**Additional Information for the CIRM ICOC Members regarding CLIN-2 11371:**

Angiocrine Bioscience greatly appreciates CIRM GWG's thorough review of our grant proposal CLIN-2 11371. As mentioned on the first page of the GWG Review, we believe AB-205 (engineered human *E4ORF1*$^+$CD31$^+$ cells derived from umbilical cords after healthy deliveries, a.k.a. E-CEL UVEC® cells) has the potential to be highly impactful to many patients in California and beyond. To remind members of the Application Review Subcommittee, E-CEL UVEC cells have already been administered to human subjects as part of AB-110, which combines matched cord-blood stem cells with E-CEL UVEC cells, the latter as ex vivo and in vivo supportive cell component for the stem cells. AB-110's pre-clinical studies and its Phase 1b clinical trial (to treat subjects with life-threatening blood cancers) were both generously supported by CLIN-1 and CLIN-2 grants from CIRM.

**The potential greater impact of AB-205 in cancer care beyond advanced lymphoma:**

We all know someone who has gone through tremendous misery undergoing chemotherapy and/or radiotherapy cancer treatments in hopes of achieving a cure. What is less known is that there are countless cancer patients who are not even offered the chance for a cure because the proven curative therapy is too harsh for them.

We at Angiocrine Bioscience want to change this paradigm for the better. Scientifically, it is well established that the same mechanism of chemotherapy and/or radiation to eliminate cancer cells also cause death of healthy cells, especially rapidly dividing cells (e.g., gastrointestinal tract, bone marrow). Despite emergence of novel targeted therapies including CAR-T therapy, many advanced cancers still can only be reliably cured by powerful but broad cytotoxic effects of high-dose chemotherapy (HDT). HDT in particular is very good at eliminating resistant cancer cells but also cause extensive collateral damage to healthy tissues. The bystander effect of HDT also damages the normal mechanism for health tissues recovery. The place where recovery starts in most tissues is known as the stem cell vascular niche. Thus, in effect, anti-cancer treatment disables the normal recovery process in patients, which drives the severity and length of misery.

Angiocrine scientists have discovered that human engineered endothelial cells (i.e., E-CEL UVEC) cells can act both as temporary players of the vascular niche in tissues and heal the vascular niche as well. If the normal recovery process can be re-established quickly and effectively, it may translate for patients to experience a much shorter and/or substantially less severe misery. In addition, quicker recovery might translate to shorter hospital stays providing an economic benefit to our healthcare system. Importantly, less patients would be turned away for a chance of a cure.

In new therapy development, especially in oncology, it is necessary to start small in a specific patient group even though the eventual goal might be highly impactful and wide ranging. Although our ultimate aim is for oncologists to employ AB-205 for any cancer patient with risk for severe toxicities from chemotherapy or radiotherapy, we need to pick the first study population.

Cancer experts we consulted unanimously suggested we study AB-205 in a smaller population with the greatest unmet medical need such as patients with recurrent or refractory lymphoma undergoing

high dose therapy and autologous stem cell transplantation (HDT-ASCT). ASCT is given to rescue the bone marrow because the HDT wipes out the marrow cells. These patients experience frequent (>80%) and multiple (at least 3) severe adverse events from the toxicity of HDT. Despite the harshness of the treatment, HDT-ASCT is the standard-of-care therapy given with curative intent for patients with refractory or relapsed lymphoma.

The main goals of the first-in-human trial are to establish initial safety and determine the recommended dose of AB-205 for later stage clinical trials. Once these goals are achieved, the results from the study will be the foundation that enables initiation of confirmatory Phase 2 and 3 efficacy studies for a broad clinical development program across multiple clinical indications where HDT or radiation are utilized. These indications may include all of autologous (e.g., multiple myeloma) and allogeneic hematopoietic stem cell transplantation for multiple hematologic and some solid malignancies, as well as severe autoimmune disorders and other severe conditions which can be cured via induction chemotherapy and/or radiation and transplantation.

In summary, the current proposal might appear to affect only a small segment of cancer patients receiving a specialized therapy. However, in the development of an innovative cancer care treatment, we are obligated to start with a selective group of patients to ensure minimum risk and maximum safety, even though the ultimate impact of novel therapy on cancer care might be large and broad.

**Additional information about the proposed mechanism of action of AB-205:**

We believe E-CEL UVEC cells work in two major ways: via a paracrine mechanism and cell-to-cell contact. Both mechanisms have been detailed to a molecular level in studies looking at the interaction of our cells with blood stem cells as well as mRNA sequencing. Multiple factors, called angiocrines, are involved and the mixture of the factors depend on the tissue and its physiologic status such as healthy versus injured versus diseased. Because of the dynamic and physiological release of factors, we have chosen to focus more on the outcome of the E-CEL UVEC cells *in vivo* versus elaborating on molecular, *in vitro* data, which may describe elements of the mechanism of action unique to E- CEL UVEC cells.

**Update on Manufacturing Plans of AB-205:**

As part of GMP qualification runs which were necessary to gain successful IND clearance by the US FDA, Angiocrine has already manufactured AB-205 investigational product that can be used for treatment of the first few patients in the trial, AB-205-001. Finally, Angiocrine has already manufactured GMP grade vector that will provide sufficient material for the entire AB-205 clinical trial. We have scheduled our next clinical manufacturing campaign to occur in January of 2019 with the hopes of being awarded this proposed CLIN-2 grant.

**Update on Clinical Sites for AB-205-001:**

Angiocrine Bioscience continues to be on schedule to operate under the timelines of the Gantt Chart submitted to CIRM via the CLIN-2 proposal and plans on working with the CIRM Alpha Stem Cell Clinic Network.