SAM LAI

TITLE: PRECLINICAL DEVELOPMENT OF A POTENT MUCO-TRAPPING ANTIBODY AGAINST SARS-COV-2 FOR INHALED IMMUNOTHERAPY AND PROPHYLAXIS AGAINST COVID-19

PRINCIPAL INVESTIGATOR: **Sam Lai**

PROJECT SUMMARY

We propose an integrated research program with three independent tracks (Aims) designed to quickly advance into the clinic, before year's end, a highly potent neutralizing monoclonal antibody (mAb) against SARS-CoV-2. This mAb, engineered by the Lai Lab, binds bivalently both to the intra- and inter-spike on the virus, and thereby neutralizes and traps in mucus with exceptional potency. In turn, our mAb actively clears the virus from infected lungs, and when given to patients diagnosed with COVID-19, should effectively prevent the spread of the infection within the lung and reduce hospitalization. The same approach against a similar respiratory virus in lambs was highly effective in preventing lung inflammation, even when dosed only after near peak viral titers.

Aim 1A seeks to complete IND-enabling development of inhaled therapy based on this unique antibody, specifically on GLP nebulization characterization and stability using Philips 510k-approved InnoSpire Go nebulizer. This effort is currently unfunded. Other aspects needed for IND, together with a Phase 1/2A study, will very likely be funded by the Department of Defense (~$4.75M, received intent to fund letter), with IND filing scheduled for October and human studies by November. This activity will directly culminate in a 6-site, 88-patient Phase 1/2A study.

In parallel (**Aim 1B**), we are seeking support to initiate the development of a production cell line for scalable GMP manufacturing of our molecule (to support Phase 3 studies and beyond), which must be initiated now in order to be ready for a large follow on clinical trial by Fall 2021, should the Phase 1/2A study be positive. This capability is critical to allow us to scale to treating tens of thousands of patients. Starting the development after Phase 1/2A results will delay treatment for thousands of patients for at least a year.

The **second Aim is to advance a systemic immunoprophylaxis for high risk patients**, specifically engineering mAbs with extended circulation kinetics and testing in primates whether adequate amounts of antibodies can extravasate into the lung airways to enable protection. We will then seek federal support to complete the primate studies for biodistribution and pharmacokinetics assessment. The proposed work will guide molecule selection, followed by preclinical development, with anticipated IND by Spring 2021. This activity will advance a new prophylactic candidate molecule and provide pivotal data for bringing in the necessary funding of ~$5M to advance into clinical development.

The **third Aim is to advance a novel vaccine candidate based on genetically editing circulating B-cells to express this highly potent neutralizing mAb**, a technology which the lab has been developing over the past 18 months. This approach bypasses traditional limitations of vaccines (induction of antibody with limited potency, poor elicitation of antibody response in elderly, slow duration to developing antibody response). This builds on an existing effort between the Lai Lab and Victor Garcia-Martinez to harness the same approach to develop a vaccine for HIV. We will focus on establishing *in vitro* proof-of-concept and seek external support to advance *in vivo* studies. This activity may advance a vaccine candidate that can tune the immune response with genetic precision. The work will provide *in vitro* proof-of-concept, providing valuable data for seeking further external support.

IMPACT TO THE STATE

My lab has developed an antibody platform that actively clears viruses from infected lungs, and also engineered a unique antibody against COVID-19 that can bind the virus with exceptional potency. When given to patients when they are first diagnosed with COVID-19, we believe that our treatment can effectively prevent the virus from spreading in the lungs, eliminate lung damage, and minimize hospitalization. We have validated this approach in large animal models (lambs) against similar respiratory viruses. If similarly effective in humans, our therapy will greatly reduce death rates associated with COVID-19 patients (particularly among vulnerable populations), and reduce the need for state-wide shutdown and possible overwhelming of the healthcare system by directly decreasing hospitalization rates.

We are seeking to advance our therapy into the clinic as soon as possible (by late 2020). We are in the final stages of negotiation with the Medical Technology Enterprise Consortium, an offshoot of the Department of

Defense, which will fund all clinical trial costs (Phase 1A/2 study in 88 patients in six sites) and a bulk of the production of clinical trial materials. However, the funding available (~$4.75M) does not cover all of the work needed to start clinical trials (we are missing GLP nebulization characterization). It also does not cover development of scalable GMP manufacturing needed to quickly advance into Phase 2B/3 trial should our Phase 1A/2 study prove to be successful (topline results available March '21). The bulk of the funding we request here would help complete the work needed to tackle these two specific challenges that must be met to quickly advance this inhaled therapy into the clinic and eventually into thousands of patients in NC. To fast track this development, we are utilizing, wherever practical, commercial vendors who can perform the work at the quality required for FDA regulatory filing and clinical trials.

MILESTONES

August 31, 2020 Milestones

(1) Execute GLP nebulization characterization study. This work will be performed at Philips Research Labs, which will then ship specimens back to the Lai Lab at UNC to complete the characterization, evaluating (i) the ability to trap in human airway mucus, and (ii) neutralize COVID-19 *in vitro*.
(2) Complete engineering antibodies that are suitable for use as (i) prophylaxis, and (ii) systemic therapy for treatment of late-stage infections. We will produce our antibody with different FcRn affinity and effector functions, and characterize their ability to trap the virus in human airway mucus and neutralize the virus. We will seek external funding (e.g. NIH) to evaluate the biodistribution and pharmacokinetics of our engineered Abs in non-human primates.

December 31, 2020 Milestones

(1) Complete the analysis of GLP nebulization characterization study (anticipated by September 30 for IND filing in October)
(2) Complete initial cell line development, where our antibody will be produced in cGMP-compliant CHO cells while maintaining their muco-trapping and neutralization potencies.
(3) Complete proof-of-concept that we can induce B-cells to secrete our engineered antibody against COVID-19. If successful, this would be a method to vaccinate people to ensure that they can produce our antibody with genetic precision.

BUDGET JUSTIFICATION

To fast track development, we are utilizing commercial vendors who can perform quality work needed for FDA regulatory filing and clinical trials. This includes GLP nebulization characterization (executed by Philips Research Labs) and cGMP cell line development. Work with both projects is to validate that antibodies retain their muco-trapping/neutralization potencies. The other two projects will be executed at UNC.

Personnel ($132,287)
Samuel Lai, **PI** (12% effort) will manage the project and monitor its progression and completion
Whitney Wolf, Research Associate (100% effort) will work on studies in Aim1A
Karthik Tiruthani, Post-doctoral Researcher (75% effort) will be involved in work proposed in Aim 1B
Carlos Cruz-Teran, Post-doctoral Researcher (100% effort) will perform experiments related to Aim 2
Jasmine Edelstein, Graduate Student Assistant (100% effort each) will work on Aim 3

Materials and Supplies ($130,000)
Aims 1A and 1B: $40,000 each
Aim 2: $40,000
Aim 3: $10,000

Contracted Services ($495,000)
Production of GMP materials for GLP nebulization studies (Aim 1A): $80,000
GLP Nebulization Characterization (Aim 1A): $120,000
Cell line development (Aim 1B): $295,000

Tuition/fees ($6,065)
For Graduate Student

Other Costs $35,000
UNC Core Facility fees ($10,000 each for Aims 1A, 1B, and 2; $5,000 for Aim 3)