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DISC2-14071
Project Title: Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells (hESC) by small molecule induction
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Appeal Letter and Public Comments to the CIRM Review Office and ICOC

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Dear CIRM Review Office and ICOC,

I would like to appeal the scientific review by the GWG for my application DISC2-14071, titled "Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells (hESC) by small molecule induction" (please see the Objective and Specific Aims below for more project information) based on demonstrable conflicts of interest (COI) that had a negative impact on the review process and resulted in a flawed review.

As defined in CIRM's COI policy for GWG, "a conflict of interest exists when a Working Group member has a real or apparent interest in the outcome of an application such that the member is in a position to gain financially, professionally or personally from either a positive or negative evaluation of the grant proposal."

A. First, though every applicant of CIRM is required to address DEI, currently CIRM do not have any diversity, equity, and inclusion (DEI) policy or any DEI office to address the biases and unfair treatments of GWG to grant applications from underserved and underrepresented racial/ethnic PIs and communities that have neither representation in ICOC nor ally in GWG. I am a woman, Asian from an underserved minority community, and my applications have been treated very unfairly by GWG and CIRM. CIRM's lack of DEI policy for GWG, in addition to our no representation in ICOC and no allies in GWG have resulted in GWG/CIRM discrimination to women and minority, and unfair scores and biased reviews for my applications. A COI exists when a Working Group member has a real or apparent interest in blocking the funding of my application to advance breakthrough hESC research such that a negative evaluation and biased score of my application put the member of GWG and his/her allies in a position to gain financially, professionally or personally, as demonstrated by the well-known fact that >99% of CIRM funding has gone to CIRM applicants who have direct or indirect connection with ICOC or GWG, dominated by men, such as Alysson Muotri of UCSD, Marius Wernig of Stanford, Joseph Wu of Sanford University. I appreciate the GWG reviewers' positive comments that show support to this application, however, the reviewers' negative comments and unfair scores also demonstrate such financial, professional, or personal COI in GWG, including:

1. The reviewers' comments such as "the field of cell replacement therapy has grown … with several new candidates being tested in clinic, the application … is not competitive to other similar project already ongoing, the work has been largely done in the past and there is little innovation" show the GWG members have a real or apparent interest in blocking funding of this application to advance breakthrough hESC research such that the members are in a position to gain financially, professionally or personally from their "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. As said by the GWG reviewers, their new candidates are still being tested in clinic and have not succeeded in any clinical trial yet, and their similar projects are still ongoing and are very likely to fail clinical trials like most of drug candidates. In fact, their iPSC (induced pluripotent stem cells) candidates and projects have already failed safety trials in clinic. And PD is still an unmet medical need that has not been solved by their new candidates and their similar projects. Such GWG comments biased towards their candidates and their similar projects of GWG or those with direct or indirect connection to ICOC or GWG (e.g., big chance of impact, competitive, and score >85), and biased against my proposal (e.g., little chance of impact, not competitive, and only score 20) are evidence or demonstration that COI exists when a Working Group member has a real or apparent interest in blocking funding of this application to advance breakthrough hESC research such that the member is in a position to gain financially, professionally or personally from a negative evaluation and biased score of this grant proposal.

2. GWG reviewers remain confidential, however, by taking the field of cell replacement therapy in PD into account, as pointed by the GWG reviewer, it is not too hard to reveal some of "the new candidates being tested in clinic or other similar project already ongoing" deemed competitive with significant chance of impact by the biased reviewers of GWG. Examples of "the new candidates being tested in clinic or other similar project already ongoing" include Marius Wernig of Stanford University who has been awarded ten of millions by CIRM GWG to do iPSC Ponzi scheme (Please see more details about iPSC Ponzi scheme below) that has not advanced any of their new candidates in safety trials, nor yielded any beneficial product for people in CA. Examples of "the new candidates being tested in clinic or other similar project already ongoing" also include DA01 of Bluerock Therapeutics/UCI/UCLA/Salk/UCSD. Both Marius Wernig of Stanford University and Bluerock Therapeutics/UCI/UCLA/Salk/UCSD have deep connection to ICOC and GWG as demonstrated by their representations in CIRM and ICOC, their collaborations, their publications, and their connections to big Pharms, like Bayer.

3. The therapeutic candidate of my application, *Xcel-hNuP*, is a novel, nuclear-localized Nurr1-positive (Nurr1+), Nestin-negative (Nestin-), human dopaminergic (DA) neuronal progenitor derived from pluripotent human embryonic stem cells (hESC) by small molecule induction (SMI). So far, there is no other candidate or similar project that can turn pluripotent stem cells into a large supply of Nurr1-positive neuronal cells at the pluripotent stage in such high efficiency or enables well-controlled neuronal lineage-specific differentiation direct from the pluripotent state of hESC, and no other cells or candidates that are nuclear Nurr-1 positive and can regenerate damaged or lost DA neurons in PD, therefore, the approach of this proposal is a big breakthrough, providing advantages of safety, efficacy, and large-scale production or scalability over other approaches for successful clinical trials, and overcomes a current bottleneck for CNS repair or regeneration. 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. The DA01 of Bluerock Therapeutic/UCI/UCLA/Salk/UCSD do not even have nuclear-localized Nurr-1 (see Piao et al., Cell Stem Cell

2021;28:217-229), suggesting DA01 of Bluerock Therapeutics/UCI/UCLA/Salk/UCSD is, in fact, not a DA progenitor, will certainly fail in their clinical trial. However, Bluerock Therapeutic has been eyeing the therapeutic candidate of my application for years, even published our large primate PD model study data from the therapeutic candidate of my application in their Nature paper without our knowing and permission (see Kirks et al., Nature 2011;480:547-551) until they retracted those data later on to avoid the consequence of scientific misconduct. Even so, they still keep using DA01 as the impostor of our true DA neuronal progenitor of this application to get NIH/CIRM funding and financial support from big Pharms like Bayer. 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/UCI/UCLA/Salk/UCSD (I believe you do not really want me to name the names here) have a real or apparent motivation or financial interest in blocking funding of our true DA neuronal progenitor of this application in order to advance breakthrough hESC research such that the members who have direct or indirect connection to Bluerock Therapeutic/UCI/UCLA/Salk/UCSD or Bayer or their allies are in a position to gain financially, professionally or personally from "the new candidates being tested in clinic or other similar project already ongoing" of GWG members or their allies/associates, such as DA01 the impostor of true DA progenitor cells, by deliberately giving a negative evaluation and biased score of this grant proposal.

4. Patent is undeniably the gold standard of innovation, originality, competitive advantage. As also noticed by the reviewer that "an advantage of the application is that their cell candidate is patented", the therapeutic candidate of this application is patented, which means we hold exclusive rights for therapeutic development of our candidate and any related products in open competition. None of "the new candidates being tested in clinic or other similar project already ongoing" of the GWG reviewers' or their allies/associates' have ever been patented, such as iPSC of Marius Wernig of Stanford University and DA01 of Bluerock Therapeutics/UCI/UCLA/Salk/UCSD. It is the proof and demonstration of COI for the GWG reviewers to make such disingenuous comments against scientific evidence, against scientific data, against USPTO's gold standard, to deem this application or proposal is "not original, not competitive, little innovation, lacks novelty" while they also recognize we in fact hold the patent, the gold standard of innovation, originality, and competitive advantage. The iPSC candidate of Marius Wernig of Stanford University is actually adult cells reprogrammed with oncogenes, or commonly-known as flawed reprogramming or oncogenesis or the origin of cancers, an adult stem cell Ponzi scheme by the Bush administration. The DA01 of Bluerock Therapeutic/UCI/UCLA/Salk/UCSD do not even have active Nurr-1, the crucial marker for DA progenitor cells or DA neurons, is in fact not a DA progenitor, cannot even regenerate DA neurons or produce any DA at all (see their publications for more details). It is proof and demonstration of COI for the GWG reviewers to make such disingenuous comments against scientific evidence, against scientific data, against USPTO's gold standard, to bias towards "the new candidates being tested in clinic or other similar project already ongoing" of the GWG reviewers' or their allies/associates' without supporting by any patent or any scientific data, such as iPSC of Marius Wernig of Stanford University and DA01 of Bluerock Therapeutics/UCI/UCLA/Salk/UCSD. It is public consensus that human embryonic stem cell (hESC) research holds huge promise for treating major human diseases that have evaded traditional medicine. Millions of people are pinning their hopes on hESC research. Of course, stem cell Ponzi schemes of the GWG reviewers' and/or their allies/associates', such as iPSC of Marius Wernig of Stanford University, iPSC of Cedar-Sinai/UCLA, iPSC of Alysson Muotri of UCSD, and DA01 of Bluerock Therapeutics/UCI/UCLA/Salk/UCSD could not openly compete with the scientific breakthroughs of hESC research, such as the patented candidate of this application, as demonstrated by that CIRM has misappropriated >$250 millions of CA taxpayers' money to iPSC, but not even one iPSC candidate

has even passed safety trial yet, as also demonstrated by DA01, though lauded by the reviewers, showing no effectiveness in clinical trials at all. So the GWG reviewers could only show the competitiveness, originality, innovation, novelty of their stem cell Ponzi schemes or stem cell scams of "the new candidates being tested in clinic or other similar project already ongoing" behind closed doors by exercising or demonstrating their COI against CIRM GWG COI policy. Without doubt, such demonstrable COI by GWG reviewers as defined by CIRM GWG COI policy had a negative impact on the review process and resulted in a flawed review of this application.

B. Second, in regenerative medicine, human embryonic stem cell (hESC) research holds huge promise for treating major human diseases that have evaded traditional medicine. Millions of people are pinning their hopes on hESC research. However, hESC research has been surrounded by decades of social and legal controversy, smeared by adult stem cell Ponzi schemes, and stonewalled public funding by the opponents of hESC research in the last decade. As a result of policy battles concerning hESC research, the opponents of hESC research created artificially-reprogrammed somatic cells -- the induced pluripotent stem cells (iPSCs) -- by over-expression of oncogenes in adult cells in order to circumvent the ethical issues associated with the derivation of hESCs in the Bush administration (please see below Letter to Senator Wicker for more details). You probably have read Reuter's article "Faked heart studies by a once-obscure scientist duped the U.S. government and medical establishment for years. Washington is still paying for it" by MARISA TAYLOR and BRAD HEATH. Induced pluripotent stem cells (iPSC) is in fact pluripotent cancer cells, or adult cells reprogrammed with oncogenes (commonly-known as flawed reprogramming or oncogenesis or the origin of cancers in the scientific world). iPSC is another scientific Ponzi scheme or adult stem cell lie that has squandered more NIH and CIRM funding and done more damages than Anversa, this time by a Nobel Prize winner Shinya Yamanaka and the Dean of Harvard Medical School, George Daley (please see my Letter to Senator Wicker below for more details).

iPSC Ponzi scam is by the Bush administration, scarlet "Red". Over the last decade, CIRM has misappropriated > $250 millions of CA taxpayer's money to iPSC, not even including any funding for shared iPSC labs, even using millions of the taxpayers' money of a "Blue" State to send the scarlet "Red" Ponzi scam to the space to ruin America's space project (collaborated by Cedar-Sinai/UCLA and Alysson Muotri/UCSD). As a result, millions of patients who would benefit from hESC research have been not only denied access to potential life-saving treatments and cures brough by the therapeutic potential of hESC, but also exposed to the harms of adult stem cell Ponzi schemes or scams awarded/funded by CA taxpayers' money. Such a huge amount of taxpayers' money flowing into a scarlet "Red" adult stem cell Ponzi scam has not only resulted in policies shifting to the "red", including Roe v. Wade, and the House turning "red", but also destroyed the hopes and dreams of millions of people to access potential life-saving treatments and cures brough by the breakthrough medical innovations of hESC research. Such a massive misappropriation of taxpayers' money and continuing misappropriation of hundreds of millions of taxpayer's money are the direct result of unaccountable, irresponsible, and flawed scientific review systems where many reviewers themselves are involved in adult stem cell Ponzi schemes or scams and have political bias and financial conflicts of interest (COI).

Political Bias and Financial Conflicts of Interest. It is political bias and financial COI for CIRM exclusively funding a scarlet "Red" adult stem cell Ponzi scheme or scam by the Bush administration (iPSC – the fake pluripotent stem cells [PSC]) created by the opponents of hESC research on one hand using the public funding of a "Blue" State, but on the other hand denying fair review and funding hESC (the real pluripotent stem cells

[PSC]) by the proponents/advocates of hESC research, even repeatedly denying funding hESC research proposals based upon breakthrough medical innovations using biased and unchecked prescreening process and/or flawed review. Such a huge amount of taxpayers' money flowing into a scarlet "Red" adult stem cell Ponzi scheme or scam by the Bush administration, instead of stem cell research, has not only resulted in policies shifting to the "Red", including Roe v. Wade, and the House turning "Red", but also denied access of millions of patients to potential life-saving treatments and cures brough by the therapeutic potential of hESC and the breakthrough medical innovations of hESC research.

Adult Stem Cell Ponzi Scheme or Scam. It is common knowledge for anyone with a doctor degree in science or medicine (PhD or MD), such as GWG reviewers, that iPSC contain oncogenes, have oncogenic potential, are in fact cancer cells, but not stem cells. CIRM GWG reviewers know, or have the full knowledge, that iPSC are cancer cells and harmful to patients, but have still knowingly misled the investing public and taxpayers, and deliberately defrauded the investing public and taxpayers by misappropriating hundreds of millions of the taxpayers' money to a scarlet "Red" adult stem cell Ponzi scheme or scam by the Bush administration – iPSC the fake pluripotent stem cells (PSC). In contrast, CIRM GWG reviewers know that my breakthrough medical innovations of hESC research would provide potential life-saving treatments and cures for a wide range of neurological and heart diseases that affect millions and cost billions, but have still deliberately defrauded the investing public and taxpayers by denying fair review and funding of such hESC research projects critical to CA's economy and healthcare.

I am a hESC research advocate/proponent, a patient advocate, as demonstrated by this application. I have long-standing scientific differences to iPSC Ponzi scammers and/or the opponents of hESC research, including George Daley of Harvard, Larry Goldstein of ICOC/UCSD, Alysson Muotri of UCSD, Marius Wernig of Stanford, Joseph Wu of Sanford University, most of ISSCR presidents/vice presidents/officers, and most of the iPSC professors in prestigious universities and GWG, as demonstrated by my Letter to Senator Wicker below; as demonstrated by my long-standing disagreement to George Daley's testimony in Congress and his false and fraudulent statement that "iPSC and hESC are identical"; as demonstrated by my long-standing disagreement to ISSCR shamelessly, intentionally, knowingly, recklessly promoting and encouraging iPSC research misconduct practices for data fabrication or falsification in PHS/CIRM-funded research with organized Ponzi scheme in international society; as demonstrated by my breakthrough hESC research being stonewalled public funding of NIH and CIRM by high-ranking, high-paid, well-connected iPSC Ponzi scammers and/or the opponents of hESC research (e.g., billions of NIH/HHS funding and >$250 millions of CIRM funding to iPSC Ponzi scheme compared to none to breakthrough hESC research, including GWG flawed review of this application); as demonstrated by my decade-long of personal experience of being prosecuted and discriminated as a woman, as a minority for doing hESC research by those high-ranking, high-paid, well-connected opponents of hESC research and/or iPSC Ponzi scammers, mostly men like George Daley of Harvard, Larry Goldstein of ICOC, Alysson Muotri of UCSD, Marius Wernig of Stanford, Joseph Wu of Stanford, who used iPSC Ponzi schemes and their well connections or demonstrable COI in CIRM GWG and NIH review committees to scam ten of millions of public funding without making any scientific breakthroughs, and such apparent and real COI have financially and professionally benefited those iPSC Ponzi scheme professors so much that catapulted them to high-ranking and high-paid positions, e.g., George Daley to the Dean of Harvard Medical School, Larry Goldstein to ICOC board, Alysson Muotri to UCSD/Sanford Center Director, Marius Wernig and Joseph Wu to Sanford Center Directors, even though none of them have made any medical breakthrough or secured any patent for their iPSC product, and then those opponents of hESC research or iPSC Ponzi scammers used their

high-ranking, high-paid, well-connected positions to prosecute the advocates/proponents of hESC research and discriminatively block funding for breakthrough hESC research and medical innovations to women like me from underserved, underrepresented minority communities.

I have been trying to alert the public and patients about iPSC Ponzi schemes for years. Examples include my communications about iPSC research misconduct to HHS/ORI, such as,

"Is Nobel Prize winner liable for research misconduct? For example, we know stem cells are difficult to make, but cancer cells are easy. The Nobel Prize winner Shinya Yamanaka could not make stem cells, so he put oncogenes in adult cells, and made cancer cells and called those adult cells reprogrammed with oncogenes induced pluripotent stem cells (iPSC). iPSC are in fact cancer cells, an adult stem cell scam. NIH has misappropriated hundreds of millions, if not billions, to it. It is common knowledge for anyone with a doctor degree that iPSC contain oncogenes, have oncogenic potential. I believe iPSC misconduct is committed intentionally, knowingly, and recklessly, there are falsification and fabrication in all iPSC grant applications and NIH awards. However, it looks like Nobel Prize winner is immune from liability of research misconduct.

Are prestigious professors and deans liable for research misconduct? For example, the Dean of Harvard Medical School, George Daley, testified in Congress that induced pluripotent stem cells (iPSC) and human embryonic stem cells (hESC) are identical, which is a false and fraudulent statement. At least, iPSC contain oncogenes, but hESC do not. He has used such false or fraudulent statements to get millions of NH funding for himself and many others lots of iPSC grants from NIH. However, it looks like he is immune from liability of research misconduct. If the Nobel Prized winner and the Dean of Harvard Medical School cannot be held liable for research misconduct, how can you hold anyone else liable?"

"PHS/NIH gave George Daley ~$20 millions of grant to do genomic analysis to validate his own claim that iPSC and hESC are identical. His 20 millions of genomic analysis funded by PHS/NIH concluded that iPSC and hESC have identical genomes. Even the genomes of identical twins or identical twin embryos are not identical, even the genomes of different hESC lines are not identical, even the genomes of different iPSC lines are not identical. hESC are derived from human embryos, and iPSC are reprogrammed from adult cells with oncogenes. With all those DNA/histone methylations and genomic imprints in adult cells that are not found in hESC, it is very hard to believe that there is no intentional, knowing, reckless research misconduct for data fabrication and falsification in his PHS-funded iPSC research. Also, is that serious conflict of interest for PHS/NIH to give that much public funding to someone to validate his own claim? Do you think George Daley would do anything to prove he was wrong or he actually lied in Congress? To maintain research integrity, PHS/NIH should give that $20 millions of grant to an independent research lab or group to validate such a critical claim that would have a huge negative or detrimental effect on public policies, public funding, and public health for years.

George Daley's claim that iPSC and hESC are identical has been only validated by himself or only a single lab, has been contradicted by many publications, including those showing abnormality and accelerated-aging of iPSC, has never been widely-accepted in the scientific community outside the ISSCR circle. To maintain research integrity, every single iPSC experiment in PHS-funded research should use at least one hESC line as the standard or control to continue validate or invalidate his claim. It is intentional, knowing, reckless research misconduct for data fabrication and falsification in almost all iPSC papers or publications coming out of PHS-funded iPSC research/NIH iPSC grants/HHS iPSC contracts, including those published in top scientific

journals, to show any iPSC experiments or data that did not use a hESC line as the standard or control, that did not do side by side comparison of data between a iPSC line and a hESC line."

Although the GWG reviewers remain confidential, it is not too hard to tell most of the GWG reviewers are opponents of hESC research by promoting iPSC Ponzi scheme or stem cell scam in their negative comments and unfair scores to breakthrough hESC research that demonstrate financial, professional, or personal COI to the advocate/proponent of hESC research of this application, such as "the field of cell replacement therapy has grown … with several new candidates being tested in clinic, the application … is not competitive to other similar project already ongoing, the work has been largely done in the past and there is little innovation, research studies are regularly published with high DA differentiation yield", which are mostly referred to iPSC or performed/falsified/fabricated by known iPSC scammers/professors funded by CIRM/NIH. Such biased comments by the opponents of hESC research in GWG have demonstrated that a COI exists when a Working Group member has a real or apparent interest in blocking the funding of my application to advance breakthrough hESC research such that a negative evaluation and biased score of my application put the member of GWG and his/her allies in a position to gain financially, professionally or personally, as demonstrated by the well-known fact that CIRM has misappropriated >$250 millions to iPSC Ponzi scheme or scam created by the opponents of hESC research who have direct or indirect connection to ICOC or GWG; as demonstrated by CIRM president, GWG, and ICOC's (e.g., Larry Goldstein who himself is a iPSC Ponzi scheme professor and opponent of hESC research, and personally misappropriated tens of millions of CIRM funding to his close ally and Fred Gage's student Alysson Muotri of UCSD) close relationship or connection to iPSC Ponzi scammers and/or opponent of hESC research like George Daley, Alysson Muotri, Marius Wernig, etc (needless to say we all remember CIRM meetings and conferences with well-known scarlet "Red" iPSC professors that completely excluded any hESC proponents/advocates, and all those exclusively scarlet "Red" CIRM iPSC meetings and conferences used the public funding of a "Blue" state given by CIRM through the flawed review of a scarlet "Red" GWG full of opponents of hESC research and adult stem cell Ponzi scammers); as demonstrated by >$250 millions of misappropriation of the Public funding of a "Blue" state to iPSC scheme or scam that have largely benefited those iPSC professors or the opponents of hESC research, including George Daley of Harvard, Larry Goldstein of ICOC, Alysson Muotri Of UCSD, Marius Wernig of Stanford, Joseph Wu of Stanford financially and professionally, and financially and professionally fueled and catapulted those opponents of hESC research to their high-ranking and high-paid positions in prestigious universities, despite all those high-ranking and high-paid iPSC professors have failed to get any of their iPSC products through any safety trial after billions of public funding spent by them; as demonstrated by those iPSC professors or opponents of hESC research who used their high-ranking and high-paid positions they obtained through misappropriation of NIH/CIRM funding to their Ponzi schemes in prestigious universities to stonewall public funding for hESC research and medical breakthroughs, to prosecute the proponents/advocates of hESC research, especially discriminative to those underserved and underrepresented minority and women like me, to give women and minority like me working in hESC research field a difficult time in job searching, in career advance, in research, in grant applications, in publications, in securing patents, in securing labs, in gaining equitable access and recognition, in advocating hESC research for patients as I have personally experienced over the last decade. In contrast, CIRM has given not even a penny of CA taxpayer's money to breakthrough hESC research of this application that would benefit millions of people in CA, bring billions of health care benefits to CA, help gain voter and CA State support for bond financing and funding, and help gain voter support for future Proposition.

To demonstrate COI, it is evident that most of the GWG reviewers' comments about iPSC are false or fabricated. There are in fact data fabrication and falsification in all US PHS/CIRM funded iPSC research, as exampled by PHS/CIRM funding for iPSC grants and contracts, and subsequent a massive amount data fabrication and falsification published coming out of those PHS/CIRM-funded iPSC research, mostly in ISSCR journals such as "Stem Cell Reports" and "Cell Stem Cells", some even in top scientific journals. If the basis is wrong (e.g., iPSC are not stem cells, but cancer cells), the conclusion or result or any data coming out of PHS/CIRM funded iPSC research is definitely false or fabricated. For example, it is normal human development for hESC to differentiate into neurons or cardiomyocytes. If the false statement of George Daley (iPSC and hESC are identical) could stand, turning iPSC into neurons or cardiomyocytes would be nothing strange. However, nobody has been able to turn cancer cells into neurons or cardiomyocytes, or even make cancer cells to differentiate into something, so cancer cell growth would slow or stop. If anyone made cancer cells or iPSC to differentiate into neurons or cardiomyocytes, we would have found the cures for cancers. It would be a huge breakthrough. That person would really deserve a Nobel prize. Why would not we have heard such huge scientific breakthroughs in the news, as lauded by the GWG reviewers? In those iPSC professors' papers or publications funded by PHS/NIH/HHS/CIRM, they have claimed they turned iPSC into DA neurons (e.g. Marius Wernig of Stanford University), or cardiomyocytes (e.g., Joseph Wu of Sanford University). If their claims could not be true, they must have falsified or fabricated a hell out of the data coming out of PHS/CIRM-funded iPSC research.

To maintain research integrity, it is common scientific practice to do side by side comparison of data from different cell lines, materials, or sources. hESC are derived from human embryos. iPSC are reprogrammed from different tissues with different oncogenes. Not only the materials and derivation sources of hESC and iPSC are totally different, the materials and derivation sources of different iPSC lines are totally different also. It is intentional, knowing, reckless research misconduct for data fabrication and falsification in almost all iPSC papers or publications coming out of PHS/CIRM-funded iPSC research, including those published in top scientific journals, not to do side by side comparison of data between a iPSC line and a hESC line, and between different iPSC lines. It is intentional, knowing, reckless research misconduct for data fabrication and falsification in almost all iPSC papers or publications coming out of PHS/CIRM-funded iPSC research, including those published in top scientific journals, not to indicate whether the data were actually from hESC or iPSC, or not to specify which "PSC" line.

Letter to Senator Wicker – "induced pluripotent stem cells -- another scientific Ponzi scheme or adult stem cell lie"

I write regarding Senator Wicker's open letter to HHS Secretary Xavier Becerra in June 2021. In particular, their statement "*Adult stem cells, induced pluripotent stem (iPS) cells, and umbilical cord blood cells have been used to create life-saving treatments for multiple diseases and conditions"* is utterly incorrect. Adult stem cells, iPS cells, and umbilical cord blood cells have not created any life-saving treatments for any diseases and conditions. Most adult stem cells and umbilical cord blood cells have failed efficacy tests in clinical trials again and again over the last two decades. And iPS cells are in fact pluripotent cancer cells or adult cells harboring multiple oncogenes, introduced by the Bush administration and some top scientists, totally a political stem cell scam. So far, iPS cells have failed safety tests in clinical trials by causing serious spontaneous mutations and harming patients.

To circumvent the ethical issue of human embryonic stem cells (hESC), induced pluripotent stem cells (iPSC) were introduced by the Bush administration and some top scientists, including the former vice president of International Society for Stem Cell Research (ISSCR), Shinya Yamanaka who ended up winning the Nobel Prize later on, and the former president of ISSCR and Dean of Harvard Medical School, George Daley, as the alternative of hESC, over a decade ago. However, iPSC are in fact pluripotent cancer cells, and cannot serve as the alternative of hESC. Over many decades of studies of cancers with billions and billions of private and public funding, now we all know that all oncogenes are in fact embryonic genes, or embryonic genes are known as oncogenes if they are abnormally expressed or activated in adult cells, and oncogenes cause cancers. What are iPSC? iPSC are adult cells that abnormally express embryonic genes or are artificially engineered or reprogrammed to express embryonic genes that are in fact rightfully known as oncogenes in adult cells. So, why should iPSC be incorrectly called stem cells, while everywhere else in the scientific world such cells are correctly known as cancer cells? One essential aspect of stem cells is their long-term genetic stability. Stem cells can maintain long-term, stable growth in culture, while cancer cells grow abnormally crazy and mutate fast. The initial cluster of iPSC papers was actually published in top scientific journals, such as *Nature*, *Cell*, and *Science*, in lightning speed, or only a few weeks, without any scientific evidence or data to show the long-term genetic stability of iPSC or iPSC could maintain long-term stable growth. And over a decade later, there is still absolutely no scientific data to show the long-term genetic stability of iPSC or iPSC could maintain long-term stable growth. Without the data of long-term genetic stability, the line between stem cells and cancer cells is bleared. In fact, iPSC have been reportedly associated with abnormal gene expression, accelerated aging, and immune-rejection following transplantation owing to introducing foreign oncogenes and instability/abnormality to the adult genome, and serious spontaneous mutations, the sign of cancer cells, have been identified in human iPSC clinical trials. iPSC are genetically engineered or reprogrammed cells harboring multiple oncogenes, show seriously adverse effects in patients, mutate as crazy as cancer cells, are absolutely not safe for any treatment or therapy, and definitely have no commercialization potential or therapeutic value at all. It is completely fraud and waste, utterly unethical, for public funding agencies --- Health and Human Services (HHS), the National Institutes of Health's (NIH), CIRM --- to misappropriate billions of taxpayers' money and continue to misappropriate hundreds of millions of taxpayers' money to fund such bogus stem cells, which have created absolutely no life-saving treatment or cure for any disease or condition, but have only largely benefited some rogue scientists who have neither scientific integrity nor moral fiber. Most of those scientists, including most of the former and current presidents and vice presidents of ISSCR, are experts and renowned professors in molecular biology and DNA/histone methylation with full knowledge that such concepts of iPSC are flawed and iPSC are bogus, but still, they have used their high-ranking positions, influences, and connections to back and promote iPSC as the alternative of hESC for their own financial gains, including millions and millions of NIH and CIRM (California Institute for Regenerative Medicine) funding to themselves and pumped-up stocks of their own companies. Those iPSC professors and their students sitting in various prestigious universities/institutions could simply do a DNA methylation or histone methylation analysis to show the stunning differences between hESC and iPSC, probably would not cost more than a few thousand dollars. They should know hESC and iPSC are different without even doing any experiment because the irreversible methylations of DNA and histones in adult cells are well-documented, and it is common knowledge that simply engineering or reprogramming with embryonic genes cannot reverse those DNA/histone modifications, only causes instability and triggers oncogenic processes, and all their research and prestige are based on such fundamentals. However, they've still backed and promoted the fraud and waste of iPSC scam for their own financial gains. Such as over $200 millions of NIH iPSC grants/awards to the professors of Broad institute of MIT and Harvard, including Eric Lander --- the disgraced former science adviser of White House, George Daley --- the Dean of Harvard Medical School, and Rudolf (Rudy) Jaenisch, the founder of Fate Therapeutics; over $50 millions of NIH and CIRM iPSC grants/awards to the student of Rudy Jaenisch --- Marius Wernig sitting in Stanford University; and hundreds of millions of iPSC grants/awards to many of their students sitting in various prestigious universities/institutions over the Country. None of these NIH/HHS/CIRM grants/awards have generated any treatment or cure for any disease or condition, even any slight progress in the stem cell field.

We all know hESC are called pluripotent stem cells (PSC) because hESC have unlimited differentiation potential. Growing evidence indicates that iPSC do not even have unlimited differentiation potential, the definition of pluripotency, completely false to call such cells PSC. hESC have unlimited differentiation potential, genomic/epigenomic/cell-line homogeneity, highly-acetylated and unmethylated, across all hESC lines. iPSC have different differentiation potential, genomic heterogenicity, cell line variations, because the different tissues they used for reprogramming have different genomic imprints and are highly-methylated that cannot be reversed by genes, causing their cell line variations, genomic heterogenicity, different differentiation potential, and also, most importantly, genomic instability and oncogenic potential. Deliberately confusing or mixing concepts or definitions or terms, falsely calling something that is not for funding, are known as scientific misconducts.

Funding iPSC is in fact a world-class fraud and staggering waste of taxpayers' money in billions, and has generated nothing to advance medicine and improve human health, but only mistrust and negative images for the public funding agencies --- HHS/NIH/CIRM --- that are neither transparent nor accountable; it is absolutely unethical to waste billions of taxpayers' money on bogus stem cells, such as iPSC. As they said: "Americans expect their tax money to be spent strategically, but at all times ethically." CIRM have misappropriated over $ 250 millions of CA taxpayers' money to iPSC scam, not even including any funding for shared iPSC labs. We urge the CA State, HHS, and the Senate/Congress to investigate the fraud and waste of iPSC scam, to establish oversight to ensure transparent and responsible funding for stem cell research, to ensure taxpayers' money to be ethically used to deliver life-saving treatments and cures for patients, not to be unethically and unaccountably distributed to profit only those few who are in power.

DISC2-14071
Project Title: Dopaminergic regeneration of a novel nuclear Nurr1-positive neuronal progenitor derived from human embryonic stem cells by small molecule induction

Objective:

Neurodegenerative diseases affect millions of the aging population. Current therapeutic approaches for neurodegenerative diseases provide symptomatic relief but none of them change the prognosis of disease. Therefore, there is a large unmet healthcare need to develop stem cell therapies to provide optimal regeneration and reconstruction treatment options to restore CNS tissues and function for neurodegenerative diseases. Parkinson's Disease (PD), a neurodegenerative disorder associated with a loss of midbrain dopaminergic (DA) neurons, has long been regarded as an ideal model for testing the safety and efficacy of various therapeutic strategies against CNS diseases. We have built a key innovative PluriXcel-SMI-Neuron platform that enables highly efficient, direct conversion of non-functional pluripotent hESC by small molecule induction (SMI) **uniformly** into a large supply of high quality nuclear-localized Nurr1-positive (Nurr1+) human DA neuronal progenitor cells (*Xcel-hNuP*) as a novel regenerative medicine therapy product [hESC-DAP] [patent: USPTO# 8,716,017]. Our preliminary data indicate that the hESC-DAP is a novel, Nurr1+/Nestin-, neuronal-lineage-specific human DA progenitor suitable for safe and effective DA neuron replacement therapy for PD, distinctly different from the prototypical epithelial-like Nurr1-/Nestin+ hESC-derived hNSC and other DA products [e.g., DA01] that show cytoplasmic localization of inactive Nurr-1. The Nurr1+/Nestin- hESC-DAP exerts its therapeutic MOA through graft-dependent DA neuron regeneration/replacement, distinctly different from the neuroprotective MOA exerted by Nestin+ hNSC derived from either CNS or hESC that have failed to demonstrate clinical efficacy of DA neuron replacement for PD.

Our PluriXcel-SMI-Neuron approach presents an innovative, more effective solution for the therapeutic needs of PD by providing a novel Nurr1+/Nestin- human DA neuronal progenitor derived from hESC by SMI in large quantity and high quality as a safe and effective regenerative therapy product adequate to regenerate the lost DA neurons for PD, thus overcoming the major bottleneck in the regenerative medicine market. Our preliminary results indicate that the hESC-DAP is a homogenous population of Nurr1+/Nestin**-** neuronal lineage-committed cells that efficiently differentiates into DA neurons expressing nuclear-localized Nurr1 and TH *in vitro*, 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 [Figs. 2-10, see our publications in ref. 22-28 for more details], demonstrating its potential for DA neuron replacement therapy, thus establishing the feasibility of this project. Based on this breakthrough innovation, we propose to investigate the safety and efficacy of the hESC-DAP for DA neuron regeneration and neurological function restoration as a much-needed therapeutic solution for PD. Accordingly, studies will be conducted to fulfill following **Specific Aims**:

Specific Aim 1: To demonstrate the hESC-DAP is a homogeneous population of neuronal lineage-committed DA progenitor cells that yield DA neurons with high efficiency *in vitro* and *in vivo*. The hESC-DAP will be characterized by marker expression, and miRNA microarray profiling, a highly sensitive assay, will be used to further affirm the homogeneity and neuronal identity of the product and confirm the absence of residual pluripotent cells that would cause safety concerns. The *in vitro* functional analysis will probe the neuronal differentiation efficiency and DA neuron subtype specification. The hESC-DAP will be transplanted into the mouse brains to assess their engraftment, migration, neurogenic potential *in vivo*, and a lack of tumors and inappropriate cell type formation from grafts will be assured for evidences of safety. **Milestones**: (1) *In vitro* efficiency: >90% of the hESC-DAP displays strong expression and nuclear localization of the DA neuron marker Nurr-1 and differentiates into DA neurons expressing DA neuron markers. The expression of Hox hsa-miR-10 cluster is induced to high levels (e.g., >100-fold upregulation) to further confirm neuronal lineage commitment; (2) *In vitro* safety: The hESC-DAP is negative (<1%) for pluripotence and other non-neuronal/neural lineage markers to ensure that it contains no residual pluripotent cells and other cellular impurities of safety concerns. The pluripotence-associated hsa-miR-302 family is silenced (100- to 500-fold downregulation) to further confirm the absence of residual pluripotent cells that would cause safety concerns; (3) *in vivo* efficiency: > 50% of the hESC-DAP yields well-dispersed/integrated human DA neurons expressing nuclear-localized Nurr1 and TH at a high prevalence following transplantation into the mouse brains; (4) *In vivo* safety: Following transplantation of the hESC-DAP into the animal brains, a lack of formation (<1%) of teratomas, neoplasms, or inappropriate tissues or cell types. Timeline: 1st year.

Specific Aim 2: To establish preclinical safety and efficacy of the Nurr1+/Nestin- hESC-DAP for DA neuron regeneration and neurological function restoration in an animal model of DA dysfunction. The *in vivo* DA neuron regenerative potential of the hESC-DAP will be assessed by functional analysis following transplantation into the brain of an animal model of DA dysfunction. Therapeutic stem cell behavior, including engraftment/cell survival/integration, migration, differentiation into DA neurons to repair or regenerate the damaged CNS structure and circuitry will be analyzed to determine the transplantation outcomes. Behavior improvement will be assessed for evidences of efficacy in repair. A lack of tumors and inappropriate cell type formation from grafts will be assured for evidences of safety. Statistically significant and reproducible therapeutic activity will be used to establish graft-dependent neurologic and behavior improvement and function recovery. **Milestones:** Following transplantation into the brains of an animal model of DA dysfunction, >50% of the transplanted hESC-DAP survives, migrates, integrates, and differentiates into DA neurons positive for nuclear-localized Nurr1 and TH, improve motor function, and <1% forms inappropriate cell types. Timeline: 2nd – 3rd year.

This DISC2 project will be critical to establishing the target product profile (TPP) for the novel Nurr1+/Nestin-hESC-DAP and provide necessary preclinical safety and efficacy data for IND-enabling studies, IND-filing, and entry into clinical development for PD.