| Application # | CLIN1-14140 #2 |
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| **Title**<br>(as written by the applicant) | IND-Enabling activities for a masked immunocytokine |
| **Therapeutic Candidate**<br>(as written by the applicant) | A masked immunocytokine comprising an anti-CD138 antibody fused to interferon alpha 2b, with a protease cleavable peptide mask |
| **Indication**<br>(as written by the applicant) | The proposed therapy is for the treatment of advanced or metastatic solid tumors with CD138 expression and multiple myeloma |
| **Unmet Medical Need**<br>(as written by the applicant) | Advanced and metastatic solid tumors and multiple myeloma are still largely incurable for the majority of patients, resulting in death in over 400,000 US residents in 2022 in indications with >50% frequency of CD138 expression |
| **Major Proposed Activities**<br>(as written by the applicant) | • Manufacturing of the therapeutic product for a phase 1 clinical study<br>• Translational research to evaluate optimal tumor indications and potential prognostic biomarkers<br>• Clinical site assessment, selection, and preparation |
| **Funds Requested** | $3,999,113 |
| **GWG Recommendation** | Tier 1: warrants funding |
| **Process Vote** | All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."<br><br>Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias." |

# SCORING DATA

## Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

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| **Highest** | 1 |
| **Lowest** | 3 |
| **Count** | 15 |
| **Votes for Tier 1** | 11 |
| **Votes for Tier 2** | 3 |
| **Votes for Tier 3** | 1 |

- 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

# KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

| GWG Votes | Does the project hold the necessary significance and potential for impact? |
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| **Yes:**<br>13 | • Interferon A (IFNA) therapy has clinical efficacy in multiple tumors but is limited by systemic toxicity. Preclinical data support the potential for the proposed therapy to provide anti-tumor effectiveness of IFNA without the dose-limiting side effects.<br>• If the study drug is indeed able to provide targeted IFNA treatment, it could result in improved patient outcomes in multiple malignancies. |

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| | • A relatively high rate of relapses in multiple myeloma after treatment with FDA-approved drugs, including CAR-T, represents an unmet medical need.<br>• New treatments for multiple myeloma have great significance and potential for impact.<br>• Although I wish the applicants had responded more directly to the GWG comments from the prior review, I believe the project merits moving to the next step given unmet need and challenges that limit the value of conducting further animal studies.<br>• Yes - the applicant has provided substantive new justification and reference citations to support that their test article crucially affects targets on cancer stem cells.<br>• It is unclear whether this interferon product will provide any improvement over the standard of care. Many recently approved and highly effective drugs for treating multiple myeloma are available, including MABs and CAR-T. The proposed drug could be more beneficial in solid malignancies.<br>• In response to the prior critique, the applicant highlighted some potential advantages over existing approved drugs for multiple myeloma. However, the biggest advantage could be lower cost and better availability/accessibility for patients. |
| **No:**<br>1 | *none* |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:**<br>11 | • Interferons (IFN) have antitumor efficacy, but the side effects associated with high dose IFN treatment have limited their therapeutic utility. The proposed therapy is being developed to minimize IFNA toxicity by targeting IFNA to the tumor site, increasing its local concentration, and reducing off-target effects by masking the IFNA during transit to the tumor.<br>• The target (CD138, also known as syndecan-1) has high expression in multiple myeloma and a number of solid tumors but is also expressed (at lower levels) on some normal epithelial and plasma cells. The tumor has enhanced expression and activity of the proteases required to release the IFN mask.<br>• Previously, an antibody therapy leveraging the same target (CD138) demonstrated a therapeutic window in patients with multiple myeloma.<br>• In vitro studies show that EC50 for the proposed therapy (targeted, masked IFNA) is greater than the EC50 for the unmasked, targeted version of IFNA, and much greater than for wildtype IFNA.<br>• Preliminary titration studies against human multiple myeloma xenografts in NSG mice (NOD scid gamma) demonstrated dose dependent effectiveness including complete regressions at higher doses.<br>• In preliminary studies, treated tumors had higher populations of activated lymphocytes and infiltrated T-cells with a higher CD8+: CD4+ ratio suggesting that the proposed therapy may alter the tumor immune environment to favor anti-tumor immune activity.<br>• In preliminary studies, cytokine induction was found to be substantially lower with masked product relative to unmasked product.<br>• Preliminary studies in pancreatic and ovarian cancer tumor animal models showed inhibition of growth but no regression. These were immunodeficient animal models, so the observed effect was likely due to direct tumor cell cytotoxicity rather than immune system activation against the tumor. Proposed studies in Aim 2 will try to address this.<br>• Overall, yes, but it is not clear what the relevance is to stem cell biology and/or stem cell-based therapies. The authors mentioned that CD138 is expressed in many types of tumor cells, including tumor stem cells. In the response to the prior GWG critique requesting more justification for this claim, the authors cite literature that indicates the potential anti-tumor effect of IFN and anti-CD138 through targeting of cancer stem cells. However, these effects are not specific to cancer stem cells (CSC) and the literature includes different IFN-based and anti-CD138 agents. The authors did not provide their own data (based on the use of their product) to support the specific targeting of CSC.<br>• Overall, yes, though specificity issues and lack of good relevant animal model make this project difficult to evaluate using standard criteria. |
| **No:**<br>3 | • Targeting syndecan-1 (CD138) is lacking in specificity. There are no data to suggest that this is specific to cancer stem cells. |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>11 | • Yes. Proposed studies, including defining Minimal Anticipated Biological Effect Level (MABEL), appear well planned and designed.<br>• Aim 1 focuses on providing FDA approvable, GMP quality product for a phase 1 clinical study. The applicant has already developed a Master Cell Bank with their collaborator and has a purification process in place. The proposal includes production scale-up activities. |

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| | • Aim 2 will further evaluate anti-tumor activity of the proposed therapy in solid tumor indications to help guide the selection of indications for the future Phase 1 trial.<br>• A valuable piece of Aim 2 will be the development and validation of an assay for measuring expression of CD138, and evaluation of human tumor panels with this assay.<br>• Aim 2 will also evaluate anti-tumor efficacy and mechanism of action of the therapy in murine models.<br>• The studies proposed in Aim 3 will be directed to the requirements for an IND submission to the FDA.<br>• Given the limitations of in vivo models, and prior primate pharmacokinetic (PK) data, FDA has agreed that a GLP toxicity study in nonhuman primates is not needed. Instead, in Aim 3a, planned with input from FDA, the applicant will determine the Minimal Anticipated Biological Effect Level (MABEL) in vitro with human peripheral blood mononuclear cells (hPBMCs) and in efficacy models. Pairing this with PK data from rodents will further support modeling of expected human exposures to determine the appropriate starting dose in the first-in-human phase I study.<br>• While the phase I trial will not be part of this grant, Aim 3 will lay the groundwork for the trial including identification of potential clinical sites for the phase 1 study, working with the clinical CRO on final protocol development and submission of the IND package to FDA.<br>• The FDA requested addition of and refinement of the clinical protocol inclusion/exclusion criteria. These requests will be included during the development of the protocol as part of this proposed work plan.<br>• Yes, but, the crowded multiple myeloma space will be a significant challenge for the trial and should be incorporated into the planning now. Definitely at least one other indication should be included as part of FDA discussions.<br>• Because CD138 is expressed on multiple normal tissues, it is important to understand how specific targeting of tumors will be achieved without any off-tumor side effects. For this reason, I recommend designing a correlative study to monitor and address CD138 specificity and off-target effects.<br>• Because antibodies do not cross-react with species other than humans and IFNA masking does not work in surrogate mouse drug-analog, animal model toxicology studies seem irrelevant. |
| **No:**<br>3 | • Biologic outcome measures need to be incorporated in order to learn whether the drug is impacting on stem cell populations. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:**<br>14 | • The studies examining correlation between efficacy and CD138 expression will be critical to a future clinical application. Of concern is how efficacy will be measured in a phase I population and whether pharmacodynamics (PD, such as measures of tumor targeting) would be a more appropriate measure.<br>• Although this is a new product, the payload IFNA2a is well-characterized and has been marketed as multiple products. IFNA2a is FDA-approved for treatment of chronic hepatitis B and chronic hepatitis C. A related product, IFNA2b, is FDA-approved for treatment of hairy cell leukemia, malignant melanoma, follicular lymphoma, Kaposi's sarcoma, chronic hepatitis B, and chronic hepatitis C.<br>• FDA has granted Orphan Drug Designation for the proposed product's use in multiple myeloma and pancreatic cancer.<br>• Companion diagnostics, such as the proposed development of an IHC assay for CD138, are not simple. There may be threshold levels that correlate with activity. Additional studies such as radiolabeled target imaging might be able to help define the target population for the agent.<br>• The project looks feasible. |
| **No:**<br>0 | *none* |
| **GWG Votes** | **Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?** |
| **Yes:**<br>14 | • For the third Aim, development of the clinical trial, the applicant indicates that the target trial accrual goal is to have the trial participant demographics match the general population.<br>• While there is no specific plan to address inclusion, the proposal indicates that they will include questions regarding each site's outreach, demographics and track record. The proposal acknowledges disparities in race, gender and age across all malignancies, but does not address the higher incidence and greater mortality for African Americans with multiple myeloma, a major focus of this study. |

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| | • They acknowledge that as a phase 1 study, the relatively small number of patients and different treatment cohorts will not be likely to demonstrate differences in safety, PK, or efficacy between demographic groups.<br>• They have preliminarily selected eight clinical sites in California as potential participants in the clinical trial. Several of these are large hospitals with significant outreach programs to nearby communities of diverse demographics.<br>• A Community Engagement Plan for the phase 1 study has not yet been established.<br>• Yes, to the extent that pre-clinical work can. The proposal suggests an intent once the clinical trial is developed.<br>• The applicant understands DEI and will address it in the clinical trial design. |
| **No:**<br>0 | *none* |

## DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

### DEI Score: 6

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

| Score | Patient Advocate & Nurse Votes | Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)? |
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| **9-10: Outstanding response** | 0 | *none* |
| **6-8: Responsive** | 5 | • An effective treatment would certainly impact CA's diverse population.<br>• These strong applicant institutions are highly capable and have demonstrated their DEI focus. |
| **3-5: Not fully responsive** | 0 | *none* |
| **0-2: Not responsive** | 0 | *none* |