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Written Public Comment to REGULAR MEETING OF THE TASK FORCE ON NEUROSCIENCE AND MEDICINE OF THE INDEPENDENT CITIZENS OVERSIGHT COMMITTEE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE Organized Pursuant To The CALIFORNIA STEM CELL RESEARCH AND CURES ACT on Jan. 23, 2024.

Dear Task force on Neuroscience and Medicine of ICOC CIRM,

Thanks for the meeting notice. I'd like to take this opportunity to bring your attention to the California stem cell research and cures act that CIRM is organized pursuant to, to those incurable or hitherto untreatable neurological diseases that destroy millions of lives and cost trillions every year, to the treatments or cures for those very costly and devastating neurological diseases promised by the California stem cell research and cures act, to human embryonic stem cell research that millions of people are pining their hopes on, to the breakthrough medical innovations of hESC research that provide therapeutic and scalable solutions to the major bottleneck in neuron regeneration and CNS repair.

Stroke, Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), spinal cord injury (SCI), traumatic brain injury (TBI), spinal muscular atrophy (SMA), and many other neurodegenerative disorders are major health problems with estimated costs of over $2 trillion annually world-wide. Those devastating and life-threatening diseases are leading causes of death or permanent disability, but there is no effective treatment or drug that can restore the damaged or lost neurological tissues and functions. The limit capacity of neuron circuitries of the brain and spinal-cord for self-repair constitutes a significant challenge to traditional medicine for neurological tissue and function restoration in seeking cures for those disorders that destroy lives. Due to lack of a scalable human neuron source, to date, the need to restore vital tissue and function for a wide range of incurable or hitherto untreatable neurological diseases remains a daunting challenge to the conventional mode of drug development. Although stem cell therapy represents a promising regenerative medicine approach closest to provide a cure for those diseases, demonstrating stem cell production at the scale and product purity adequate to heal the damaged or lost tissues that have naturally limited capacity for

repair, such as the human heart and brain, has been a big challenge for traditional cell sources or products.

The successful derivation of human embryonic stem cell (hESC) lines from the *in vitro* fertilization (IVF) leftover embryos is considered as one of the major breakthroughs of the 20th century life sciences. Pluripotent hESC can maintain long-term, stable growth and differentiate into clinically-relevant lineages, providing an inexhaustible source of replacement cells for human tissue and function restoration. It is public consensus that hESC research holds huge promise for treating major human diseases that have been challenging for traditional medicine, and California voters even passed 2 propositions to establish CIRM to fund hESC research in order to find treatments or cures for many major health problems. However, after almost 2 decades, after $4 or 5 billion of CA taxpayer money later, there is still no CIRM award in CIRM pipeline or portfolio that can provide effective treatment or therapy to restore the damaged or lost neurological tissues and functions for those very costly neurological disorders that destroy lives.

A major challenge for clinical translation of hESC research for neurological diseases is how to turn non-functional pluripotent cells efficiently and reproducibly into a large supply of human neurons we need for CNS repair. We have developed the key breakthrough technology to solve this problem, enabling well-controlled, highly efficient, direct conversion of non-functional clinical-grade hESC at the pluripotent stage by small molecule induction into a large supply of functional human neuronal progenitor cells as novel, effective regenerative medicine advanced therapy (RMAT) products for neuron-circuitry regeneration, overcoming the major bottlenecks in the regenerative medicine market (USPTO patent# 8,716,017). Our innovative hESC Platform is a game-changing enabling technology to provide RMAT products in large quantity and high quality with adequate cellular capacity to regenerate the neuron circuitry, ensuring high degrees of efficacy and safety of the hESC-derived therapeutic products, thus robust clinical benefit leading to therapies. It not only constitutes clinically representative progresses in human neuronal therapeutic products for treating a wide range of incurable or hitherto untreatable neurological diseases, but also offers manufacturing innovation for production scale-up and creation of replacement tissue or organ products. Our breakthrough innovations present hESC as a novel, advanced therapeutic strategy for a wide range of incurable or hitherto untreatable neurological diseases, having tremendous impact on economy, health, future medicine, and patient care. Our innovative hESC Platform enables direct conversion of pluripotent hESC into a large supply of human neurons for neuron circuitry repair and nerve tissue bio-fabrication, also providing a practical scalable solution for CNS regeneration.

The difficulty of crossing “the valley of death” in drug development is the pounding consequence of a vast amount of Federal and private investments only go to maintain the status quo of mainstream biomedical research in the non-human model organisms or systems that do not reflect the complexity of humans, thus have little implications for the prevention and treatment of human diseases. Without a

readily accessible and effective human model system to unlock the mysteries of human development and disorders, the road of desperately seeking cures has become all but a dead end to real world remedy. Due to the restriction on human embryonic and fetal materials available for study, there is a fundamental gap in our knowledge regarding the molecular networks and pathways underlying human embryogenesis. As a result, the normal human developmental pathways that generate the enormous diversity of CNS neurons remain poorly understood. Development and utilization of hESC models of human embryonic development will facilitate rapid progress in identification of molecular and genetic therapeutic targets for the prevention and treatment of human diseases. Our technology breakthrough enables neuronal lineage-specific differentiation direct from the pluripotent state of hESC with small molecule induction, providing much-needed *in vitro* model systems for investigating molecular neurogenesis in human embryonic development. It opens the door for further unveiling genetic and epigenetic programs embedded in the human CNS development using genome-wide high-throughput high resolution profiling approaches.

Today, cutting-edge hESC technology platforms have been developed, some even commercialized, for defined media and culture systems to derive high quality clinical-grade stable hESC lines suitable for human trials, for large-scale production of clinical-grade hESC-derived CNS-related human stem/progenitor/precursor cells, accessory cells/glial cells (e.g., oligodendrocytes, astrocytes), and functional human neuronal cell/tissue/organ products to support clinical trials of neuronal regeneration or replacement therapies as well as CNS tissue/organ biofabrication for those most-costly neurological diseases, such as Stroke, Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), spinal cord injury (SCI), traumatic brain injury (TBI), spinal muscular atrophy (SMA). To fulfill the California stem cell research and cures act, to gain both the public and State supports for bond financing, there is an urgent need for CIRM Task force on Neuroscience and Medicine to put derivation of clinical-grade hESC lines and banks, establishing world-class hESC training courses and training centers, building cutting-edge most-advanced stem cell centers and infrastructures, supporting developing hESC medical innovations for a wide range of incurable or hitherto untreatable neurological diseases, facilitating collaborations or sharing between teams/organizations/companies that hold critical IP or patents, supporting highly promising hESC products moving into clinical trials of those very costly and devastating neurological diseases on the agenda.

Despite that hESC research innovations could provide urgently-needed life-saving treatments or cures for major health problems that affect millions and cost trillions, the science or scientific, format, and eligibility criteria aspects of CIRM guidelines and instructions for grant application packages set by former CIRM Presidents/Staff have prevented the most translational research – human embryonic stem cell research -- from translating to clinics, as CIRM has done in almost 2 decades. The walls arbitrarily erected by CIRM former Presidents/Staff for DISC, TRAN, and CLIN grant application programs only suit for traditional drug development have restricted the highly promising hESC products or regenerative medicine advanced therapy (RMAT) products from moving into human trials. Traditional drug development usually starts with drug leads discovered in non-human simple model organisms, thus

requires lengthy and costly both demonstration in animal model testing and establishment of proof-of-concept and safety in human trials. As a result, almost no CIRM DISC awards selected by CIRM President/Staff for full review could progress to CIRM TRAN, and almost no CIRM TRAN awards selected by CIRM President/Staff for full review could progress to CIRM CLIN. As a result, all CIRM CLIN awards have encountered the very high failure rate of traditional drug development in human trials, no CIRM CLIN award has led to any market approval, and no CIRM CLIN award has provided any cures or even meaningfully effective treatments for a host of very costly and devastating neurological disorders promised by the California stem cell research and cures act, such as Stroke, Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), spinal cord injury (SCI), traumatic brain injury (TBI), spinal muscular atrophy (SMA), after almost 2 decades, and after $4 or 5 billion of CA taxpayer dollars spent by CIRM. Unlike traditional R&D, hESC-based RMAT products have been developed directly with human cells with proof-of-concept already established in humans, which simplifies the development process, lowers the costs, shortens the time consumption, and increases the probability of clinical success dramatically.

hESC research is intrinsic translational by nature. To accelerate regulatory review/approval and patient access to new therapies brought by the breakthrough medical innovations of hESC research, even FDA has passed the Regenerative Medicine Advanced Therapy (RMAT) Designation Program and the FDA Modernization Act 2.0 to legitimize alternatives to animal testing for advancing a drug or product to human trials. However, after almost a year since the FDA Modernization Act 2.0 was enacted into law, CIRM TRAN still requires "preclinical animal model data relevant to the target clinical indications" to even apply, even though most of CIRM TRAN awards only have failed "preclinical animal model data relevant to the target clinical indications" that have failed to demonstrate the efficacy in their animal models, e.g., failed animal data that have failed to regenerate, repair, or replace the diseased or damaged tissues or organs, which have resulted in their total failure to progress to CIRM CLIN and their total failure in CIRM-funded human trials. Preclinical animal model data provide little implication for human trials. Companies use tens of thousands of animals for animal tests each year. Yet more than nine in 10 drugs that enter human clinical trials fail because they are unsafe or ineffective. The only role that CIRM TRAN requirement of "preclinical animal model data relevant to the target clinical indications" set by the very ignorant former CIRM Presidents/Staff serves is to prevent the most translational research – hESC research -- from translating to clinics, stalling CIRM's mission and bond financing with the State. To fulfill the California stem cell research and cures act, to gain both the public and State supports for bond financing, CIRM Task force on Neuroscience and Medicine should ensure CIRM comply with the law and remove those unscientific, arbitrary, obsolete, discriminative, even conflict of interest (COI) barriers in CIRM grant applications set by CIRM former Presidents/Staff for successful human trials and accelerated market approvals of hESC-derived RMAT products targeting those very costly and devastating neurological diseases.

Current state of hESC research has provided much-need therapeutic solutions for a wide range of incurable or hitherto untreatable neurological diseases, and has laid the foundation for neurological

tissue and function restoration as well as for bridging the key knowledge gap in human CNS development. It is crucial for CIRM Task force on Neuroscience and Medicine to prioritize such frontier of regenerative medicine to ensure that these reachable treatments or cures brought by the breakthrough medical innovations of hESC research for those costly and devastating neurological diseases are near, to ensure CA taxpayer money be used to pave a successful path in the war against diseases, and to ensure CIRM's future sustainability.