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November 15, 2021

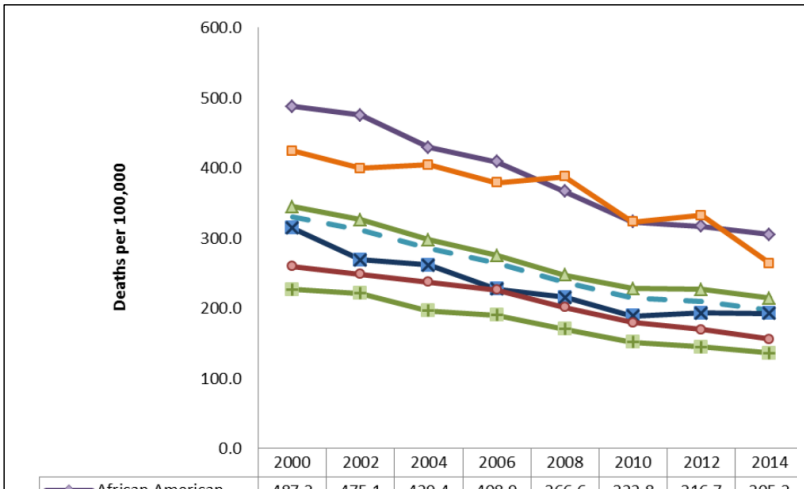
Re: Application Review Subcommittee Meeting for TRAN 1-12893 "Targeting Stromal Progenitors to Prevent the Development of Heart Failure"

Dear ICOC,

We are deeply grateful to CIRM GWG for recommending our above referenced grant proposal for funding. Reviewers agreed that the therapeutic product developed in this proposal "**would impact an unmet medical need"** with **"a novel therapeutic approach"** and **"inhibition of remodeling post MI would be high impact".** The GWG overwhelmingly (13/14 reviewers) considered the rationale to be sound and the proposal "**to be well planned and designed"**. The reviewers highlighted the "**resubmitted proposal to have a pathway forward for a successful pre IND meeting",** thus achieving a primary goal of the RFA.

***PROJECT IMPACT ON UNDERSERVED COMMUNITIES*:**

All of the GWG reviewers considered **the "project to serve the needs of the underserved community"** as "**MI and heart failure disproportionately impact the underserved communities"**. Reviewers considered the "**therapeutic product developed to be a cost effective measure"** and **"positively impact the underserved communities"**.



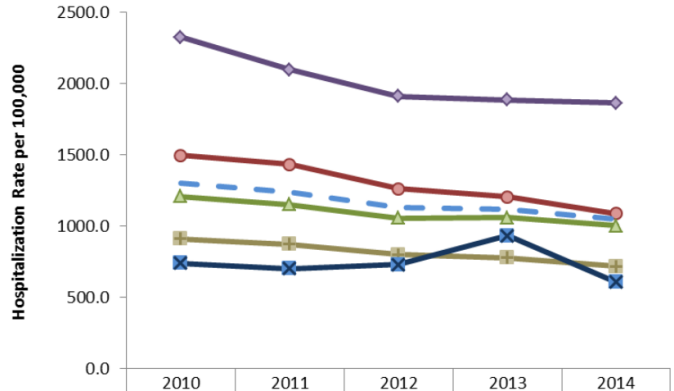
	2000	2002	2004	2006	2008	2010	2012	2014
African American	487.3	475.1	429.4	408.9	366.6	322.8	316.7	305.3
Pacific Islander	424.4	399.3	404.5	379.0	387.8	323.1	332.5	264.0
White (non-Hispanic)	344.9	326.3	297.8	275.1	247.6	228.4	226.8	214.5
California overall	329.7	312.0	285.0	264.9	237.5	215.1	210.2	197.6
Native American	314.6	269.3	261.8	227.7	215.4	188.7	193.2	192.6
Hispanic	259.9	248.4	237.6	226.5	201.3	179.7	169.9	156.4
Asian	227.0	221.1	196.2	190.0	170.1	151.7	145.0	136.3

Source: California Death Statistical Master File, 2000-2014

Fig 1. Age adjusted cardiovascular disease mortality by race/ethnicity in California (2010-2014).

Heart failure is the burgeoning epidemic of this century. More than 6 million individuals have heart failure in the United States alone and 700,000 individuals are newly diagnosed every year. **Once a diagnosis of heart failure is made, the 5 year survival is approximately 50%**. Myocardial infarction (heart attack) is the leading cause of heart failure and contributes to 40-70% of all cases of heart failure. In California, the statistics mirror the national average. Death from cardiovascular disease accounts for

one in three deaths in the state and over 8 million Californians have some form of heart disease that predisposes them to the development of heart failure. Moreover, in contrast to national trends where mortality from heart failure has declined from 2000-2014, **mortality secondary to heart failure has increased in California from 2000-2006.** The precise reasons behind this trend are not clear **but thought to be secondary to large disparities in health equity and socio-economic diversity in the state of California.** For instance, **death from heart failure and cardiovascular disease are substantially higher among African Americans and Pacific Islanders than other groups (Fig 1). Heart failure hospitalization rates are also the highest for African Americans and Hispanics (Fig 2).** Moreover, other common forms of heart failure such as hypertensive heart disease (addressed in this proposal as per reviewer suggestions) are also more common in African Americans (hypertension prevalence of 45-60%). **In addition to the health of the affected individual, heart failure significantly impacts the financial status of family members as valuable resources either need to be directed towards health care or in many instances, the affected individual is no longer able to maintain employment.**



	2010	2011	2012	2013	2014
African American	2324.6	2097.5	1911.7	1885.3	1863.1
Hispanic	1495.2	1434.9	1263.6	1205.7	1088.0
California overall	1303.6	1241.0	1130.6	1117.6	1049.7
White (non-Hispanic)	1209.2	1151.5	1056.5	1059.9	1003.4
Asian/PI	913.0	874.0	799.4	779.9	719.2
Native American	739.4	703.7	731.7	933.6	608.8

Source: California Office of Statewide Health Planning and Development, 2010-2014
PI = Pacific Islander

Fig 2. Heart failure hospitalization rates by race/ethnicity in California for those age >65 (2010-2014)

***COST-EFFECTIVE STRATEGY*:**

The therapeutic agent developed in this proposal will be used to treat both myocardial infarction as well as non-ischemic causes of heart failure such as hypertension. **As a single monoclonal antibody which can be injected at the time of diagnosis of myocardial infarction or shortly thereafter, this serves as a cost-effective measure to thwart the development of heart failure**. (Reviewers also commented on the strength of the cost-effective nature of the therapeutic product). **If heart failure can be prevented, the impact on the underserved community is immense both from a health as well as economic perspective**.

The GWG reviewers considered the resubmitted proposal to be highly responsive to reviewer comments. As per initial reviewer recommendations, we have included a hypertensive animal model, additional safety studies as well as a consultant with specific expertise in safety studies of monoclonal antibodies.

***EFFICACY OF THE PROPOSED APPROACH*:**

Reviewers commented on how the resubmitted proposal related to the **efficacy of the proposed therapeutic approach compared to current approaches.** Despite optimal medical therapy, almost 50% of individuals with heart failure will not live 5 years. We need innovative approaches to decrease mortality in heart failure and our therapeutic agent is in a position too achieve that.

***COST OF CURRENT THERAPIES*:**

The reviewers **mentioned that current approaches are relatively inexpensive**. Despite optimal medical therapy, heart failure remains one of the most expensive financial burdens on society. More than $30B is spent annually on the treatment of heart failure or heart failure related complications and one in 5 deaths have a diagnosis of heart failure. Moreover, a single dose of a monoclonal antibody

administered at the time of diagnosis of MI to prevent heart failure would be cost effective as it would attenuate or prevent the development of heart failure and minimize costs related to repeated hospitalizations and complications.

PREVENTION OF HEART FAILURE: THE TRANSLATIONAL SIGNIFICANCE OF OUR PRODUCT:

Myocardial infarction contributes to 40-70% of all cases of heart failure and our therapeutic product by preventing the development of heart failure from its most common cause will thus significantly impact the incidence of heart failure.

In summary, heart failure is a disease of gargantuan significance and new therapies are desperately needed. It ravages our underserved communities and minorities physically, mentally and financially. The therapeutic product developed in this proposal will prevent the development of heart failure after heart attacks and thus be of immense significance and impact to our communities. We are deeply appreciative of the GWG recommendations and enthusiasm for our proposal and we are committed to bringing this therapeutic approach to the people of California and beyond.

Sincerely,

Arjun Deb, MD
Professor of Medicine
David Geffen School of Medicine, UCLA