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To:
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)

Re: Comments regarding DISC2-13413 (PI: Wang): **In Utero *Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing***

Dear ICOC Members,

We would like to thank you for considering our application "In Utero *Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing*" for funding, and would like to briefly address the Grants Working Group's comments on this proposal. The funding recommendation for this proposal is "Do not fund". **However, this proposal scored an 84, and received *the same score* as the two other proposals recommended for funding by the Minority Report**. We appreciate that CIRM grant funding is a fair competition and would greatly appreciate your consideration for funding this project, given that our proposal had the same merit as the other two grants that scored an 84. Funding this proposal will allow the significant and innovative work we do to move forward without delay. Described below are two impactful aspects of the work and one concern raised by the reviewers, where I would like to provide more details:

1. **Significance - a Potential Cure for a Rare Disease Before Disease Onset**

This is the ***only*** proposal within the DISC2 grants under consideration that is focused on developing an mRNA based non-viral gene editing for disease treatment *in utero* and will open the door to numerous therapeutic opportunities, given the tremendous versatility of mRNA.

Duchenne muscular dystrophy (DMD) is one of the most common fatal genetic disorders affecting 1 in 3500 male births. The onset of DMD symptoms occurs as early as 2 years of age and rapidly progresses where patients are usually wheelchair bound by age 12. The life expectancy of DMD patients is 25 years old. The overall goal of this proposal is to develop a new therapy, potentially a cure, for DMD. Our proposed therapy is comprised of lipid nanoparticle (LNP)/mRNA complexes that will be administered *in utero*, which will target and edit muscle stem cells before birth, correct dystrophin mutations, and restore full-length dystrophin expression in patients with devastating point mutations. **DMD affects fewer than 200,000 Americans and is therefore classified as a rare disease and medically underserved.** DMD patients can greatly benefit from solutions to rare-disease problems, including a lack of research activity, long waits for diagnoses, and expensive treatments. DMD patients with point mutations are **VERY RARE**. As the reviewers pointed out, "*point mutations make up a smaller proportion of causative mutation"* for DMD patients. On June 16, 2022, CIRM announced to have joined the Bespoke Gene Therapy Consortium (BGTC), a national public-private partnership that brings together the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), and multiple public and private sector organizations **to streamline the development and delivery of gene therapies for rare diseases**. As Dr. Maria Millan, CEO and president of CIRM said, "*the move is intended to advance the field, overcome obstacles and lead to breakthroughs for many rare and ultra-rare diseases*." Our project aligns well with CIRM's move into this critical area.

2. **An Innovative Strategy with Strong Preliminary Data**

In our **Preliminary Studies**, we demonstrated that *in utero* delivery of LNP/mRNA complexes can efficiently deliver mRNA to the heart and diaphragm, organs that are critical in maintaining respiratory and circulatory function for DMD patients. These experiments are ***the first* demonstration of targeted gene editing in the heart and diaphragm** using mRNA based non-viral gene editing *in utero*. If successfully accomplished, this proposed therapeutic will be a cure for DMD, and the treated fetus will be born without disease symptoms and will not need extensive medical treatments.

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3. Feasibility of the Study - the only concern from the reviewers

Overall, reviewers in favor of funding the application thought "*there was a significant unmet need for DMD treatments"* and praised our *"innovative approach of using lipid nanoparticles for targeted gene editing in utero*". These reviewers also thought "*the preliminary data were strong, the proposed project was highly innovative, and the team was well-qualified to complete the work*". We like to thank the Grants Working Group for recognizing the strengths of the application. As stated in the Minority Report, the greatest divergence between high scoring (funding recommended) and lower scoring (not recommended) panelists was in **criterion 4: feasibility of the project**. Reviewers in favor of funding thought the timeline was feasible and the team was qualified; reviewers not in favor of funding said the project was too ambitious, uncertain, and/or had too many milestones. No reviewer expressed doubts about the proposed team. The reviewers commented that our proposal consisted of "*Too many milestones. Human studies in (milestones) 6 and 7 seem outside scope of application; focus should be on studies in vivo*."

We appreciate but respectfully disagree with these reviewers' comments. As stated in the Quest award **PROGRAM ANNOUNCEMENT:** "*For a gene therapy candidate that is not a stem cell therapy: disease/injury modifying activity must be demonstrated using a clinically relevant model; and evidence that the gene therapy candidate will target or have activity on **a clinically relevant human cell population must be established"***. To be tightly consistent with the **PROGRAM ANNOUNCEMENT's** requirements, we proposed to include ***a clinically relevant human cell*** study. In fact, we have already obtained the ***clinically relevant*** patient-derived cells and successfully carried out preliminary studies with these cells. Additionally, the proposed work will be carried out by two well established labs across two UC campuses, the Wang lab at UC Davis and the Murthy lab at UC Berkeley. Some of the proposed work will be carried out simultaneously in the two labs. Most importantly, I would like to assure the reviewers and ICOC that we would certainly work closely with the CIRM team to ensure that the milestones are feasible and met on time.

Finally, I would like to highlight my team's outstanding track record for translating pre-clinical studies into clinical trials. Our team at UC Davis, led by Dr. Diana Farmer and me, have successfully acquired IND approval (IND# 24097) from the FDA for our *in utero* spina bifida treatment, and we are **currently conducting a first-in-human Phase 1/2a clinical trial (NCT04652908) for *in utero* treatment of spina bifida**. These clinical studies were made possible by CIRM support (PC1-08103, CLIN1-11404, CLIN2-12129), and we have a track record of using CIRM grants to generate impactful translational outcomes, that the voters of California want and paid for. I would like to assure the reviewers and ICOC that, if funded, we will rapidly move the current project into clinical trials by leveraging our experience in fetal medicine and IND approval.

Thank you for considering these comments. We would be happy to provide more details if needed.

Sincerely,

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