[EXT] Public Comments to CIRM ICOC/ARS Meeting on September 26, updated

Public Comments to CIRM ICOC/ARS Meeting on September 26

Xuejun Parsons, PhD
Founder/CEO/President, San Diego Regenerative Medicine Institute,
website; https://www.sdrmi.org
Founder/CEO, Xcelthera, website: https://www.plurixcel.com

Dear CIRM,

Thanks for the meeting notice and thank you for this opportunity to present my Public Comment.

I'd like to make a public comment, because CIRM Review continues to not follow the standards, regulations, and laws for a CA State Agency, and unreasonably requires the applicants to demonstrate conflict of interest (COI) without even disclosing to the applicants who are the reviewers, please see below, which makes any appeal impossible. Also, I thought everybody had to demonstrate COI before appealing in front of ICOC. I just realize I do not see any other applicants' appealing letters have to demonstrate any financial COI at all. Is the demonstrate COI requirement for appeal in front of ICOC only for me or a general CIRM requirement for all applicants?

I am writing regarding the conflicts of interest (COI) of CIRM Review that CIRM has not disclosed to the public according to the COI law of the State of California about its employees, which has resulted in flawed and biased review summary and deliberately very biased score for our cutting-edge human embryonic stem cell (hESC)-based technology innovation that would provide breakthrough treatment or cure for a major health problem Parkinson's Disease (PD) and bring hopes to millions of patients and tremendous benefit to CA healthcare system and economy, exactly the stem cell research breakthrough that California voters passed 2 Propositions to fund. Such flawed and biased review summary and deliberately biased score of CIRM Review are not based on scientific merits, but on COI and on false and fraudulent statements, please see below. Such flawed and biased reviews and deliberately biased review scores not based on scientific merits can also be found at the top of the list of the Summaries CIRM Review presents to the ICOC board that contain many false and fraudulent statements against scientific evidence. Such flawed and biased CIRM reviews and deliberately biased scores not based on scientific merits have resulted in CIRM continued and accelerated misappropriation of tens and hundreds of millions of taxpayer money of a "Blue" State to induced pluripotent stem cells (iPSC) that are in fact adult cells reprogrammed with oncogenes or cancer cells – the scarlet "Red" adult stem cell Ponzi scheme of the Bush Administration to only benefit the greedy financial interest of CIRM Review. Such flawed and biased CIRM reviews and deliberately biased scores not based on scientific merits have completely tarnished the credibility of taxpayer-funded CIRM programs.

Anyone, any CA taxpayer, any CA voter, would wonder why a cutting-edge stem cell technology breakthrough with patents to address a major unmet medical need (DISC2-16732 Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction, please see the graphic abstract at https://www.sdrmi.org) still only got a very low score of 20 after resubmission that has addressed all the concerns of the reviewers, please see the resubmission statement below; why fraudulent induced pluripotent stem cells (iPSC) projects based on their intentional, knowing, or reckless faked data, faked differentiation protocols, and fabricated and falsified iPSC organoids against the code of scientific conduct could score 95 and make to the top list of CIRM Awards again and again, presented by CIRM Review to ICOC Board, including DISC2-16738 Developing a universal CRISPR gene therapy approach to treat C9orf72 ALS, DISC2-16715 Drug discovery for Charcot Marie Tooth Disease using hPSC-derived Schwann cells, DISC2-16562 Human induced pluripotent stem cells-derived glial enriched progenitors for the treatment of mild traumatic brain injury, and could even get a preferential minority report treatment for a totally fraudulent DISC2-16686, Development of iPSC-derived neural progenitors secreting GDNF for the treatment of ALS; why those projects that do not even meet CIRM's own eligibility criteria and positive selection requirements in the CIRM application package and are unrelated to CIRM mission, that is "to accelerate world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world", could make to the top list of CIRM Awards again and again, such as DISC2-16725 to develop an HIV antibody. It is shocking to the public how terrible and fraudulent of those applications at the top of the CIRM Review list are, which bears witness to the gross financial COI of CIRM Review.

It is self-demonstration of financial COI by CIRM Review themselves to intentionally put my application at the bottom of the CIRM Award list, and deliberately give a very unfair, obviously biased low score of 20 again and again without even pointing out any significant flaw in the application, while knowingly gave my mentor and her-cofounder's companies' iPSC products high scores and awards (see CLIN2-15547 & CLIN2-14300) against the code of scientific conduct with plagiarized data from my hESC research that they had no part of it. As said in my previous comments (Please also see the resubmission statement below) to demonstrate COI, the hESC-based prototype Xcel-hDANP of my PluriXcel-SMI-Neuron Platform has previously been tested using the systemically MPTP-lesioned non-human primate (NHP), the most authentic animal model of the actual human disease not only mimics all of the human symptomatology but also all the side-effects of treatment in CIRM award TR1-01267 to my former mentor Evan Snyder (for my NIH award K01AG024496, titled "Epigenetic controls in hESC dopaminergic fate") to fully evaluate and identify the optimal stem cell type for a cell-based therapy for Parkinson's disease (PD). We compared head-to-head behavioral analysis of stem cell transplanted MPTP-lesioned non-human primate (NHP) for 8 candidates derived from CNS or hESC, and identified the hESC-derived ventral mesencephalic precursor (hVM) I developed and secured patent [USPTO# 8,716,017], now renamed as Xcel-hDANP in this project, as a single developmental candidate for cell-based

therapies for PD that showed consistent and dramatic improvement in severely Parkinsonian NHP (i.e., a significant decrease in Parkinsonian symptoms), reflecting a restitution of DA function by these hESC-derived Xcel-hDANP (unpublished data, please see CIRM translational award# TR1-01267 on CIRM website www.cirm.ca.gov). Please also see my previous publications with Evan Snyder for hESC-derived hVM and CNS-derived hNSC candidates compared for cell-based therapies for PD in CIRM award TR1-01267. Part of the NHP study data of the hESC-based prototype Xcel-hDANP of my project were published in Kirks et al., Nature 2011;480:547-551 by Jeffrey Kordower of Ryne Bio/Kenai Therapeutics and Lorene Studer of Bluerock Therapeutics against the code of scientific conduct, after Evan Snyder's UCSD graduate student Dustin Wakeman, who I had been mentoring on the monkey study for 5 or 6 years, went to Jeffrey Kordower's lab in Chicago for less than half year. Part of the NHP study data of the hESC-based prototype Xcel-hDANP we hold patent have been used by my former mentor Jean Loring (for my NIH award K01AG024496, titled "Epigenetic controls in hESC dopaminergic fate") and her company Aspen Neuroscience in CIRM CLIN2-15547 for their iPSC product ANPD001, and also by Jean Loring's co-founder, who was never involved in the NHP study, in CIRM CLIN2-14300 for their iPSC product RNDP-001, against the code of scientific conduct, even though they have absolutely no data no protocol no publication to show they could turn iPSC into DA neurons, even though they have no data no protocol no publication to show they have any iPSC-derived DA progenitor/product that is Nurr1 positive and could generate those primate study data they used in CIRM awards and for FDA approval for their iPSC products.

To demonstrate significant financial COI, Bluerock Therapeutics has used their plagiarized preclinical large animal safety and efficacy data of the hESC product Xcel-hDANP of PluriXcel-SMI-Neuron Platform of this project for their hESC/hiPSC product DA01 against the code of scientific conduct to raise a few hundred million from private investors, which allowed them to sell Bluerock Therapeutics to the big Pharm Bayer for ~$ 1 billion. My former mentor Jean Loring and her company Aspen Neuroscience have also used their plagiarized preclinical large animal safety and efficacy data of the hESC product Xcel-hDANP of PluriXcel-SMI-Neuron Platform of this project, which we hold patent, for their iPSC product ANPD001 against the code of scientific conduct to raise ~$250 million private investment. Jean Loring's co-founder and Jeffrey Kordower have also used their plagiarized preclinical large animal safety and efficacy data of the hESC product Xcel-hDANP of PluriXcel-SMI-Neuron Platform of this project, which we hold patent, for the iPSC product RNDP-001 of Ryne Bio/Kenai Therapeutics against the code of scientific conduct to raise ~$ 80 million Series A private investment. All three companies have obtained IND from FDA using their plagiarized monkey study data generated from the hESC product Xcel-hDANP of PluriXcel-SMI-Neuron Platform of this project s for the iPSC products of Aspen Neuroscience and Ryne Bio/Kenai Therapeutics and DA01 of Bluerock Therapeutics, and ready to go into clinical trials. The only problem is that they do not have the original Nurr1 positive hESC product that was injected into those monkeys and used to generate those monkey study data they used for FDA approval, and we own the patent for that product. The financial COI is unavoidably serious and huge. We all know the PD therapeutic market is huge. With such huge financial interest, COI is sadly unavoidable when those members in

GWG, who have direct or indirect connection to Bluerock Therapeutic, Aspen Neuroscience, Ryne Bio/Kenai Therapeutics, UCI/UCLA/Salk/UCSD, and big Pharms like Bayer and J&J/Janssen, have a real or apparent motivation or financial interest in blocking funding of our true DA neuronal progenitor of this application for advancing breakthrough hESC research such that the members who have direct or indirect connection to Bluerock Therapeutic/Aspen Neuroscience/Ryne Bio/Kenai Therapeutics/UCI/UCLA/Salk/UCSD/Bayer/J&J/Janssen or their allies are in a position to gain financially (e.g. hundreds of millions of private investment and millions of CIRM grants shown above), professionally (e.g., professor, director, CEO positions in their institutions or companies shown above) or personally from "the new candidates being tested in clinic or other similar project already ongoing" of GWG members or their allies/associates by deliberately giving a negative evaluation and biased score of this grant proposal, DISC2-16732 Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction, please see the summary below and the graphic abstract at https://www.sdrmi.org.

To continue demonstrate COI as CIRM Review required, in fact, during 2017-2020, my former mentor Jean Loring even arranged for me to present my research data to investors or pitch to investors in San Diego Biocom a few times for her Company Aspen Neuroscience to raise hundreds of millions from private investors, including google venture and domain associate, which I was totally unaware of, until a few years later (~2022) CIRM asked me to demonstrate COI for my CIRM PD application. Somewhere between, I even received emails from those involved in the pitches, and found out they were all no longer with Biocom, which I thought was very weird at that time. Domain associate was my website that soon lost all my web content and told me they could not find it for a couple of years, which forced me have to start a new website. I wonder who was at google at that time. I am sure you all know it was another Duke professor and our dear FDA commissioner Robert Califf, which explains why FDA fast-approved several iPSC products last year despite its strict regulations regarding any product harboring oncogenes, including Japan's Jun Takahashi's iPSC product CT1-DAP001 for PD using his faked iPSC animal study data published in Nature for CIRM Alpha Stem Cell Clinics of UCSD to continue repeat his sham iPSC study with California taxpayer money, and Jean Loring's iPSC product ANPD001 for PD using her plagiarized preclinical animal safety and efficacy data of the hESC product Xcel-hDANP of PluriXcel-SMI-Neuron Platform of this project in CIRM CLIN2-15547. My former mentor Jean Loring was a frequent member of NIH study sections. To demonstrate financial COI, in fact, Jean Loring of Aspen Neuroscience and Lorene Studer of Bluerock Therapeutics and their cohorts have been abusing the NIH 3 or 4 reviewer triage process and sitting on multiple NIH study sections to triage my proposals for years, giving my significance very biased score 8 or 9 (NIH review score 1 is the highest) even though all my grants address unmet medical needs, and other very negative, false, fraudulent comments in the summary statements that do not comply with the guidelines and instructions of NIH CSR, very similar to the CIRM GWG flawed and biased review summary and biased score below. I am sure you all know the professional way to do it is by licensing and collaboration. Deliberately, knowingly, and recklessly giving me a hard time and unfair treatment to apply

for public funding with my original hESC research breakthrough innovations using their ties in CIRM Review, just like what they did in NIH study section, is very unprofessional and dirty, particularly playing on such a public stage.

Therefore, we, the CA taxpayers and voters, would like to urge ICOC to fund the cutting-edge human embryonic stem cell (hESC)-based technology innovation that would advance breakthrough treatment or cure for a major health problem Parkinson's Disease (PD) and bring hopes to millions of patients and tremendous benefit to CA healthcare system and economy (DISC2-16732 Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction), but not to give CA taxpayer dollars to the fraud and waste projects with no scientific merit at all at the top of CIRM Review list to only benefit CIRM Review's greedy financial COI, presented to the ICOC Board by CIRM very unqualified new President even according to CIRM's own presidential search criteria, who was directly responsible for massive misappropriation of billions of California taxpayer money to iPSC Ponzi scheme in > $ 1 billion of CIRM iPSC awards and other scams in > $ 2 billion of CIRM awards demonstrated by over 150 total failures and wastes in CIRM clinical trial awards during his term.

DISC2-16732: Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction
Project Summary:
Stem cell therapy represents a promising therapeutic approach to restore the lost nerve tissue and function for PD, however, it has been a major challenge for traditional cell sources/products to achieve stem cell production at the scale and product purity adequate to regenerate the lost DA neurons. We have built an innovative PluriXcel-SMI-Neuron platform enabling highly efficient direct conversion of hESC**uniformly** into a large supply of high quality Nurr1+/Nestin- hDANP [patent: USPTO# 8,716,017] that efficiently differentiates into DA neurons, yields well-dispersed/integrated DA neurons at a high prevalence following transplantation into the brains, contains no residual pluripotent cells and other cellular impurities of safety concerns, safely engraftable, thus suitable for safe and effective graft-dependent DA neuron replacement therapy, distinctly different from the prototypical epithelial-like Nurr1-/Nestin+ hNSC and other DA products. Therefore, we propose to further establish preclinical safety and efficacy of the hESC-derived Nurr1+/Nestin- hDANP for DA neuron regeneration and neurological function restoration in animal models of PD and establish TPP for IND-filing and entry into clinical development for PD. This project enables clinical translation of hESC technology/IP for DA neuron regeneration and neurological function restoration as a much-needed therapeutic solution for PD. The outcome will have a transformative impact on translational research priority by presenting hESC as a novel, advanced therapeutic strategy for a wide range of incurable or hitherto untreatable neurological disorders and stroke.
Resubmission Statement:
We appreciate the GWG reviewer comments, which enable dramatic improvements of this application, including: the approach in itself (cell replacement in PD) holds great promise

to meet an unmet clinical need; present options for progression from successful candidate discovery to translation; an advantage of this application is that their cell candidate is patented; the milestones are specific, logical, and achievable in the timeline; the team has access to necessary resources; the project uphold the principle of DEI as best as possible, discussed impact regarding African-Americans and Asian-Americans in particular;
To address the reviewers' concerns about the novelty, competitiveness, and impact of this application compared to other similar projects/products ongoing or already beyond (**Please see p22-25 and Table1**):

Innovation/Novelty: The innovative PluriXcel-SMI-Neuron platform of this award enables highly efficient, direct conversion of non-functional pluripotent human embryonic stem cells (hESC) **uniformly** into a large supply of high quality nuclear-localized Nurr1-positive human dopaminergic (DA) neuronal progenitor cells (hDANP) by small molecule induction (SMI) as a novel regenerative medicine advanced therapy (RMAT) product [patent: USPTO# 8,716,017]. Our PluriXcel-SMI-Neuron platform presents an innovative, more effective solution for the therapeutic needs of PD by providing a novel Nurr1+/Nestin- human DA neuronal progenitor in large quantity and high quality as a safe and effective RMAT product adequate to regenerate the lost DA neurons for PD, thus overcoming the major bottleneck in the regenerative medicine market.

Innovative Approach to Ensure Clinical Safety and Efficacy: The game-changing PluriXcel-SMI-Neuron approach of this award is unconventional and exceptionally innovative, enabling well-controlled, highly efficient, neuronal lineage-specific differentiation direct from the pluripotent state of hESC by SMI, fundamentally different from conventional hESC multi-lineage differentiation approaches through germ-layer induction. Those previous hESC/hiPSC-derived products through conventional multi-lineage differentiation protocols consist of a heterogeneous population of mixed cell types, including fully differentiated cells, high levels of various degrees of partially differentiated or uncommitted cells, and low levels of pluripotent hESC, posing a constant safety concern when administered to humans [29-31]. The PluriXcel platform dramatically increases the clinical efficacy of graft-dependent repair and safety of pluripotent cell-derived cell therapy products, a game-changer for human trials of hESC derivatives, including benefits in safety, stability, low tumor risk, high purity, high efficacy, as well as large-scale production over all other existing cell sources or products.

Novel Stem Cell Product for Effective DA Regeneration: The proposed therapeutic candidate is a novel, nuclear-localized Nurr1-positive and Nestin-negative (Nurr1+/Nestin-) hDANP derived from hESC by SMI, which we hold patent, the gold stand of innovation, novelty, and competitiveness. The hESC-derived Nurr1+/Nestin- DA product hDANP of this project efficiently differentiates into DA neurons strongly expressing nuclear-localized Nurr1 and TH, yields well-dispersed/integrated DA neurons at a high prevalence following transplantation into the brains, contains no residual pluripotent cells and other cellular impurities of safety concerns, and is safely engraftable, thus suitable for safe and effective graft-dependent DA neuron regeneration/replacement therapy. The hESC-derived Nurr1+/Nestin- hDANP is distinctly different from the prototypical epithelial-like Nurr1-negative and Nestin-positive (Nurr1-/Nestin+) hESC/hiPSC-derived human neural stem/progenitor cells (hNSC) [e.g., ANPD001 of Aspen Neuroscience and RNPD-001 of

Ryne Bio/Kenai Therapeutics] and other DA products [e.g., DA01 of Bluerock Therapeutics] that show cytoplasmic localization of inactive Nurr-1 (Nurr1-) (**Table 1**). The neuronal lineage specific transcription factor Nurr-1 is essential for maintenance of maturing and adult midbrain DA neurons, or an essential marker for DA progenitor cells or DA neurons. Those similar projects or products ongoing or already beyond of the GWG reviewers, including ANPD001 of Aspen Neuroscience, RNDP-001 of Ryne Bio/Kenai Therapeutics, DA01 of Bluerock Therapeutic, do not even have nuclear-localized Nurr-1 [20], indicating those projects/products are actually not DA progenitor and will certainly fail in their clinical trials. In addition, it is undeniable scientific fact that all induced pluripotent adult/stem cell (iPSC) products contain oncogenes, and there are serious safety concerns to implant iPSC/cancers into patients. Transplanting the iPSC product ANPD001 of Aspen Neuroscience (CIRM CLIN2-15547) and RNDP-001 of Ryne Bio/Kenai Therapeutics (CIRM CLIN2-14300) in PD patients would cause brain tumors/cancers for sure, seriously harming patients.

New Mechanism of Action (MOA) to Ensure Robust Clinical Benefit Leading to Therapy: The hESC-derived Nurr1+/Nestin- hDANP of this project exerts its therapeutic MOA through graft-dependent DA regeneration or cell replacement, distinctly different from the neuroprotective MOA or "Chaperon Effect" exerted by traditional stem cells (e.g., Nestin+ hNSC either isolated from CNS or derived from hESC/hiPSC, including ANPD001 of Aspen Neuroscience, RNDP-001 of Ryne Bio/Kenai Therapeutics, DA01 of Bluerock Therapeutic) that have failed to demonstrate clinical efficacy of DA neuron replacement for PD (**Table 1**). Please see **Table 1** in p24 about the novelty, competitiveness, and impact of this application compared to other similar projects or products ongoing or already beyond.

Health Impact: This project enables clinical translation of hESC technology/IP for DA neuron regeneration and neurological function restoration as a much-needed therapeutic solution for PD, having a groundbreaking impact on advancing medicine and improving human health. Fulfilling the goals of this project will offer critical insights into viable therapeutic strategies against PD as well as provide robust preclinical evidences of *in vivo* safety and efficacy to meet the entry criteria for TRAN1 for further development, and facilitate future therapeutic discovery and development for safe and effective hESC-based therapies for a wide range of incurable or hitherto untreatable neurological disorders and stroke, having tremendous impact on economy, health, future medicine, and patient care. The outcome of this project, which is fundamentally different from traditional strategies, will have a transformative impact on translational research priority by presenting hESC as a novel, advanced therapeutic strategy for a wide range of incurable or hitherto untreatable neurological disorders and stroke, potentially shifting current research and clinical practices, and creating new scientific paradigms for CNS repair.

To address the reviewers' demand that the candidate must be tested in more than one model:

The proposed therapeutic candidate has previously been tested using another model, the systemically MPTP-lesioned non-human primate (NHP), the most authentic animal model of the actual human disease not only mimics all of the human symptomatology but also all the side-effects of treatment in CIRM award TR1-01267 to my former mentor Evan Snyder (for my NIH award K01AG024496) to fully evaluate and identify the optimal stem cell type

for a cell-based therapy for PD. We compared head-to-head behavioral analysis of stem cell transplanted MPTP-lesioned NHP for 8 candidates derived from CNS or hESC, and identified the hESC-derived ventral mesencephalic precursor (hVM) I developed and secured patent [USPTO# 8,716,017], now renamed as hDANP in this project, as a single developmental candidate for cell-based therapies for PD that showed consistent and dramatic improvement in severely Parkinsonian NHP (i.e., a significant decrease in Parkinsonian symptoms), reflecting a restitution of DA function by these hESC-derived hDANP of this project (unpublished data, please see CIRM translational award# TR1-01267 on CIRM website www.cirm.ca.gov). Please also see my previous publications with Evan Snyder (including refs. 6, 7, 23, 29) for hESC-derived hVM [now renamed as hDANP in this project] and CNS-derived hNSC candidates compared for cell-based therapies for PD in CIRM award TR1-01267. Part of the NHP study data of the proposed therapeutic candidate were published in ref. 19 [Kirks et al., Nature 2011;480:547-551] by Jeffrey Kordower of Ryne Bio/Kenai Therapeutics and Lorene Studer of Bluerock Therapeutics against the codes of scientific conduct, after Evan Snyder's UCSD graduate student Dustin Wakeman, who I had been mentoring on the monkey study for 5 or 6 years, went to Jeffrey Kordower's lab in Chicago for less than half year. Part of the NHP study data of the proposed hESC-derived therapeutic candidate we hold patent have been used by my former mentor Jean Loring (for my NIH award K01AG024496) and her company Aspen Neuroscience in CIRM CLIN2-15547 for their iPSC product ANPD001, and also by Jean Loring's co-founder, who was never involved in the NHP study, in CIRM CLIN2-14300 for their iPSC product RNDP-001, against the codes of scientific conduct, even though they have absolutely no data no protocol no publication to show they could turn iPSC into DA neurons, even though they have no data no protocol no publication to show they have any iPSC-derived DA progenitor/product that is Nurr1 positive and could generate those primate study data they used in CIRM awards and for FDA approval for their iPSC products. Please see more in my Letters to the Board in CIRM ICOC meetings and on our websites https://www.sdrmi.org and https://www.plurixcel.com.

Table 1. Comparison of the hESC-derived Nurr1+/Nestin- hDANP with Other Stem Cell Products in the Market for PD

Derivation Source	Stem Cell Product	Large Scale Production	Nurr-1 (DA Marker)	Nestin (Epithelial Marker)	DA Neuron Replacement (MOA)	Safety	Ref./ CIRM Award
hESC	DA01 (BlueRock Therapeutics)	Yes	Negative (Cytoplasmic localization, Inactive)	Positive	No	Contain residual pluripotent cells of safety risks	19-21

hiPSC	ANPD001 (Aspen Neuroscience)	Yes	Negative (Cytoplasmic localization, Inactive)	Positive	No	Cancer risks (contain oncogenes)	CIRM CLIN2-15547
hiPSC	RNDP-001 (Ryne Bio/ Kenai Therapeutics)	Yes	Negative (Cytoplasmic localization, Inactive)	Positive	No	Cancer risks (contain oncogenes)	CIRM CLIN1-14300
hESC	hNSC	Yes	Negative (Cytoplasmic localization, Inactive)	Positive	No	High incidents of teratoma/neoplasm formation	8-10
Fetal CNS	hNSC	**No**	Positive (Nuclear localization, Moderate expression)	Positive	No	Safe	5-7, CIRM TR1-01267
hESC	**hDANP (SDRMI/ Xcelthera)**	**Yes**	**Positive (Nuclear Localization, Strong expression)**	**Negative**	**Yes New MOA: Graft-dependent DA neuron regeneration**	**Safe (no residual pluripotent cells of safety risks, no oncogenes)**	**22-32, CIRM TR1-01267**

DISC2: Quest Review 24.1 – Review Summary
Application: DISC2-16732
Xuejun H Parsons — San Diego Regenerative Medicine Institute
Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction

Application #	**DISC2-16732**

Title (as written by the applicant)	Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction
Research Objective (as written by the applicant)	The therapeutic candidate is a hESC-derived Nurr1+/Nestin- dopaminergic (DA) neuronal progenitor (hDANP) suitable for safe and effective DA neuron regeneration therapy for Parkinson's Disease (PD).
Impact (as written by the applicant)	This project enables clinical translation of hESC technology and IP as a much-needed therapeutic solution for PD, overcoming a major bottleneck and having a groundbreaking impact on advancing medicine.
Major Proposed Activities (as written by the applicant)	• To demonstrate hDANP is a homogeneous population of DA neuronal progenitors. Milestone: >90% positive for Nurr1 and differentiate into DA neurons but negative (<1%) for pluripotence/nonneural markers. • To affirm its homogeneity and neuronal identity with no residual pluripotent cells of safety concern by highly sensitive miR profiling. Milestone: >100-fold-down of miR-302, >100-fold-up of miR-10b. • To demonstrate the hESC-derived hDANP is highly neurogenic and safely engraftable following transplantation into the brain. Milestone: > 50% yields DA neurons and a lack of tumor formation (<1%). • To establish preclinical safety and efficacy of the hDANP for DA neuron regeneration in an animal model of PD. Milestone: >50% of the graft yields DA neurons and <1% forms inappropriate cell types. • To develop the target product profile (TPP) for the hDANP and conduct INTERACT meeting. Milestone: The TPP with preclinical safety and efficacy data is established for entry into TRAN1.
Statement of Benefit to California (as written by the applicant)	In regenerative medicine, hESC research holds huge promise for treating major human diseases that have been challenging for traditional medicine. Millions of people are pinning their hopes on hESC research. This project enables clinical translation of hESC technology/IP as a much-needed solution for PD, presenting hESC as a novel, advanced strategy for a wide range of incurable or hitherto untreatable neurological diseases, bringing tremendous benefits to California economy and healthcare.
Funds Requested	$2,804,000
GWG Recommendation	***(1-84): Not recommended for funding***

Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data
Final Score: 20
Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	19
Median	20
Standard Deviation	9
Highest	35
Lowest	10
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Key Questions and Comments
Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	**Does the project hold the necessary significance and potential for impact?**
Yes: 1 **No:** 14	• PD is an incurable disease that causes symptoms and signs through loss of dopaminergic neurons. Current treatments such as drugs and deep brain stimulation address symptoms but the disease remains progressive. Cell therapy is theoretically a realistic approach for PD to reduce dopamine deficiency. • There is an unmet clinical need for regenerative and reparative therapies for PD but this proposal is not likely to contribute to this for several reasons. There is no clear advantage of this cell

	product over once that are years ahead in development and have already shown safety and efficacy in clinical trials. • The program is unlikely to produce anything novel that will address the need for cell therapy for PD. • There is a lack of critical distinction of this cell product from competitors aside from various critical statements about the value of other programs. • Responses to the prior GWG review are tangential. The applicant indicates that nuclear localised Nurr1 sets the product apart from that of other competitors who "will certainly fail in their clinical trials." The applicant criticizes iPSC cells as likely to cause cancer. • Regarding animal model testing, the applicant launches into criticisms about other researchers without addressing the question. • The ability to effectively treat PD with cell therapy remains unclear, although some promising reports exist, and the learning in the field has been extensive. As the understanding of PD has deepened, the approach of only providing dopamine replacement is currently regarded as an over-simplification. • The candidate will provide neural progenitors with dopaminergic identity cells at scale. • The methodology to generate the neuronal progenitors seems to have been developed around 2011 and patented in 2014, and it is not clear why it hasn't progressed more quickly. • There is no clear plan for translation in humans and many missing details.
GWG Votes	**Is the rationale sound?**
Yes: 0 **No:** 15	• There is a very long and extensive history of tissue and cell transplantation for PD. Significant challenges included graft rejection and survival and circuit integration with modest evidence of benefits. Even with significant survival of cells and increased PET signal there may be little clinical benefit. Disease progression may also involve the transplanted cells. • Given the clinical effects of PD including dementia and autonomic dysfunction there is now a more realistic view of the scope for DA neural cells to have clinical effects, which are basically to provide a source of dopamine within the relevant circuit. • In this proposal there are several major flaws in rationale. The first one being that pure progenitors generates pure dopaminergic (DA) grafts and that this is better than grafts with a mix of mature cells. There is no evidence for this, and in fact several studies shows

	that non-DA neurons, such as astrocytes, can have an important role in supporting survival and maturation of DA neurons. • The idea that a pure population of neural progenitors will maintain in vitro features after implantation is flawed as there are many signals that may affect phenotype. • It is incorrect that the previous therapies are not based on cell replacement. • Additionally, the strategy based on grafting into the proposed location may be successful in rodents but the distance in the human brain is much much larger and not likely to have a therapeutic effect. • Many groups well ahead in this field and applicants repeated criticism of these approaches are unfounded. Other investigators have produced very well characterized and well validated dopaminergic cells for use in PD. • Applicants state this candidate is superior to others through graft dependent neural regeneration as compared to neuroprotection. However, no engraftment data are provided. • Preliminary data do not demonstrate any unique features of the new product. Immunostaining of poor quality and in particular does not show convincing nuclear localization of Nurr1. • Applicant's claims for their differentiation protocol is unsubstantiated. Methods for assessment of off target cell types inadequate and poorly validated. • There is extensive background work that supports the cell derivation project using hESC and the proposed platform. However, there is very little data about how the cells behave after being implanted into the brain. • The lack of testing of the cell product in PD animal models makes it difficult to anticipate the possible efficacy. • No data are provided to support the statements made. • Scientifically this is a largely incorrect proposal.
GWG Votes	**Is the project well planned and designed?**
Yes: 0 **No:** 15	• The applicant institute has hESC platform therapeutics, apparently at scale, for the cell derivation. The small molecule that induces differentiation appears to be a molecule which also leads to Nurr 1 nuclear translocation. Superiority over hiPSC sources is claimed. • Preliminary data in cell differentiation in vitro are not sufficient to convincingly support claims on superior differentiation into DAs. The in vivo data are sparse and do not allow for assessment of key parameters such as graft survival, maturation, function and innervation.

	• Without functional characterization of cells in vitro, or adequate characterization, this project will not get to a defined endpoint. • Methods for assessment of off target cell types inadequate and poorly validated. • No, no functional assessment of DA cells. Inadequate assessment of off-target cells. No mechanism of action data from in vitro or in vivo work; any improvements seen in the animal model could be due to unspecified trophic effects of grafted cells. Functional integration is not assessed in the animal model. • There is a substantial amount of work proposed to be done by a TBD scientist. The facilities for the conduct of PD-animal experiments are not evident. • The ability to conduct animal studies is unclear. • No experimental details. • No immune suppression in the xenograft. • Program de-risking forward from TPP is not discussed. Two patents are awarded, but the potential to partner around the expensive downstream requirements is not discussed.
GWG Votes	**Is the project feasible?**
Yes: 0 **No:** 15	• The project is unlikely to produce any product ready for further development. • Based on prior publications and provided preliminary data, it seems that some milestones (1-2) may already have been achieved, and animal brain engraftment is the main result to be accomplished to provide proof of concept to define a Target Product Profile. • The animal models used are standard in the field but where the graft will be placed, when and how it will be assessed and outcome evaluated is not clear. Also, the plan is to use wildtype rats and only use immune suppression as a contingency plan even though the need to protect the grafts from rejection in a xenograft setting is well documented. • Access to animal PD models and relevant testing is unclear. • The ability to carry out Milestone 4 is unclear. Animal numbers and power analysis are not provided. Milestone 5 cannot occur without the success of Milestone 4. • The project is controlled fully by applicant PI with some infrastructure support and advisors. Based in the application, the PI lacks sufficient knowledge of the field and models used. • The PI is a stem cell scientist; no other staff members are identified. It's not clear if the PI has experience in rodent PD models. • No expertise in PD is demonstrated.

	• The project is not realistic, with PI and one postdoctoral fellow. • The annual travel budget is high.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 6 **No:** 9	• This is discussed to some extent in proposal. • PI advocates for DEI. • Application states: "PD affects persons of all races, ethnicities, and genders, including 39% of Latino/Hispanics, 36% white, 15% Asian, 6% black, < 1% Natives in California". It's not clear where these figures come from and they are not accurate. • The PI indicates that they are a stem cell advocate. • Applicant claims her advocacy has influenced federal policies to increase stem cell access but no evidence is provided. • Statement contains some assertions that lack support.

Additional Review Information

Application Score & Review Summary

CIRM's board-appointed Grants Working Group (GWG) conducts the scientific evaluation of applications submitted to CIRM. The GWG scores DISC applications on a scale that ranges from 1 – 100, with 100 being the highest achievable score. An application's median score determines the funding recommendation as follows:

85-100 = exceptional merit and warrants funding, if funds are available

1-84 = not recommended for funding

DISC applicants receiving median scores from 80 to 84 can bypass the initial 'positive selection' step in a future review cycle, proceeding directly to full GWG review.

The Review Summary provides information on how the GWG panel scored, whether each review criterion was met, and specific bulleted comments that reviewers provided following the discussion. The Review Summary is not an exhaustive critique and does not cover all the factors that may have contributed to the final score.

Response to Review

An applicant may appeal the scientific review by the GWG based only on a demonstrable financial conflict of interest. All appeal requests must be made through the CIRM Review Office within 10 days of CIRM making the Review Summary available.

Future Resubmission

Applicants that do not receive funding can revise and resubmit the same project in a future DISC review. Application deadlines are posted in the Funding Opportunities section of

CIRM's website. Applications are available under 'Open Programs' in CIRM's Grants Management Portal about one month before the deadline.
Returning applicants must create and populate a new application and must download and populate the most recent application materials. The proposal template includes a section for addressing prior reviewer critiques in overview. CIRM staff seek to have at least one prior reviewer critique a revised, resubmitted application. The GWG will have access to this Review Summary.

Application Review Subcommittee Meeting
Funding decisions are made by the Application Review Subcommittee (ARS) of CIRM's governing board, the Independent Citizens Oversight Committee (ICOC). The ARS may consider GWG scores, public Review Summaries, recommendations from CIRM leadership, public comment, and/or programmatic factors (such as availability of funds, overall grant portfolio, RFA priorities, strategic considerations, the applicants' approach to issues of diversity, equity, and inclusion) in its decisions, with the aim of funding applications that are both scientifically meritorious and that bring programmatic value to the CIRM portfolio.
The meeting is conducted virtually and is open to the public. Members of the public, including applicants for CIRM funding, may provide signed, open letters to the ARS and/or make public comments (not exceeding 3 minutes, time dependent on the number of members of the public wishing to speak) to the ARS on matters related to the meeting agenda. Notify Scott Tocher (stocher@cirm.ca.gov) and Claudette Mandac (cmandac@cirm.ca.gov) if you plan to attend, send an open letter or make a public comment. Any correspondence that relates to an appeal of a funding recommendation by the GWG will be redirected to the CIRM Review Office (see "Response to Review" above).

Award Notification
CIRM staff notify funded awardees by email following the ARS meeting.