Keck School of Medicine of USC

DEPARTMENT OF STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

CARUSO DEPARTMENT OF OTOLARYNGOLOGY – HEAD AND NECK SURGERY

Neil Segil, Ph.D.

October 7, 2018

Gilberto Sambrano, PhD
Independent Citizens Oversight Committee
California Institute for Regenerative Medicine

RE: Quest award proposal **DISC2-11183: A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs** (Score 87).

Dear Dr. Sambrano and the ICOC,

Talk about adding insult to injury! Imagine that you are the parent of a 4 year old child who has just been diagnosed with a deadly pediatric cancer. You are told that, in spite of this horrible diagnosis, a cure is possible, with a good chance of success. However, the cure has an extremely common side-effect, namely that your child will likely go deaf as a result of the chemotherapy. In fact, more than 60% of kids treated for pediatric cancer end up profoundly deaf. These children, in addition to likely will having to endure a subsequent operation for a cochlear implant, will face a lifetime of playing catch-up with their peers in language and cognitive development. Some will do better than others, but all will be affected.

What do you say as a parent? Of course you will take the treatment, knowing full well that your child will never be the same. But, what if there was a drug that could be administered, along with the chemotherapy, that could block, or at least reduce, the hearing loss, without affecting the effectiveness of the chemotherapy.

That is exactly the purpose of our proposal, and I think a goal of this QUEST CIRM grant mechanism. To invest in the development of tools, which in this case, will ultimately improve the lives of childhood cancer survivors. To develop such a drug, we have built a screening platform using direct-reprogramming of iPS cells to a sensory hair cell fate. These are the very cells that are killed by cisplatin chemotherapy used in pediatric cancers. In this proposal, we are asking for money to develop this nascent tool into a drug screening platform, that can be used to identify new drugs that protect the sensory hair cells. Our proposal was highly rated by the GWG scientific review, receiving an 87 and being recommended for funding.

However, the final decision actually comes down to you, the members of this board. I hope you will consider funding this innovative and much needed effort. Advocacy for this problem is in its infancy. Just last month, the first symposium ("Childhood Cancer Hearing Loss" https://www.youtube.com/watch?v=boPJLbizZbk) was held to hear from scientists, clinicians, and patients about the nature of this problem, and supported by several Cancer Survivor foundations (The Children's Brain Tumor Foundation, Momcology, and the Children's Cause; Cancer Advocacy). This new awareness is invaluable, but without more resources, these patient-advocates will continue to be frustrated.

Thank you for your attention, and I hope you will consider our efforts to develop a treatment for this overlooked problem.

Sincerely,

Neil Segil, Ph.D.
Professor of Research
Department of Regenerative Medicine and Stem Cell Biology
Caruso Department of Otolaryngology - Head and Neck Surgery

Co-Director, USC Hearing and Communication Neuroscience Training Program,

University of Southern California
1425 San Pablo St., Los Angeles, California 90089-9080; Tel: 323 442 1549; nsegil@med.usc.edu

Eli and Edythe Broad Center
for Regenerative Medicine & Stem Cell Research
Keck School of Medicine of USC

3 October 2018

Independent Citizens' Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application: DISC2-11183

Title: A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs

Principal Investigator: Neil Segil, Ph.D.

Dear Members of the ICOC,

I am the primary Research Associate leading the bench-work of the above referenced grant application that addresses an important scientific gap in the CIRM portfolio, e.g., **a small molecule-based approach to discover drugs offering protection from chemotherapy-induced hearing loss**. I am also profoundly deaf in both ears and use a cochlear implant.

Cisplatin-based chemotherapy is a major life-saving treatment for many types of cancer, especially pediatric cancers. These groups now have an excellent survival rate, close to 90%; however, this life-saving treatment leaves many childhood cancer survivors profoundly deaf. Many will require a cochlear implant; and most will suffer from developmental delays in language acquisition and cognitive development, even with extensive therapy. They will require intensive treatment and training for many years. Our project seeks to develop a human iPSC-based screen to discover new drugs that mitigate chemotherapy-induced hearing loss. It also has the potential to substantially improve the standard of care for such patients, by eliminating the need for additional surgery in the form of cochlear implant, and permitting even more effective chemotherapy regimens.

Unmet medical needs: While patients do not die as a result of hearing loss, it is nonetheless a major quality of life issue among cancer survivors who have undergone cisplatin-based chemotherapy. More than 50% of breast cancer survivors suffer from significant hearing loss following such therapy, while an even higher number of young children undergoing high-dose chemotherapy for childhood cancers, such as neuroblastoma, are also profoundly affected. No current adjuvant therapy is available to mitigate hearing loss and degradation in quality of life that follows cisplatin

chemotherapy. Consequently, drugs aimed at protecting sensory hair cells during chemotherapy would be extremely welcome, as would a means of testing newly developed drugs for hair cell-damaging qualities prior to FDA testing.

First steps: Experimentation, to discover new drugs that can protect sensory hair cells during chemotherapy, requires that large numbers of sensory hair cells be grown in the laboratory. However, due to their inaccessibility deep in the temporal bone of the head, and their small numbers, these cells have been unavailable. Additionally, animal models can only partially reflect the effectiveness of potential drugs for human use.

To overcome these problems, we have adapted a state-of-the-art strategy called "direct lineage reprogramming" to generate human hair cells in the lab. We show preliminary data that mouse and human hair cells grown in the lab have properties extremely similar to normal hair cells, including an extreme sensitivity to chemotherapy drugs.

In the entire history of CIRM, only three hearing loss-related grants have been awarded. This is not an oversight of CIRM, but rather a reflection of the paucity of experimental approaches for studying problems related to hearing loss in humans. Our approach can now overcome these problems, and the work described in this proposal will allow us to simultaneously improve the efficiency of our direct-reprogramming technique from human iPSCs, while allowing us to immediately begin pilot testing small libraries of FDA-approved drugs for hair cell-protective qualities during cancer treatment.

Transformative potential: The reviews of the proposal were extremely positive, with no negative comments offered for any of the four key review questions. Most critically, the GWG felt the proposal has the necessary significance and potential for impact because "**platin toxicity for cancer patients is a huge problem and the applicants have a unique model for use to screen drugs to protect against this**" and "**development of a means of protecting sensory hair cells from ototoxicity with small molecules would be extremely important, and would also have potential implications from protecting against other aspects of cisplatin toxicity**."

Upon recovering from chemotherapy, there are many thoughts going through young patients' heads when faced with the harsh reality that they may lose their hearing: "***Will I ever hear again? How will I hear my family and friends? Will I be able to function in the hearing world?***" Despite a >80% 5-year survival associated with chemotherapy treatments, we still have no effective adjuvant treatment to protect against chemotherapy-induced hearing loss. As a former sufferer of tinnitus, which resolved only after I received the cochlear implant (when the brain loses sound input, it fills the gap with buzzing din), it is my hope that you will consider funding this application, to help attain our goal of translating the first proven prophylactic treatment to ameliorate these significant side effects, so cancer survivors worldwide will not have to resort to extreme measures such as the cochlear implant.

I think I can speak on behalf of my fellow hearing loss sufferers in conveying in the strongest possible term to urge you to support this study. We have no other options for this unsolved medical problem.

Sincerely,

Robert Rainey, Ph.D.

Research Associate
Neil Segil Laboratory
Eli and Edythe Broad CIRM Center
Keck School of Medicine of USC