CLINICAL

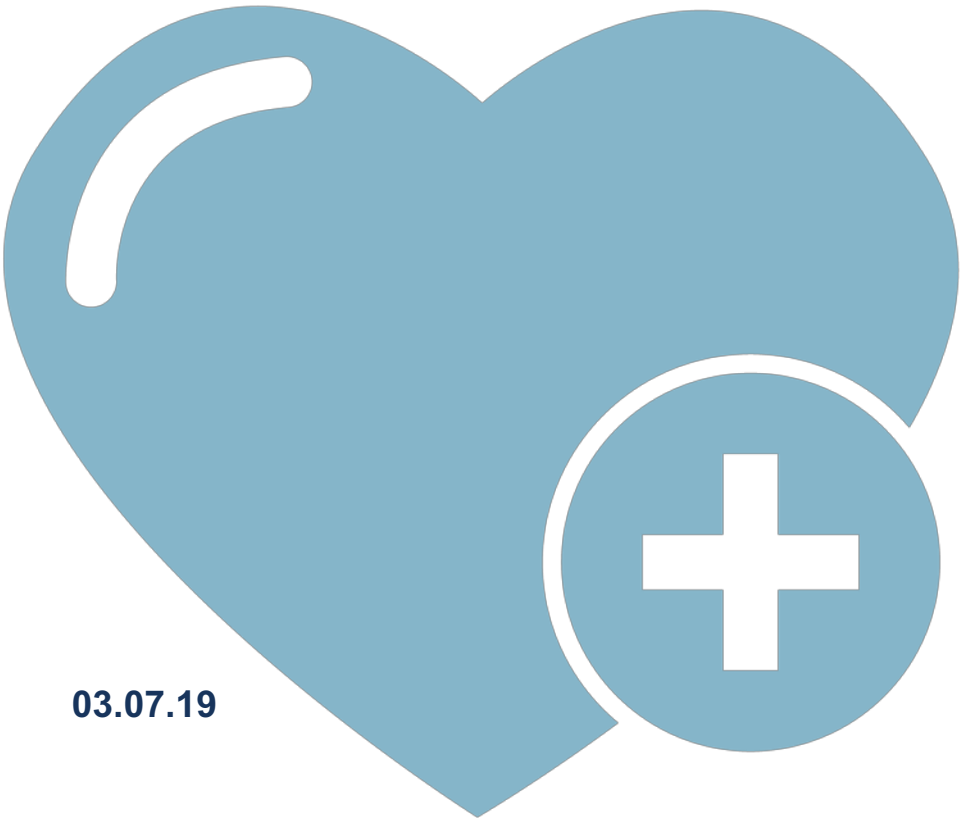
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

IND enabling development of an endogenous stem cell reactivation therapy to enhance bone healing in the elderly

Application Number: CLIN1-11256 (Revised Application)	Review Date: 28 February 2019

Late Stage Preclinical Project Proposal (CLIN1)



03.07.19

IND enabling development of an endogenous stem cell reactivation therapy to enhance bone healing in the elderly

APPLICATION NUMBER: CLIN1-11256 (Revised application)

REVIEW DATE: 28 February 2019

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

A liposomal formulation of recombinant human WNT3A protein that is intended to enhance the osteogenic properties of autografts in elderly

Indication

Patients with Degenerative Spondylolisthesis (DS) undergoing a spinal fusion surgery

Therapeutic Mechanism

WNT proteins are potent pro-osteogenic signals. L-WNT3A is the investigative prototype material of the therapy. Treated autografts exhibit enhanced cell survival and reduced apoptosis. As a consequence of osteogenic gene up regulation, the osteogenic properties of the autograft are enhanced: compared to control (untreated) autografts, L-WNT3A treated autografts exhibit a significantly increased new bone formation.

Unmet Medical Need

When the first line therapies with non-surgical approaches fails, patients undergo a spinal fusion procedure, which utilizes an autograft. But autografting is unreliable in older patients. The unmet medical need is an autograft that retains its osteogenic capacity, even in elderly patients.

Project Objective

Initiation of a Phase 1/2 clinical trial

Major Proposed Activities

Conduct a GLP toxicology study in a rabbit model

GMP manufacture of the therapy to support proposed clinical studies

Prepare and conduct an Investigational New Drug filing

Funds Requested

$3,994,246 ($998,562 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 3 GWG members

Votes for Score 3 = 0 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation.

Review Overview

This application proposes preclinical studies, manufacturing, and regulatory filing for a treatment to enhance bone fusion in patients with degenerative spondylolisthesis undergoing spinal fusion surgery. Overall, the reviewers thought the treatment was promising and a potentially safer alternative to current products on the market. There were some concerns regarding the aggressive timeline for the proposed studies and clinical project timeline. In addition, there were aspects of the clinical protocol that need significant clinical input and would benefit from a spine surgeon on the team. However, the reviewers felt these concerns could be resolved during the award period with CIRM guidance and recommended the application for funding.

Review Summary

Does the project hold the necessary significance and potential for impact?

YES	15	NO	0

a) Consider whether the proposed treatment fulfills an unmet medical need.

- The proposed treatment addresses the need for a spinal fusion material that can increase the chance for a solid bony union in the lumbar spine. There are other products on the market that fulfill this need but have safety concerns that have been raised in the past.

b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

- The intended biological outcome of an attempted fusion is solid bony union. This does not occur in a large portion of patients undergoing inter-transverse fusion. If the material enhances fusion, the treatment will be an improvement over the current standard of care for the intended patient population. In addition, there are other orthopedic indications beyond this particular population where a therapy like this could be useful.

c) Consider whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

- The value proposition will be a function of the ultimate cost of the product compared to its efficacy. There is some value to offering an additional material that enhances spinal fusion more reliably than autograft fusion alone or with other available materials (e.g. BMP-2).

Is the rationale sound?

YES	15	NO	0

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

- The proposed project is based on sound scientific evidence and clinical rationale. Autologous bone graft is not nearly as effective in compromised populations - immunocompromised, geriatric, smokers, etc. Furthermore, spine fusions in this population are also a unique opportunity to examine various agents to facilitate bone healing due to the high rate of complications in these procedures.
- The preclinical data shows potential advantages of the investigational material compared to BMP-

2.

b) Consider whether the data supports the continued development of the treatment at this stage.

- The existing data provided by the researchers supports the continued development of this agent for clinical application. The preclinical data suggests high fusion rates and low observed rates of local swelling and heterotopic bone formation, which are two complications associated with BMP-2.

Is the project well planned and designed?

YES	**11**	**NO**	**4**

a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

- The project is appropriately planned and designed.
    - There are concerns from some reviewers regarding the FDA interactions. The FDA made it clear that the proposed preclinical model was suitable only for posterolateral surgical approach in the clinical trial. The applicants confirmed in the resubmission that posterolateral surgery would be the only approach in the clinical trial but there were still references to other surgical approaches in the application. Complete alignment of the proposed surgical approach to the FDA recommendations is needed.
    - Most of the endpoints in the proposed preclinical toxicity and efficacy studies are subjective, therefore it will be important to blind all readers to the treatments.

- There were several concerns regarding the clinical protocol that would benefit from additional clinical input from a spine surgeon:
    - It is essential that all patients receive the exact same surgical procedure (ie. posterolateral instrumented fusion with pedicle screws with no interbody device or interbody fusion) as any variation could impact fusion outcomes:
        - The researchers need to be explicit that no additional material such as cages will be added to the spinal fusion arm where only autologous bone graft is used.
        - It is unclear if pedicle screws will be used in all patients; the revised draft states that the surgical approach will be "standardized e.g. intertransverse lumbar spinal fusion procedure." This can be performed with or without pedicle screws, which is important to clarify. The use of pedicle screws would affect the fusion rate, which is the primary measurement of this study.
    - The protocol details fusion assessment by CT at multiple time points. This would impart a large degree of ionizing radiation to the enrolled patients, above and beyond what is used in typical care.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- The experiments in the project plan are essential and they create value that should advance CIRM's mission.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- Reviewers raised a few concerns regarding the timeline for the eventual clinical trial:
    - There is concern about the project timeline with respect to clinical enrollment. As a single site study, it may be challenging to find the number of patients sought and have all the necessary endpoints without having drop off, which did not appear to be accounted for in the study outline.
    - The estimated time to meet the primary objective is 6 months. For radiographic fusion, this might be sufficient. However, this would not be considered sufficient for clinical outcomes. Thus, the total duration of 18 months for this phase of the study may not be feasible.

Is the project feasible?

YES	**14**	**NO**	**1**

a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- While the team will likely be able to achieve their objectives, the time line is very aggressive with respect to patient enrollment and follow-up. The specific inclusion and exclusion criteria are a strength but that will also limit patient eligibility.

b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

- The team, with the addition of a CRO, would be able to complete this study. However, a spine surgeon does not appear to be on the trial team or involved in the study design. For the clinical study to be successful, it is imperative that a spine surgeon be engaged as soon as possible.

c) Consider whether the team has a viable contingency plan to manage risks and delays.

- Each component of the preclinical project timeline is dependent on the completion of the prior activity, which may mean a delay in the overall timeline if any one aspect is delayed.
- The data safety monitoring board appears to be a reasonable measure to manage the risks and potential complications of the clinical trial. However, additional contingency plans related to the clinical study should be considered. As with any clinical study, delays and challenges with recruitment must be expected.

CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).