

September 22, 2026

**To:** California Institute for Regenerative Medicine (CIRM) Independent Citizens' Oversight Committee  
**Re: CLIN2-20316 — Request for Funding Approval, or Alternatively, a Time-Limited Collaborative Path to Resolution**

Dear Members of the ICOC:

We write to you today with both hope and urgency, on behalf of families affected by Fanconi anemia (FA) who are waiting for the potential of a breakthrough in care that CIRM was created to bring. Our proposal, CLIN2-20316: *"In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia"*, aims to bring a maternally derived stem cell product through clinical development so that it can be used before birth to prevent blood and immune dysfunction that otherwise define this devastating genetic disease. We have great respect for the thoughtful, careful process the ICOC and CIRM Leadership bring to every funding decision, and it is in that spirit of partnership — not confrontation — that we make our request: given the merits of the application and alignment with CIRM's mission and strategic priorities, we ask the Board to approve funding for CLIN2-20316, consistent with the Grants Working Group's (GWG) unanimous, top-scoring recommendation, so that families facing this diagnosis have the possibility of a different option in front of them. If the ICOC is not able to take this step immediately, in light of this unique situation, as an alternative, we ask the Board to grant CIRM Leadership the ability to work together with our Stanford/UCSF team, quickly and collaboratively, to transparently discuss and align on an approach that gives this promising, clinic-ready California-based program a chance.

The record supports finding a path forward, and we hope it gives the Board confidence in the strength of this proposal. The application received a top score of 90 and the support of all fifteen GWG reviewers — a level of consensus reviewers reserve for proposals they consider important, rigorous, and achievable. Reviewers described the science as having “a strong, extremely clear rationale and value proposition,” addressing “a genuine, otherwise-unsolvable unmet need,” and carrying “the potential to fundamentally change the treatment paradigm.” Further, they alluded to the practicality of this proposal with “clear milestones and feasible timeline.” A fuller record of the review comments, together with a detailed, point-by-point response to each concern raised by CIRM Leadership, is provided in the Appendix.

### **This Program Embodies CIRM's Founding Mission and the CLIN2 Program's Purpose**

CIRM exists because California's voters believed that patients facing serious, unmet medical needs should not have to wait on the slow timelines of traditional funding, and that our state should lead the world in turning stem cell science into cures. We do not believe there could be a clearer expression of that founding mission than CLIN2-20316. This is precisely the kind of program CIRM was built to carry forward: a scientifically rigorous, high-risk high-reward pivotal clinical trial, with an efficient track to approval, for a devastating rare genetic disease, led by an experienced and devoted California team, with no other viable path to funding. The CLIN2 mechanism itself exists to “support the completion of an interventional phase 1, 2, or 3 trial for an innovative stem cell-based or genetic therapy addressing a serious unmet need and with the potential for transformative benefits to patients, families and the health care system,” and to help “advance four to seven rare-disease projects toward a Biologics License Application (BLA).” This proposal was designed, from its earliest days, around those exact ideals — an innovative stem cell therapy, a defined and de-risked regulatory path toward approval, and a platform that has the potential to be extended to other rare blood disorders beyond FA. We believe, with genuine conviction, that it fulfills CIRM's mission and the CLIN2 program's purpose as fully as any application the Board will consider this cycle.

## **The Human and Scientific Case for This Program**

FA is a devastating DNA-repair disorder for which today's only option is reactive: postnatal allogeneic transplantation with genotoxic chemotherapy and immune ablation after bone marrow failure or hematologic malignancy is the standard-of-care, though this carries significant morbidity, mortality, and a subsequent lifetime risk of aggressive cancers. The only alternative under development is gene therapy which our team has also been involved with, but this is uniquely challenging in FA due to the fragility of FA patient cells and the underlying defects that result from diverse disease-causing mutations in 23 different genes. This proposal offers something fundamentally different — early prevention rather than rescue, with a universal and cost-effective product, that could be used for all FA patients.

By transplanting a maternally derived stem cell product during the developmental window in which the fetal immune system tolerates maternal antigens, this approach aims to establish durable donor engraftment with stabilization of the blood and immune system through an outpatient procedure without the toxic chemotherapy, immunosuppression and prolonged inpatient hospitalization that postnatal treatment requires. Based on strong preclinical data across three independent FA mouse models from two independent research groups, we believe this product could give children with FA the opportunity for a full, normal life. These are not abstract outcomes to us — they are for the real families that have approached us for support, who have shared with us how frightening this diagnosis feels, and how much hope even the possibility of prevention offers them. The stakes of inaction are not abstract either — the data shows an estimated 44% of families who receive a prenatal FA diagnosis say they would consider pregnancy termination given the inadequacy of currently available therapies (Lum et al., Prenat Diagn 2026).

Working together with FA advocates, the Fanconi Cancer Foundation, maternal-fetal medicine specialists, hematologists, and genetic counselors in California and around the world, we are ready to efficiently identify and support the rare families with a prenatal diagnosis of FA. We have already had families approach us in this situation giving us confidence in our enrollment ability, but without funding to initiate the clinical trial, our hands are tied. Today the choices for these families are limited leaving them to make very challenging decisions for themselves and their families. We would like to be able to provide them with this additional option of investigational in utero stem cell transplantation for consideration.

## **Value Creation to CIRM and the People of California**

In addition to its scientific merits, our proposal is equally strong on execution and value creation. It unites Stanford and UCSF investigators with complementary, leading expertise in fetal therapy, hematopoietic transplantation, GMP-grade cell manufacturing, regulatory strategy, immunologic monitoring, clinical operations, and long-term follow-up — exactly the cross-institutional model CIRM's Alpha Clinics Network was built to enable. It also directly and efficiently leverages manufacturing capability, FDA relationships, and clinical trial infrastructure built through CIRM's prior investments in FA and in utero transplantation, allowing CIRM to extract meaningful value from earlier investments rather than letting this go unrealized. Our team has also proven its ability to execute, and this program could unlock value and has the potential to bring a near-term win to the CIRM portfolio. The unique characteristics of this stem cell product that is an individualized therapy that addresses the underlying cause of disease also enables alternative and accelerated approval paths, and the FDA has already confirmed that it is being appropriately regulated on a path to a BLA with Fast-Track designation. Further, we now provide a non-binding letter of intent in the Appendix from a biotech partner, Orca Bio, that has expressed direct interest in continued development of this stem cell product if promising clinical data is obtained through this CIRM investment. This ensures there is a partnered path to commercialization of this product to give the ICOC and CIRM team additional confidence that this is a valuable program to add to the CIRM portfolio.

The proposal also advances CIRM's equity mission. FA disproportionately affects Hispanic/Latino families in California, who make up a substantial share of the Stanford-UCSF FA cohort and often face compounding barriers of insurance access, language, distance, and access to specialized transplant care. A one-time, cost-effective, maternal-donor intervention has the potential to narrow, not widen, that gap, and offers substantial financial savings against the \$500,000–\$1 million typically required for postnatal transplantation and the \$3–\$5 million projected for gene therapy. And because this approach uses maternal stem cells rather than a bespoke genetic correction, it is inherently mutation-agnostic — usable across FA genotypes — and, over time, potentially adaptable to other inherited marrow failure disorders and hemoglobinopathies. A successful treatment would also lead to improved prenatal diagnosis and screening which could universally become available to all pregnant women further enabling greater equity in care. Notably, a California-based diagnostics company, BillionToOne, has already announced near-term commercial availability of non-invasive fetal risk screening for Fanconi Anemia C variant which further increases our confidence in clinical trial enrollment and the need for this treatment.

We hold CIRM Leadership's diligence in the highest regard, and we take their programmatic concerns — involving enrollment feasibility, scale of impact, lessons from prior CIRM-supported programs, and the likely outcome and return of the investment — seriously and in good faith. We simply, and respectfully, see the picture differently. While we appreciate that this is a high-risk high-reward proposal, we believe each concern is addressable through clarification, milestone structuring, and/or adjustment in scope and budget size, without abandoning a program the GWG unanimously found scientifically compelling and operationally sound. A full, concern-by-concern response explaining our rationale, together with concrete and constructive paths to further resolution for each, appears in the Appendix.

### **Our Specific Request to the Board**

**Primary ask:** that the ICOC act on the strong record before it with the additional information provided and approve funding for CLIN2-20316, consistent with the GWG's unanimous recommendation.

**Alternative ask:** if the Board is not able to approve funding today, that the ICOC instead ask CIRM Leadership to sit down and work with our Stanford and UCSF team, promptly and collaboratively, rather than let a difference of view between the GWG and CIRM Leadership become the final word on a program that could benefit these families. We propose the following 30-day process:

**1. Leadership meeting within 10 business days.** CIRM Leadership and the Stanford/UCSF team would review each programmatic concern together and distinguish issues resolvable by adjustments in scope, milestones, budget, enrollment strategy, and/or co-funding for any issue CIRM considers fundamental.

**2. Written programmatic requirements.** CIRM would then provide a concise, written set of conditions or modifications that, if satisfied, would resolve the identified concerns — giving the investigators a defined target rather than asking the Board to choose between two review perspectives.

**3. Rapid Stanford/UCSF team response.** The investigators would return a focused amendment addressing those requirements, including any revised milestones, enrollment triggers, site strategy, budget size or staging, contingency funding, and/or regulatory and commercialization deliverables.

**4. Leadership recommendation back to the ICOC.** CIRM Leadership would assess the revised plan and report whether the concerns have been adequately mitigated, allowing the Board to decide on a record that reflects both the GWG's scientific assessment and CIRM's current programmatic priorities.

Either path preserves CIRM Leadership's role in portfolio stewardship and respects the GWG's scientific judgment. Both paths ensure that a highly rated, innovative stem cell program is not lost to concerns we believe are resolvable, as there is no fundamental scientific or programmatic disqualification presented.

## The Need for Funding is Now

We do not use the word “urgent” lightly. Fanconi anemia is a fatal disease if left untreated, and the window in which this therapy can be given — during pregnancy, after a prenatal diagnosis and before birth — is measured in weeks, not years or even months. Families do not get to choose when this diagnosis arrives, and once it does, they face it with sub-optimal options: today, nearly half consider ending an otherwise wanted pregnancy simply because no adequate treatment exists. These families have approached us, we know their names and stories, and we feel their distress. Every month this decision remains unresolved is a month in which another eligible family may receive this diagnosis without this option, because this trial has not yet opened its doors. We are not asking the Board to rush a decision it is not ready to make. We are asking for consideration, as gently as we can while still conveying the potential of this trial. We hope that a resolvable, operational-level disagreement not become the reason a family loses a preventive option that could be available to them. This program is ready to move forward into the clinic today, and our team is ready today as well; the only missing piece is funding which could be obtained through CIRM's support, hence, we ask that the Board to provide a potential path forward for this important and feasible program, that may or may not work, but has the possibility to change the course of this genetic disease and others.

CIRM exists, at its heart, to give families exactly like these a chance that nothing else can offer them: the possibility for an innovative, homegrown California stem cell therapy, built by a devoted and experienced team, aimed squarely at a challenging disease with no optimal treatment today. Moreover, this application has been specifically designed to create meaningful value over the course of the award that enables further product development giving this therapy the opportunity to reach those in critical need. Approving CLIN2-20316 would be a direct, tangible expression of everything CIRM and the CLIN2 program were created to do. We respectfully and hopefully ask the ICOC to fund this program — or, at the very least, to give it the brief, good-faith opportunity described above to work with the CIRM team to determine if it can be adjusted to meet CIRM's current programmatic requirements and strategic priorities.

Thank you, sincerely, for your time, your compassion, and for CIRM's unwavering commitment to advancing regenerative medicines so they can assist patients with serious unmet needs like the children and families this program was built to help.

Sincerely,



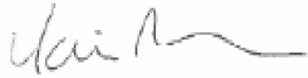
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## Appendix A: Review Record Supporting Alignment with CIRM Priorities

The following review comments illustrate why we believe this application aligns directly with CIRM's strategic direction: "strong scientific rationale, unanimous GWG support, and potentially transformative benefit of the proposed treatment"; "proposed approach could be transformative by avoiding genotoxic conditioning and immunosuppression, using the mother as the donor, and potentially applying across FA genotypes"; "use of maternal cells eliminates the need to identify a matched donor and is mutation agnostic, which could address an important access barrier"; "strong, extremely clear rationale and value proposition"; "potentially transformative value proposition"; "a genuine, otherwise-unsolvable unmet need"; "potential to fundamentally change the treatment paradigm"; "could be a potential standard of care"; "unique solution to the risk benefit ratio"; "outstanding, well-positioned multi-institutional team"; "unusually well-matched to the complexity of this project"; "realistic clinical execution plan"; "well thought out enrollment strategy, evidence-based accrual predictions"; and "clear milestones and feasible timeline."

The application also directly fulfills CIRM's own stated priorities: it is "an interventional phase 1, 2, or 3 trial for an innovative stem cell-based or genetic therapy addressing a serious unmet need and with the potential for transformative benefits to patients, families and the health care system," and it advances CIRM's goal of "advancing four to seven rare-disease projects toward a Biologics License Application."

## Appendix B: Detailed Responses to CIRM Team Concerns and Potential Paths to Resolution

*We offer the following, in a spirit of partnership rather than dispute, addressing in turn each concern raised by CIRM Leadership in declining to recommend funding for CLIN2-20316, notwithstanding the GWG's unanimous, top-scoring endorsement. Each response is followed by a brief, constructive note on how that specific concern could be converted into a concrete, fundable condition through a collaborative process.*

### 1. Discordance with the Grants Working Group

CIRM Leadership's own summary acknowledged "the strong scientific rationale, unanimous GWG support, and potentially transformative benefit of the proposed treatment," and that the approach "could be transformative by avoiding genotoxic conditioning and immunosuppression required for allogeneic bone marrow transplant in these DNA damage prone patients." That review record is unambiguous: the proposal received a top score of 90, with all fifteen GWG reviewers voting to fund it, and reviewers independently described it as having a "strong, extremely clear rationale and value proposition" with "potentially transformative value proposition." The GWG bylaws also highlight that members of CIRM's scientific review team are to provide guidance and information regarding CIRM's programs, portfolio and procedures to aid the GWG in making informed evaluations. A funding decision that departs from a unanimous, high-scoring GWG recommendation for a treatment approach explicitly recognized as a potential optimal option for FA — one that removes cytotoxic conditioning and immunosuppression entirely — warrants further justification and exploration of a path forward.

**Potential resolution path:** *We raise this not to relitigate the review, but because we believe it matters: this is the foundation against which the concerns below should be weighed, and we would welcome the chance to walk through the concerns together with CIRM Leadership as the starting point for any structured discussion. We believe the stated concerns may be misunderstandings or may be addressable, and we would appreciate the opportunity to align on them with the CIRM Leadership team.*

### 2. Size of Impact

FA is an unforgiving disease, and the human cost of waiting for better options is measured now, not hypothetically: an estimated 44% of families who receive a prenatal FA diagnosis would choose, or

seriously consider, terminating the pregnancy because no sufficiently adequate treatment exists (Lum et al., Prenat Diagn 2026) — an option that, moreover, is not legally available in every state. There is a roughly 5–15% mortality rate from current postnatal stem cell transplants which are required in ~ 90% of FA patients due to severe hematologic disease, and of those who receive postnatal transplants, virtually all go on to develop deadly cancers in their teenage years or early adulthood. While we recognize the high-risk high-reward nature of this approach where success is not guaranteed, this proposal represents a possible best answer to address the current unmet need, with reviewers characterizing it as addressing “a genuine, otherwise-unsolvable unmet need” and noting its “potential to fundamentally change the treatment paradigm.” Because the approach uses individualized, maternal, semi-allogeneic stem cells rather than a bespoke genetic correction, it is also inherently mutation-agnostic and cost-effective — unlike many targeted therapies in development — it does not exclude patients on the basis of genotype, and it also carries potential for extension to patient populations well beyond the initial treated cohort.

**Potential resolution path:** *We welcome a discussion of the risk tolerance of CIRM and which impact measures CIRM Leadership would find most reassuring. We are prepared to incorporate specific impact-related milestones into the award, or as an alternative adjust the scope or budget of the proposal.*

### **3. Ability to Enroll**

Reviewers already recognized the team's readiness on this front, describing an “outstanding, well-positioned multi-institutional team” that is “unusually well-matched to the complexity of this project,” with a “well thought out enrollment strategy” and “clear milestones and feasible timeline.” The trial pairs two CIRM Alpha Clinics with complementary strengths, allowing Stanford and UCSF to execute efficiently while deliberately limiting the initial site footprint — a choice made for focus, not a constraint born of necessity or ignorance. Several additional centers in California and beyond have already expressed interest in joining as follow-on sites, which will ease the travel burden on families if early clinical signal is obtained. Enrollment will begin in a slow, staggered fashion by design, both to confirm efficacy before scaling and to match the budget's own milestone-gated structure (smaller investment in years one and two, increasing thereafter). This caution reflects careful planning rather than doubt about referrals: the team has never struggled to enroll its prior FA trials, which have consistently run ahead of schedule, and several families with a prenatal FA diagnosis have already approached the team in recent years. Further, the team has had success in various other clinical trials utilizing in utero therapies across disease indications. We are cognizant of the rare nature of prenatal FA diagnoses today, however, the team has established a strong FA referral network, has an active collaboration with the well-coordinated Fanconi Cancer Foundation, and has dedicated program-specific FA advocates to support this effort — this will ensure awareness of the clinical trial option to eligible families and will provide timely patient-support for those interested. These FA-specific relationships are augmented by strong relationships with iFeTIS, NAFTNet, and other maternal-fetal medicine and prenatal genetic counseling communities, and the program will be further supported by multilingual outreach and telehealth screening to ease access. Diagnostic capacity is also improving in the field and trial's favor — amniocentesis with whole-genome sequencing is increasingly recommended when ultrasound anomalies are detected, and non-invasive prenatal testing for genetic disorders is advancing rapidly. The team is already in close communication with a California-based diagnostics company, BillionToOne, that has recently developed non-invasive fetal risk screening for FANCC mutations and is working to expand its panel, a development expected to meaningfully broaden the pool of eligible families. Thus, the team is confident in its ability to enroll and treat patients on the proposed clinical trial schedule.

**Potential resolution path:** *Rather than treating enrollment uncertainty as binary, CIRM could require prespecified referral, screening, enrollment, and/or site-activation milestones before later-year funds are released, with staged expansion to additional California or national sites triggered by defined trial criteria and evidence of prenatal diagnoses across different geographies.*

#### 4. Outcome of Investment

Unlike many CIRM CLIN2-funded Phase 1 studies that generate only preliminary safety or exploratory data, this trial was deliberately designed as a potential pivotal study — one that could create tangible value and is capable of directly supporting a Biologics License Application (BLA) and market approval. The regulatory pathway is also not speculative: the FDA has been an active and responsive partner throughout development, and the ASH-FDA education program invited the team to brief the agency on emerging FA treatment approaches even before the IND was submitted. That regulatory confidence and close communication is grounded in direct experience running two prior FA clinical trials — one gene therapy, one antibody-conditioned allogeneic transplant — giving the team a well-informed view of appropriate endpoints and realistic development milestones. The trial's  $\geq 1\%$  donor chimerism endpoint at 3 months post birth was negotiated deliberately with the FDA for two reasons: it is the threshold the agency wants in place before treating additional patients, absent which the protocol would need modification to improve efficacy; and it is also the level believed sufficient to support tolerance and, if needed, a booster transplant from the same donor. However, this treatment may result in substantially higher donor chimerism, especially with increased follow-up time, due to the competitive advantage of the healthy donor stem cells over the patient's failing FA stem cells. Because the in utero transplant approach delivers roughly 10- to 1,000-fold more healthy stem cells than is feasible in FA gene therapy — where cells must be harvested from FA patients themselves and cultured for gene modification, a process that is expensive and leaves them comparatively fragile — engraftment may progress considerably faster than in the gene-therapy setting, where despite the inherent product limitations, robust efficacy with  $\geq 20\%$  MMC resistance was still achieved in many patients between 6–12 months post-treatment. Preclinical data in FA mouse models also show substantial engraftment within 4 weeks of treatment, the earliest time point assessed, indicating the possibility of high donor chimerism early post treatment in the clinical trial (see Background Data). Given the FDA's Plausible Mechanism and Accelerated Approval Pathways available for individualized genetic disease therapies for serious conditions, it is conceivable that as few as one to three patients with sufficiently compelling clinical data in the initial Phase 1 cohort could support a BLA submission — potentially before the full clinical trial concludes and within the 4-year CIRM funding period, obviating the need to treat all 12 patients currently proposed. Nonetheless, the trial's specified 2-year post-birth follow-up and Phase 2 expansion cohort preserve flexibility in monitoring and dataset size to ensure generating a sufficiently robust dataset, since the rate of engraftment cannot be known with certainty before the trial begins. Contingency funding from philanthropic and institutional sources has already been secured to ensure full follow-up on all patients if needed. Finally, the team's own track record argues against the concern that feasibility will stall the program: none of its prior FA or in utero therapy trials has been deterred by feasibility issues. Where earlier programs slowed, it was because commercial partners lost interest in a rare-disease market, or, in the case of an earlier in utero alpha thalassemia transplant trial, because of underlying disease biology that proved too challenging to overcome — not because trial infrastructure or execution fell short. For these reasons, we are confident in the ability to obtain critical data and reach important development milestones over the course of the award to enable further advancement.

**Potential resolution path:** *CIRM could tie continued funding to defined regulatory interactions (e.g., FDA meeting milestones), donor-chimerism performance thresholds, enrollment milestones, and evidence that a viable approval and commercialization path remains intact — giving the Board a checkpoint rather than a one-time, all-or-nothing decision. Alternatively, the scope and budget of the award could be adjusted to fund only the Phase 1 portion of the clinical trial thereby de-risking the application.*

#### 5. Challenges with Past Trials

CIRM Leadership's caution, likely informed by CIRM's earlier investment in in utero transplantation for alpha thalassemia, may not directly translate to this proposal. That earlier trial differed from the current

application in several important respects: the alpha thalassemia patient community has been small and poorly defined because most affected fetuses have historically not survived to birth, and those who do rarely share the same postnatal complications seen in FA patients; the trial was conducted a decade ago, before telehealth was a standardized tool for reaching patients; the safety and feasibility of the underlying procedure were unknown at the time, since it was the first-in-human application; and no efficacy was observed in the first patients, a result likely driven by the underlying disease biology rather than any flaw in trial execution, which understandably dampened enthusiasm for continuing. Despite that, the trial still safely treated six patients, establishing a foundation of feasibility and safety that this FA in utero program can now build upon directly, utilizing the same stem cell product and manufacturing plan. Separately, the team's own two FA clinical trials — one in gene therapy with an industry sponsor, one in antibody-conditioned allogeneic transplantation with CIRM support — have consistently run ahead of schedule and under budget, to the point that savings from the allogeneic trial allowed the team to open an additional treatment arm. Where those programs have slowed, the cause has been commercial rather than scientific: the biotech partners holding rights to those products have pulled back from rare-disease investment more broadly. If anything, that dynamic favors this proposal, since the team would retain full internal control to ensure approval and commercialization of this product if clinical success is observed, rather than depending on a partner's continued interest — though biotech interest in this program does exist as is documented in the non-binding letter of intent in the Appendix from Orca Bio, which showcases a path to additional financing, product development, and commercialization through a capable and optimal industry partner if the program is de-risked and positive clinical data is obtained through this award. That said, we do appreciate the difficulty of this nature of a clinical trial and the potential for biological challenges and lack of efficacy with this type of treatment. Hence, we have proposed a moderated clinical trial enrollment plan and milestone-based funding structure.

***Potential resolution path:*** *A revised award could explicitly incorporate lessons from these or other CIRM-funded programs through early efficacy checkpoints and stop/go criteria specific to this application's biology, patient population, and product — rather than applying the experience of a materially different disease and program as a general presumption against funding. Alternatively, the scope and budget of the application could be adjusted, requiring positive data to de-risk the program before consideration of any further funding.*

## **6. Cost Effectiveness and Return on Investment**

FA is undoubtedly a rare disease, with an estimated 1 affected birth per 136,000, and because eligibility for this trial depends on a timely prenatal diagnosis and maternal/fetal suitability, the immediately treatable population is smaller still. However, the population is also almost certainly undercounted for California specifically: Hispanic communities within our referral network have been discovered to carry FA founder mutations originating in Mexico at disproportionate rates, suggesting the true state prevalence may exceed the national average, even as the disease continues to affect families of every ethnic background. The financial case also remains compelling even at modest patient numbers. Current standard-of-care or developing treatment — allogeneic transplant or gene therapy — runs roughly \$500,000–\$1 million and is expected to be \$3–\$5 million per patient, respectively; whereas this approach is projected to cost a fraction of this price, because it uses maternal stem cells, has cost-effective manufacturing, and could be administered as an outpatient procedure, representing meaningful savings to the state even if only a handful of children are ultimately treated under this award instead of receiving alternative therapies. Beyond direct cost, if successful, cancer prevention in this population would generate savings on its own and produce human data that could inform cancer-prevention strategies for other diseases. Product approval in a rare pediatric disease could also lead to value generation through a priority review voucher (with an estimated value of \$150–\$300 million) and we intend to request Orphan Drug Designation from

the FDA in order to pursue additional financial and regulatory incentives, including market exclusivity, tax credits on qualified clinical testing costs, and a prescription Drug User Fee Act (PDUFA) application fee waiver. Additionally, the underlying platform may also be reusable: if validated in FA, it is a plausible foundation for treating other bone marrow failure syndromes with further downstream potential in hemoglobinopathies. There is a screening dividend as well — the visibility this trial brings to FA is already motivating collaborations to improve carrier and prenatal detection of FA and, potentially, other single-gene disorders.

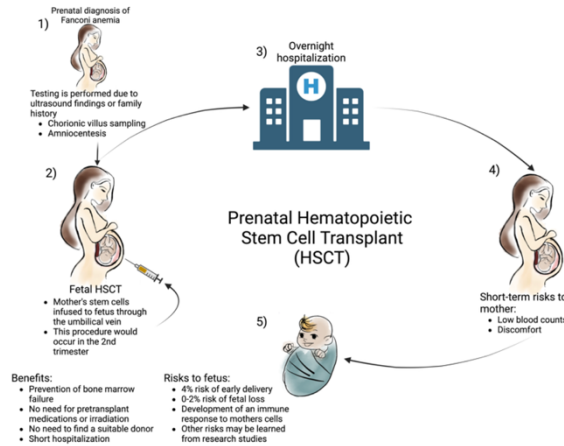
**Potential resolution path:** *If CIRM's current priorities call for greater leverage or reduced exposure, the parties could evaluate a small initial funding tranche, smaller total grant size, co-funding requirements, or milestone-gated release of expansion funds — preserving the opportunity to generate decisive clinical data while limiting CIRM's initial commitment.*

## **7. Alignment with CIRM's Mission and the CLIN2 Program**

CIRM's own funding priorities call for supporting “an interventional phase 1, 2, or 3 trial for an innovative stem cell-based or genetic therapy addressing a serious unmet need and with the potential for transformative benefits to patients, families and the health care system,” and for “advancing four to seven rare-disease projects toward a Biologics License Application (BLA).” This proposal was built to do precisely that, and we believe it embodies the spirit in which California voters created CIRM: to give patients with the most serious, otherwise unmet needs a path to a cure that the traditional funding system could not otherwise provide. FA is exactly such a disease, and this program is on exactly such a path — a pivotal-intent clinical trial, grounded in strong, independently replicated preclinical data, with an active FDA relationship and a credible route to a BLA submission. While we recognize the high-risk, high-reward nature of this trial – that may or may not work – we have also developed this application, so it has the possibility for success. It aims to fully complete an interventional Phase 1 clinical trial with all follow-up visits and obtain the primary endpoint in the Phase 2 cohort — this elegantly sets up the product for potential approval in this disease indication and/or enables subsequent development with an industry partner to ensure access of this treatment to patients of California and the world. This application reflects the CLIN2 mechanism's specific purpose: supporting transformative stem cell products through clinical trials for rare and serious diseases that otherwise have no viable path to the clinic. CIRM also has the resources available to fund this application; without that support, families facing a prenatal FA diagnosis are left to make challenging, time-critical decisions with no appealing therapeutic alternatives. Our institution and the Fanconi Cancer Foundation, though a comparatively small advocacy organization, have both already fundraised to support the underlying preclinical work and have pledged additional support that could serve as contingency funding for a clinical trial — but we cannot finance a clinical trial of this scale on our own. Funding now would set this potentially transformative treatment up for success and enable it to reach the patients with the highest unmet need. The program is prepared to begin: no further development is needed, nothing would change by waiting for a future funding cycle, an additional administrative review cycle would only re-utilize the same precious resources used in this evaluation, and every additional cycle of delay is a cycle in which eligible families cannot be offered this potentially meaningful new option. We urge the Board to consider approving support of this application.

**Potential resolution path:** *If any aspect of the current application does not fully reflect CIRM's evolving strategic priorities, we would be grateful if CIRM Leadership could specify those aspects directly, so that our team can propose targeted amendments in that same spirit of shared mission, rather than have the application declined without a defined path to alignment.*

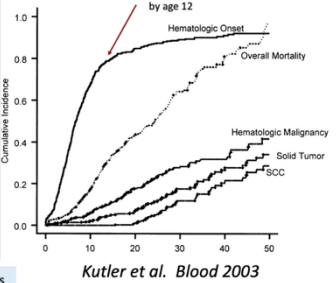
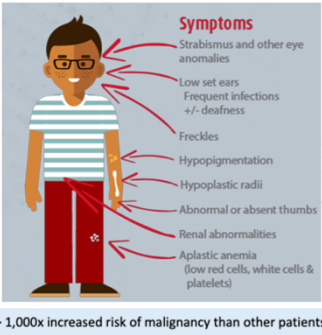
Appendix C: Supporting Background Information and Data



**Figure 1:** Schematic of prenatal HSCT process developed for families in collaboration with the Stanford, UCSF and FCF teams demonstrating ease of treatment compared to postnatal transplant approaches. *From Lum et al. Prenat Diag 2026.*

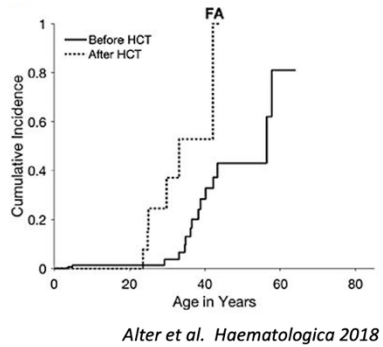
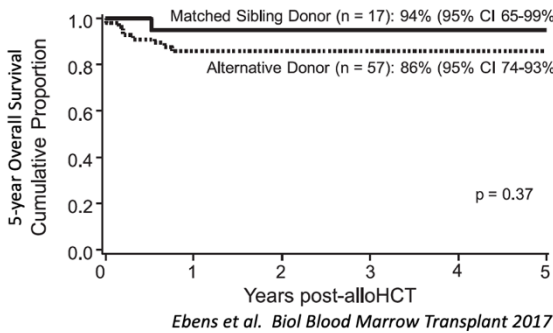
Fanconi Anemia

- Genetic disease caused by abnormal protein in FA pathway (23 genes)
- Defective ability to repair DNA leading to interstrand cross-links (ICLs)

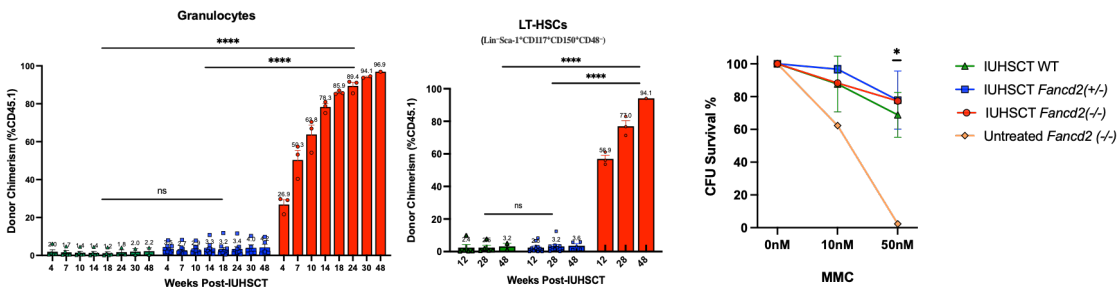
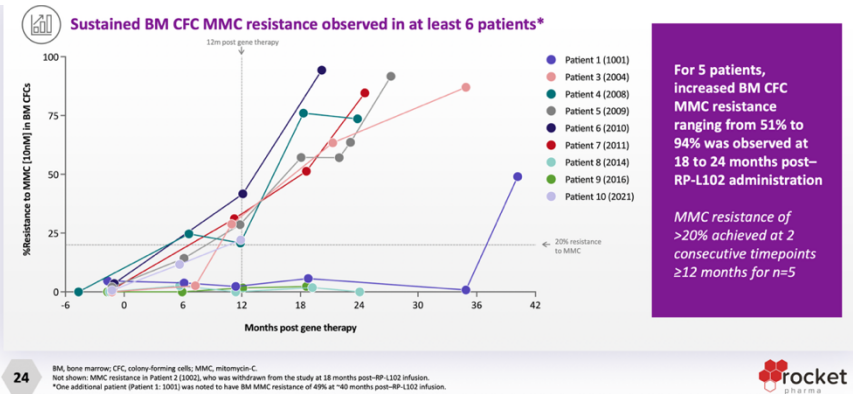


**Figure 2:** Fanconi Anemia (FA) background information demonstrating congenital anomalies that can lead to suspicion for FA on prenatal ultrasound, as well as high incidence of blood and immune disease, cancer and overall mortality. *From Kutler et al. Blood 2003.*

**Figure 3:** Despite improving outcomes of postnatal HSCT, this is a resource-intensive treatment requiring weeks of hospitalization and months of isolation. High rates of serious complications occur including premature death and accelerated malignancies due to FA patients receiving current chemotherapy- and/or irradiation-based HSCT treatments, especially with alternative, non-matched sibling, donors.



**Figure 4:** Reported results of unconditioned ex vivo FANCA lentiviral gene therapy demonstrating rapid engraftment of gene-corrected HSPCs in treated FA patients with sustained resistance to DNA-damage with MMC challenge. Biomarkers derived from these studies set a precedent for endpoints for FDA approval. Despite strong clinical data, gene therapy is a resource-intensive treatment approach and approval has been challenged by a need for corporate reprioritization. *From Rocket Pharma Corporate Deck 2023.*



**Figure 5:** Prenatal HSCT uniquely allows for robust donor engraftment of surrogate stem cell product in homozygous FA (*Fancd2*<sup>-/-</sup>) mice as early as 4 weeks post birth, which increased with time due to the competitive advantage of wildtype stem cells over failing FA stem cells. Importantly this was achieved without any toxicity, and no genotoxic chemotherapy or immune suppression was required to achieve high donor engraftment with resistance to DNA-damage. *From Swartzrock et al. Bld Adv 2024.*

September 24, 2026

**To: CIRM ICOC Committee**

**Re: Enthusiastic Support for Funding CLIN2-20316: In Utero Hematopoietic Stem Cell Transplantation for Fanconi Anemia**

Dear Members of the CIRM ICOC Committee:

It is with great enthusiasm that Stanford Alpha Clinic confirms its support for funding **CLIN2-20316: In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia**, a clinically ready and potentially transformative approach to treating the blood and immune defects in children with Fanconi anemia (FA) – a grievous genetic DNA-repair disorder. We concur with the assessment of the Grants Working Group which makes clear that this proposal addresses a profound unmet medical need for a rare disease population with a scientifically compelling, operationally feasible, and equity-centered stem cell therapy strategy that once successful can have broader applications.

As indicated by the strong support of the Grants Working Group reviewers, there is no question as to the scientific merit of this proposal. It also offers a fundamentally different paradigm to the current treatment options for FA. The proposal is also unusually well positioned for execution, bringing together an outstanding, multidisciplinary team with deep expertise. This proposal exemplifies the kind of multi-institutional collaboration that aligns with the mission of the CIRM Alpha Clinics network which is steadfastly committed to streamlining and accelerating the delivery of cell and gene therapies to patients who need them by fostering partnerships like these across the network.

We understand CIRM's concern regarding enrollment for this trial. As Stanford Alpha Clinic, we are committed to ensuring success in enrollment for all of Stanford Medicine's cell and gene therapy trials, including this proposal, through equity-centered approaches to increasing trial access.

We believe this equity-centered proposal would fit neatly into CIRM's portfolio because it addresses an optimal treatment option for a population with great unmet need. It directly addresses California's diverse population, including Hispanic/Latino families who comprise a substantial portion of Stanford's FA cohort and may face disproportionate barriers related to insurance, language, geography, and access to specialized surveillance and transplantation services. Our families confronting a prenatal diagnosis of FA must make extraordinarily difficult and timely decisions in the setting of limited therapeutic options and the prospect of lifelong medical complications. This proposal gives eligible families a scientifically grounded, carefully regulated, and ethically reviewed opportunity to pursue a preventive treatment strategy. Without CIRM support, there is no realistic pathway to generate the clinical evidence needed to advance this innovative approach.

As a member of the CIRM Alpha Clinics network, we deeply align with CIRM's mission to support this kind of bold, high-impact stem cell science: a program that addresses an urgent unmet need, advances an innovative and practical therapeutic platform, is led by a highly experienced and collaborative California-based team, and has the potential to improve outcomes and equity for patients who currently have few acceptable options.

For these reasons, we respectfully urge CIRM to provide funding for CLIN2-20316: In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia.

Sincerely,



Matthew Porteus MD, PhD  
Sutardja Chuk Professor of Definitive and Curative Medicine  
Director, Center for Definitive and Curative Medicine  
Laurie Kraus Lab Research Director, CDCM  
Department of Pediatrics  
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Stanford, CA 94304

**Re: Support for CIRM Application – CLIN2-20316: In Utero Stem Cell Transplantation to Prevent Bone Marrow Failure and Cancer in Fanconi Anemia**

Dear Dr. Czechowicz,

On behalf of Orca Bio, I am writing to express our enthusiastic support for your grant application to the California Institute for Regenerative Medicine (CIRM). Your team's groundbreaking research establishing that *in utero* hematopoietic stem cell transplantation (IUHSCT) can achieve robust, progressive multi-lineage engraftment and disease correction without pre-HSCT conditioning in Fanconi anemia models represents a paradigm shift in treating severe inherited hematologic disorders. Further, your team's proven ability to safely and feasibly enroll and treat patients in the alpha thalassemia indication sets this program up for near-term success.

At Orca Bio, we are pioneering the high-precision manufacturing and clinical advancement of engineered cell therapies to replace conventional bone marrow transplants. Our proprietary platform enables precise control of donor cell compositions to improve therapeutic outcomes while minimizing graft-versus-host disease (GVHD) and toxicities. The fundamental premise of your CIRM proposal—delivering an allogeneic engineered stem cell therapy *in utero*—aligns seamlessly with Orca Bio's core drug development and regulatory expertise, manufacturing and commercialization capabilities, and strategic mission.

As an industry leader in cell therapy, Orca Bio possesses extensive operational, clinical, regulatory, and commercial infrastructure. Our team has successfully advanced engineered cell therapy products through registrational clinical trials toward commercialization by establishing robust cGMP manufacturing protocols, scalable distribution networks, and strong regulatory pathways. Recognizing the immense potential of your work, Orca Bio is actively pursuing discussions to explore licensing this technology and seeking a Biologics License Application (BLA) to manufacture, market, and distribute this life-saving therapy.

While Orca Bio is uniquely positioned to scale and commercialize this innovation, our optimal resource allocation window follows early-stage clinical de-risking. CIRM funding is critical at this pivotal juncture to bridge translational development, support early-phase clinical evaluations, and establish initial human proof-of-concept and safety profiles. Grant support from CIRM will provide vital catalytic capital to de-risk the program, enabling Orca Bio to step in with significant commercial capital, manufacturing capacity, and regulatory capabilities for late-stage development and commercialization.

We strongly endorse your application and look forward to partnering with you to bring this next-generation prenatal stem cell therapy to patients and families in need.

Sincerely,

*Nathaniel Fernhoff*

CEO

Orca Bio, Inc.