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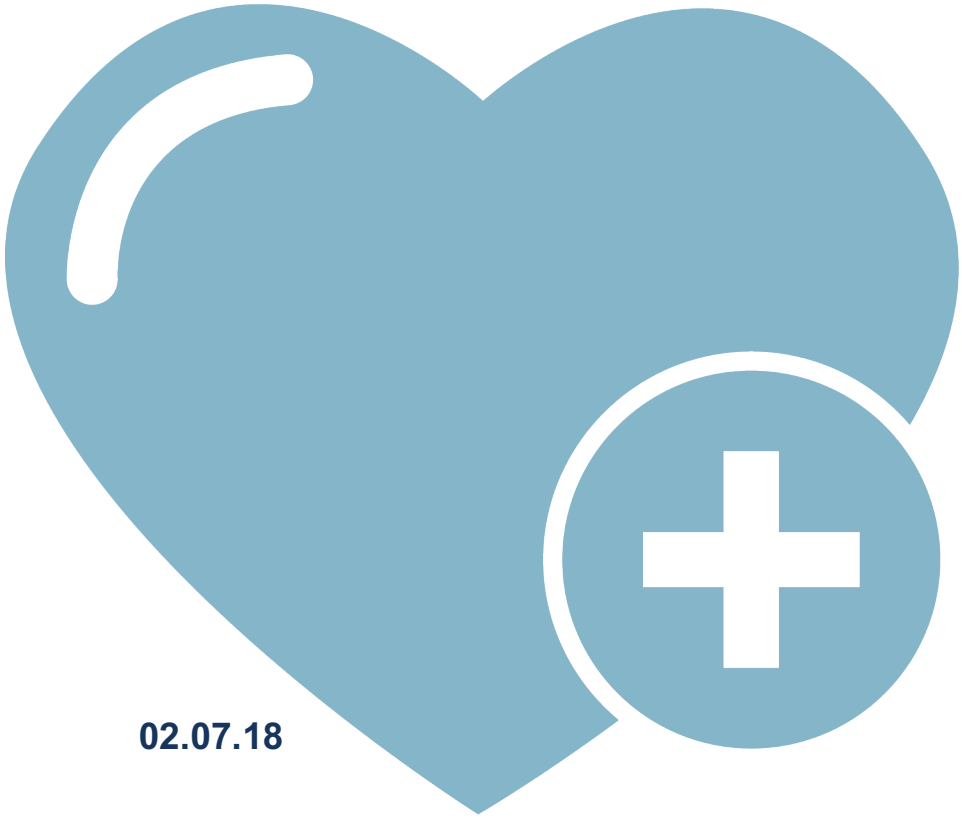
Grants Working Group Public Review Summary

IND Enabling Development of a Natural Killer Cell Immunotherapy for Cancer Derived from a Human Inducible Pluripotent Stem Cell

Application Number: CLIN1-10893	Review Date: 25 January 2018

Late Stage Preclinical Project Proposal (CLIN1)



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IND Enabling Development of a Natural Killer Cell Immunotherapy for Cancer Derived from a Human Inducible Pluripotent Stem Cell

APPLICATION NUMBER: CLIN1-10893

REVIEW DATE: 25 January 2018

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

A Natural Killer Cell Immunotherapy for Cancer Derived from a Human Inducible Pluripotent Stem Cell Line

Indication

Monotherapy for patients with advanced cancer and in combination with approved ADCC-competent monoclonal antibodies

Therapeutic Mechanism

The drug product is comprised of natural killer (NK) cells derived from a clonal human induced pluripotent stem cell (iPSC) master cell line that has been genetically modified to express a high-affinity variant of immunoglobulin FcgammaRIIIa (CD16a) receptor and to prevent cleavage by the metalloprotease ADAM17. Both modifications enhance NK cell targeting and elimination of cancerous cells by release of cytolytic granules, cytokine activation, and antibody-dependent cellular cytotoxicity.

Unmet Medical Need

The product is designed to exhibit innate anticancer activity and to synergise with therapeutic monoclonal antibodies to significantly improve outcomes for patients with progressive cancer and few other effective therapeutic options

Project Objective

Full readiness to initiate Phase 1 clinical trial

Major Proposed Activities

Complete manufacturing process control and release assay development. Complete engineering-, process-qualification and clinical manufacturing runs

Completion of IND-enabling preclinical studies, investigational new drug application preparation and submission

Complete clinical trial database construction and clinical site identification and study initiation

Funds Requested

$5,649,684 ($1,979,405 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 7 GWG members

Votes for Score 2 = 5 GWG members

Votes for Score 3 = 0 GWG members

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- 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.

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Review Overview

Overall, reviewers were very positive about the potential impact of this therapy to improve the treatment of multiple types of solid tumors. The therapy would provide an additional option for patients who have progressed on existing therapies. Reviewers noted the applicant team is experienced in developing early phase cell therapy products, and the product addresses a few of the major obstacles in the NK therapy field. The approach makes use of induced pluripotent stem cells (iPSC) to produce large quantities of uniform NK cells that are engineered to enhance their interaction with tumor cells and to resist the immunosuppressive tumor microenvironment. Some concerns were raised about the need for more definitive comparisons of the combination therapy to antibody therapy alone in the preclinical stage and clinical study design to more accurately assess the effectiveness of the combination therapy over current antibody treatments. Ultimately, the majority of reviewers recommended the application for funding.

Review Summary

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

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

- The proposed NK cell and combination with monoclonal antibody therapy is a potentially novel approach in patients with advanced disease and an improvement over current therapy options.
- There is still a very high unmet medical need for more efficacious treatments for solid tumors, and this approach has the potential to expand to multiple solid-tumor types.

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

- Approved antibody therapies currently favor patients with the high-affinity CD16 variant (about 10% of overall population). In addition, patients with low NK cell counts exhibit worse outcomes. The application identifies poor responders to current monoclonal antibody therapies as ideal candidates. If successful, this approach would be a valuable option for patients who are refractory to existing therapies.

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

- The value proposition will depend on safety and efficacy results seen in clinical trials.
- This approach has the potential to boost response rates for many patients if it is shown to successfully enhance the antibody dependent cell-mediated cytotoxicity (ADCC) against multiple tumor types.

Is the rationale sound?

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 approach of combining NK cell therapy with antibody therapy is based on sound scientific and clinical rationale.
- The proposed approach of deriving NK cells from induced pluripotent stem cells overcomes several manufacturing hurdles and results in a uniform, reproducible product.
- Some reviewers were not convinced that the *in vitro* and preclinical *in vivo* data gathered showed a clear advantage of the combined NK cell and antibody therapy over antibody monotherapy. More preclinical data demonstrating a significant difference of the combination therapy over antibody alone is needed.
- The proposed genetic engineering of the iPSC-derived NK cells to enable high affinity interactions with tumor cells and to resist the immunosuppressive tumor microenvironment is based on sound scientific rationale.
- The *in vitro* and *in vivo* data supports the hypothesis that the engineered NK cells are more uniform and have higher activity than cord blood or apheresis-derived NK cells.

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

- The data supports continued development of the product.

Is the project well planned and designed?

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 planned in accordance with FDA recommendations and is highly likely to yield a successful IND application.
- The clinical trial and correlative study design does not truly test whether the engineered cells make a real difference in patient response compared to antibody monotherapy. Since the treatment depends on the antibody component to work it would be important to demonstrate the effectiveness of the combination therapy as compared to the antibody therapy alone.
- The clinical trial enrollment criteria includes patients who have progressed on antibody therapy but does not re-assess the patients' tumors for expression of the antibody target prior to the proposed combination treatment.
- Reviewers were concerned that the proposed maximum dose in the phase 1 trial is only equivalent to an NK cell count obtained from a single apheresis.
- NK cell persistence is an overall concern. The clinical protocols should more clearly quantify the persistence and expansion of the cells *in vivo*.
- Since the product does not appear to be engineered to avoid rejection, the HLA type of the patients should be recorded and monitoring of rejection mechanisms should be included in correlative studies.

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

- The regulatory path is well laid out, the concept is sound, and if positive in phase I, will support CIRM's mission.
- If successful, the project will enable iPSC-derived cell therapies for other indications.

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.

- The work outlined in the application has been deemed essential by the FDA and the project plan proposes a streamlined development process aimed at achieving IND submission in the required 18 months.

Is the project feasible?

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

- The timeline is aggressive but achievable.

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 is very experienced and has engaged competent contract research organizations (CROs).
- The applicants plan to open a site at an Alpha Stem Cell Clinic and other sites with specific expertise in immunotherapy.
- It was not clear how much regulatory experience the team has with respect to authoring and publishing the IND in eCTD format.

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

- All risks including manufacturing, regulatory (FDA feedback and requests during pre-IND meeting), clinical and financial risks have been discussed in detail. Contingency plans are available for critical items.

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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 with award amount of $4,000,000, which aligns with recently approved award maximum for a CLIN1 project.