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Letter of Support for INFR6.2-15475 Proposal from Cedars-Sinai

To the CIRM Application Review Subcommittee,

We would like to submit this letter in further support of our application INFR6.2-15475 - A Shared Resource Laboratory for Advanced Stem Cell-Based Modeling.

We thank the reviewers for their many positive comments regarding our unique SRL core facility at Cedars-Sinai that will train the next generation of stem cell scientists and physicians in cutting edge microfluidic human "organ-chip" and organoid technologies. Cedars-Sinai has positioned itself as a global leader in the development and application of both technologies, evidenced by our leading publications in these areas and long-standing collaboration with the leading organ-chip company Emulate, Inc. The Cedars-Sinai Shared Resource Laboratory (CS-SRL) for advanced stem cell-based disease modeling will utilize our strength in human iPSC production and differentiation and close collaboration with Emulate. This will enable a diverse group of students, trainees, and researchers throughout California to access this exciting and powerful new organ-chip technology, which allows for multi-tissue growth, enhanced cellular maturation, unique biomechanical stimulation, improved drug screening workflows, and physiologically-relevant disease modeling applications.

Overall, reviewers for our proposal were enthusiastic about the unique organ-chip technology that would be the specialty of this core, and felt that the course offerings were broad, well-described, and well-integrated with existing curricula. Our proposal received a Tier 2 recommendation by the Grants Working Group, with 1 vote for Tier 1 and 13 votes for Tier 2. However, we have noticed that other Tier 2 applications were recommended for funding, while receiving lower scores. Respectfully, we would like to address the reviewer comments associated with our application below, as we believe we are well-positioned to succeed if receiving this funding.

1. *While reviewers were enthusiastic about the partnership with the organ on a chip company and training/services on their systems, it was not clear how trainees from outside institutions would benefit from this training long-term, since these systems are not widely available. Please comment on this aspect of the proposal's impact.*

Thank you for this comment. Our institute has a strong collaboration with Emulate, Inc, leading to a number of high impact publications focused on organ-chip technology in leading journals such as *Cell Stem Cell*. Emulate has an international reputation as a leader in organ-chip culture and instrumentation (emulate.com), and we have obtained a strong support letter from their leadership in our INFR6.2 application. We believe that it will be straightforward for any California institution to purchase both the system and the organ-chips for their studies once they are trained at the CS-SRL. Alternatively, many of the training methodologies presented in our proposal and course curriculum are universally applicable to organ-chip and organoid culture, independent of using the Emulate systems. These methods and techniques include human iPSC differentiation to multiple cell types (cardiac, neuronal, gut, bone, blood, etc), organoid derivation and culture from these diverse cell types, transcriptomic and functional analyses of cells grown either within organoids or organ-chips, and maintenance of microfluidic organ-chip systems similar to the Emulate system. Thus, we believe that our CS-SRL will have a broad range of offerings to fit any user's interests and training needs.

2. *Reviewers also expressed concern that the core's organ on a chip equipment may be inadequate for the volume of research and training proposed. Please provide additional details on how the use of this equipment will be allocated between these activities.*

Thank you for this concern. We are well poised to scale the equipment required to succeed with this proposal, with strong support from Emulate. We will have 4 Emulate Zoe automated systems at the CS-SRL, each of

which can hold 12 organ-chips. Experiments will generally run for 14-28 days. This will allow us to train a minimum of 4 labs simultaneously on the system each month, which means 48 labs per year could be trained. This is only part of the overall training, which would also involve generation of the cells to go into the chips and post-analysis of the chips (both effluent analysis and cellular/molecular/genetic analyses). These downstream analyses can also be learned independently of the Emulate organ-chip culture, if the user does not want to focus on that aspect of the training. For contingency planning, we also have 6 Emulate Zoe systems present within the Board of Governors Regenerative Medicine Institute on the Cedars-Sinai main campus that could also be employed for training, in the case of excess demand.

3. *Several reviewers felt that aspects of day-to-day core operations could be better described. For example, are booking sheets adequate to manage the number of expected users? Are there sufficient staff to support the expected number of users/projects? Please provide more details on how typical core operations will be managed.*

Thank you for this concern. We have a long experience of running core facilities at Cedars-Sinai, and will have ample booking sheets and staff to match the users of the system as detailed in the grant. Dr. Maria Gabriela Otero, who is on the grant at 100% effort as the CS-SRL on-site manager, has a long experience with both organoid generation from iPSCs and Emulate organ-chip utilization and will coordinate all aspects of the core in the new space that Cedars-Sinai has set aside for this activity. Cedars-Sinai has allocated approximately 1500-2000 sq feet of new research space for this INFR6 program that will house the equipment for training requested in this proposal. This space will be located in the Cedars-Sinai North Campus, which also houses the Board of Governors Innovation Space and the Cedars-Sinai Biomanufacturing Center. Furthermore, Cedars-Sinai will contribute 20% of the operation costs of running this shared resource from CIRM as outlined in the budget. Notably, resources and personnel from the nearby Cedars-Sinai Biomanufacturing Center, which houses our world-class GMP Core and human iPSC derivation facilities with nearly 50 affiliated staff members, can be used in the case of excess demand.

4. *Reviewers felt that the DEI outreach plans included in the proposal were strong, but other aspects of DEI were not as clear. Specifically, please provide concrete goals and plans regarding obtaining and offering diverse cell lines and regarding course enrollment.*

Thank you for this comment. We did not budget to make a new set of iPSC lines in this proposal, but the iPSC Core facility at the Cedars-Sinai Biomanufacturing Center has over 1,000 iPSC lines available. Thus, we can select a diverse set of patients from this facility for this training program. Notably, the Cedars-Sinai Biomanufacturing Center is the recent recipient of a CIRM INFR5 award to further expand their GMP and biomanufacturing capabilities, including derivation of human iPSC lines from diverse individuals. An important way to serve underserved communities is to be able to provide more appropriate starting cell material (iPSC banks) that would be better immune-matched to the intended recipient population receiving and iPSC-derived cell and gene therapy. There is a paucity of GMP-compliant iPSC lines from ethnically diverse populations. Through the active INFR5 award, the Cedars-Sinai Biomanufacturing Center will procure starting material (whole blood or cord blood units) under GMP compliance to generate iPSCs from diverse populations, different ethnic backgrounds and haplotypes. This will be done by sourcing licensed blood bank registries and Cedars-Sinai clinics with IRB approval to enable procurement of PBMCs/ blood cells from Latino, Asian or Pacific Islander and African American ethnicity with the goal to create GMP-compliant diverse iPSC banks. Our team has a strong commitment and a good track record of promoting DEI by providing educational opportunities to underserved communities and by devoting research to help underserved populations. The CS-SRL facility will aim to engage directly with researchers and scholars from minority and underserved communities. This is in similar fashion to our current CIRM-funded programs, where we have been working closely with local universities that engage with these communities (i.e. CSUN, Channel Island, Long Beach, CSUSB).

5. *Several reviewers felt that the core director's limited experience managing multi-investigator projects or core facilities might be a challenging. Please provide additional details describing how the director will be supported by additional team members.*

Thank you for this comment. We agree that Dr. Sharma is a young independent investigator, but he has significant experience in pluripotent stem cell culture, organ-chip workflows, and managing complex scientific projects. Although currently an assistant professor, he has received exceptional training as a PhD in Stem

Cell Biology from Stanford University (with world-renowned cardiac human iPSC expert Dr. Joseph Wu and associated CIRM training funding), and postdoctoral training in cardiovascular genetics and organ-chip biology at Harvard Medical School and Cedars-Sinai, respectively. Notably, he is currently leading a multi-million dollar, highly-complex project funded by NASA focusing on in-space biomanufacturing. While leading this project, he has coordinated biweekly with multiple engineering and technical support teams across multiple US institutions (University of Colorado, Axiom Space, NASA Kennedy Space Center) to successfully conduct experiments aboard the International Space Station, while interfacing with NASA astronauts. He has also been successful in running a multi-year American Heart Association Career Development Award, focusing on cardiac organ-chip culture, to grow his laboratory to four members. These experiences, his highly collaborative nature, and strong track record in the stem cell and organ-chip field, should enable him to be successful in running this core facility. However, to further strengthen this proposal, we will bring in associate professor Dr. Josh Breunig who has over 8 years of experience running our Regenerative Medicine Imaging Core at Cedars-Sinai. Dr. Breunig will assist Dr. Sharma with coordinating the activities of the CS-SLR as an advisor. Finally, associate program director Dr. Clive Svendsen, will be overseeing all activities within the core and is an active user of the organ-chip technology. Dr. Svendsen is the director of the Board of Governors Regenerative Medicine Institute at Cedars-Sinai, is well-versed in complex project management, and is the director of multiple CIRM clinical trial stage projects.

In summary, we believe that our team is well positioned to address any and all concerns brought forth by the review panel. We believe that our proposal is worthy of funding under the CIRM INFR6.2 mechanism because of our significant expertise in organ-chip and organoid culture and applications, education of diverse and underserved populations as well as derivation of diverse human iPSC lines from these populations, and our institution's sustained demonstration of successfully executing CIRM education and infrastructure projects. We believe that our proposal presents a unique expertise, focus, and technology in organ-chip and organoid cultures that is reflected in Cedars-Sinai's position as a state, country, and world-level leader in this area, and which could provide far-reaching benefits to scientists throughout the state of California.

For these reasons, we believe that the Application Review Subcommittee should strongly consider approving our INFR6.2 proposal for funding. Thank you for your consideration.

Sincerely,

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