MEMORANDUM

Date: July 20, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05352

Enclosed is a petition letter from Dr. Timothy Hoey of OncoMed Pharmaceuticals, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 18, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

OncoMed
PHARMACEUTICALS

July 18, 2012

Dr. Jonathan Thomas
Chairman, Independent Citizen's Oversight Committee

Dr. Alan Trounson
President and Chief Scientific Officer, CIRM

Dear Drs. Trounson and Thomas,

We are submitting this "extraordinary petition" in response to our application for funding for RFA 10-5 Disease Team Development Therapy Award, "A New Therapeutic to Reduce CSC Frequency in Breast Cancer". We would like to clarify some potential misunderstandings about our program that arose during the review process and provide an update on the status of the program.

The concept that stem cell pathways are often inappropriately regulated in tumor cells is now widely viewed as an important hypothesis in cancer research and numerous drug discovery efforts are underway to develop new anti-cancer therapeutics by targeting stem cell self renewal pathways hyperactive in cancer. CSCs have been shown to be resistant to many current therapies and to mediate disease recurrence and metastasis. At OncoMed Pharmaceuticals, we have developed a novel monoclonal antibody, OMP-52M51, targeting the Notch pathway, a key stem cell pathway which is frequently dysregulated in cancer. This antibody is part of a broad collaboration on the Notch pathway with GSK, and this antibody is the lead program in that collaboration based on the ability to pre-select responding tumors using a simple biomarker. Based on the literature and our internal research there is a strong rationale for inhibiting this pathway in numerous types of cancer, and again, particularly in a pre-selected way in breast cancer. We have developed an easy to use biomarker to identify patients with [REDACTED] [REDACTED]. We have established a collaboration with Dr. Laura Esserman, a world-renowned researcher, clinician and clinical investigator in the field of breast cancer at UCSF to pursue pre-clinical research and also clinical development of OMP-52M51 for the treatment of breast cancer. OMP-52M51 has been extensively tested in preclinical models utilizing patient-derived tumors, has demonstrated significant reductions in cancer stem cell frequency utilizing an *in vivo* limiting dilution assay to measure cancer stem cell frequency, has progressed through IND enabling safety studies and has been scaled up and manufactured at commercial scale levels. Dr. Esserman, co-PI of this application, is the coordinator of the I-SPY2 clinical trial network. I-SPY2 is an NIH Foundation Biomarkers Consortium sponsored Ph2 program that enables rapid investigation of novel therapeutics in neo-adjuvant breast cancer. Importantly, this trial also facilitates the testing of easy to use biomarkers developed by OncoMed, to easily identify the subset of

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patients for whom the drug is most successful. This represents a fast track pathway for accelerated regulatory approval for effective agents for use in the adjuvant/neoadjuvant setting. The new pathway using the model development in the I-SPY trial was developed by a consortium of academic investigators (principally Dr. Esserman), industry, the NCI and the FDA and has been described in a recent article in the *Journal of the American Medical Association* (Esserman, L.J. and Woodcock, J. *Accelerating Identification and Regulatory Approval of Investigational Cancer Drugs*. JAMA. 2011. **306**, 2608-9.)

OMP-52M51 is part of our funded collaboration with GlaxoSmithKline (GSK) on the Notch pathway. The structure of our contract with GSK entails that we carry out initial pre-clinical and clinical development of two Notch antibodies, and GSK will move those two antibodies into late stage clinical development, choosing indications based on our early work. This award gives us the chance to have multiple shots on goal, and at this stage, this pre-selected triple negative, [REDACTED] patient population is at the top of that priority list. We have GSK's strong support for the development of OMP-52M51 in breast cancer as shown in the letter of support from Jason Gardner (Vice President, Head of Regenerative Medicine Discovery Performance Unit at GSK). We believe that there may have been a misunderstanding about the priority at OncoMed and GSK for developing OMP-52M51 for the treatment of breast cancer. We are making this appeal to clear up the misunderstanding about our partnership with GSK and to bring forward new information regarding the validation of Notch pathway in breast cancer.

Key points to consider regarding our application -

- We have a novel antibody therapeutic manufactured in commercial quantities targeting a key stem cell pathway
- This is a high priority program at OncoMed, supported by our collaboration with GSK, and we are filing an IND for OMP-52M51 next month, August of 2012, enabling us to enter clinical trials in September 2012. The filing of that IND secures a large milestone payment from GSK, providing specific funding for this Notch1 antibody.
- We have demonstrated that inhibition of Notch signaling with our antibody reduces cancer stem cell frequency in patient derived breast tumors
- Our data indicates that OMP-52M51 has superior efficacy and therapeutic index relative to other Notch antagonists in breast tumors with activated Notch signaling and OMP-52M51 is the first antibody targeting Notch1 to enter the clinic
- Through the I-SPY2 clinical trial network, we have identified [REDACTED] patient population that can be pre-selected through our biomarker test and who are in need of a new therapy and generated proof-of-concept data in pre-clinical studies
- We have developed a biomarker strategy to select patients who would benefit most from this therapy and have made significant progress in developing a clinically feasible diagnostic test
- Using this biomarker test, we have new data obtained after the submission of our proposal showing that a sizable proportion of triple negative breast cancer patients

display evidence of Notch pathway activation and we think it is feasible to conduct clinical studies in this indication

- Pre-clinical work indicates that Notch1 inhibition is more effective in this targeted population than inhibiting other stem cell pathways, thus we think we are in an excellent competitive position
- As stated in the Review Report "This collaboration between industry and academic researchers and clinicians appears to be ideally suited to such a project and the team is fully able to implement this study."
- We have a plan in place to achieve early clinical proof-of-concept in biomarker selected patients which could come in late 2013 or early 2014 and would fulfill CIRM's mission to bring stem cell-directed therapies to the clinic and to the market
- If we were to be successful in early clinical trials, we have the commitment from GSK to advance this program through clinical development and to commercialization. This indication is high priority on our collaboration because it utilizes a biomarker to pre-select a group of patients who have no other options: triple negative, chemo-refractory breast cancer patients who can be readily identified screened through the I-SPY2 clinical network.

We hope you will reconsider our application in light of this new data and our updates on the molecule's progress. We are flexible regarding the details of the proposed budget and will work with CIRM to resolve any issues. It would truly be a loss to the program if this promising application was not funded due to a misunderstanding of the priority and importance of this agent both to us and to GSK. This is especially true because the team we assembled has the capacity for rapid evaluation and has provided a path for accelerated approval of the agent if it should turn out to be successful.

Sincerely,

Timothy Hoey

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