Stanford University

PHILIP BEACHY, PH.D.
Ernest and Amelia Gallo Professor
Stanford University School of Medicine

October 5, 2018

Independent Citizens' Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650 Oakland, CA 94612
Principal Investigator: Philip Beachy, Ph.D.
Title: “Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer”
Application: **DISC2-11105**

Dear members of the ICOC:

I write in regard to our CIRM DISC2-11105 proposal "Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer.” To briefly summarize the status of our application, the scientific review was highly positive and ranked our proposal in a tie for 3rd position among forty-one applications. In July we were surprised to learn that our application was not selected for funding, whereas four proposals ranked below ours were funded. We have subsequently learned that an important component of the funding decision made by the ICOC is comments from scientists and patient advocates. We wish to have the opportunity to present our comments at the October 11 ICOC meeting, at which our proposal will be considered. Four scientists involved in this proposal will be attending the meeting, including myself (Philip Beachy, Ph.D.), Kyle Loh, Ph.D., Lay Teng Ang, Ph.D., and Joe Liao M.D., Ph.D. We are all researchers in the field of bladder cancer and stem cells, and Dr. Liao is a urologic oncologist who treats bladder cancer patients. Our publications on bladder stem cells and bladder cancer have been published in Nature (Shin et al. 2011), Nature Cell Biology (Shin et al. 2011), and Cancer Cell (Shin et al. 2011), and our papers on embryonic stem cell differentiation in Cell Stem Cell (Loh et al. 2014), Cell (Loh et al. 2016), and Cell Reports (Ang et al. 2018).

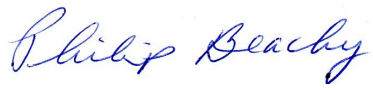
With regard to the application itself, in the time elapsed from the scientific review, we have made significant additional progress as follows: (i) we have found a relatively straightforward way to remove the pre-existing bladder lining (an important step that precedes transplantation) by instillation of an imidazolium salt synthesized and tested expressly for its exfoliation ability; and (ii) we have established a collaboration with three experts in information theory and machine learning from the Stanford Physics and Computer Science Departments to develop new computational tools capable of using single cell RNA sequence data to identify the extensive premalignant lesion that must be replaced for a definitive cure.

Finally, I would like to reiterate, as mentioned in the proposal itself, that bladder cancer represents an unparalleled opportunity to realize the potential benefits of stem cell therapy, both because of the suffering and morbidity that would be averted, but also because the bladder represents an accessible organ that is highly favorable for stem cell therapy approaches.

Stanford Institute for Stem Cell Biology & Regenerative Medicine, Stanford Cancer Institute,
Departments of Urology and Developmental Biology
279 Campus Drive, Lokey Stem Cell Building Rm G3120A, Stanford, CA 94305 T 650.723.4521 E pbeachy@stanford.edu

As an attachment I include here additional supporting letters from several bladder cancer patients, from the Bladder Cancer Advocacy Network (BCAN), and from The Greenberg Bladder Cancer Institute at Johns Hopkins. Please see also the supporting letter from Don Reed. Thank you for your consideration.

Yours sincerely,



Philip Beachy

Stanford Institute for Stem Cell Biology & Regenerative Medicine, Stanford Cancer Institute,
Departments of Urology and Developmental Biology
279 Campus Drive, Lokey Stem Cell Building Rm G3120A, Stanford, CA 94305 T 650.723.4521 E pbeachy@stanford.edu

July 26, 2018

California Institute for Regenerative Medicine
ICOC Board
1999 Harrison St., Suite 1650
Oakland, CA 94612

RE: Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer

Dear Members of the Independent Citizen's Oversight and Application Review Committee:

My name is Emilio P. Darpino (5275). I am writing in support of Dr. Beachy and Dr. Liao's proposal to develop a new definitive treatment for bladder cancer using stem cells.

I am registered at the VA Palo Alto Health Care System, where I receive all of my medical care. I was first diagnosed with bladder cancer in 2007. My diagnosis has fluctuated from low grade to high grade papillary non-invasive urethelial carcinoma. Over the past 11 years, I have had multiple cystocopies. My most recent TURBT surgery was on October 17, 2017. In 2011, I completed six weeks of BCG treatments, as well.

My quality of life, and that of others with bladder cancer, would be greatly improved by not having to have further urologic procedures if a cure for bladder cancer is achieved.

My heartfelt appreciation to Dr. Liao, his medical associates, and the staff members at the VA Hospital/Palo Alto, CA, is immeasurable.

Sincerely,

Emilio P. Darpino

(ECD/mld)
(*)

Vernon A. Brown, DDS
943 W. Carmel Valley Rd.
Carmel Valley, Ca 93924

California Institute for Regenerative Medicine
ICOC Board
1999 Harrison St., Suite 1650
Oakland, CA 94612

July 24, 2018

RE: Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer

Dear Members of he Independent Citizen's Oversight and Application Review Committee:

My name is Vernon Brown and I am writing in support of Dr. Philip Beachy and Dr. Joseph Liao's proposal to develop a new definitive treatment for bladder cancer using stem cells.

I have recently been treated for bladder cancer with the current day procedures of surgery and BCG treatments. In spite of these treatments, the recurrence rate for this cancer is very high. I will be required to have frequent follow-up cystoscopy appointments to make sure there are no recurrences.

My involvement with bladder cancer is very personal to me not only for my own experience, but from a personal friend who recently died from this cancer.

It is my greatest hope that there could be a definitive cure for this cancer that could help not only me, but many others.

Sincerely yours,

Vernon A. Brown

Vernon A. Brown, DDS

BCAN
Bladder Cancer Advocacy Network
Leading the way to awareness and a cure

September 13, 2018

California Institute for Regenerative Medicine
RCOC Board
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Re: Pleuripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer.

To Whom it May Concern:

On behalf of the Bladder Cancer Advocacy Network (BCAN), we write this letter in support of Dr. Philip Beachy's application to the California Stem Cell Research Program for his project, "Pleuripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer." This project, which focuses on the concept of using stem cells to replace the premalignant urothelium in patients with bladder cancer, addresses a tremendous need in the bladder cancer community.

BCAN is the first national non-profit organization devoted to advancing bladder cancer research and supporting those impacted by the disease. Through a comprehensive program of research, education and advocacy, BCAN is the leading voice for bladder cancer.

As outlined in Dr. Beachy's application, the burden of bladder cancer is significant and growing. Bladder cancer is one of the most common cancers, with a high risk of recurrence. In 2018 alone, it is estimated that more than 18,000 people will die from this disease.

A bladder cancer diagnosis has enormous physical, emotional, psychological and financial impacts on patients and their families. For patients with muscle invasive bladder cancer, there are limited approved medical treatments available, requiring the majority of those patients to undergo bladder removal and reconstruction of the urinary system. This is major life-transforming surgery, with significant potential for surgical complications and mortality.

We strongly support Dr. Beachy's proposal to investigate new stem cell transplantation-based therapy as a definitive cure for bladder cancer. This work has the possibility of altering the trajectory of this disease, allowing patients to live longer and with their natural bladders intact. BCAN believes that bladder cancer patients deserve better treatment options.

Sincerely,

Diane Zipursky Quale
Co-Founder

Andrea Maddox-Smith
Chief Executive Officer

4915 St. Elmo Avenue, Suite 202 • Bethesda, MD 20814 • 301-215-9099 • info@bcan.org • www.bcan.org

David J. McConkey, Ph.D.
Director, Johns Hopkins Greenberg Bladder Cancer Institute
Professor, James Buchanan Brady Urological Institute

Johns Hopkins Greenberg Bladder Cancer Institute
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Email: djmcconkey@jhmi.edu

JOHNS HOPKINS
MEDICINE

October 4, 2018

To whom it may concern:

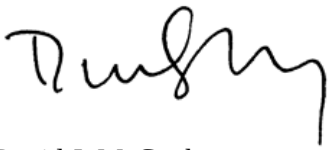
I write this letter as the inaugural director of the Greenberg Bladder Cancer Institute at Johns Hopkins Medicine in enthusiastic support of the research project described in Dr. Philip Beachy's CIRM application "Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer". The Johns Hopkins Greenberg Bladder Cancer Institute serves as the hub of an institutional and international community of researchers who share a commitment to advancing the scientific understanding of bladder cancer and improving its treatment.

One of the most challenging aspects of bladder cancer treatment is its frequent recurrence. Thus, even after successful cystoscopic excision of a tumor, the remaining cells of the bladder lining often give rise to new tumors, despite appearing normal at the time of surgery. Although radical cystectomy potentially represents a definitive long-term therapy, this treatment has significant lifestyle consequences and complication rates are as high as 60-70%. Local cyctoscopic excision, on the other hand, requires continual monitoring to reduce the risk of recurrence with progression to invasive disease.

Dr. Beachy's work has established that frequent bladder cancer recurrence is likely due to the presence of a precancerous lesion that extends well beyond the boundaries of the primary tumor, thus corrupting all or most of the bladder lining. His proposal, conceptually simple, is to replace the corrupted lining with pristine bladder lining cells as a way to prevent recurrence and provide a definitive cure. Dr. Beachy proposes to generate these pristine cells by differentiation of bladder lining progenitors from embryonic stem cells. He is uniquely positioned to execute this proposal given his strong collaborations with Dr. Joe Liao and other members of the Urology Department at Stanford and with Professor Kyle Loh and Siebel Investigator Lay Teng Ang, who are world-class experts in embryonic stem cell differentiation.

In sum, I would close by saying that the approach presented in this proposal represents the kind of visionary thinking that the field of bladder cancer needs. As a matter of fact, we tried to recruit Dr. Beachy as Scientific Co-director of the Johns Hopkins Greenberg Bladder Cancer Institute and a Bloomberg Distinguished Professor at Johns Hopkins, based on his previous work in bladder cancer and his record of innovative, basic and disease-relevant research. Although he elected for personal reasons to remain at Stanford, his commitment to developing a more effective bladder cancer therapy is clear, and I look forward to working with him in the future to achieve this goal.

Sincerely,



David J. McConkey
Director, Johns Hopkins Greenberg Bladder Cancer Institute