F. M. KIRBY FOUNDATION SOLICITATION EVALUATION FORM

DATE: August 9, 2024 **REQUEST DATE:** July 22, 2024
Program Area: Health
Grant Type: Board Grant

APPLICANT:
Cold Spring Harbor Laboratory
One Bungtown Road
Cold Spring Harbor, NY 11724

CONTACT: Mr. Bruce Stillman, President & Chief Executive Officer

AMOUNT REQUESTED: $250,000
BUDGETED AMOUNT: $125,000

NATURE OF REQUEST: Support of the Chemistry for Biology Program at CSHL

GRANT HISTORY

SUPPORT: 2006-2023

 # OF APPROVED GRANTS: 15 **TOTAL DOLLARS:** $1,620,000

LAST GRANT DATE: 09/15/2023 **LAST GRANT AMOUNT:** $120,000

FYE DATE: 12/31 **AFS DATE:** 05/01/2024

Year Approved	Approved Amount	Approval Date	Grant Purpose
2023	$120,000	09/15/2023	Support of research in the lab of Dr. John Moses
2022	$115,000	09/12/2022	Support of research in the lab of Dr. John Moses
2021	$115,000	09/13/2021	Support of research in the lab of Dr. John Moses
2020	$115,000	06/30/2020	Toward the purchase of a Nuclear Magnetic Response (NMR) machine
2019	$100,000	04/15/2019	Toward construction and outfitting of an organoid testing facility

LAST SITE VISIT DATE: September 9, 2021

APPLICANT: Cold Spring Harbor Laboratory

ENDORSEE: N/A

FINANCIAL ANALYSIS COMMENTS: The FY24 budget is projecting a $2.1M operating deficit, which includes capital expenditures and an anticipated $3.4M draw from cash reserves. The net deficit for laboratory operations is expected to grow by nearly 68%, thanks to a 5% expected increase in expenses and a marginal decrease in income. FY23 saw a $1.2M deficit across all divisions and a $10M laboratory operations deficit. While still lagging behind FY19 figures, FY23 saw the highest laboratory income since the onset of the pandemic, $140M, which represented a 4% increase since FY20. The 2023 FMKF grant of $120K represented 0.5% of laboratory individual and foundation support. As of December 31, 2023, CSHL had $1.4B in total assets, $19M of which was cash and $766M of which was investments. Net assets without donor restrictions totaled $327M. Net assets increased by $149M in FY23, thanks to an $80M operating surplus (not including capital expenses) and $68M in investment income. CSHL had $33M in assets available for expenditure within one year. The organization is paying off bonds from 1999 and 2006, both used to finance construction costs. Total bonds payable at the conclusion of FY23 were $96M. Endowment funds total $781M. Program expenses represented 71% of total expenses.

ORGANIZATION DESCRIPTION: Cold Spring Harbor Laboratory (CSHL) addresses critical needs in biological research. The organization works to advance our understanding of fundamental life processes and develop innovative solutions for human health and environmental challenges.

CSHL serves a diverse population, including researchers, scientists, students, and educators from around the world. Its educational programs serve learners ranging from middle school students to postdoctoral researchers, fostering scientific literacy and cultivating the next generation of scientific leaders.

While CSHL's main campus is located on Long Island, New York, its impact is global. The institution hosts thousands of scientists annually for Meetings and Courses at its New York campus and its facility in Suzhou, China. Through its research publications, collaborations, and educational outreach, CSHL's influence extends worldwide, contributing to scientific advancements that benefit populations across the globe.

GINA BEVIGLIA COMMENTS: At Cold Spring Harbor Laboratory (CSHL), the Moses Laboratory is the first and only synthetic chemistry research group. As a biology-focused institution, CSHL benefits immensely from the presence of Dr. John Moses, a renowned click chemist, who promotes advanced scientific investigation made possible by the pairing of chemistry and biology. The Moses Lab’s research is focused on synthesizing new molecules that can serve as treatments for diseases that are typically unresponsive to traditional therapies. They do this with a method known as click chemistry, in which different elements of naturally-occurring molecules with disease-fighting properties are “clicked” together to create more potent derivatives. This research can be more easily transferred to clinical applications through the marriage of the Moses Lab’s synthetic chemistry work and CSHL’s extensive biology resources. This symbiosis has an even larger impact through the Chemistry for Biology program (C4B). C4B, founded by Dr. Moses in 2022, aims to educate and train the next generation of scientists with an understanding of the importance of merging chemistry and biology to achieve life-saving scientific breakthroughs. To expand the international scope of the C4B program’s principles while continuing the rigorous

scientific investigation occurring in the Moses Lab, CSHL is requesting a two-year grant of $250,000.

In recent years, the Moses Lab has been researching the potential for naturally-occurring chemical compounds known as natural products to become targeted therapies. Some natural products, like one known as jerantinine A, demonstrate unique disease-fighting properties. Through the deployment of click chemistry, the Moses Lab can refine these natural products to become even more potent and targeted. The research on jerantinine A has shown that a novel derivative of the compound created in the Moses Lab is particulary effective at targeting triple-negative breast cancer, one of the most dangerous forms of the disease. Similary, using a newly-identified vulnerability in pancreatic ductal adenocarcinoma, the Moses Lab created a derivative of a natural omega-3 fatty acid that can target this vulnerability. This discovery has the potential to revolutionize the treatment of pancreatic cancer, a diagnosis with one of the lowest five-year survival rates. Finally, while much of the natural product research being done in the Moses Lab is centered on cancer treatment, Dr. Moses has also discovered a way to "shapeshift" common antibiotics with click chemistry that make them once again effective against resistant bacteria, like MRSA. I am inspired by how the research we are supporting at institutions like Memorial Sloan Kettering so closely impacts the work being done at CSHL. Dr. Parada of MSK is working to genomically profile a dangerous form of brain cancer in an attempt to identify potential vulnerabilities in the cancer. The identification of a cancer's vulnerabilities, like the recently discovered pancreatic cancer vulnerability, allows a chemist like Dr. Moses to develop a compound that could be used as a new therapy. This demonstrates the important role of CSHL's interdisciplinary approach in the broader scope of the pipeline to cures.

Over the course of the next two years, the Moses Lab is committed to advancing the development of natural products and broadening their application. As mentioned previously, the compounds being studied have disease-fighting properties naturally, but require synthesis via click chemistry to become more effective and safe. In a similar way, click chemistry can be utilized to make the effects of these compounds more permanent and targeted. While many drugs interact with their therapeutic targets in a reversible fashion, molecules called covalent drugs can form irreversible bonds. Additionally, covalent drugs are more specialized, meaning that they do not interact with non-targets and cause potentially harmful side effects. In the process of creating jerantinine A derivatives, the Moses Labs discovered a new mechanism of action: the jerantinine A derivative covalently reacts with a protein known as KRAS, which mutates to cause aggressive cancers like non-small cell lung cancer and pancreatic cancer. In other words, this natural product derivative has the positive elements of permanence and specificity that make covalent drugs so effective. Derivatives that act with these properties are known as covalent mimetics. Since this discovery, the Moses Lab has identified numerous covalent mimetics that irreversibly react with the cancer-promoting KRAS. Now, the objective is to design and synthesize additional covalent mimetics, using advanced screening and validation techniques to create mimetic libraries that can be used in drug development. In the first year, the Moses Lab will select natural products that cause a diverse range of anti-cancer effects, such as disruption of cancer cell mitochondrial function, apoptosis (cell self destruction) induction, and modulation of enzymes involved in cancer proliferation. The covalent mimetics that the Moses Labs synthesizes from these selected natural products will then be tested in 2D cancer models of pancreatic, small cell lung, and triple negative breast cancers. From this research, five lead compounds will progress to be studied further. In the second year, the

collaboration of CSHL's chemists and biologists will become relevant as these five compounds undergo extended biological testing in patient-derived organoids. Upon confirming that these covalent mimetics are reaching the intended targets, the most promising will progress to be studied in animal models of cancer. Using human tumor cells implanted in mice, the inter-disciplinary research team will monitor how effective the covalent mimetics are in preventing and reversing tumor growth.

As is evident from the research outlined above, much of CSHL's C4B program is designed to promote the translation of research findings into clinical settings. Because CSHL operates a graduate program, the next generation of post-doctoral fellows and PhD candidates will receive training that promotes the intersection of chemistry and biology. Collaborations between the two disciplines take place beyond the bounds of CSHL as well, with scientists at institutions across the Tri-State area coming together to advance therapeutic innovations. With an understanding of the "in the lab" aspects of C4B, I will outline some of the other elements of the program that Dr. Moses hopes to expand in the coming years. The launch of the C4B seminar series will bring together distinguished researchers from CSHL's partner institutions to discuss relevant cross-discipline topics. Additionally, CSHL plans to commence a public lecture series that might educate diverse audiences on a range of scientific topics. Because the courses currently offered to graduate students at CSHL are largely biology-focused, Dr. Moses plans to develop a lecture course with topics such as organic synthesis, click chemistry's applications in biology, and chemical biology. With a mind towards eventually attracting another chemistry primary investigator to CSHL, Dr. Moses also hopes that CSHL will host an international click chemistry conference. An event of this kind will further situate the Moses Lab as a major player in the click chemistry world and promote C4B's principles to an international audience. All of these efforts are being developed with the understanding that meaningful breakthroughs in disease treatment are not possible without the free flow of ideas between disciplines. Further, Dr. Moses explained to me during a recent phonecall that the nature of most PhD and post-doctoral training causes scientists to become siloed in their fields, never deploying even the most basic principles of other scientific disciplines once they move past the undergraduate level. Dr. Moses views this rigid separation of focus areas as a barrier to scientific discovery. With the expansion of C4B, he imagines a future in which CSHL becomes a worldwide model for training young scientists to be scientifically well-rounded and collaboration-minded.

FMKF has been supporting CSHL since 2006 with $1.6M in total grants across that period. Much of our support has been designated for equipment purchases and operation of CSHL's shared data and technology resources. Since 2021, however, FMKF has had the opportunity to support CSHL's movement in a new direction: bringing a click chemist to a biology institution. Dr. Moses was mentored by Dr. K. Barry Sharpless, the "father" of click chemistry and two-time Nobel laureate. Dr. Moses is truly a pioneer in this field, bringing both an innovative research product and mindset to the institution. While Dr. Moses has only been with CSHL since 2020, he is already having an outsized impact, both inside and outside of the lab, exemplified by the C4B program. As a translational research institution, CSHL fits neatly within the Foundation's cancer research area of interest. I think there is also a case to be made that support of the Moses Lab aligns with our interest in supporting early career investigators. While we are not directly supporting a post-doctoral research project, several tenets of C4B are designed to change the traditional models of siloed early career study. As C4B's audience beyond CSHL grows, more graduate institutions

might adopt this approach. In recognition of the exciting work happening in the Moses Lab, a positive site visit earlier this year, and excellent stewardship from the CSHL team and Dr. Moses himself, I recommend a grant of $250,000, payable over two years, in support of research in the Moses Lab.

RECOMMENDATION: I recommend a grant of $250,000, payable over 2 years, designated for support of research in the lab of Dr. John Moses.

JUSTIN J. KICZEK COMMENTS: There is no question that Dr. Moses – and thereby CSHL – is trying to stake a claim for Cold Spring, NY, being a global center of innovation when it comes to the interplay of "click chemistry" and biology discovery. What began as almost a "pet project" a few years ago has now transformed into a veritable hub of educational offerings, workforce development programs, and international opportunities and partnerships. While one might think that the involvement of chemists and chemistry in biomedical clinical research is commonplace, as GEB shared with me, PhDs in chemistry are often picked off by pharmaceutical companies, leaving a dearth in the field of biomedical research. Moses appears to be expanding efforts beyond his own research into jeratinine A and other natural compounds, with the intention of building a program that will outlive him.

This seems to be a particularly exciting time to be funding this program, as it grows in reach and scope (not to mention in the impact of its research, which seems more promising by the day in addressing potential therapies for the devastating pancreatic cancer, as well as antiobiotic resistance). We should be excited by the fact that, as I see it, our support is now doing more than just funding bench research; it is building a program, with broad applicability, that breaks down silos, builds a pipeline of talent, and harnesses the charisma and energy of a very talented leader. It is worth noting here that Dr. Moses is not just an ivory tower researcher. He takes the time to get to know his supporters and build connections between his funders and the research. He is almost a development officer himself, again, a signal to me that he is a multi-faceted leader with the ability to build something much larger than his own line of research. Therefore, I am in favor of the multi-year grant proposed by GEB.

RECOMMENDATION: I recommend a grant of $250,000, payable over 2 years designated for support of research in the lab of Dr. John Moses.

APPLICANT: Cold Spring Harbor Laboratory

DISPOSITION:

( ) Declination

( ) Hold for review on/about:

(**X**) Approval for: **$250,000**

(**X**) Recommended Grant Payment(s): **Support of research in the lab of Dr. John Moses**
2024: $125,000
2025: $125,000

(**X**) Hold for Board Review: **September 6, 2024**

( ) Payee Other Than Addressee:

( ) Insert Information:

(**X**) Other: **Include multi-year grant letter.**

Initials: JJK Date: 8/9/2024

Check #_____ Date:_____