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June 18, 2926

Members of the Application Review Subcommittee (ARS)
California Institute for Regenerative Medicine
San Francisco, CA 94102

Dear Members of the Application Review Subcommittee,

I am writing on behalf of the PDEV-19729 team to highlight several points that we respectfully believe are critical for your consideration during the decision-making process.

Our program will deliver scalable, low-cost, one-time and durable treatment options for type 1 diabetes and late-stage type 2 diabetes in California on an accelerated timeline, enabled by existing human clinical data and GMP-ready cells capable of large-scale production within months of project launch.

The PSC-beta cell field has experienced repeated setbacks in immune protection through encapsulation, and we have learned from them. As the Grants Working Group affirmatively noted, our program has clinically demonstrated, that new encapsulation technologies can substantially improve engraftment and long-term survival. That clinical data, generated by the same medical team and using the same encapsulation technology proposed here, but incorporating donor islets, demonstrated excellent in-human performance without fibrosis. Leveraging the existing clinical experience, team and technology materially de-risks the regulatory path for the proposed program and establishes **a clear and rapid path to clinical trials and patient accessibility**.

The core of our cell therapy is a market-leading, GMP-grade iPSC generation and differentiation platform that achieves currently unmatched efficiency compared with other programs in the industry, with >95% purity of PSC-derived beta cells versus the 50–60% purity reported by some other programs. This performance has been validated across dozens of iPSC lines, rather than relying on the highly selected line(s) typically used by others, a potential choke points down the road. Our program offers a clear advantage in achieving **industry-level manufacturing scale and consistency at substantially lower cost** than prevailing growth factor- and chemical-based methods, enabled by our patented mRNA differentiation protocols.

The only technical critique appears to be based on a misunderstanding that the shelf life of the Aiβ Spheroids encapsulation combination product is only 72 hours. In fact, what we described was our operational plan to maintain a tight logistical window, such as 72 hours, between final product preparation and transplantation to ensure rapid patient access. The intrinsic shelf life of our product following cell packaging into the encapsulation device under shipping conditions is validated at **5 days,** and up to one week, without significant loss of cell viability or device integrity.

Additionally, while genome editing to reduce immune attack on transplanted therapeutic cells has the potential to provide clinical benefit, emerging data suggest that such immune evasion may be temporary, lasting only about a year. Over time, the immune system may recognize the transplanted cells and initiate rejection, potentially necessitating immune suppression after all. Reliance on either short-term, high-cost cell therapies or long-term immune suppression is undesirable and limits accessibility for many Californians with type 1 diabetes or late-stage type 2 diabetes.

Finally, access is not a downstream consideration for this program, it is a consequence of its core design, and it aligns directly with CIRM's mission under Proposition 14 to bring affordable therapies to all Californians, particularly those in underserved and harder-to-reach communities. Three features drive this. First, an unlimited iPSC-derived cell source removes the supply ceiling, allowing the treatment of a population rather than a select few. Second, because the system requires no chronic immunosuppression, it is suitable for patients who cannot tolerate immunosuppressive regimens and eliminates a major lifetime cost, monitoring, and safety burden. Third, a one-time treatment manufactured at substantially lower cost, with a validated multi-day shipping window, can be delivered beyond a handful of elite academic centers, extending reach to communities across the state where a patient's location should not determine whether a therapy is available to them.

For these reasons: We respectfully ask the ARS to fund PDEV-19729 and bring this California-developed therapy to patients in dire need across the state.
Sincerely,

Sincerely,

Jiwu Wang, Ph.D.
President and CEO
Allele Biotechnology & Pharmaceuticals, Inc.