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Developing Accurate 3D Structure-Based Tools for Rapid Detection and Screening of the SARS-CoV-2 Virus

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OVERVIEW

The coronavirus pandemic has dramatically impacted human interactions and the global economy. A barrier to lifting social distancing restrictions is the lack of rapid and effective detection and screening. Dr. Mickey Kosloff of the Department of Human Biology at University of Haifa recognizes the need for new and effective tools that can address these challenges. His on-going research is positioned to identify tools to address the current crisis and avoid the need for future global quarantines.

The Kosloff Lab at University of Haifa combines computational and experimental approaches to better understand how the "wiring together" of protein interaction networks drives cellular communication in health and disease. This agenda strongly intersects with the current focus on protein interactions being used by the coronavirus to replicate. Dr. Kosloff and his lab are eager to accelerate work on the Rapid Detection and Screening Project, which has the potential to contribute substantially to the global efforts to fight the coronavirus pandemic.

The Kosloff Lab has applied for funding for this research from the Israel Science Foundation, the Israeli Ministry of Science and Technology and to the Israel Innovation Authority through Carmel Ltd. While these grants are pending, additional support is needed to accelerate this important work, to:

- Procure the specialized equipment needed to establish a recombinant viral proteins production unit
- Hire two dedicated post-doctoral researchers to advance the experimental and the computational components of the project

RESEARCH OVERVIEW

Specific interactions between viral and human proteins are the gateway through which the SARS-CoV-2 (COVID 19) virus enters human cells. Since the functional infectivity and virulence of the virus depend on these critical protein-protein interactions, decoding them at the individual amino-acid level can be leveraged to develop better in vitro methods for detecting the virus and/or for testing/developing therapeutics, antibodies, and vaccines.

Antibody-based approaches are already employed and further developed for diagnostics of prior SARS-CoV-2 infections, complementing Real Time (RT)-PCR based methods. Nevertheless, the use of antibodies for direct in vitro detection of virus particles can be impeded due to many limitations. Particularly worrisome are mutations in viral proteins that can negate antibody recognition – rendering antibody-based assays useless. Such mutations are a frequent occurrence in viruses – as was

demonstrated in the closely related MERS CoV. Indeed, numerous mutations that change viral infectivity and recognition have already been identified in SARS-CoV-2. This rapid evolutionary process can also lead to a re-emergence of a new, more virulent form of the virus, which might be capable of bypassing the immune resistance that accumulated in the population (herd immunity) during the current outbreak. Finally, identifying and characterizing small molecules that could inhibit virus cell binding to human tissue are high on the global research priority list, but searching for such potential drugs is hindered by the lack of simple and straight-forward in vitro assays to gauge direct binding between the virus and human cells.

We are addressing this need by developing in vitro assays for detecting the virus and for testing/developing therapeutics and vaccines, based on recombinant redesigned variants of human and SARS-CoV-2 proteins that will be optimized for stability and affinity using our in-house 3D-structure based computational pipeline.

SARS-COV-2 RESEARCH AGENDA

The Kosloff Lab's agenda strongly intersects with the current focus on protein interactions being used by the coronavirus to replicate. To further our novel research, we need to establish a protein production unit that will express the recombinant and engineered human and viral proteins in eukaryotic cells. We aim to rapidly advance our research agenda in the following areas:

1. Utilize the unique 3D structure-based computational approaches developed in the Kosloff Lab to accurately map the interactions between human and viral proteins at the individual amino-acid level. Our approach produces computational maps that quantify individual contributions to protein-protein interactions, and thereby can also directly and accurately guide orthogonal experimental efforts, such as antibody and vaccine development or anti-viral drug design.

2. Develop an in vitro virus detection assay based on human proteins, redesigned by our computational pipeline. This requires local production of these engineered proteins at the University of Haifa.

3. Establish a screening assay for small molecules that can disrupt virus binding to human cells by adapting the assay above.

4. Based on the assay above, set up a rapid assay for screening antibodies (e.g., in blood) based on the actual interactions that are required for viral entry into cells.

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ACADEMIC LEADERSHIP

Dr. Mickey Kosloff is a computational and experimental biologist. After graduating with a PhD in Structural and Molecular Biochemistry from the Hebrew University, he studied computational biology at Columbia University. He then continued his post-doctoral studies at Duke University Medical School, where he combined his experimental background with structural bioinformatics to determine how to decode selective recognition among signaling proteins. He has contributed to the annual joint Broad-ISF symposiums for several years and is a member of its scientific committee, which have been funded by the Klarman Family Foundation.

The University of Haifa is dedicated to investing the time, resources, and talent to support the important research Dr. Kosloff and his team want to undertake. As an institution grounded in multidisciplinary education and research, this project harnesses the University's expertise to address one of the most important areas of study seen in recent years.

As Israel emerges from its quarantine, the University's researchers, faculty and students are working to address today's challenges and develop solutions to avoid future crises. The country will need its strongest institutions to navigate through the challenges ahead; University of Haifa will lead the response, driving recovery and growth and serving as a beacon of support and stability for the northern region and country.