitive landscape here; and please let us know any comments on the landscape.

This is a notable model to drive forward, collaboration between such competitive academic organizations; JDRF is a model to drive this forward and we look forward to seeing progress ahead. Drs. Hebrok, Kim, Kowalski, Rakeman, and Bluestone surely have incredible conversations ahead - stay very tuned!

--by Ursula Biba, Rhea Teng, Martin Kurian, and Kelly Close