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Re: Rationale for *not* reducing frequency of PDEV grants to just once-per-year

Dear ICOC Members.

Most of you know that I have been, and continue to be, one CIRM's staunchest advocates dating back to its birth when I was involved in the grassroot activities of putting together, campaigning for, and defending Prop. 71, subsequently serving on the CIRM President's Advisory Council. CIRM was initially conceived to immunize California scientists, clinicians, and patients from the politically-driven vagaries of Washington DC in the early 2000's. In so doing, it made California science – even beyond stem cell biology and regenerative medicine – the envy of the world. The subsequent 2 decades, during which such flagrant assaults on our science seemed to ebb, may have lulled us into a false sense of security. The past year, however, during which the integrity of the scientific principles and approaches we hold dear have come under renewed baseless attack should be a stark reminder that **now is not the time for CIRM to soften its core mission**: ensuring that the greatest number of California citizens benefit from data-driven science and cutting-edge technologies, even if those imperatives have been forsaken elsewhere. I view further reducing the number of cycles for Preclinical Development (PDEV) Proposals to be vetted and funded as just such a compromise of CIRM's *raison d'être.*

Indeed, the surge in applications to CIRM is a symptom of precisely the lack of support so much of the research we value no longer receive from – in fact, are discriminated against by – the federal government: for example, use of fetal or embryonic cells, early human development, biological diversity, types of gene therapy (e.g., those using mRNA), types of immunotherapy, certain infectious diseases, health disparity, accessibility/affordability – and even the suspension of such bedrock funding mechanisms as SBIRs/STTRs. CIRM's response should *not* be to reduce opportunities but rather to figure out – *creatively* (see below for some suggestions) – a way for California scientists, clinicians, businesses, and patients to circumvent these obstacles.

Not so long ago, robust pre-clinical and clinical development defined CIRM, making California the paragon for translational research advocacy. While I appreciate the immense burden this emphasis placed on CIRM staff, the apogee of CIRM's productivity and innovation was, indeed, when there were biannual DISC grants (bringing a nascent project to the stage of an INTERACT meeting), which then transitioned into a TRAN grant (bringing that project to the stage of a Pre-IND meeting), which, in turn, allowed it to blossom to the point of competing for monthly CLIN1 grants (with IND filing as a goal) & CLIN2 grants (for launching a clinical trial). The output and successes were mind-boggling and helped propel us to passage of Prop. 14. This reliable menu of funding opportunities -- uniquely and innovatively conceived by CIRM – was prescient and effective because it was so accurately in tune with the tempo and dynamic of pre-clinical development – longer times for gestating a novel idea, more rapid progression through the regulatory milestones. I took pride in saying that CIRM was better and more responsive than NIH (despite its 3 reliable cycles) to the needs of California science and patients.

Indeed, the climate, opportunity, and support created by CIRM was such that even an academic PI like me, in a relatively small non-profit research institution – not a company, not a huge hospital-based enterprise – could take an idea I had nurtured at the bench for decades (regarding how to neuroprotect against the most common brain injury in babies using fetal-derived neural stem cells) through the regulatory pipeline to the point of being poised for IND-enabling studies. Neither I – nor the babies I hope someday to benefit from this unique

approach – could ever have gotten to this point without CIRM under the old funding model.

Under the proposed once-per-year PDEV funding scheme, our success would never have happened; we would never have been able to compete against the large companies that would now glut the annual application pool. Even now, with the present system, which itself is a departure from the old model, we are stalled in the queue (despite having successfully completed our TRAN milestones thanks to CIRM's investment in us) for obtaining funding for our IND-enabling studies, and we simply do not have the resources to stay whole for another year as large pharma/biotech companies & large hospital enterprises might.

Simply stated, cutting-edge pre-clinical and clinical research cannot languish unfunded and unactualized for an entire year. With applications being accepted only annually, the time gap between completion of a DISC and/or a TRAN project and movement to the next phase grows so long that, for lack of funding, teams disperse and expertise is lost: technicians and research associates are laid-off, graduating PhD students and post-docs are not replaced, data and approvals grow stale, momentum wanes.

The proposed PDEV funding schedule would certainly discriminate against the involvement of academics and small businesses, only rewarding the biggest companies with reserve capital to sustain itself for a year until the lottery opens again (and with so many applications stacking up over the course of a year, a lottery is, indeed, what it becomes among the top 20% of hundreds of applications. The competition for few slots and the ability to distinguish among excellent worthy grants will be even worse. We saw that, after CIRM's nearly year-long hiatus, during which NIH was unraveling, the number of CIRM applications increased to the unmanageable number encountered now. With solely an annual cycle, the volume of backlogged applications will grow even more oppressive and the ability to distinguish among meritorious grants even more unreliable.

I understand the workload and financial challenges confronting CIRM to fulfill its mission – and am most appreciative. However, the answer to alleviating these burdens, in my view, without compromising our mission, is *not* fewer cycles, but, perhaps some of the suggestions below:

- Giving smaller dollar amounts-per-grant while maintaining (or even increasing) the frequency of cycles.
    - Each PDEV award does not need to be for the full $13M; most PDEV-type projects from most applicants other than big Pharma are not ready to go the full distance.
        - "Early PDEV only" is an option
        - For those projects that have already been through the earlier stages of the CIRM pipeline, "Late PDEV only" is an option
        - Combined early + late PDEV (mirroring NIH's combined Phase 1 + 2 fast-tracked SBIRs) may be appropriate for some projects, likely those from big companies or hospital-based institutions.
- Institute a *merit*-based (not just preference-based) *short* letter-of-intent (LOI) pre-selection process
- Shorten & simplify applications for reviewers to read (eliminate the redundancy that has been typical of PDEV applications).
    - Some details may be appropriate only after a merit-based, fundable score is attained

I fear that if PDEV cycles are reduced to just once-per-year, CIRM will cease becoming responsive to the needs of California academicians, clinicians, businesses, and patients at a time when they need CIRM's protection & support the most. Such a funding schedule would never have enabled the birth of our project (ready now for IND-enabling studies) and certainly would now strike its death knoll. Other programs in which CIRM has already made an investment would be in similar jeopardy.

Thanks for considering another solution other than so drastically reducing PDEV granting frequency.

Sincerely,

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