Statement of Work

Proposal Number: MTEC-20-09-COVID19-029

Organization: Lumen Bioscience, Inc. (Seattle, WA)

Title: COVID-19 Rapid Response (b) (4) : Rapid, scalable, and inexpensive (b) (4) for treating G.I. symptoms of Covid-19 and blocking transmission

ACURO and/or HRPO Approval: Approval should not be required from ACURO: As noted in Section Error! Reference source not found.~~2.5.1~~(c) of the Enhanced White Paper, well-validated animal models of SARS-CoV-2 infection have not yet been reported. HRPO approval will be required for the assessment of GI proteolytic stability described in Task 1(c).

EGS #: MT20009.029

Introduction/Background

Reducing viral burden. The most recent data found that a majority of non-hospitalized Covid-19 patents had both GI and respiratory symptoms, and 25% had only GI symptoms[1]. Historically, 25% of MERS cases[2] and 16-73% of SARS cases in 2002-2003[3] presented with significant gastrointestinal distress. SARS-CoV-1 is able to replicate in the GI tract and live virus can be isolated from stool samples[4]. SARS-CoV-2 shares these characteristics. Both use the ACE2 receptor, which is expressed on intestinal epithelial cells at levels nearly 100 times greater than on respiratory epithelial cells[5]; capsid proteins from SARS-CoV-2 has been identified in GI epithelial cells from Covid-19 patients[6]; viral RNA is present in rectal and stool samples in 53% of hospitalized patients and detected in stool samples in 23% of patients after respiratory symptoms have resolved and nasopharyngeal swaps test negative[6,7]. SARS-CoV-2 also clearly infects GI tissues of the best available animal model, shedding live virus in the stool[8]. In populations with weakened immune systems (e.g. the elderly) GI colonization may result in self-infection of the airways. The systemic inflammatory response associated with GI infection may exacerbate pulmonary disease. (b) (4)
(b) (4)

Blocking transmission. The Amoy Gardens SARS super-cluster was traced to faulty engineering that enhanced fecal-oral transmission[9]. Very high amounts of SARS-CoV-2 viral RNA are present in stool samples[6], even in patients who never suffer any respiratory symptoms[1]. Like norovirus, Covid-19 outbreaks occur on cruise ships and in nursing homes[10], where the risk of fecal-oral transmission is especially high. Similarly, a US aircraft carrier was recently forced to return to port after a Covid-19 outbreak, demonstrating the implications of the disease for operational readiness[10].

Therapeutics and preventatives to treat this documented route of infection, this reservoir of ongoing viral disease and potential means of transmission should not be overlooked. (b) (4) . ***Lumen Bioscience***
(b) (4)

Scope/Project Objective

The **objective** of the proposed project is to use Lumen's (b) (4)
(b) (4)
(b) (4)

A **complete solution** to Covid-19 will require a multifaceted response, including social control measures, small molecule therapeutics, traditional vaccines, and the product proposed here: (b) (4)
Lumen's (b) (4)
(b) (4)

Requirements

Lumen (b) (4)
(b) (4) Lumen's (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

The project is divided into three phases as follows.

Phase 1: Development of lead anti-SARS-CoV-2 (b) (4)

The objective of Phase 1 of this project is to finalize (b) (4)
(b) (4) ***and IND preparation.***

Task 1(a): Improved versions of (b) (4)

A VHH discovered by the McClellan team[17] was raised against the SARS-CoV-1 RBD and then shown to bind with high affinity to the SARS-CoV-2 RBD due to conservation of the epitope (Kd=39 nM). This epitope differs between SARS-1 and SARS-2 by only a single amino acid (Arg426->Asn). A dimeric version of this VHH neutralizes SARS-CoV-2 in a pseudovirus infectivity assay.

(b) (4) Lumen, (b) (4)
Lumen (b) (4)
. (b) (4)
(b) (4)
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(b) (4)

(b) (4)

Figure 6. Lumen (b) (4)

Task 1(b): (b) (4)

To augment this collection of (b) (4) Lumen (b) (4)

(b) (4)

(b) (4)

(b) (4) Lumen's (b) (4)

(b) (4)

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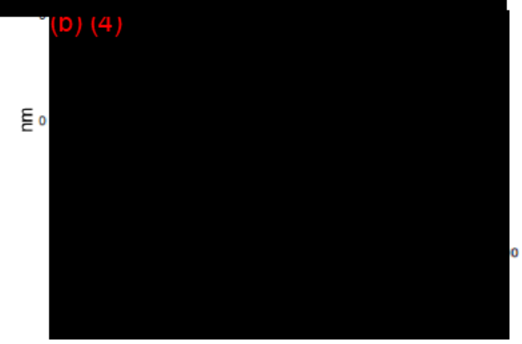
Task 1(c): [redacted]

[redacted] Lumen [redacted]



[redacted] Lumen

[redacted]

[redacted], Lumen [redacted]

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(b) (4)

Phase 2: (b) (4)

The objective of Phase 2 of this project is to (b) (4)

Task 2(a): (b) (4) (b) (4)

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Lumen's (b) (4)

Lumen (b) (4)

(b) (4)

(b) (4) Lumen's (b) (4)

(b) (4)

(b) (4)

(b) (4)

, Lumen (b) (4)

(b) (4)

(b) (4)

In response to reviewer comments, Lumen has considered additional risk mitigation strategies related to drug development in (b) (4)

Additional Risk Considered	Likely?	Mitigation Strategy
(b) (4)	(b)	Lumen (b) (4)

Additional Risk Considered	Likely?	Mitigation Strategy
		(b) (4) , Lumen (b) (4)
(b) (4)	(b)	(b) (4) Lumen's (b) (4) Lumen (b) (4)

Task 2(b): FDA pre-IND briefing

FDA staff previously reviewed detailed briefings from Lumen that described all elements of the (b) (4) (b) (4) contemplated by this proposal. The FDA staff concurred in all material respects with Lumen's proposed development plan, which means that there is little remaining regulatory risk to be cleared in a pre-IND meeting.

However, to de-risk subsequent development, it would be best to brief the FDA staff on the clinical plan for Lumen's anti-Covid-19 therapeutic. Consequently, during Phase 2 of the project, Lumen's Chief Medical Officer, working with the Lumen project management team, internal quality team, and external regulatory consultants at (b) (4)), will develop a Phase 2 clinical trial synopsis, CMC quality plan, and other elements required for a formal pre-IND meeting under the Prescription Drug User Fee Act (PDUFA). This briefing package will be submitted following a request for a formal pre-IND meeting under PDUFA, including a request for expedited scheduling. A pre-IND meeting will be held if granted by the FDA, however this is not expected given the anticipated lack of novel issues in Lumen's pre-IND briefing package. The costs associated with preliminary planning for the planned Phase 2 study and development of the clinical trial synopsis are included in this Task 2(b), as such materials will need to be included in the pre-IND briefing package. The team will meet in person with MIDRP personnel during this phase to review program status.

The FDA's written responses (and, if a meeting is granted, the pre-IND meeting minutes) will guide development of the IND application in Phase 3 of the proposed project.

Phase 3: IND application, and scale-up planning activities

The objective of Phase 3 of this project is to (b) (4)

(b) (4)

Task 3(a): FDA IND application

All studies required for FDA IND submission will be performed: (b) (4)

(b) (4)

scale under cGMP conditions; lot-release assay qualification, shelf stability testing, and other CMC (b) (4) (b) (4) (b) (4) Lumen's (b) (4) (b) (4) (b) (4) This task of the work plan incorporates the written guidance previously provided to Lumen by the FDA in Lumen's pre-IND meeting for (b) (4). The budget likewise derives from Lumen's prior real-world experience carrying out such activities.

Study	Purpose	IND Module
Pre-clinical efficacy & safety studies		
(b) (4)	(b) (4)	3.2.S.4.2
(b) (4)	(b) (4)	3.2.S.3.1, 3.2.S.4.2
(b) (4)	(b) (4)	2.6.6.8, 4.2
(b) (4)	(b) (4)	3.2.S.3, 2.6.4
(b) (4)	(b) (4)	5.3
Pre-clinical development studies		
(b) (4)	(b) (4)	3.2.S.2
(b) (4)	(b) (4)	2.6.4, 4.2, 3.2.P.4
(b) (4)	(b) (4)	3.2.S.2
(b) (4)	(b) (4)	3.2.S.3
(b) (4)	(b) (4)	3.2.S.2.6
(b) (4)	(b) (4)	3.2.S.4.2, 3.2.S.4.3, 3.2.P.4.2, 3.2.P.4.3

Table 1. IND enabling studies required by FDA for products on the Lumen platform that are similar to that proposed here.

In brief, Lumen anticipates that the IND will describe a Phase 2 efficacy trial that includes some or all of the following endpoints: (b) (4) . (b) (4) (b) (4) The length of exposure to may be varied after results of an initial 10-day treatment. We anticipate collaboration with the network of C-19 investigators already in place in (b) (4), where Lumen is

headquartered: The Public Health Laboratories of the (b) (4), the (b) (4); the Division of Allergy and Infectious Diseases, (b) (4); the Vaccine and Infectious Disease Division, (b) (4). The costs associated with preliminary planning for this study and development of the clinical trial synopsis are included in Task 2(b) (pre-IND briefing), as such materials will need to be included in the pre-IND briefing package. In response to reviewer comments indicating concerns regarding the risk of (b) (4), a portion of the FDA engagement work stream has been advanced to Task 1. In this preliminary FDA work, Lumen will meet with the FDA to discuss the (b) (4) and (b) (4) with FDA staff under a PDUFA "Type C" meeting. This will further de-risk the CMC elements of the IND submission, leaving additional time to respond to any FDA concerns, and streamline the standard PDUFA "Type B" pre-IND meeting to be held a few months later, allowing it to focus closely on the clinical trial design (see Task 1(a) above).

Costs associated with full protocol development and establishing the contractual arrangements required to initiate the study immediately following FDA clearance of the IND are included in this Task 3(a) as such activities will need to be completed prior to IND submission in order to avoid delays in trial initiation. All such cost estimates were developed by referencing Lumen's actual costs incurred in similar previous drug development programs.

Task 3(b): Scale-up preparatory activities

Working with (b) (4), Lumen will conduct a detailed review of current process status and establish a detailed scope of work for an engineering partner firm including vendor qualification process, establishment of site selection criteria, engineering milestones, preliminary engineering and permitting schedule and provisional budget.

Lumen will conduct a vendor selection process with several prospective FEED partners to identify a suitable partner. Once a partner has been selected and contracted, the FEED partner will work with Lumen engineering staff to finalize site and facility requirements and initiate preliminary engineering work, including process equipment specification and costing, detailed infrastructure requirements, mass & energy balances, etc. The FEED partner will work under supervision of Lumen staff and (b) (4) to identify appropriate available facilities in (b) (4) (b) (4) and conduct suitability analysis. For a limited subset of suitable facilities, preliminary site engineering work will be conducted, including determination of infrastructure improvements required, initial interaction with local officials, physical plant layout, and related work. As FEED work is completed, Lumen will initiate selection of a construction partner to conduct final facility build-out.

As initial FEED sizing work is completed, facility drying capacity and light supply requirements will be available. Because of the long lead time for acquisition of these specialized pieces of equipment, Lumen will initiate purchase and pay initial order deposit on the (b) (4) (after initial go/no-go in September 2020) and (b) (4) (after final go/no-go in January 2021) to ensure the facility can be commissioned and enter service in mid-2021.

At the end of Task 3(b), Lumen and its partners will have selected a preferred site and up to three backup sites, have developed a fully vetted process layout, procurement plan, infrastructure, and permitting requirements ready for initiation of construction.

Deliverables

1. A report (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
2. A report describing a submitted FDA IND application covering a Phase 2 clinical efficacy trial.
3. A report describing timelines and budget for the commercial scale cGMP manufacturing scale-up.

Key References (full references available upon request)

(b) (4)
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Milestone Schedule

Milestone Number	Task No.	Event	Due Date	Government Funds	Cost Share	Total Funding
1	n/a	Project kickoff	6/1/2020	(b) (4)	-	$ 20,000
2		Q2 Report (May-June Technical & Business Reports)	7/25/2020	-	-	-
3	1(a)	Improved versions of lead (b) (4)	7/31/2020	(b) (4)	(b) (4)	(b) (4)
4	1(b)	Isolate and characterize new (b) (4)	8/31/2020	(b) (4) ~~90~~	(b) (4)	(b) (4)
5	1(c)	Evaluate and select final therapeutic (b) (4)	9/30/2020	(b) (4) (b) (4)	(b) (4)	(b) (4)
6	-	Go/no-go-decision #1	9/30/2020	-	-	-
7	3(b)	Key long-lead equipment order payment (b) (4))	9/30/2020	-	(b) (4)	(b) (4)
8	-	Preliminary report describing fina (b) (4)	10/15/2020	-	-	-
9	-	Q3 Report (July-Sept. Technical & Business Reports)	10/25/2020	-	-	-
10	2(a)	Build and select final set of therapeutic (b) (4)	11/30/2020	(b) (4)	(b) (4)	(b) (4)
11	2(b)	FDA pre-IND briefing (PDUFA)	11/30/2020	(b) (4) (b) (4)	(b) (4)	(b) (4)
12	-	Report describing commercial cGMP plant timeline and budget	12/31/2020		-	-
13	-	Outside deadline for final go/no-go decision	1/31/2021	-	-	-
14	3(a)	FDA IND application submission	1/31/2021	(b) (4) (b) (4)	(b) (4)	(b) (4)
15	3(b)	Key long-lead equipment order payment (b) (4))	1/31/2021	-	(b) (4)	(b) (4)
16	3(b)	Report describing commercial cGMP plant timeline, budget	1/31/2021	(b) (4) (b) (4)	-	(b) (4)
17	-	Report describing submitted IND application	1/31/2021	-	-	-
18		Q4 Report (Oct-Dec Technical & Business Report)	1/25/2021			
19	-	Final technical report (within 60 days of completion of work)	3/31/2021	-	-	-
20		Final business report (within 90 days of completion of work)	4/30/2021	-	-	-
		Total		$3,376,609~~3~~ ~~93,329~~	(b) (4) (b) (4)	(b) (4) (b) (4)