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Dear Maria Bonneville and ICOC subcommittee members:

We are respectfully writing to you regarding our application titled, "Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia" (TRAN1-12891), which will be reviewed at the meeting of the ICOC/Application Review Subcommittee (ARS) on November 23rd, 2021. We would like to thank the Grants Working Group (GWG) for their constructive review and their many positive comments. **Our application received a median score of 85, which is considered of exceptional merit and warrants funding.** There was unanimous consensus that our proposal was significant and served the needs of underserved communities. A few highlights of the GWG Reviewer Comments include:

- The science is outstanding and a major strength.
- The project is based on sound rationale.
- The major strength of this proposal is that the applicants intend to use a unique cell population that they have developed and studied over the last decade. They have demonstrated that their cells impact both cognitive and motor defects in animal models of white matter stroke. The project is unique and highly significant.
- The [cell] differentiation protocol is robust and should be applicable to other pluripotent cell lines.
- A product that treats white matter stroke would have significant impact.
- The need for better therapies for treatment of white matter stroke, or for any kind of stroke, is enormous. Current therapies are of marginal value, and this application provides a promising new approach.

Underserved Communities:

This grant addresses a disease of significant societal cost and cost to communities traditionally under-represented in receiving the benefits of medical innovation. Stroke is the leading cause of adult disability and affects 15 million people each year, worldwide. By 2030, there will be an estimated 72 million people >65 years old (19% of the population), and women will increasingly outnumber men with stroke disability. ***Stroke mortality rates are higher in Black Americans, American Indians, Alaska Natives, Native Hawaiians, and Other Pacific Islanders, compared with White Americans.*** These populations also present a higher risk of cognitive impairment associated with stroke. These data indicate that the patient populations that suffer the most from this disease are the underserved communities.

Besides affecting the patients, stroke also places a heavy emotional, psychological, social, physical, and financial burden on families of stroke patients. Since stroke is a sudden reason for chronic disability, families are obliged to undertake a number of responsibilities related to the stroke patient's treatment without any preparations. Anxiety and depression are common mental illnesses in stroke caregivers, resulting in significant stress to the emotional health of caregivers. The process of caregiving also disrupts tremendously the economic balance in families. Often caregivers suffer from loss of employment, reduced incomes, and increases in expenditures. ***Poorer patients and families tend to have poorer post-stroke functional outcomes.*** In the United States, the medical and nonmedical costs of caring for patients with stroke during the first year after their stroke are approximately $50,000/patient. Making this disease an immense burden not only for patients but for their

families. Yet, there is no specific medical therapy for stroke or vascular dementia. This TRAN1 proposal develops a stem cell-based therapy for this disease.

We thank the GWG for their critical review and recommendations for improving the proposal and we would like to take this opportunity to emphasize a few key aspects of our proposal, and modifications that we have made in response to the GWG's recommendations.

Manufacturing – Scale-Up & Expertise:

We agree with the reviewers concerns that the approach to rely on "open 6-well plates dishes for manufacturing and scale-up may not prove to be practical". But as the reviewers indicated, **the likelihood of the proposed team to solve this problem is high**. In fact, we have built a strong team of manufacturing experts with which we have had detailed discussions to elaborate our manufacturing plan. As described on Milestone 2.1 and the Organization team section, our manufacturing team will be led by Tracy Janus (Senior Vice president, regulatory affairs, and CMC at GLOBAL regulatory writing and consulting) and will be supported by Drs. William Lowry, Jerome Zack (CIRM funded PIs whose groups are involved in Good Manufacturing Practices (GMP) manufacturing other iPSC cell products, including RPE cells for retinal diseases) and Gary Steinberg (CIRM funded PI whose group is involved in GMP manufacturing neural stem cell products use in several clinical trials to treat chronic ischemic cortical strokes). We have taken into consideration the reviewers' comments and to guarantee the successful completion of milestone 2.1, we developed in parallel other manufacturing approaches to which we can transition if problems with the current manufacturing plan arise. The use of bioreactors, closed systems, spheroid growth and cell stacks are some of the approaches that this team has considered during ongoing discussions to improve our manufacturing plan. Lastly, we will also work closely with other GMP cell production labs in the CIRM portfolio to explore other expansion conditions.

In conclusion, we thank the GWG for its constructive review and positive feedback of our research proposal. If successful, the therapeutic product developed on this proposal has the potential to positively affect the lives of millions of patients that suffer from white matter stroke and vascular dementia but more specifically to benefit underserved communities which suffer the most from these diseases. We hope the ICOC will support this project to develop a therapeutic product that directly addresses a clear unmet medical need.

Sincerely,

Irene L. Llorente, PhD