



האוניברסיטה העברית בירושלים  
THE HEBREW UNIVERSITY OF JERUSALEM

## The Hebrew University of Jerusalem's Mobilization in the Fight against the Coronavirus

The Hebrew University of Jerusalem is applying its full scientific and medical expertise and resources to combatting the coronavirus. Many of the top Israeli scientists in the fields of virology, microbiology, immunology, cellular biology, epidemiology, computer science, chemistry, physics, and nanotechnology are members of the Hebrew University community and have joined forces to win this battle. Our scientists and scholars are working intensively on broad aspects of the viral epidemic, with the aim of enhancing and scaling up virus detection efforts, developing new tools to identify the virus and its carriers as well as new protocols for patient treatment, the prevention of infection, and the development of new vaccine. They are studying the impact of social isolation, of the economic crisis, of the crisis on particular populations, and building upon existing research platforms to improve filters, infection-proof surfaces, and more.

### LEADING THE EFFORT

Leveraging its areas of scientific strength, its wide breadth of disciplines as well as its interdisciplinary capabilities, the Hebrew University has established a **Coronavirus Steering Committee (HUCSC)**, composed of internationally leading scientists, to guide and support these efforts. The Committee identifies main fields of required research, enhances interdisciplinary collaborations, and sets priorities in allocating staff, equipment, and funding among the various research projects.

In the following pages, a brief overview of some of the promising projects planned or in progress at laboratories of the Hebrew University is provided. These projects include efforts in seven main areas:

**1. Diagnostics and Genetics:** Hebrew University researchers are designing and testing rapid diagnostic kits, shortening the test time needed for virus identification and developing innovative ways for scaling up testing. We are also developing means to identify individuals who have been exposed to the virus, even without showing symptoms, or have recovered from the disease and now harbor in their blood antibodies to the virus. This may enable us to identify people who are already resistant to the virus, improve isolation modes and minimize the spread of the epidemic.

**2. Creating model systems to study the COVID-19 virus and develop new anti-viral drugs:** Animal models for the disease are essential for testing any new management protocols. Mice, for example, are not infected by the virus, because they don't carry the human ACE2 receptor

through which the virus enters cells. Our scientists are designing mice that are genetically engineered to carry the human ACE2 receptor in their lungs. These “humanized” mice may be infected by the virus and develop human-related disease, and will then serve as a models on which vaccines and other newly developed anti-viral drugs will be tested.

**3. Improving the capacity of the immune system to combat the virus:** The immune system plays the role of a double-edged sword in its encounter with the viral disease. Some immune cells, such as those that produce antibodies, are helping to defeat the virus, while other immune cells produce factors that aggravate the disease, particularly the virus-induced pneumonia. Our scientists are designing novel approaches to reinforce the constructive immune components and weaken the destructive ones of the immune system.

**4. Drug development to block the virus infection and reduce the tissue damage caused by the virus.** Our cellular biologists and pharmacology scientists are experimenting with repurposing clinically-approved drugs and even food additives to reduce infectivity and prevent either direct or indirect tissue damage caused by the virus.

**5. Development of advanced matrices for the neutralization of pathogens.** Our scientists work extensively to develop advanced matrices for the neutralization of pathogens. The matrices will be applied as components in masks or ventilation systems. The active neutralization matrices will be based on nanoparticle catalysts or biocatalysts and “green” chemical components.

**6. Molecular epidemiology studies to identify virus-susceptible and -resistant populations:** Genetic variations among people may explain why some people are infected and others not, and why some develop more severe disease than others. Israel’s population is one of the world’s most diverse, and the study of genes affecting virus infectivity and spread as well as immune-response genes may teach us how to halt this and other epidemics. We are constructing a new patient sample bio-bank which will offer unique opportunities to understand the genetic factors contributing to disease susceptibility; and our computational scientists, epidemiologists and geneticists will join forces to screen and study the relevant genes.

**7. Addressing the social and societal implications of the disease.** Addressing public health issues, psychological effects of isolation, financial aspects and other social issues is vital to understanding the consequences of the current situation and offering possible ways to address the challenges.

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None of these efforts would be possible without the Hebrew University’s outstanding and motivated students. Numerous ideas and execution efforts are driven by these brilliant and highly motivated young minds. Our research students are working day and night in the labs, often abandoning their own studies to now focus on the corona epidemic. These students are not only supporting the research but the community as a whole: medical students are volunteering with Magen David Adom to collect swab samples from potential carriers in the community to test for the virus; they are visiting at-risk individuals, such as those who have

received kidney transplants, to collect blood samples, so that these patients do not have to visit the hospital and risk infection; they are volunteering as babysitters to take care of the children of doctors and nurses, freeing these professionals for their essential healthcare work; and they are manning routine hospital laboratories to cover for absent personnel.

## Contents

1. Diagnostics and Genetics.....	8
Developing Quicker and Simpler Testing for COVID19 .....	8
Dr. Eitan Lerner, The Silberman Institute of Life Sciences, Faculty of Science .....	8
Developing a new fast and simple diagnostic kit for COVID-19.....	8
Prof. Eylon Yavin, School of Pharmacy, Faculty of Medicine.....	8
Investigating genetic predispositions to COVID-19 infection and differential expression .....	9
Dr. Yotam Drier, Faculty of Medicine .....	9
Developing Mass Testing for COVID-19 .....	9
Prof. Nir Friedman, The Benin School of Computer Science and Engineering and the Silberman Institute of Life Sciences and Dr. Naomi Habib, ELSC.....	9
Semiconductor Nanocrystals that can detect Corona on Surfaces.....	10
Prof. Uri Banin, The Institute of Chemistry and the Center for Nanoscience and Nanotechnology.....	10
Ultrasensitive, Ultrafast Electrical Detection of Coronavirus .....	11
Prof. Danny Porath, The Institute of Chemistry and the Center for Nanoscience and Nanotechnology and Prof. Yuval Dor, Faculty of Medicine .....	11
Integrated nanophotonic chip scale technology for detection and sensing of COVID-19 RNA .....	12
Prof. Uriel Levy, Department of Applied Physics and the Center for Nanoscience and Nanotechnology.....	12
Fast and ultrasensitive detection of COVID-19 RNA for point-of-need diagnostics.....	13
Prof. Eilon Sherman, The Racah Institute of Physics.....	13
Characterizing the RNA cis-acting elements in the SARS-CoV-2 viral life-cycle .....	13
Dr. Michal Rabani, The Silberman Institute of Life Sciences, Faculty of Sciences.....	13
Identifying genetic factors influencing the severity of COVID-19 infection.....	14
Dr. Shai Carmi and Prof. Asaf Hellman, Faculty of Medicine .....	14
2. Creating model systems to study the COVID-19 virus .....	16
Generating biological models for testing treatment and preventive protocols .....	16
Dr. Lior Nissim, Faculty of Medicine .....	16
Construction and validation of a clinically-relevant platform for high throughput analysis of inhibitors against Covid-19.....	16
Prof. Amos Panet and Prof. Dana Wolf .....	16

3. Improving the capacity of the immune system to combat the virus.....	18
Generating monoclonal antibodies for COVID-19 .....	18
Prof. Jacob Hochman, The Silberman Institute of Life Sciences, Faculty of Sciences .....	18
Identifying protective antibodies targeting SARS-CoV-2 from recovered patients.....	18
Prof. Alexander Rouvinski, Faculty of Medicine.....	18
Deciphering the virus-host tango: A network of interactions through evolution, structure, dynamics, and computational design.....	19
Dr. Dina Schneidman-Duhovny and Prof. Michal Linial, The Silberman Institute of Life Sciences and The Benin School of Computer Science and Engineering.....	19
Characterization and structural studies of neutralization epitopes on SARS-CoV-2 spike (S) protein to facilitate the design of an effective vaccine.....	20
Dr. Alexander Rouvinski, Faculty of Medicine; Dr. Netanel Tzarum, The Silberman Institute of Life Sciences, Faculty of Science .....	20
T-cell cytokine analysis and manipulation as a novel therapy mode for severe COVID-19 patients .....	21
Dr. Micha Berger, Faculty of Medicine.....	21
Targeting neutrophils as a therapy for severe COVID-19 infection.....	22
Prof. Zvika Granot and Prof. Zvi G. Fridlender, Faculty of Medicine.....	22
Orally available, highly potent Integrin avb3/avb5 inhibitor: A promising agent for coronavirus SARS- CoV-2 infection therapy.....	23
Prof. Chaim Gilon and Prof. Amnon Hoffman, Faculty of Medicine.....	23
Neutrophil Involvement in refractory coronavirus infection .....	24
Prof. Zvika Granot and Dr. Alex Rouvinski, Faculty of Medicine .....	24
A Systematic Search for New Drugs that Restrict SARS-CoV-2 infection .....	24
Dr. Oren Parnas, Faculty of Medicine .....	24
Metabolic Control of SARS-CoV-2.....	25
Prof. Yaakov Nahmias, the Center for Nanoscience and Nanotechnology and the Alexander Grass Center for Bioengineering .....	25
Human co-stimulatory receptor mimetic peptides: Potential therapeutics against coronavirus infection. 26	
Prof. Raymond Kaempfer, Faculty of Medicine.....	26
Blocking of SARS-CoV-2 infection using antibodies and fusion proteins .....	27
Prof. Ofer Mandelboim, Faculty of Medicine .....	27
Preventing lung-collapse in coronavirus patients through the development of inhibitors for trigger enzymes .....	28
Prof. Gil Shoham, Institute of Chemistry, Faculty of Science .....	28

Repurposed drugs and vaccine for COVID-19 treatment .....	29
Prof. Yechezkel Barenholz, Department of Biochemistry & Molecular Biology, Faculty of Medicine.....	29
Identifying genes involved in the pathogenicity of COVID-19 for potential drug therapy .....	30
Prof. Nissim Benvenisty, Azrieli Center for Stem Cells and Genetic Research, The Silberman Institute of Life Sciences, Faculty of Science .....	30
Drug treatments and simple blood tests for the early detection of COVID-19 biomarkers and risk factors through a combined computational biology, virology and proteomics approach.....	31
Prof. Dana Reichmann, Silberman Institute of Life Sciences, Faculty of Science, Prof. Ora Furman, Faculty of Medicine, Dr. Alex Rouvinski, Faculty of Medicine .....	31
Harnessing antimalarial drugs for the potential treatment of COVID-19.....	32
Dr. Ahmad Masarwa, Institute of Chemistry, Faculty of Science .....	32
Smart Screening of Disinfecting Materials and Anti-Coronavirus Drugs .....	33
Prof. Uri Raviv, Institute of Chemistry, Faculty of Science .....	33
Discovery of drugs to inhibit coronavirus function .....	34
Prof. Amiram Goldblum, School of Pharmacy, Faculty of Medicine .....	34
Rational design of anti-SARS drugs by applying machine learning and quantum chemical methods to existing drugs .....	35
Dr. Igor Schapiro, Institute of Chemistry, Faculty of Science .....	35
Relieving lung disease in Covid-19 patients through ribozyme-loaded microcapsules delivered into the lungs as aerosols .....	36
Prof. Itamar Willner, Institute of Chemistry, Faculty of Science and Prof. Eli Pikarsky & Prof. Moshe Kotler, Faculty of Medicine.....	36
Systematic computational drug repositioning to treat COVID-19 .....	37
Dr. Yuval Tabach, Faculty of Medicine .....	37
Design, coordination and production of tools to reduce viral transmission .....	38
Prof. Ami Citri, the Edmond and Lily Safra Center for Brain Sciences (with Itamar Frachtenberg, ELSC)	38
Development of anti-Ceacam1 antibodies for the treatment of Coronavirus infection NO PR .....	39
Prof. Francesca Levi-Schaffer, School of Pharmacy, Faculty of Medicine.....	39
Identifying novel drug targets for blocking the COVID-19 virus using large-scale proteomics and AI.....	39
Dr. Haitham Amal, School of Pharmacy, Faculty of Medicine.....	39
5-MER peptide to ameliorate coronavirus-induced inflammation of the upper respiratory tract and lungs .....	40
Prof. David Naor, Faculty of Medicine .....	40
Testing a potential therapeutic treatment for Corona .....	41
Prof. Ariella Oppenheim, Faculty of Medicine.....	41

Mass spectrometry screening for effectors on the dynamics of the COVID-19 spike protein.....	42
Prof. Nir Kalisman, Faculty of Science.....	42
5. Development of advanced matrices for the neutralization of pathogens.....	43
Neutralization of pathogens using advanced matrices as components in masks or ventilation systems	43
Prof. Itamar Willner, Institute of Chemistry, Faculty of Science and Prof. Eli Pikarsky, Faculty of Medicine	43
Development of Disposable Active Antiviral Filters.....	43
Prof. Shlomo Magdassi, Prof. Daniel Mandler and Prof. Uri Banin, Institute of Chemistry and the Center for Nanoscience and Nanotechnology .....	43
State-of-the-art real-time, powerful and safe technology for fighting and eliminating viral and bacterial pathogens.....	44
Dr. Hani Gnayem and Prof. Yoel Sasson, Institute of Chemistry, Faculty of Science .....	44
Long-lasting antiviral coatings for public surfaces.....	45
Prof. Avi Domb, School of Pharmacy, Faculty of Medicine .....	45
Environmentally friendly nontoxic coating which prevents virus adhesion .....	45
Prof. Meital Reches, Institute of Chemistry and Center for Nanoscience and Nanotechnology .....	45
Copper-based antiviral agents to prevent surface contamination .....	46
Prof. David Avnir, Institute of Chemistry and Dr. Zvi Hayouka, Robert H. Smith Faculty of Agriculture, Food & Environment .....	46
Reusable, mass-produced, affordable, anti-viral face masks to combat the spread of Coronavirus.....	47
Prof. Gershon Golomb, School of Pharmacy, Faculty of Medicine .....	47
Improving disinfection treatments against coronavirus for surfaces and hands.....	48
Dr. Nadav Kashtan, Plant Pathology and Microbiology, Robert H. Smith Faculty of Agriculture, Food and Environment.....	48
7. Addressing the social and societal implications of the disease.....	49
Israel's health policy actions to cope with COVID-19 pandemic .....	49
Shuli Brammli, Hebrew University-Hadassah Braun School of Public Health and Community Medicine, Faculty of Medicine .....	49
Social distancing in health and cognitive deterioration: A view from the brain.....	49
Prof. Shahar Arzy, Faculty of Medicine .....	49
Mental wellbeing of migrant careworkers in Israel during COVID-19: Vulnerabilities of migrant careworkers and their employers.....	50
Prof. Yehuda Neumark, Hebrew University-Hadassah Braun School of Public Health and Community Medicine.....	50
Smoking behaviours and quit attempts during COVID-19 .....	51

Dr. Yael Bar-Zeev and Prof. Yehuda Neumark, Hebrew University Hadassah Braun School of Public Health and Community Medicine .....	51
Community responses and initiatives for underprivileged and vulnerable populations during the COVID-19 pandemic .....	53
Dr. Yael Bar-Zeev, Dr. Milca Dunchin and Prof. Yehuda Neumark, School of Public Health and Community Medicine .....	53
A Simulation Model of the Spacial Contagion of the Coronavirus in Israeli Cities .....	54
Prof. Daniel Felsenstein and Dr. Yair Grinberger, Department of Geography, Faculty of Social Sciences	54
Saving for Retirement and Emergencies and use of Robo-Advisors .....	55
Prof. Orly Sade, the Jerusalem Business School (with Prof. Olivia S. Mitchell, and Dr. Abigail Hurwitz) .	55
The effects of social Isolation on the body’s basic regulatory physiological processes and COVID-19 susceptibility .....	55
Dr. Shir Atzil, Department of Psychology, Faculty of Social Sciences .....	55
Cognitive-psychological aspects of the pandemic and new ways to improve wellbeing in times of crisis..	56
Prof. Ran Hassin, Department of Psychology, Faculty of Social Sciences.....	56
Improved food security through the decentralization of food manufacturing.....	56
Prof. Oded Shoseyov and Prof. Ido Braslavsky, Robert H. Smith Faculty of Agriculture, Food, and Environment and the Center for Nanoscience and Nanotechnology.....	56
Autonomous, portable living units for coronavirus patients (individuals, families, and communities) during the pandemic .....	57
Prof. Amotz Agnon with respective teams, Fredy & Nadine Herrmann Institute of Earth Sciences, Faculty of Science .....	57
Social Acceptance of Technological Innovations among Senior Citizens Facing COVID-19 .....	58
Prof. Elyakim Kislev, Federmann School of Public Policy and Government, Faculty of Social Sciences...	58

## 1. DIAGNOSTICS AND GENETICS

### Developing Quicker and Simpler Testing for COVID19

*Dr. Eitan Lerner, The Silberman Institute of Life Sciences, Faculty of Science*

Dr. Eitan Lerner's lab has diverted its expertise to developing more efficient testing for COVID19. Diagnosis of COVID19 is currently done via RNA extraction & RT-PCR, which is labor-intensive, takes time per sample and requires use of existing kits or, owing to high demand, preparing their contents specially. The specificity in this kit relies on hybridizing nucleic-acid fluorescent probes and relying on PCR amplification (Polymerase Chain Reaction which makes copies of specific DNA samples).

An alternative mode of identification involves high-sensitivity fluorescence detection of the specific factors in the virus, without amplification. Using this method will save time, labor efforts and (bio)chemical resources to produce highly specific results, even when the targets are at low concentrations. In order to do this, Dr. Lerner's lab is using confocal-based fluorescence detection of one particle at a time. They are currently developing two alternative:

- 1) In-situ identification of viral particles one at a time, directly from the sample, based on two measured signals: the particle size and the binding to their host receptor protein, ACE2. When the two signals are synchronized in time, a particle with specific binding to ACE2, with the appropriate size of the virus (~100 nm) is identified.
- 2) Fluorescence detection of dye-labeled hybridizing probes, with a known change in their fluorescence signal upon binding to the viral RNA. Unlike in RT-PCR, this method enables the virus' detection even if the extracted viral RNA is in miniscule concentrations.

Dr. Lerner's team is currently performing proof-of-concept measurements, and the next step would be to prepare the involved proteins/probes components and to test them at first against model systems embedded with the COVID19 spike proteins. The goal would be to test these modalities against pseudovirions, or other safe(r) modes of the virus particle.

### Developing a new fast and simple diagnostic kit for COVID-19

*Prof. Eylon Yavin, School of Pharmacy, Faculty of Medicine*

There is a clear and urgent need to develop simple and quick diagnostic tests that are able to diagnose the coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

The Yavin lab is using highly specific molecular probes (termed Peptide Nucleic Acids, or PNAs) that will be attached to the surface of a simple 96-well plate. This will enable them to "fish out"



viral RNAs that, in turn, will allow them to introduce two additional elements that are commercially available: (1) SARS-CoV-2 RNA-specific DNA molecules, and (2) positively-charged gold nanoparticles (Au NPs) or a fluorescent molecule that binds to dsDNA (e.g. TOTO). Should a noticeable change in color ensue (due to the interaction of the Au NPs with DNA) or in fluorescence (TOTO binding to dsDNA), this will confirm the infection by SARS-CoV-2.

The test is expected to (1) enable the early detection of infection in an individual with COVID-19, prior to the emergence of symptoms; (2) be readily applied to multiple samples with a turnover of thousands of tests within 2-3 hours; and (3) be cheap and easily performed by minimally-trained staff.

### **Investigating genetic predispositions to COVID-19 infection and differential expression**

*Dr. Yotam Drier, Faculty of Medicine*

This study explores whether and how genetic differences among patients affect the severity of COVID-19 disease expression, by comparing the DNA sequences of patients of similar age who exhibit different disease severity. The Drier lab will focus on elderly patients in whom the course of the disease varies greatly, but also on young individuals with severe disease presentation (if a sufficient number of such cases is available) to identify genetic variants that renders different individuals more or less susceptible. Focusing on genes related to COVID-19 response, they will analyze the sequence of the genes themselves as well as surrounding regions that regulate these genes. Such regulatory regions will be identified by data mining in existing databases. This work will have two main implications: the first is to identify population groups that may be at a higher risk of severe disease expression once contracted, and the second is to improve our basic understanding of how COVID-19 genes are regulated, which may help identify the relevant cell types targeted by the virus and enable us to propose new therapeutic strategies.

### **Developing Mass Testing for COVID-19**

*Prof. Nir Friedman, The Benin School of Computer Science and Engineering and the Silberman Institute of Life Sciences and Dr. Naomi Habib, ELSC*

The test currently used for the SARS-CoV2 virus uses molecular methods for detecting presence of viral RNA sequences in subject samples. This is the approved gold standard in the field. The current application of this test requires several cumbersome steps that are labor intensive and require non-trivial reagents (which are becoming a bottleneck worldwide). It is clear that the next steps in managing the COVID19 pandemic will require large scale testing.

This project is developing an approach that harnesses high-throughput sequencing methods to test samples. The working guideline is to adhere to current collection protocols and clinical test

definitions and standards. The pair are aiming to replace labor intensive molecular steps with alternative ones that are based on their expertise in high-throughput genomics.

The approach will allow a single technician to process thousands samples per day by using a simple protocol. Thousands of samples (10,000 or more) will be read by a single sequencing run, with straightforward calling of results using simple bioinformatic tools.

The benefits of this new method include:

- Use of the same set of probes as in the current gold standard tests;
- Readout will be directly comparable to current tests and can adhere to the same standards;
- High-throughput, i.e. processing of thousands of samples;
- Automation friendly, i.e. can be readily automated;
- Low cost in terms of reagents and readout

### **Semiconductor Nanocrystals that can detect Corona on Surfaces**

*Prof. Uri Banin, The Institute of Chemistry and the Center for Nanoscience and Nanotechnology*

Early and diverse detection of the coronavirus is the first step to battle the current epidemic, which by now is already the most severe epidemic of the new age. The virus can be spread by people without specific symptoms, preventing physiological diagnostics, resulting in the self-isolation of a large portion of the population with a significant impact on our daily life and global economics. Banin's group aims to develop a rapid and sensitive toolkit, which will facilitate parallel diagnostics and outdoor detection of the coronavirus, and future similar threats. Specifically, Prof. Banin is working to develop a rapid and sensitive tool for detection and diagnosis of specific viral RNA in the lab and the field.

The virus is a single strand RNA virus with a protecting envelope, which stabilizes it on different surfaces, allowing it to infect even after being left for 2-3 days on plastic and stainless steel surfaces. Moreover, it can be spread by people who do not display specific symptoms, preventing physiological diagnostics. Therefore there is an urgent need for fast and sensitive tools to detect the virus in human samples and on a wide range of substrates.

Semiconductor nanocrystals (SCNC) are highly developed and available exceptional fluorescent tags for imaging biomolecules. In these applications, the nanocrystals are functionalized with biological molecules, such as antibodies, peptides, or nucleic acids that are conjugated to their surface and specifically recognize a target molecule. This yields a unique system that exhibits outstanding advantages, including very high sensitivity due to a combination of high light sensitivity, high fluorescence quantum yield, and large surface area that allows multi-labeling, high photochemical stability, and high selectivity.

SCNCs have also been used as donor molecules in FRET (fluorescence resonance energy transfer). FRET is the radiationless transmission of energy from a donor molecule (such as SCNC) to an acceptor molecule. The donor molecule is the dye or chromophore that initially absorbs the energy and the acceptor is the chromophore to which the energy is subsequently transferred.

Prof. Banin's group is focused on the synthesis, surface functionalization and characterization of light-emitting SCNCs, allowing them to finely tune the SCNC towards specific applications specifically based on their utilization as donors in FRET-based applications.

Banin is developing a viral RNA sensing toolkit based on SCNCs fluorescence and FRET. First, nanocrystals and organic dyes couples, compatible with FRET reaction, will be functionalized by two proximate complementary sequences of the desired viral RNA. Upon binding of the two to the viral RNA and light excitation, this will result in high proximity and efficient FRET reaction with the nanocrystals, acting as light-sensitive donors, and the dyes acting as acceptors. This offers a highly sensitive platform for sensing viruses.

The development of this system will allow its functionality in multiple scenarios, from fast and sensitive large parallel diagnostic of the virus in human samples, to a sensitive mobile toolkit for the sensing of patients and viral contaminations in the field.

### **Ultrasensitive, Ultrafast Electrical Detection of Coronavirus**

*Prof. Danny Porath, The Institute of Chemistry and the Center for Nanoscience and Nanotechnology and Prof. Yuval Dor, Faculty of Medicine*

Early, rapid, mobile, widespread and cheap detection of viral infection in humans is crucial in the battle against Corona, the worst epidemic of the last one hundred years. The virus is characterized by a specific single strand RNA and its detection is the key to identifying infection.

Infection detection is currently done by PCR (Polymerase Chain Reaction which makes copies of specific DNA samples) in central laboratories and takes hours. Another limitation of current detection methods is they are unable to detect a few mutants simultaneously. Patients infected by the Coronavirus become aware of their infection or illness after few days at the earliest, and in some cases never. During this period they spread the virus and infect others. Therefore, the creation of rapid, mobile and ultra-sensitive tools for multiplex detection of the virus in humans everywhere, such as at the entrance to buildings or public transport, is the key to limiting the spread of the epidemic. In addition, this method would enable the containment of the virus without halting the worldwide economy.

Prof. Danny Porath and Prof. Yuval Dor are working on a novel technology for ultrasensitive, ultrafast detection of minute amounts of DNA and RNA in biological samples. This method, radically different from the current PCR method, is based on Electrical Detection of Nucleic Acids (EDNA).

In recent experiments, Porath and Dor showed that a double-stranded DNA that is 100 bases long can be connected to two metal nanoparticles and can transport significant current when placed between nanofabricated metal electrodes. This forms an electrical circuit. If a segment in one of the two strands is missing then the device they are working on it will only transport current when the missing segment matches. In this case the missing segment is part of the Corona RNA sequence.

With silicon technology, these mass produced devices, will be able to perform the detection for several sequences simultaneously. Each device will detect multiple times by releasing the captured RNA through heating the double strand and recapturing another target RNA. This large array of devices, where each device detects multiple times, will enable an unprecedented sensitivity, and multiplex detection, thus enabling very early detection of the infection.

Porath and Dor expect to demonstrate a single operating detection circuit within 4-6 months and plan to form collaborations that will help them demonstrate a prototype device within 12-18 months. Commercial development of a detection toolkit will then follow.

### **Integrated nanophotonic chip scale technology for detection and sensing of COVID-19 RNA**

*Prof. Uriel Levy, Department of Applied Physics and the Center for Nanoscience and Nanotechnology*

Chip scale photonics technology is developing rapidly for diverse applications, from communication and computation to various types of sensing. The Levy group has pioneered various chip scale photonics technologies, including high Q resonators, integration of light sources and detectors on chip, integration of microfluidics and photonic devices, paving the way for the discipline of optofluidics, and more.

In this project, they will integrate chip scale high Q micro and nanoresonators together with microfluidic/nanofluidic delivery systems and surface chemistry for the purpose of detecting RNA. To achieve specificity for the RNA, the microresonators will be functionalized with an antibody such that the specific analyte (such as the COVID-19 RNA) will be attached to it. The resonance frequency of the resonator will be monitored using an active feedback loop. A reference resonator that will NOT be exposed to the analyte will also be implemented and the signal will be detected in common mode rejection. In this way, environmental fluctuations (for example temperature) will be eliminated. The Levy group has already built a system on chip with  $10^{-8}$  relative precision in refractive index, and can improve it even more towards the  $10^{-9}$ , which is more than sufficient to detect the RNA.

The chip scale device will be constructed within 3-4 months and tests on liquid samples will be initiated. The goal is to achieve significant results within 10-12 months from initiation of the project.

## **Fast and ultrasensitive detection of COVID-19 RNA for point-of-need diagnostics**

*Prof. Eilon Sherman, The Racah Institute of Physics*

A major cause for the current corona pandemic is the lack of immediate, accurate and widely accessible diagnostic capability of the COVID-19 virus. Such means will be sorely needed in the near future for the on-going containment of the disease. Current testing is performed using the polymerase chain reaction (PCR) as a gold standard, and is thus slow (hours to days), expensive, and requires expert equipment, reagents and well-trained personnel.

The Sherman lab for Biophysics at the Racah Institute has developed a unique technology for the ultra-sensitive and fast (< 1min) detection of a range of pathogens (bacteria and viruses). The technology relies on the detection of single molecular interactions using cutting-edge fluorescence microscopy. It thus eliminates the need for molecular amplification of PCR, along with its complexity and operational and availability limitations.

The technology has been demonstrated on both proteins and DNA molecules as proof of concept. It will be commercialized via Yissum (the Hebrew University's IP and technology transfer company).

In this project, the Sherman group intends to adapt this technology for the detection of single COVID-19 RNA molecules, in the form of a disposable, low-cost kit. This kit will be used in conjunction with a compact and handy optical device that is currently under development.

Thus, their tests will become available at point of care (e.g. hospitals, regional clinics, etc.) and at point of need (including airports, central bus and train stations, etc.). It will be able to be operated by untrained personnel, and will provide an immediate and simple yes/no answer for the presence of the virus. The test results will be shared with the appropriate medical staff. Future development will allow the application of these tests at home.

## **Characterizing the RNA cis-acting elements in the SARS-CoV-2 viral life-cycle**

*Dr. Michal Rabani, The Silberman Institute of Life Sciences, Faculty of Sciences*

Our ability to develop diagnostic tools and therapeutic approaches to fight the new SARS-CoV-2 virus could be greatly enhanced by an understanding of the viral life-cycle and the organization of its genome. SARS-CoV-2 is an RNA virus, with a positive-sense, single-stranded genome of ~30 kb, and is the newest member of the genus betacoronavirus, together with SARS-CoV-1 (80% homology) and MERS-CoV (50% homology).

Cis-acting RNA elements are an essential part of the life-cycle of RNA viruses, and play key roles in the molecular mechanisms of their genome replication, gene expression and genome packaging. The boundaries of many essential betacoronavirus cis-acting elements have been

defined, and the RNA secondary structures of these regions are understood. However, how these cis-acting structures and sequences interact with the viral and host cell components to allow viral growth and replication is still not clear.

The Rabani lab is studying molecular mechanisms of RNA regulation, and has developed both experimental and computational tools to study different aspects of RNA biology. In particular, they recently developed an approach to decode RNA cis-acting element, which combines a Massively Parallel Reporter Assay (MPRA) within the zebrafish embryo model system, and a linear regression computational analysis. Their assay introduces RNA molecules directly into the cytoplasm of cells by microinjection, providing a parallel approach to the cytoplasmic life-cycle of betacoronaviruses.

They will use our expertise in RNA biology as a strategy to decipher cis-acting elements in the SARS-CoV-2 viral life-cycle. They will first use comparative genomics of the coronavirus family members in order to identify RNA cis-signals in the viral genome. They will use a methodology that considers RNA-specific features to guide their analysis, such as structure-preserving compensatory mutations and non-canonical base pairing. Next, they will use the growing number of SARS-CoV-2 viral sequences from multiple patient samples to determine the mutation landscape of the virus, and compare it to viral gene expression in order to gain functional insights. Finally, using their MPRA strategy, they will build libraries of RNA reporters that cover the landscape of viral cis-elements, and test how their interaction with molecular components, derived either from a host cell or from the viral genome, affects RNA stability, translation and replication.

Their results will resolve viral cis-elements which are likely to be critical for the expression of viral transcripts and for viral replication inside the host cell. This improved molecular understanding of the SARS-CoV-2 life-cycle will greatly enhance the set of possible diagnostic and therapeutic approaches to effectively fight this virus.

### **Identifying genetic factors influencing the severity of COVID-19 infection**

*Dr. Shai Carmi and Prof. Asaf Hellman, Faculty of Medicine*

The COVID-19 pandemic is an emergency public health event, with hundreds of thousands of infected individuals worldwide and an astronomic economic toll. A marked characteristic of COVID-19 infection is the wide variability in its disease course. A substantial fraction of affected individuals are asymptomatic, with some affected individuals developing a mild form of the disease, while other individuals develop a severe disease that requires critical care and may result in death. Furthermore, huge differences in mortality rates have been observed across countries, which cannot be explained by the relative quality of health systems.

Risk factors for death currently include older age, smoking, underlying health conditions, and, possibly, male gender. However, all known risk factors combined do not explain the wide

variability in disease severity among patients. The particular DNA sequence of the patient is likely to be at least partly responsible for these differences, as observed for other infectious diseases. Genetic factors could also explain the wide differences in mortality across countries.

Carmi and Hellman propose to search for and identify genetic variants that affect susceptibility to COVID-19 and disease severity. Such studies have been previously applied successfully in the context of other infectious diseases. Discovery of genetic variants that modify infection outcomes will have a dramatic impact in multiple crucial fronts. First, it will allow a much-refined personalized risk estimate. This could aid policy-making by stratifying the population: low-risk individuals could return to normal life and restore normal economic activities, while high-risk individuals would be encouraged to exercise extra caution. Second, it could hint at underlying reasons for the differences in susceptibility witnessed across countries, which would be crucial for guiding policy in the wake of the emerging economic crisis. Third, it has a strong potential to improve our understanding of the molecular mechanisms behind COVID-19 infection. Finally and importantly, the discovery of genes associated with susceptibility and severity may suggest novel drug targets.

The Carmi-Hellman team will map the DNA sequence of patient samples using current technologies that cover common human genetic variants. To analyze the data, they will employ state-of-the-art statistical methods for generating high quality information on the genetic variants carried by each individual, and for statistical association of these genetic variants with clinical outcomes such as severity of the disease, treatment received, and the response to the treatment. They will account for variables such as age, sex, and underlying health conditions.

\$500K - \$1M

## 2. CREATING MODEL SYSTEMS TO STUDY THE COVID-19 VIRUS

### Generating biological models for testing treatment and preventive protocols

*Dr. Lior Nissim, Faculty of Medicine*

Studying the course of SARS-CoV-2 viral infection and disease, and the testing of new vaccines and drugs, require animal models. For example, mice and rats can be infected with the virus and then tested with different treatment protocols. Unfortunately, these rodents are not susceptible to COVID-19 infection since the virus only interacts with the human version of the ACE2 proteins in the lungs, and cannot interact with the mouse version. It is therefore necessary to genetically engineer mice such that the human ACE2 is present in their lungs, enabling their susceptibility to this viral infection. Conventional genetic engineering (or breeding of existing engineered mice) will require months.

To overcome this difficulty and enable the immediate generation of a temporary mouse model, the Nissim lab will deliver the human ACE2 into mouse lungs via an engineered virus that carries this human gene. The engineered virus will infect the lungs, integrate into the mouse genome, and generate the ACE2 receptor, thereby enabling infection with the COVID-19 virus.

The Nissim group has already designed appropriately-engineered carrier viruses, allowing consistent or time-controlled presentation of the human ACE2 in the lungs. In addition, they have added synthetic peptides and membrane anchors to some ACE2 variants to enhance the display of this receptor in mice.

They will produce large amounts of concentrated engineered ACE2 delivery virus and deliver it into mice, which will then be subject to testing of multiple candidate drug and vaccination treatments developed in the research community.

### Construction and validation of a clinically-relevant platform for high throughput analysis of inhibitors against Covid-19

*Prof. Amos Panet and Prof. Dana Wolf*

A collaborative project of the Hebrew University and the Hadassah Medical Center

The collaborative research of these two investigators in the past involved a variety of viral human diseases, such as Influenza, Herpes simplex, cytomegalovirus, etc., and for this project they have prepared two platforms suitable for fast selection of promising drugs against COVID-19. In particular, they are interested in the analysis of various small inhibitors and antibodies with potential therapy. To this end, they are preparing a virus vector based on the Lenti virus (pseudotype) that is coated with the membrane of COVID-19, including the three COVID-19 membrane proteins. This engineered virus, expressing a reporter gene, will now serve



as a screening mechanism of various potential inhibitors and antibodies to COVID-19. (1) The first step will be to infect human cultured cells derived from the upper and lower respiratory system, in the presence of the tested inhibitors. (2) The promising viral inhibitors will be further examined in its activity against COVID-19, using a unique human ex vivo organ culture system developed in the Panet and Wolf labs. Over the last twenty years, the Panet and Wolf labs have developed organ culture systems for various viral disease studies, derived from different human tissues, including the lung and more recently, the upper respiratory tract (nasal mucosal organ culture), obtained from the operation room. Tissue viability ex vivo was optimized for each of the tissues used for the viral studies ex vivo. This novel clinically-relevant nasal mucosal organ culture system will now be applied to the study of COVID-19 and potential therapies. Moreover, the same viable tissue in organ cultures can be tested for potential toxicity of the potential drug. The Panet and Wolf team have already established appropriate assays to monitor tissue toxicity of potential drugs. Due to the absence of a validated experimental system for the analysis of therapies against COVID-19, this ex vivo system should enable a fast track development for clinical studies with promising inhibitors to COVID-19.

This project is already in a stage of advanced development and will soon be ready to analyze new potential drugs for COVID-19. This team is open to collaboration with scientists from around the world on this subject.

### 3. IMPROVING THE CAPACITY OF THE IMMUNE SYSTEM TO COMBAT THE VIRUS

#### Generating monoclonal antibodies for COVID-19

*Prof. Jacob Hochman, The Silberman Institute of Life Sciences, Faculty of Sciences*

The overall objective of the Hochman lab is to generate monoclonal antibodies directed against signal peptide (SP) and envelope proteins of COVID-19 for subsequent immune therapy and putative vaccination in the clinical setting.

The group's approach is to use synthetic and/or recombinant peptides comprising the SP and Envelope of the virus for immunization of mice. Mice with positive sera will be used for the generation of the monoclonal antibodies. These will be tested against the different peptides for validation. Positive monoclonals will then be sent out to an authorized laboratory for validation against COVID-19. Positive monoclonals after this step will be humanized for further studies in the clinic. A positive immune response may also suggest that the antigens used for immunization could also be applied as putative vaccines.

Hochman's group has a long standing experience with the generation and application of monoclonal antibodies against cancer cells. Specifically, they have generated such antibodies against Signal peptide epitopes of a virus (MMTV) that is associated with human breast cancer. These antibodies have been used for both diagnosis of MMTV-associated human breast cancer as well as for the inhibition of breast cancer tumors (that contain the virus) in mice.

#### Identifying protective antibodies targeting SARS-CoV-2 from recovered patients

*Prof. Alexander Rouvinski, Faculty of Medicine*

The Rouvinski lab is aiming to address two urgent needs related to COVID-19: treatment and diagnostics. Inoculation using the plasma of survivors who have acquired protective antibodies is a promising approach to treat COVID-19. However, the supply of immune plasma is severely limited, and treating the huge number of patients in the current pandemic will require more advanced methodologies. Rouvinski's team proposes to identify and clone the genes that encode for protective antibodies in recovered patients. This will allow the mass production of recombinant, protective anti-SARS-CoV-2 antibodies that will be available for therapy and diagnosis. To achieve this goal, they are currently using computational biology, structural data and modeling, and novel knowledge about the SARS-CoV-2 virus biology, to design a set of proteins predicted to mimic crucial components of the virus and thus expose its Achilles heels. Importantly, these antigens – regions that can be used to stimulate the immune system – are frequently complex. Next, they will produce large amount of these “protective antigens” using our in-house capabilities. Having these antigens on hand will lay the foundation for two key projects as follows:

1. A novel approach for immune therapy: Using antibody-producing cells obtained from the blood of recovered patients, they will clone the genes encoding antibodies that bind to antigenic regions of the virus. To this end, they have designed a method to tag each antigen with a fluorescent DNA “barcode”, allowing them to detect which antibody-producing cell binds such a fluorescent antigen. The team will then use single cell transcriptomic methodology to identify the structure of the binding antibody. Computational analysis will reveal the sequence of a plethora of antibodies that possess such binding ability. Next, the protective power of each antibody will be assessed using several models, including infected cell lines and animal models, before progressing to clinical trials. In this manner, they expect to be able to rapidly identify potent, targeted, and safe anti-SARS-CoV-2 antibodies. This methodology can be applied to multiple antigens from various pathogens.

2. Diagnosis, epidemiology and vaccine design. Using their set of protective antigens, the Rouvinski team proposes to develop a rapid innovative diagnostic tool that will allow detection of protective antibodies in blood and/or saliva of individuals, thus enabling the identification of those who are no longer at risk. The proposed assay will include tagging the protective antigens each with a different DNA barcode, followed by tagging the antibodies of each individual with other, distinct DNA barcodes. Next, the antigens and antiserum will be mixed, and combined molecular and computational analysis will expose antigen-antibody interactions. This method will allow the massive parallel testing of blood extracted from a large number of individuals and multiple protective antigens, providing a rapid assessment of the immunity status of many individuals within the community.

Rapid serological (blood) screening will help in crucial epidemiological surveys. In particular, it will help to answer the key question: What is the proportion of silent SARS-CoV2 recovering patients in the population? Identifying those recombinant antigens that are the targets of the most potent protective antibodies will serve to inform vaccine designers.

### **Deciphering the virus-host tango: A network of interactions through evolution, structure, dynamics, and computational design**

*Dr. Dina Schneidman-Duhovny and Prof. Michal Linial, The Silberman Institute of Life Sciences and The Benin School of Computer Science and Engineering*

All viruses make extensive use of the host capacity for completing the infectious cycle – from the initial attachment to the host receptor up to the release of hundreds of viruses from an infected cell. Upon cell entry, the COVID-19 viral proteins interact with hundreds of human host proteins. Atomic resolution structural characterization of these interactions will shed light on the mechanisms of infection and provide insight into druggable targets while also determining which are the most successful ones.

While there has been a successful effort in characterizing structures for many of the 12 virus proteins using cryo-Electron Microscopy and x-ray crystallography, rapid structural

characterization of hundreds of virus-host interactions remains a challenge. Even with a complete structural atomic view of the viral proteome, the temporal aspect of viral maturation within the host cell is hard to capture from a static structural view. An additional difficulty that specifies COVID-19, as well as other RNA-viruses, concerns the constant changes that the virus undergoes due to its high mutation rate. Computational tools are necessary for high-throughput characterization of structures, dynamics, and mutation effects of virus-host protein interactions.

To achieve this goal, Schneidman-Duhovny and Linial propose to rely on comparative modeling, template-based and ab initio protein-protein docking algorithms, molecular dynamics simulations, and mutation analysis tools. They have recently applied this methodology to characterize the SARS-CoV2 spike protein for the domain that interacts with the human ACE2 receptor. By comparison with other coronaviruses (natural isolates and a designed version), they found that the viral interface with its receptor mutates and it is thus not an attractive candidate for future drugs. This finding is of utmost importance as the combination of the dynamics of the interface, binding affinity, and degree of conservation can be used for prioritization of druggable targets among the hundreds of such possible targets.

Using their methodology, Schneidman-Duhovny and Linial will identify and classify protein-protein interactions, understand sequential steps in viral infection, and suggest the most successful therapeutic strategies.

### **Characterization and structural studies of neutralization epitopes on SARS-CoV-2 spike (S) protein to facilitate the design of an effective vaccine**

*Dr. Alexander Rouvinski, Faculty of Medicine; Dr. Netanel Tzarum, The Silberman Institute of Life Sciences, Faculty of Science*

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that emerged in China at the end 2019 and spread to the vast majority of countries worldwide, is the third newly-emerged coronavirus that has caused outbreaks in the past two decades (together with SARS-CoV (2002) and the middle east respiratory syndrome (MERS, 2012-2013)). The recurring outbreaks of new coronaviruses suggest that these viruses will continue to pose a global health concern and highlights the urgent need to develop a cross-protective vaccine against multiple coronaviruses.

Coronaviruses surface spike glycoprotein (S) is the receptor-binding protein that mediates viral entry into host cells. The S protein is composed of two functional sub-units, S1 and S2, that mediate cell attachment and the fusion of the viral to the host cell membrane, and is the main target for neutralizing antibodies (NABs). Therefore, structural studies of coronaviruses S protein in complex with NABs are critical for the identification and characterization of S cross-protective epitopes (the part of an antigen molecule to which an antibody attaches itself) and can provide essential information on sites of vulnerability in the virus to guide structure-based vaccine design.

Utilizing Rouvinski's, Tzarum's and Wolf's combined experience and expertise in functional and structural studies on RNA enveloped viruses spike proteins (Dengue, Zika, Influenza A, and Hepatitis C viruses), they will characterize coronaviruses S protein cross-protective epitopes to facilitate the design of an effective vaccine. In the first step, they are currently expressing, as a recombinant protein, the ectodomain and the subunits of the S protein of SARS-CoV-2 viruses that were isolated from infected patients. In parallel, they will express SARS-CoV and MERS S proteins. The recombinant proteins will be used for isolations of epitope-specific Abs from infected patients using the tagged-antigen B-cell sorting method that they have developed in a joint effort collaboration with the Departments of Microbiology and Biochemistry of the Faculty of Medicine. The use of this method will provide them with a plethora of antibodies linked to their given antigen. The isolated Abs will be expressed, their epitopes will be mapped, and the neutralization potency of the isolated Abs will be tested in viral neutralization assays. Selected NAbs will be advanced to co-crystallization experiments with their antigen and the cross-protective epitopes will be characterized. This knowledge will be then applied to the development of a novel prophylactic vaccine against coronaviruses to limit the spread of SARS-CoV-2 as well as the emergence of new coronaviruses outbreaks.

### **T-cell cytokine analysis and manipulation as a novel therapy mode for severe COVID-19 patients**

*Dr. Micha Berger, Faculty of Medicine*

The clinical manifestation of COVID-19 in patients varies from mild flu-like symptoms to severe pneumonia, respiratory failure, sepsis and death. Although data regarding epidemiology and the clinical characteristics of COVID-19 are accumulating, studies investigating the cytokine profile in these patients are scarce. Cytokines are the most important factors regulating inflammation, which are secreted by a variety of immune cells and other cell types.

Several pro-inflammatory cytokines, including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6 and IL8, were reported to be increased in severe acute respiratory syndrome (SARS). This profile suggests that a particular type of immune cell, called a "T helper" (Th, in this case Th1) is involved in mediating immunity. Reports on the cytokine profile of COVID-19 –infected patients suggest a similar Th1-associated profile. However, in SARS patients with severe disease, the immune reaction appears to be skewed towards a different program – Th2 – with increases in different cytokines. This is notable in SARS patients with fatal outcome, as compared to patients who have recovered. The Berger team proposes to analyze the cytokine characteristics of COVID-19 patients with mild, moderate and severe disease expression.

Data regarding cytokine profiles of COVID-19 patients can be used to further evaluate the efficacy of therapeutic targeting of specific cytokines active in severe cases. This can be achieved by utilizing biological agents, such as dupilumab, which are currently approved for other

diseases such as severe asthma and atopic dermatitis. Thus this research has the potential to introduce a novel therapeutic modality that can reduce mortality rates from COVID-19.

### **Targeting neutrophils as a therapy for severe COVID-19 infection**

*Prof. Zvika Granot and Prof. Zvi G. Fridlender, Faculty of Medicine*

COVID-19 is a new, highly infectious virus that infects the respiratory system. Severe COVID-19 infection is associated with respiratory failure which may be lethal. One of the major causes for lethal respiratory failure in critically ill COVID-19 patients, is Acute Respiratory Distress Syndrome (ARDS). ARDS is a rapidly deteriorating condition where components of the immune system react excessively and cause severe lung tissue damage. While it is clear that the COVID-19 virus is capable of initiating the ARDS cascade, this pathology is propagated by neutrophils, the most abundant subset of white blood cells. After the viral replication triggers hyperinflammatory conditions and cytokines storm, an influx of activated neutrophils is the next step in this deleterious process.

Neutrophils, a central type of immune system white blood cells, are primarily involved in protecting the host from microbial infections and inflammatory processes. However, under extreme conditions, such as COVID-19 -induced ARDS, they play a deleterious role and cause life threatening damage to the lungs. Moreover, a study published this month shows that refractory COVID-19 patients in Wuhan, China (the epicenter of the COVID-19 outbreak) present with a significant increase in neutrophil numbers compared with recovering COVID-19 patients. This observation, together with the established role neutrophils play in ARDS, highlights neutrophils as a potential therapeutic target in complicated severe COVID-19 cases.

Over the past several years, Granot and Fridlender have been developing a neutrophil-specific drug delivery platform. The specificity of this platform provides an opportunity to deliver potentially toxic drugs to neutrophils with minimal effect on other cells in the body. Using several mouse models of disease, they have proved that this platform may be used to modulate neutrophil function in vivo. As neutrophils appear to be an attractive target in treating severe COVID-19 cases, they will study the possibility of utilizing this platform as a potential therapy for severe COVID19 patients. This therapy will have two complementary arms: A. they will use this platform to deliver a toxic molecule to neutrophils and reduce their number without harming other components of the immune system; and B. they will deliver specific inhibitors that will limit the extent of neutrophil-induced tissue damage. To test the therapeutic potential of targeting neutrophils in this context, they will use both mouse models of ARDS and mouse models of coronavirus infection. They will assess how limiting neutrophil numbers, limiting neutrophil activity, or limiting both, improves survival. Granot and Fridlender have already successfully adjusted the neutrophil-specific drug delivery platform to human neutrophils. This suggests that if their experiments in mice are successful, they could be rapidly translated into a life-saving therapy.

## Orally available, highly potent Integrin avb3/avb5 inhibitor: A promising agent for coronavirus SARS-CoV-2 infection therapy

*Prof. Chaim Gilon and Prof. Amnon Hoffman, Faculty of Medicine*

A wide array of viruses utilize integrins as receptors to mediate multiple functions such as viral entry and activation of signaling events. Integrins are integral membrane proteins that mediate a variety of functions including cell adhesion and signaling events. Integrins are arranged as heterodimers on the cell surface composed of two transmembrane subunits: an  $\alpha$  and a  $\beta$  subunit. The integrin heterodimers have a large extracellular domain to mediate binding to ligands, such as extracellular membrane proteins, including fibronectin or vitronectin, either through the I- (or A) domain within the  $\alpha$  subunit or through an interface formed by the  $\beta$  propeller domain of the  $\alpha$  subunit with the I- domain of the  $\beta$  subunit. Oftentimes integrins recognize and bind to their ligands through short, linear integrin-binding motifs, such as the arginine–glycine–aspartic acid (RGD) motifs. Integrins have a short cytoplasmic domain that can elicit the activation of signaling pathways and can promote cytoskeletal rearrangement within the cells.

Pneumonia caused by the new coronavirus SARS-CoV-2 has caused serious damage to people's lives and health. The initial route of infection is the binding of the spike protein (S protein) of the virus to the angiotensin-converting enzyme 2 (ACE2). From bioinformatics analysis, it was found that the S protein of SARS-CoV-2 produced an evolutionary mutation of K403R compared with the S protein of SARS-CoV, forming an adjacent RGD motif at the interaction surface.

As the RGD motif is considered as a ligand for many cell surface integrins, Gilon and Hoffman propose that the binding of S protein of SARS-CoV-2 with integrins may facilitate the infection process of the virus. Therefore they performed high-throughput virtual screening by choosing the key residues of S protein interface of SARS-CoV-2 and the adjacent RGD motif as potential binding site, to search for the potential agents targeting interaction of S protein of SARS-CoV-2 with both ACE2 and integrins as potential therapeutic drugs.

It was already shown that Zika virus (ZIKV), a close relative of the coronavirus SARS-CoV-2, uses integrin avb5 to infect neural stem cells. Gilon and Hoffman have developed a highly potent, orally available integrin avb3/avb5 inhibitor. They propose to test whether this inhibitor will block the entry, activation and signaling events used by the coronavirus SARS-CoV-2 for infection.

## Neutrophil Involvement in refractory coronavirus infection

*Prof. Zvika Granot and Dr. Alex Rouvinski, Faculty of Medicine*

Neutrophils are the most abundant white blood cells in the blood circulation system. They are primarily involved in protecting the host from microbial infections and inflammatory processes. Over the past two years Granot and Rouvinski have been studying how neutrophils modulate the response to West Nile virus infections. The hypothesis they have been testing is that neutrophils take up viral particles, in an antibody-dependent manner, and act as Trojan horses, propagating the infection by both sheltering the virus and disseminating the viral particles throughout the body.

Their research highlights neutrophils as an attractive therapeutic target to treat infected individuals. With the global spread of COVID-19, their attention shifted towards testing this concept in this context. This hypothesis is supported by two studies – the first is a study published this month, showing that refractory COVID-19 patients in Wuhan, China (the epicenter of the COVID-19 outbreak) present with a significant increase in neutrophil numbers compared with recovering COVID-19 patients. The second study focused on SARS-CoV and showed that old mice are less responsive to treatment compared with younger mice. The noticeable difference between the two age groups was the increased number of circulating neutrophils in older mice.

These studies suggest that neutrophils may be involved in facilitating refractory COVID-19. If this is indeed the case, targeting of viral particles uptake by neutrophil may serve as a therapeutic strategy to treat refractory COVID-19 patients. To test this hypothesis Granot and Rouvinski will use mouse models of coronavirus infection and ex vivo experiments with human neutrophils.

## A Systematic Search for New Drugs that Restrict SARS-CoV-2 infection

*Dr. Oren Parnas, Faculty of Medicine*

A novel severe acute respiratory syndrome-related coronavirus, SARS-CoV-2, is the virus behind the global COVID-19 pandemic. COVID-19 has already killed more than 40,000 people and continues to spread quickly. The major cause of death is lung failure but it is not fully clear how the virus enters the lung and which cell type allows viral replication and spreading. The suggested entry mechanism for coronaviruses includes the spike protein that is expressed on the virus envelope and binds to ACE2 – a receptor that is expressed by the host.

In this project we will take three steps to find new drugs that can reduce ACE2.

First we will generate single-cell data from the lung and upper respiratory tract tissue, and in addition build on existing single-cell data, to map all the cells that express ACE2 and therefore can be a potential entry site for the virus. Second, we will screen to search for genes that regulate ACE2 expression. The result of this experiment is a set of genes that can be targeted to reduce the expression of ACE2 on the cell membrane. Lastly, we will perform computational



screen for known drugs that inhibit the relevant genes that were found in the screen and test their ability to reduce ACE2.

The expected outcome of the study are drugs that reduce the level of ACE2 and therefore can inhibit infection and spreading of the virus in the body after the initial infection and clinical signs.

## Metabolic Control of SARS-CoV-2

*Prof. Yaakov Nahmias, the Center for Nanoscience and Nanotechnology and the Alexander Grass Center for Bioengineering*

Viruses like COVID-19 need to hijack patient metabolism to replicate. This is the soft spot in the virus lifecycle as human proteins don't mutate as fast as viruses do. In this project, it is proposed to use known molecules that target specific metabolic pathways on which the virus rely in order to stop the virus from replicating in patients.

The SARS-CoV-2 infection is expected to infect over 40% of the world population and its associated COVID-19 pandemic to cause pulmonary disease in 5% to 20% of patients. Current anti-viral compounds were developed for other infections but have some efficacy in mitigating the virus replication. However, new compounds that target virus proteins might require significant safety assessment due to possible side effects and toxicity affecting over 95% of all investigated compounds.

One alternative is to target host-pathogen interactions, specifically virus reliance on host metabolic pathways for replication. The Nahmias lab has previously shown that the HCV virus lifecycle can be blocked by targeting host nuclear receptors that control metabolic pathways on which the virus relies. In recent work, they identified that inhibition of HNF4 $\alpha$  or up-regulation of PPAR $\alpha$  or FXR could block virus proliferation. This approach has the advantage of identifying FDA approved drugs such as fibrate or obeticholic acid as potential HCV anti-virals with a known safety record, hastening the pathway from discovery to the clinic.

The aim of this project is to develop a comprehensive model of lung epithelial metabolism by integrating metabolic fluxes with their underlying transcriptional elements of control thus enabling the rational design of transcriptional-metabolic interventions which will minimize SARS-CoV-2 assembly, replication, and release.

Recently, the Nahmias lab developed an advanced tissue culture model that couples metabolic flux balance with transcriptional regulatory analysis, identifying and systematically perturbing nuclear receptors to unravel the host-pathogen interactions of the Hepatitis C Virus. This technology detects changes in metabolic fluxes induced by viral infection to guide the transcriptional regulatory analysis, identifying precise regulatory hubs that can be systematically perturbed to target cause-effect relationships. Importantly, the work showed that HCV induces

glucose metabolism through HNF4 $\alpha$  and its inhibition can block viral replication. Moreover, we showed that activation of lipid metabolism through PPAR $\alpha$  and FXR was anti-viral. Induction of nuclear receptors using FDA-approved drugs such as fibrates or obeticholic acid blocks the viral lifecycle.

### **Human co-stimulatory receptor mimetic peptides: Potential therapeutics against coronavirus infection**

*Prof. Raymond Kaempfer, Faculty of Medicine*

Coronavirus kills by evoking an inflammatory cytokine storm, especially in the lungs. In a paradigm shift, the Kaempfer lab provides a novel, host-oriented therapeutic approach to protect broadly from lethal coronaviruses, particularly emerging pandemic strains, thus containing outbreaks and preventing virus spread. The Kaempfer group has been working full-time on host-oriented therapeutics directed against such a cytokine storm. Their discovery is that the homodimer interfaces of the human CD28 receptor and of its B7 co-ligands control formation of the B7/CD28 co-stimulatory axis, pivotal to pro-inflammatory signaling that is harmful.

The group created short mimetic peptides derived from distinct regions in the CD28 and B7 receptor dimer interfaces that show potent ability to attenuate, yet not eliminate, signal transduction through B7/CD28 for inflammatory cytokine expression, and demonstrated the relevance in vivo of this host control mechanism in protecting mice from pandemic H1N1 (California 2009) and avian H5N1 influenza A virus infection – prominent examples of virus-induced lethal inflammatory cytokine storm. Their approach preserves a basal response necessary for pathogen clearance. Relevant to coronavirus, excessive expression of pro-inflammatory cytokines induced in the lungs by H5N1 avian influenza virus infection, essential to pathology, was effectively reduced by a CD28 dimer interface mimetic peptide, coupled with markedly enhanced survival rates. The group's next-generation B7-1 and B7-2 dimer interface mimetic peptides are even more promising in attenuating the cytokine storm in primary human immune cells and protect mice from lethal bacterial infections, even at 300-fold lower peptide doses. The Kaempfer team plans to evaluate their ability to attenuate inflammatory cytokine responses of human antigen-presenting cells induced via a set of Toll-like receptors (TLRs) that mediate the pathology of coronavirus during infection upon lysis of infected cells, using commercially available TLR agonists – for example, in attenuating expression of a major human mediator of acute lung injury, IL-6, when induced by double-stranded RNA, a major product of coronavirus replication acting through the TLR3 receptor.

Positive pilot data on their ability to attenuate TLR3 and TLR4 signaling in human cells support this hypothesis as correct. Moreover, the team has entered into a collaboration with an American scientist on coronavirus infection in the human ACE2 receptor transgenic mouse model, aiming to test their most potent B7 receptor mimetic peptides for protective activity

against Covid-19 in vivo. The aim is to develop a therapeutic candidate(s) against lethal coronavirus infection, effective not only against the current COVID-19 epidemic but – because they are dealing here with host-oriented therapeutics that target the human immune response itself – are predicted to be effective also against future outbreaks of novel coronavirus strains. This should create a powerful market opportunity, first in the current crisis, and then – as the world has become keenly aware of pandemic threats – will demand regular stocking of the selected therapeutic(s) in hospitals and medical centers worldwide.

#### **4. DRUG DEVELOPMENT TO BLOCK THE VIRUS INFECTION AND REDUCE THE TISSUE DAMAGE**

##### **Blocking of SARS-CoV-2 infection using antibodies and fusion proteins**

*Prof. Ofer Mandelboim, Faculty of Medicine*

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in 2019 in Wuhan, China, and has since spread globally. While the majority of cases result in mild symptoms, some progress to severe pneumonia. The rate of deaths per number of diagnosed cases is on average 3.4% and is approximately 15% in patients over 80 years old.

Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The spike protein is the protein responsible for allowing the virus to attach to the membrane of a host cell. Studies have shown that SARS-CoV-2 used its spike (S) protein to bind human ACE2 which is the receptor for the original SARS virus strain.

Thus, a therapeutic agent that will block the interaction between the S protein of the virus and the ACE2 protein on the host cells will block the entry of the virus into the cells and consequently block infection. The Mandelboim lab proposes generating 4 types of therapeutics against SARS-CoV-2. They propose generating fusion proteins composed of the extracellular domains of ACE2 and S proteins fused to human IgG1. These fusion proteins will be used as decoys to prevent virus infection. In addition, they propose generating blocking antibodies against ACE2 and S which will block virus entry. These reagents can be used either alone or in combination.

## Preventing lung-collapse in coronavirus patients through the development of inhibitors for trigger enzymes

*Prof. Gil Shoham, Institute of Chemistry, Faculty of Science*

Since it is a relatively new virus, the precise behavior of the Coronavirus and its virulence is not yet clear. Nevertheless, even at this early stage it is generally accepted that it is not the direct action of the virus that may make it life-threatening but rather its indirect lung-collapse effects. A main factor involved in such lung collapse is the *Pseudomonas aeruginosa* (Pa) bacterium, a major bacterial infection that is extremely hard to cure even with intensive antibiotic treatment. Pa infection is the main cause of disease and mortality in several lung conditions, leading to the lungs becoming severely coated with mucus and a biofilm. The elderly and those with pre-existing illnesses — whose natural immune systems are significantly weakened — are particularly susceptible to it. Pa is highly potent, mainly due to its secretion of a variety of toxic and lung-degrading enzymes (biological substances that increase the rate of chemical reactions). These include four relatively well-characterized enzymes and a recently identified one called PaaP. Preliminary studies have shown that PaaP triggers the other four enzymes, with all five joining forces to damage the lung tissues of the infected person. PaaP, it appears, is the key enzyme that must be shut down. This means understanding it better — by characterizing its 3D structure and its exact mode of action — and using that knowledge to develop an approach to inhibit the action of PaaP that can then be tested, adjusted and improved.

Prof. Shoham's defined goal is to develop PaaP inhibitors that can be used to treat Pa infection as part of a "cocktail" with existing inhibitors of the other four Pa enzymes. Based on the lessons learnt from HIV treatment, he expects that this "cocktail of inhibitors" will significantly reduce the virulent impact of Pa and, thereby, of the Corona virus.

The Shoham lab recently cloned, over-expressed, purified and partially characterized PaaP. Their initial findings show that it has some unusual properties. They have found that it is critical to rapid bacterial growth and also for virulence, and have also found that it has non-catalytic and other specific characteristics that make it a promising and attractive candidate for a new concept in selective inhibition treatment approaches for lung infections.

The focus of the project is to clarify the structure and function of the relatively uncharacterized PaaP enzyme, and its potential role in various lung infections. The lab has already purified mature PaaP-56, which is likely to be the active form secreted by the Pa bacterium in its physiological environments. The lab recently succeeded in obtaining reasonable single crystals of both the monomeric form and the dodecameric form of PaaP-56. At this point, both of these crystals are relatively small (30-60 microns) and display only relatively weak X-ray diffraction (of about 3.6Å resolution). These crystals will be improved in the near future, to the point that a high-resolution 3D structure of PaaP will be determined. On the basis of this structure, the lab

will then adjust and refine its current inhibitors. In parallel to its PaaP research, the lab is conducting a complementary structural study using an enzyme isolated from a bacterium called *Bacillus subtilis* (BsaP), with characterization of its 3D structure now in final stages. In the short-term, BsaP will serve as the initial target for inhibitor design — and, in the mid- and long-term, will also serve as an alternative target should the current structural studies of PaaP fail to lead to a reasonable 3D structure of the protein.

### **Repurposed drugs and vaccine for COVID-19 treatment**

*Prof. Yechezkel Barenholz, Department of Biochemistry & Molecular Biology, Faculty of Medicine*

Prof. Barenholz is focusing his lab activities on four projects, all aimed at re-purposing drugs and treatment approaches for different stages of, and using known active ingredients for, viral infection.

Project 1: aims to stop and/or reduce viral penetration and the severe inflammation caused by the viral infection by repurposing a well-established and clinically used active pharmaceutical ingredient targeting infected lungs. A trial formulation is ready for lab models.

Project 2: aims to inhibit intracellular processing of the virus that has reached cells in the lung, using a different formulation and active ingredient with completely different modes of action than Project 1. A well-established and clinically used active pharmaceutical ingredient targeting infected lungs is being repurposed and a trial formulation is ready for lab models.

Project 3: aims to treat Acute Respiratory Distress Syndrome (ARDS), the last stage of viral infection that lead to severe morbidity and death. This is a collaboration with Prof. Yoram Weis of Hadassah-University Hospital and the University of Lausanne (Switzerland) who has shown the feasibility of this approach in treatment of ARDS. Currently at formulation stage, and ready with all the reagents and assay required for development. This Project is a totally different approach from Projects 1 and 2 and is based on a totally different active ingredient. Projects 1-3 have promising potential based on in vitro or lab model studies.

Project 4: aimed at vaccine development. The Barenholz Lab and Bio-Lab Ltd have developed and patented a novel potent adjuvant that shows excellent results as a vaccine against other viruses, and that may be applied to the development of an anti-COVID-19 vaccine. This means that all the knowledge and methods exist for the development of a vaccine that can elicit both the excellent antibodies and cellular responses needed for an effective vaccine against COVID-19. This is a joint project with Prof. Gabriel Nussbaum, an immunologist at the Faculty of Dental Medicine.

## Identifying genes involved in the pathogenicity of COVID-19 for potential drug therapy

*Prof. Nissim Benvenisty, Azrieli Center for Stem Cells and Genetic Research, The Silberman Institute of Life Sciences, Faculty of Science*

COVID-19 is a coronavirus that infects human cells through interaction with the membrane protein ACE2. We are still not familiar with the molecular pathogenicity of this virus and the genes that are involved in its virulence. Identifying genes that regulate its pathogenicity should enable generating resistance to this virus, and offer new ways to treat the devastating disease caused by COVID-19.

The Benvenisty team aims to define the genes in which mutation would confer resistance to COVID-19. They have recently generated lines of haploid embryonic stem cells (Sagi et al., Nature 2016), which are optimal for genetic screenings. Using these haploid cells, they established a genome-wide loss-of-function library (Yilmaz et al., Nature Cell Biology, 2019; Yilmaz and Benvenisty, Cell Stem Cell, 2019). In this largest mutant library in human cells, they targeted nearly all coding genes (>18,000) with more than 180,000 sgRNAs. They have recently utilized this library to study Zika virus-host interactions using this genetic screening, and will now use it to study COVID-19. The aim is to analyze the genetic basis of coronavirus-mediated infection and cell-death, and to screen for mutations that would confer resistance against COVID-19.

As preliminary data, the Benvenisty lab has already demonstrated that human embryonic stem cells have low levels of ACE2 (the membrane protein that interacts with COVID-19). However, after only 4 days of differentiation into endoderm, in the lineage that includes lung tissue, the expression of ACE2 is upregulated more than 50 fold. They thus have an in vitro system to test the pathogenicity of COVID-19. The group will next infect their extensive genome-wide mutant library of human cells with COVID-19. For this step they need access to the virus and to a BL4 tissue-culture facility. At the end of a week, they will extract the DNA of the surviving cells and prepare synthetic DNA libraries, and perform next-generation sequencing on them (as we have previously done). They will thus identify all the genes related to the pathogenicity of COVID-19. Such genes can expose the mechanisms by which the virus is infecting and killing the cells, provide information on the response of different patients to the virus, and suggest potential avenues for therapy. Since for many genes we already have inhibitory molecules, this analysis should enable the development of new strategies for drug therapy for COVID-19.

## **Drug treatments and simple blood tests for the early detection of COVID-19 biomarkers and risk factors through a combined computational biology, virology and proteomics approach**

*Prof. Dana Reichmann, Silberman Institute of Life Sciences, Faculty of Science, Prof. Ora Furman, Faculty of Medicine, Dr. Alex Rouvinski, Faculty of Medicine*

This project has two aims: (1) Identification of virus-human interactions that can serve as drug targets; (2) development an initial screening test for biomarkers for COVID-19 onset and progression.

The current CoV-2 pandemic poses a novel unprecedented threat to humanity that requires coordinated response in terms of early diagnosis and prevention of the SARS-CoV-2 infection. This project brings together and the efforts and expertise of three teams: computational biology (Ora Furman), virology (Alex Rouvinski) and proteomics (Dana Reichmann). The joint team will seek answers to two main questions: 1. How does SARS-CoV-2 interact with human cells and which receptors beyond ACE2 are hijacked by the virus? 2. Why do specific individuals develop a severe form of the disease, while others are asymptomatic and are these differences encoded in the human proteome?

The characterization of virus-host interaction and definition of the differences in plasma proteome of individuals with diverse response to the SARS-CoV-2 infection will not only allow create the basis for promising drug targets, but also for the development of a simple blood test for the detection of early biomarkers and risk factors for COVID-19 progression. The team's specific plan is:

1. Map and characterize virus-host protein interactions: Since the SARS-CoV outbreak in 2002, significant advances in the structural characterization of the SARS-CoV and SARS-CoV-2 viruses have shed light on the spike protein and its interaction with the human ACE2 receptor. However, it is evident that the SARS virus interacts with additional host factors in order to hijack cellular behavior for its own benefit. We propose a structure-based, computational approach to identify, on a large scale, the host proteins that are contacted by the SARS-CoV-2 virus and are then used by it to hijack cellular behavior (Furman lab). Identified potential targets will be matched with complementing available proteomic studies of protein expression, focusing on age-related and tissue-specific proteomic studies. This will shed light on the distinct infection pattern (associated with age and infection rate) of the SARS viruses from the 2002 and 2020 outbreaks, and will point to clinically promising human and viral drug targets. To narrow down the list of potential candidates, we will conduct cross-linking mass spectrometry analysis (Reichmann lab) to validate promising interacting pairs, as well as mapping interacting sites. These newly identified virus-host interactions can then be specifically targeted using two approaches: (a) The repurposing of existing drugs known to target the specific identified host receptors, and (b) the structure-based design of peptidic inhibitors of the virus-host interactions, using stabilized peptides and

peptidomimetics. Candidate molecules will be tested for their effect on viral infection and propagation in model systems, and in infected human samples (Rouvinski lab).

2. Comparative proteomic analysis of plasma proteins using blood and saliva samples (provided by Dana Wolf, Hadassah-Medical Center): The Rouvinski lab will extract plasma proteins, which will be evaluated by high-resolution mass spectrometry in the Reichmann lab. We will analyze samples from patients varying in age and the COVID-19 disease progression phase. Bioinformatic analysis will be used to define distinct proteome profile and biomarker identification, with a predictive power.

### **Harnessing antimalarial drugs for the potential treatment of COVID-19**

*Dr. Ahmad Masarwa, Institute of Chemistry, Faculty of Science*

Goal: Development of a novel synthetic methodology for the synthesis of a new family of hydroxychloroquine analogs to be used as a potential therapy for COVID-19.

COVID-19 is an emerging global health crisis, with over 300,000 confirmed cases to date and about 13000 deaths globally. The pandemic continues to expand, meaning that the rapid development of specific antiviral drugs is of the highest urgency. Recently, hydroxychloroquine (HCQ), a medication used for the prevention and treatment of certain types of malaria, has shown great potential for the treatment of COVID-19. However, the library of its analogs (novel drugs with structural and pharmacological similarities to the original) is extremely limited. Based on the hypothesis that the development of new HCQ analogs could lead to more efficient therapeutic interventions, the Masarwa lab will pursue a unique methodology for the synthesis of a wide range of analogs of the HCQ family that are highly promising candidates for COVID-19 treatment. This involves Dr. Masarwa's current work on the modification of reactions of selected sites on the HQC structure.

The growing significance of these new, modified reactions has been illustrated by their incorporation into the synthesis of complex natural products and biologically active molecules. Moreover, the late-stage functionalization/diversification of selected sites in molecules is an area of contemporary importance with wide-ranging implications for organic synthesis and the effective use of natural resources, and drug discovery.

The Masarwa research team is actively engaged in the pursuit of innovative solutions to the selective synthesis of bioactive-architectural complex molecules based on late-stage site diversification. It is envisaged that these methods could eventually be easily applied to the late-stage diversification of HQC in order to create a new family of analogs.



This method offers a future platform for the efficient process of late-stage site functionalization of HQC derivatives through the incorporation of novel functional groups that can make HQC more powerful.

### **Smart Screening of Disinfecting Materials and Anti-Coronavirus Drugs**

*Prof. Uri Raviv, Institute of Chemistry, Faculty of Science*

Coronavirus is a 120-nanometer lipid enveloped ssRNA spherical virus with a capsid (protein coat) of helical symmetry. The lipid membrane that envelops the virus contains spike proteins. An antiviral drug may either disassemble the capsid and/or destabilize the lipid bilayer.

The Raviv lab will use experimental and analyses approaches developed in its earlier work on virus assembly and lipid membrane stability in order to direct, tune, and control the assembly and disassembly reactions of Coronavirus, and develop disinfecting materials and antiviral drugs.

The Raviv research group's focus and expertise is in the study of macromolecular assemblies in realistic solution conditions. It has been developing pioneering state-of-the-art solution X-ray scattering-based technology which it has combined with cutting-edge data analysis tools developed in the lab and then integrated with simulations, theory, and various advanced algorithms in order to elucidate the structures and intermolecular interactions in complex, weakly ordered, and dynamic self-assembling biological structures. Research subjects include both virus self-assembly and lipid membranes, which are highly relevant to determining novel approaches for combatting Coronavirus.

The lab has done rigorous, high-precision thermodynamic, kinetic, and structural analysis of the assembly and disassembly processes of the Hepatitis B virus (HBV) and the simian vacuolating virus (SV40). To date, it has resolved the interactions of SV40 with various ions and the pH stability and disassembly mechanism of wtSV40; elucidated the most basic interactions that take place between lipid membranes; and determined how different ions, polymers, and osmolytes mediate the structure, dynamics, stability, and interactions between membranes.

The lab's work has revealed the paths and conditions that allow virus capsid subunits to successfully work together and form stable capsids and determine when assembly is likely to go irretrievably off-path. This unique knowledge has direct implications for the development of antiviral drugs. The lab has shown that in order to successfully form capsids, the association energy has to be within a narrow window — if below a critical value, assembly cannot take place and if above a certain threshold, then kinetically trapped states rapidly form, deplete the available free subunits, and limit the possibility to form a complete capsid. The lab also found that in reaction conditions that successfully lead to capsids, the most compact and stable intermediates form. Outside successful assembly conditions, it showed why assembly does not start, or lead to kinetically trapped states.

Prof. Raviv's hypothesis is that a similar narrow window exists in coronavirus. He plans to test a range of osmolytes and FDA-approved drugs that are likely to change the association free energy

between coronavirus subunits and prevent or reverse the assembly process. These molecules would serve as potential antiviral drugs or as sanitizing or disinfecting materials to be used on different surfaces.

The Raviv lab will perform the lab's existing tests on HBV and realistic model lipid membranes (for example 1:1 mixture of DPPC and DMPC) and suggest a list of materials to be tested on coronavirus; and then work directly on coronavirus model systems and fine-tune the efficiency of the antiviral drugs and disinfecting materials.

### Discovery of drugs to inhibit coronavirus function

*Prof. Amiram Goldblum, School of Pharmacy, Faculty of Medicine*

Several years ago, Prof. Goldblum and his team developed a prize-winning algorithm which, in recent years, has been the basis of patents and publications for over 60 drug candidates for diverse conditions: blocking immune system reactions, treating fatty liver disease, reducing iron load in cancer, anti-obesity compounds, and molecules that prevent the death of beta cells in pancreas (anti-diabetes).

The generic novel algorithm, called "Iterative Stochastic Elimination" (ISE), is unprecedented in its ability to cut through an immense number of solution possibilities and swiftly identify excellent solutions for extremely complex combinatorial problems such as in drug discovery. The Goldblum lab's most advanced project to date is the result of modeling nano-liposomal drug delivery based on the properties of drugs and their stability in the blood vessels.

The lab aims to reach clinical studies of several anti-SARS-2 drug candidates in less than a year and then improve them based on research results. They envisage uncovering "multi-targeted" small molecules that simultaneously inhibit two or more of the pathways of SARS-CoV-2 (SARS-2). It is focusing on four SARS-2 proteins: 3C-like proteinase (3CLPro); papain-like proteinase (PLPro); RNA-dependent RNA polymerase (RdRp); and angiotensin converting enzyme-2 (ACE2), which is the viral "gate" into the host cell. Multi-targeting by single molecules has well known advantages in both drug delivery to the disease location and in binding to more than one disease target. The Goldblum lab already has an impressive track record in finding multi-targeted molecules using its algorithm.

The modeling algorithm (Iterative Stochastic Elimination or ISE) allows for the very rapid screening of millions of molecules, obtained from commercially available or combinatorial databases, that are scored by its models and prioritized for experimental testing. These ISE models are sets of physiochemical properties that distinguish between bioactive molecules on a specific target and random molecules. Following screening, the most promising molecules are purchased or synthesized, tested for solubility, and sent for cellular studies in collaborating labs.

ISE is a machine-learning platform with several major advantages:

- It can discover large sets of active molecules in screenings of some 20 million.

- It provides extremely fast results: modeling takes a few days, screening another few days.
- 99% of molecules discovered have never been tested for any activity.
- Over 60 molecules in seven different projects have been patented recently.
- Three start-up companies are based on our algorithm.
- Anti-obesity molecules have been licensed to another start-up
- All discovered molecules are patented in the “any pharmacological activity” category.

## Rational design of anti-SARS drugs by applying machine learning and quantum chemical methods to existing drugs

*Dr. Igor Schapiro, Institute of Chemistry, Faculty of Science*

This study aims at a molecular-level understanding of how specific drugs bind a drug to the main enzyme — a protease called Mpro — in SARS-CoV2. In order to interrupt the life cycle of the virus, the candidate drug must bind to the protease and inhibit enzyme activity; this means that it is essential to both characterize and quantify the drug-protein interaction. The Schapiro lab plans to characterize this interaction in two steps: first, a large library of known drugs will be screened; then accurate quantum chemical calculations will be applied to the best candidates, with the results used to identify and quantify the interactions between the specific drug and Mpro. The results of this process will then be used for drug repurposing. In contrast to the development of brand new drugs, this approach represents an efficient strategy to discover effective drugs within a shorter time in terms of approvals and at a reduced cost. Furthermore, the comprehensive insights gained from the computer simulation will provide guidelines for better drug design.

The Coronavirus disease (COVID-19), a pandemic caused by the SARS coronavirus (SARS-CoV2), spreads at a significantly high reproductive rate, several times higher than other related RNA viruses. The main challenge of SARS-CoV2 is its animal origins. Because the DNA/RNA chain in animals is not recognized by the human immune system, this means that the human immune system and vaccinations cannot combat animal viruses. While this is a major drawback, it also carries an advantage that can be leveraged for drug development to combat SARS-CoV2.

The enzyme Mpro has been identified as the optimal target for Coronavirus drugs. Mpro is essential for processing the protein chains, which are translated from a viral RNA. Hence, if its activity can be inhibited by short peptide-mimicking drugs, it would block the viral replication. It is at this stage that the animal origin of SARS-CoV2 becomes a strategic advantage — there is no human protease that has similar specificity to Mpro, meaning that a drug developed to target Mpro would be non-toxic for humans.

This target was previously identified in 2003 for SARS-CoV, which is 80% similar to SARS-CoV2. Subsequently, a series of drug were developed and tested. Several days ago, the crystal structure of the main protease in SARS-CoV2 was solved, including the binding of four potential drugs that could act as inhibitors of Mpro. The Schapiro lab intends to analyze the structure with the bound

inhibitor and then analyze the interactions using quantum chemical calculations. This will provide a guideline as to which binding sites are suitable for improvement in order to ensure strong binding. Working in collaboration with Prof. Olexandr Isayev of Carnegie Mellon University, a world-leading expert in the application of machine learning to chemical problems, the lab will also conduct a virtual screening that will make use of Prof. Isayev's extensive library of previously developed drugs which will first be trained to recognize the SARS-CoV and then compared to experimental data. The lab will use accurate multiscale modelling as the basis for training the machine-learning approach. The multiscale modelling will comprise a hybrid of quantum mechanics and molecular mechanics (QM/MM), Nobel-prize winning method (Nobel prize 2013 by Warshel, Levitt and Karplus) that allows for the division of the entire system into two subsystems. A smaller subsystem describes the site of interest using quantum mechanics and the remaining, larger system is described at a lower accuracy. The advantage is that the entire system doesn't require a full quantum mechanical description and can be calculated in less time. Moreover, it offers higher precision than docking or force-field approaches, which also require extensive benchmarking. This combined QM/MM method means that the focus is on the high accuracy of the active binding site where the inhibiting drug is bound to the protein which in turn means that a large number of compounds can be screened at a very high level of accuracy. The drugs with the most promising compounds will then be tested on SARS-CoV2 and the most effective would be made available to experimental groups free of charge in order to speed up the search for a cure to the COVID-19.

Dr. Schapiro expects to screen a large library of drugs and produce accurate predictions of their binding to the main protease. This approach replaces or narrows down expensive and time-consuming drug tests while also pinpointing specific site for drug binding for the development of de novo (computer-assisted molecular design) drugs.

### **Relieving lung disease in Covoid-19 patients through ribozyme-loaded microcapsules delivered into the lungs as aerosols**

*Prof. Itamar Willner, Institute of Chemistry, Faculty of Science and Prof. Eli Pikarsky & Prof. Moshe Kotler, Faculty of Medicine*

The major cause of death from COVID-19 is lung disease, with examination of lung tissue from COVID-19 patients and those afflicted in the previous SARS outbreak indicating that the major trigger of the lung disease are cytopathic viral effects which kill the pneumocytes, which are the cells in lungs that mediate oxygen and CO<sup>2</sup> transfer to and from the blood.

This team brings together experts in ribozyme/DNAzyme engineering and the in-vitro characterization of the catalytic functions of ribozymes/DNAzymes and experts in the synthesis of stimuli-responsive nucleic-acid-loaded CMC microcapsules. Ribozymes are catalytic nucleic acids that catalyze specific biochemical transformation, and can be easily engineered to cleave any specific RNA molecule. A single ribozyme can cleave multiple copies of a specific RNA.

Ribozymes are unlikely to be immunogenic and rarely elicit a cellular innate immune response. Smart carboxymethylcellulose (CMC) microcapsules carry loads, including nucleic acids, into cells, and release the loads by cellular triggers. A single microcapsule can carry hundreds of ribozymes units. CMC is routinely used as a drug carrier and reveals a superb toxicity profile.

The team's research project aims to engineer several ribozymes that target viral genetic elements (particular targets include S=spikes, RNA-dependent RNA polymerase, and leader sequences residing at the 5'-end of the genomic RNA and at the 5'-end of each of the sub-genomic mRNAs associated with specific corona viruses). The respective ribozymes will be loaded in microcapsules, and delivered as aerosols into the lung. The microcapsules delivered into the pneumocytes will be unlocked by K<sup>+</sup>-ions present in the cells. It is expected that, on delivery of the ribozyme to a major number of pneumocytes, there will be a significant attenuation of the cytopathic effect which will serve to improve lung capacity and the patient's condition, and allow the immune system to mount an effective response to achieve cure. The microcapsules will be tested on avian infectious bronchitis virus, the first corona virus, or — as the research progresses — on the COVID-19 virus itself (in appropriate laboratories).

### **Systematic computational drug repositioning to treat COVID-19**

*Dr. Yuval Tabach, Faculty of Medicine*

There is an urgent need for the development of preventive and treatment strategies for the SARS-CoV-2 (COVID-19) outbreak. Viruses depend on their hosts to reproduce and can only survive by hijacking and rewiring the host's cells during infection. For example, coronaviruses are known to interact with the human gene ACE2. The Tabach lab suggests a strategy that focuses on targeting the proteins and networks in the human cells that are manipulated by the virus. By incorporating massive amounts of data and applying cutting-edge computational approaches, they will effectively map new drug targets that can perturb these proteins and networks. One very effective and efficient drug discovery strategy involves finding new uses for existing, FDA-approved, drugs. This strategy can reduce both the cost and time it would take to develop, and acquire approval for, COVID-19 treatments as compared to de-novo drug discovery. The lab is pursuing three complementary research directions:

1. Comparative genomics and data integration - They will construct a map of the network of human genes connected to SARS-CoV-2 infection. They will start with known virus interacting genes, and integrate comparative genomics (comparing the genetic data of multiple species) across over 1000 species with data from the literature, known protein-protein interactions, and others, to construct the virus interaction network. They will identify drugs which will perturb the network that is critical for viral infection.
2. Gene activity profiles - Viruses change the gene activity profiles of cells they infect. This unique profile will be utilized by the Tabach group to develop a list of drugs which exclusively target the human proteins interacting with the virus or associated with the disease. They will be

able to classify other diseases with similar gene activity profiles and identify the drugs that treat those same diseases. They will identify drugs that cause similar or reverse gene activity profiles to the SARS-CoV-2, which will allow them to know both which medications are effective in treating cases of SARS-CoV-2, and which will make the infection worse.

3. Clinical health records - Using clinical health records from Hadassah Medical Center in Ein-Kerem as well as other sources, the group will identify drugs that correlate with mitigating severity of disease in different age groups and clinical conditions. They will employ these datasets both to validate their predicted repurposed drugs, and to identify new ones.

In preliminary results, the Tabach group has already identified a list of drugs that target genes in the ACE2 network, including drugs against diabetes, the previously reported-on and much debated Ibuprofen, and more. Throughout this project, they will improve their methods of comparative genomics and data integration, develop and employ novel methods of data analysis, and dramatically increase the amount of data they analyze. This work will suggest specific, FDA-approved, drugs which can be rapidly deployed to treat coronavirus infection related diseases.

### **Design, coordination and production of tools to reduce viral transmission**

*Prof. Ami Citri, the Edmond and Lily Safra Center for Brain Sciences (with Itamar Frachtenberg, ELSC)*

A large proportion of virus dissemination is through exposure to common surfaces (door handles, cart handles, elevator buttons etc.). The Fabrication Laboratory at the Edmond and Lily Safra Center for Brain Sciences is designing simple and easy-to-manufacture solutions for reduction of the interaction of exposed hands with these surfaces. Furthermore, the Fabrication Lab is set to coordinate the activity of the 'Maker' community around Israel (including, for example the Industrial Design department in Bezalel) – to provide a common platform for sharing designs and coordinating production. The designs will be open-source and disseminated broadly.

As an example of one such product, the lab is designing a tool to be used as a substitute for hand-performed operations for utilization in various scenarios such as opening doors, pressing switches and more. The tool will act as a pocket knife that will be affixed to the smartphone protector, thus turning the smartphone into a torque lever during operation.

The smartphone itself - an object that transmits infections - is usually held in the hand and touches the ear. The tool will also act as an external skeleton that holds the smartphone in display position when mounted on a surface. The tool's contact areas and positioning device will be embedded with copper to reduce the accumulation of virus on them.

The purpose of this effort is to reduce the risk of being immediately infected via contact with various surfaces in regular daily functioning, by developing a relatively cheap tool that can be

quickly designed and manufactured, unrestricted by stringent safety standards as this is not a medical device. A second product example is a copper extension to be placed on door handles, enabling the door to be opened with the elbow rather than the hand.

### **Development of anti-Ceacam1 antibodies for the treatment of Coronavirus infection NO PR**

*Prof. Francesca Levi-Schaffer, School of Pharmacy, Faculty of Medicine*

Viruses are small infectious agents that can only replicate inside the living cells of an organism. In order to infect host cells, viruses use several proteins on their surface that bind and attach to the host cells. This stage allows the virus to penetrate the host cells and as such, it is a crucial step in the development of the disease. Ceacam1, a receptor expressed on immune cells and other cell types, has been shown to be a molecule that regulates cell interactions and that affects a variety of cellular processes and reactions. Ceacam1 is also an inhibitory receptor that, after activation, blocks the immune cells' response against pathogens. Previous studies showed that various pathogens (including bacteria and viruses) bind to Ceacam1 in order to inhibit the immune response and to infect the host cells. However, upon induction by viruses, Ceacam1 was found also to activate several processes that aim to suppress viruses. Several studies indicate that Coronaviruses may bind to ceacam1, and Prof. Levi-Schaffer has hypothesized that COVID-19 may also use Ceacam1 to infect the body cells.

By blocking Ceacam1/COVID19 interactions with an antibody, she and her lab are aiming to block the virus infection and its propagation, and strengthen to body's immune cells to fight the virus. The lab has developed several anti-Ceacam1 antibodies which may offer the potential for broad antiviral efficacy by:

- 1) binding to cell membrane Ceacam1 and thereby stimulating anti-viral activity in the lungs, epithelial cells, lung dendritic cells, and other immune cells expressing Ceacam1.
- 2) competing with virus Ceacam1 binding to the cell surface Ceacam1.
- 3) binding to virus Ceacam1 and therefore trigger its binding to the cell surface Ceacam1.

This novel immune-therapy approach could be very effective for the treatment of coronavirus patients.

### **Identifying novel drug targets for blocking the COVID-19 virus using large-scale proteomics and AI**

*Dr. Haitham Amal, School of Pharmacy, Faculty of Medicine*

Identifying the molecular events underlying the disease caused by COVID-19 is essential to finding the best treatment for those infected by the virus. Using the blood samples of people infected with the Corona Virus (COVID19), Dr. Amal and his lab plan to combine a state-of-the-art proteomics platform with bioinformatics techniques that include Artificial Intelligence (AI) in

order to identify novel clinically relevant molecular targets for blocking the pathogenic effect of COVID-19 virus. Proteomics, the study of the entire complement of proteins in a cell, can be used to probe their function and their interaction with viruses. Using a human lung cell culture, the scientists will test potential drug interventions, with the aim of blocking the disease-triggering activity of the virus. Based on their hypothesis that altered signaling, and oxidative and nitrosative stress contribute to the pathology of COVID-19, the Amal team will examine the virus-induced changes in the proteome of critical proteins and in signaling pathways. Alongside this AI approach, they also plan to pursue a large-scale study to detect potential molecular targets for novel and effective drug interventions.

The study comprises three stages:

1. Detection of the most significant changes in protein expression caused by COVID-19, using blood samples from healthy volunteers and patients infected with COVID-19 infection. The samples from both sexes in two age groups will be analyzed using methods that allow full analysis of protein activity.
2. The obtained proteomics data will undergo intensive AI analysis to identify high-risk targets.
3. Outlining possible drug interventions to combat COVID-19. The therapeutic effect of these drugs will be tested on human lung cells, representing a potential first step towards the translation of these novel effective therapies against COVID-19 into clinical practice.

### **5-MER peptide to ameliorate coronavirus-induced inflammation of the upper respiratory tract and lungs**

*Prof. David Naor, Faculty of Medicine*

This study will test the hypothesis that treatment with a peptide comprising five units (5-MER), and that is administered by injection or oral delivery, will substantially reduce chronic inflammation of the upper respiratory tract and lungs, thus ameliorating the effects of the Coronavirus disease. This will be achieved by targeting a major pro-inflammatory protein called SAA which plays an active role in the development of the disease. Furthermore, it is anticipated that the 5-MER peptide may also activate genes that provide resistance to chronic inflammation mediated by Coronavirus.

Prof. Naor's research is based on his lab's finding that a synthetic 5-MER peptide MTADV (methionine, threonine, alanine, aspartic acid, valine), derived from the sequence of a human pro-inflammatory protein (CD44), substantially reduced inflammation in models of rheumatoid arthritis, inflammatory bowel diseases and multiple sclerosis. Studies in his lab point to Serum Amyloid A (SAA) as the target for this peptide, which is also capable of activating genes that may contribute to resistance against chronic inflammations. In SARS, the previous Coronavirus global epidemic disease, SAA was found to increase significantly and was proposed as a suitable marker for the disease. The Naor lab has already shown the 5-MER peptide inhibits inflamed tissues stimulated with SAA.



## Testing a potential therapeutic treatment for Corona

*Prof. Ariella Oppenheim, Faculty of Medicine*

The Oppenheim lab has developed an innovative drug with high efficacy against severe lung illness (acute respiratory disease syndrome or ARDS) that is triggered by a severe disease-based infection. The novel drug comprises the outer shell — called a ‘capsid’ — of a small virus SV40 that has been declared by the NIH as non-pathogenic, meaning that it does not cause disease. Prof. Oppenheim has called the nanoparticles “nanocapsid” or NCs. The virtue of this drug lies in its mode of action, as investigated in rats that were inflicted with the severe infection sepsis. Sepsis is a major worldwide killer, second only to heart failure. The only treatment to date is antibiotics alongside hospitalization in intensive care units where patients are sedated and ventilated. Sepsis is not as well-known as cancer, mainly because while 30% of sepsis patients die within days, cancer patients may live with it for many years and may even fully recover. All previous efforts to develop treatments for sepsis have failed due to the high complexity of the disease which affects a wide range of biological functions.

The results of the Oppenheim lab’s study of the novel NC drug — in which no antibiotics were administered — showed a 75% survival rate in those rats inflicted with sepsis and treated with the NCs, while all the non-treated septic rats died within days. The study focused on the lungs and showed that unlike antibiotics, which directly kill the infecting pathogens, the NCs are able to beat severe infection by dramatically enhancing the host response. This is achieved by triggering multiple biological functions through the activation of thousands of genes and numerous cellular pathways. Furthermore, the study showed that the elicited pathways become modified with time, thus adjusting the recovery process of the treated lab models. Significantly, the control group of healthy rats was essentially unaffected by the drug, indicating that there would be no side effects for treatment with the NCs.

Additional studies indicate that the basis for the unique properties of the nanocapsids is their ability to utilize normal cellular mechanisms in order to “sense” the malfunctions of the cells as soon as they enter them. Consequently, they restore the cells to normal, healthy conditions. This same mechanism accounts for the dynamic changes in the genes and cellular pathways that are activated during the recovery process.

Prof. Oppenheim anticipates that treatment of Covid-19 patients with NCs will enable them to fight the virus and fully recover. Moreover, the novel mode of action of the NCs would stymie the development of drug resistance by generating agents that would kill any threatening microbes. It is highly unlikely that Covid-19 would develop resistance to the wide scope of host functions elicited by the NCs. The lab’s core hypothesis is that the unique property of the nanocapsids, developed through eons of virus-host coevolution, is driven by the ‘selfish’ goal of the non-pathogenic SV40 virus to propagate in a healthy organism.

## Mass spectrometry screening for effectors on the dynamics of the COVID-19 spike protein.

*Prof. Nir Kalisman, Faculty of Science*

The aim of the Kalisman lab is to establish a fast screen for inhalable drugs that have an effect on the flexibility of the spike protein. In order to interact with the surface protein ACE2 on the lung cells, the spike protein must undergo a significant conformational change. Drugs that inhibit or slow this conformational change are potential therapeutic agents. Yet, measuring the dynamics of a protein in solution is often difficult and time consuming. Kalisman and his team propose that mass spectrometry can quantify such dynamics in molecular detail by analyzing the yields of certain cross-linking reactions on the protein of interest. Multiple experimental conditions (such as the addition of different drugs) can be prepared in parallel and analyzed in the mass spectrometer within the same day. Importantly, the effect on protein dynamics of promising compounds can be later verified on intact viruses with the same approach.

The team proposes to establish a mass spectrometry assay in which different cross-linking reagents are applied on recombinant spike protein. They will verify that the cross-links indeed report on the relevant conformational change by monitoring the variations in their intensities upon addition of ACE2. They will then test whether these changes can be inhibited when inhalable drugs are added to the solution.

Timeline for achievable goals: The basic mass spectrometry assay can be set up, calibrated and verified within 6 weeks. Testing of different drugs will take an additional 6-10 weeks (depending on the number of drugs to be tested). Verification of the effect of promising compounds on intact viruses requires collaboration with a lab certified to higher safety levels, and may take an additional 2-3 months.

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## 5. DEVELOPMENT OF ADVANCED MATRICES FOR THE NEUTRALIZATION OF PATHOGENS

### Neutralization of pathogens using advanced matrices as components in masks or ventilation systems

*Prof. Itamar Willner, Institute of Chemistry, Faculty of Science and Prof. Eli Pikarsky, Faculty of Medicine*

The goals of this project include efforts to develop advanced matrices for the neutralization of pathogens. The matrices will be applied as components in masks or ventilation systems.

Active neutralization matrices — which trigger chemical reactions that dissipate harmful processes or effects — are based on the combination of nanoparticle catalysts and/or biocatalysts with “green” chemical components (such as glucose/fructose and ascorbic acid-vitamin C). In the presence of these catalysts/biocatalysts and chemical ingredients, reactive oxygen species (ROS are chemically reactive chemical species containing oxygen) called hydroxyl radicals are formed; they act as ROS for the neutralization of pathogens. The activity of the matrices originates from the catalyzed aerobic oxidation of glucose/fructose to yield — under breathing humidity conditions (or humid air) — hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) which serves as the compound needed to generate the ROS hydroxyl radicals. Previous lab studies by Profs. Willner and Pikarsky demonstrated a unique catalyzed feedback mechanism for the catalytic generation of ·OH hydroxyl radicals in the presence of H<sub>2</sub>O<sub>2</sub>/ascorbate (Nano Lett. 2018, 18 (6), 4015–4022).

As part of these studies, it was discovered that ·OH radicals can be generated in the presence of the iron oxide Prussian blue and its structural analogs. Accordingly, the neutralization composites will include H<sub>2</sub>O<sub>2</sub> generation catalysts such as glucose oxidase, fructose oxidase, Au or CeO<sub>2</sub> nanoparticles; the catalysts generating ·OH radicals; and the reactants glucose/fructose and ascorbate. These composites would be incorporated into fabrics, paper, or nonreactive particles such as silica or alumina.

### Development of Disposable Active Antiviral Filters

*Prof. Shlomo Magdassi, Prof. Daniel Mandler and Prof. Uri Banin, Institute of Chemistry and the Center for Nanoscience and Nanotechnology*

The goal of this project is to develop active antiviral filters that will provide better protection against a wide variety of viruses including COVID-19 in various scenarios, from masks to filtering systems.

Current particle filtering systems are based on a mechanical process which prevents the penetration of particles larger than the filter pores. Yet, most of the existing filters, used in

diverse applications, such as masks, office and airplane filters, are not made for viruses as small as a few tens of nanometers. Hence, to exterminate viruses efficiently, existing mechanical filtering is insufficient and additional virus eradication mechanisms should be used.

This project will work to develop an additional air-permeable active layer for filters. It is anticipated that these active filters will provide optimal protection against viruses in a cost effective way, solving both the limitations of the conventional disposable masks and current air filtration systems used.

### **State-of-the-art real-time, powerful and safe technology for fighting and eliminating viral and bacterial pathogens**

*Dr. Hani Gnayem and Prof. Yoel Sasson, Institute of Chemistry, Faculty of Science*

Numerous studies have suggested that photocatalysis technology — which harnesses the natural process in which a light-triggered chemical reaction results in the breakdown of organic matter at the molecular level — is one of the most promising and effective methods for fighting bacterial and viral pathogens. Viruses are known to withstand harsh environmental conditions such as sunlight, temperature fluctuations, chemical and physical treatments. Moreover, since they lack enzymes and cellular structure, the only part of them that can be targeted for virus deactivation is the capsid, which is the virus' protein shell. Fortunately the capsid can be destroyed using ROS (Reactive Oxygen Species are chemically reactive chemical species containing oxygen). ROS damages the capsid proteins and binding sites by means of fragmentation and aggregation that results in the loss of the proteins' biological activity, and ultimately leads to deactivation of the virus.

While the most common photocatalytic processes use Titanium dioxide (TiO<sub>2</sub>) and its derivatives, they have many drawbacks which render them ineffective or impractical for deactivating the Coronaviruses on an ongoing basis. Dr. Gnayem and Prof. Sasson will fight Coronavirus spread by leapfrogging photocatalysis technology — which already has proven to be extremely effective in fighting viruses and bacteria under lab conditions — to the forefront and the realities of the day-to-day environment by introducing boosted capabilities and effectiveness. The novel materials family, which will be developed by startup company Catalife founded by Dr. Gnayem, will ensure extremely effective photocatalysis under regular outdoor and indoor light conditions. Indeed, the researchers expect that these materials will overcome many, if not all, the drawbacks and deficiencies of existing photocatalytic materials.

Dr. Gnayem and Prof. Sasson envisage that their new materials will be embedded into the outer layers of medical fabrics, facemasks and non-woven items. This will allow solar or artificial daylight to activate the embedded photocatalytic materials, thus leading to the safe and absolute elimination of the Coronavirus and any other viruses that have penetrated the items. Introducing the photocatalytic materials into medical fabrics worn by health care personnel will create an automatic “self-cleaning” process that will eliminate airborne viruses and disinfect the

environment — and thus stop the spread of the Coronavirus. Likewise, embedding the new materials in air-conditioning system filters in hospitals or any public enclosed space such as airports, airplanes, and other forms of public transportation will prevent the accelerated spread rate of the Coronavirus and provide clean, fully disinfected breathable air. **\$300 – 400K**

### **Long-lasting antiviral coatings for public surfaces**

*Prof. Avi Domb, School of Pharmacy, Faculty of Medicine*

The Domb lab's objective is to develop a self-sterilizing anti-coronavirus coating which can be applied to public surfaces that are commonly touched by people. The coating would deactivate viruses and microbes upon surface contact, thereby reducing transmission of the virus via surfaces that have been previously touched by an infected person. The coating should be easy to apply without damaging the surface, have a short virus-deactivation time (minutes), a 99% deactivation rate, be safe for contact and effective for weeks.

The coating materials to be used are considered safe and composed of compounds that have been used in the pharmaceutical industry.

The active antiviral agents to be applied are active polymers and oxidizing agents that destroy any microbial agent, including viruses.

The coating will be applied to metal, plastic, stone and other common surfaces. Testing against viruses can be by any virus or MS2 surrogate.

### **Environmentally friendly nontoxic coating which prevents virus adhesion**

*Prof. Meital Reches, Institute of Chemistry and Center for Nanoscience and Nanotechnology*

The goal of this project is to develop an environmentally-friendly and non-toxic coating that would prevent the adhesion of viruses.

The Reches research group has already developed a peptide-based coating that prevents adhesion of proteins to surfaces, in this way avoiding attachment of bacteria, fungi and other organisms. The peptide is a short peptide comprising only three amino acids and therefore its synthesis is simple and can be done on a large scale. The peptide spontaneously forms a coating on various surfaces (metals, polymers, oxides, etc.). The Reches lab has recently found that this peptide can also self-assemble into capsules that can adhere to surfaces and prevent protein adhesion. They then encapsulated enzymes inside the particles and showed that the enzymatic activity is maintained. The Reches lab is currently studying the encapsulation of anti-viral enzymes in the capsules to degrade the viruses.

COVID-19 is a unique virus in that it can survive for a relatively prolonged time on surfaces. The virus comprises an RNA molecule surrounded by the viral capsid made up of proteins. Since the

peptide-based coating developed by the Reches lab can prevent protein adsorption to surfaces, it is expected that it would prevent the adhesion of viruses. This project will test this hypothesis initially with similar viruses (Infectious Bronchitis Virus, IBV) and later use a lab that can work with COVID-19. In parallel, the ability of the peptide-based capsules that contain anti-viral enzymes to degrade viruses will be studied.

The resulting coating developed could not only prevent the adhesion of COVID-19, but the adhesion of all viruses, bacteria and other microorganisms. Such a peptide can already be manufactured in large scale (hundreds of Kg and more) and can be sprayed onto different surfaces. It could be useful for coating surfaces in hospitals, food preparation and production areas, on public transportation and much more.

### **Copper-based antiviral agents to prevent surface contamination**

*Prof. David Avnir, Institute of Chemistry and Dr. Zvi Hayouka, Robert H. Smith Faculty of Agriculture, Food & Environment*

Recently published research studied the aerosol and surface stability of HCoV-19, the novel human coronavirus that emerged in China in late 2019 and triggered the current pandemic. According to the study's findings, HCoV-19 remained most stable on plastic and stainless steel, with the viable virus still detectable up to 72 hours after application. Interestingly, no viable virus could be measured after just four hours on a copper surface. Since contaminated surfaces may cause severe infection, these findings are highly significant for the battle against HCoV-19.

The Avnir and Hayouka labs have been working together over the past few years, with the aim of developing novel copper composites that are resistant to pathogenic bacteria and are based on a new family of materials that Avnir has termed "organically doped metals" (organics@metal). These hybrid materials combine two very different chemical families —metals and any organic molecules — which have a synergetic effect in various applications, including biological and medical ones. The general approach for the preparation of the metallic composites involves a room-temperature, one-pot, reduction of the metal cation (its positively charged ions) in the presence of the desired organic molecule while using carefully selected reducing agents. Using this approach, the team has developed novel antimicrobial-doped copper in which antimicrobial peptides or small antibacterial molecules are entrapped. It has demonstrated the new materials' high efficacy both *in vitro* and as a novel crop protection agent in plants.

Prof. Avnir and Dr. Hayouka will expand their current study to develop efficient copper-based antiviral agents. They will explore the entrapment of various agents, mainly antiviral peptides and chloroquine which have been suggested as capable of tackling HCoV-19. The designed compounds will be tested on HCoV-19. The researchers are negotiating to conduct the tests in China. They are also exploring the potential of converting the compounds into a product with an Israeli start-up specializing in nanometric copper.

## Reusable, mass-produced, affordable, anti-viral face masks to combat the spread of Coronavirus

*Prof. Gershon Golomb, School of Pharmacy, Faculty of Medicine*

There is an urgent need for 'particulate respirator' face masks that protect medical staff, patients and the general population from infection by the Coronaviruses, and by Covid-19 in particular. Human-to-human transmission of Coronaviruses is primarily thought to occur when in close contact via respiratory droplets generated by sneezing and coughing. Currently, only the N-95 type masks (and better types) provide adequate protection for the wearer and the surroundings. This is a three-part problem: the shortage of masks; the need for economical mass production, the development of reusable masks. Prof. Golomb's suggested solution: Instead of woven masks made from different types of textiles, a mask based on a semi-permeable materials known as polymeric membranes into which an anti-viral compound would be embedded. This polymeric mask could be made from a blend of biocompatible polymers (e.g., polyurethanes or polyacrylates) and a leachable component (e.g., polyethylene glycol (PEG) or others).

The latter leachable component is extracted in solvents that do not affect the main matrix of the polymeric mask, but create pores with massive tortuosity (flow ability). Following leaching of PEG to create a tortuous structure, Prof. Golomb developed a polyurethane membrane that can filter particles of sizes ranging from ~100 nm (the size of the COVID-19) to 300 nm (the effective filtering size of N-95 masks). This membrane was originally prepared and tested for controlling slow drug release in various drug delivery systems. Prof. Golomb envisages using this same concept to produce masks by 3D printing, a simple technology that would enable the mass production of tailor-made polymer masks. 3D printing technology encompasses a variety of processes whereby material is joined or solidified, under computer control, to create a three-dimensional object. Its characteristics of precision, repeatability, and material range mean that it is suitable for industrial-scale production. Following several hours of usage, masks made using this process would be sterilized by simple washing with 70% ethanol/isopropanol and then dried for reuse by conventional means.

Milestones:

Phase I: Formulation of polymeric blends (HUJI lab), 3D printing, and testing according to Occupational Safety and Health Administration (OSHA) standards.

Phase II: Embedding an anti-viral compound in the polymeric mask, using advanced matrices that can neutralize pathogens. The active neutralization matrices will be incorporated as components in masks or in ventilation systems.

## Improving disinfection treatments against coronavirus for surfaces and hands

Dr. Nadav Kashtan, Plant Pathology and Microbiology, Robert H. Smith Faculty of Agriculture, Food and Environment

While there is growing evidence that COVID-19 survives for a surprisingly long time on various surfaces — even several days — it is not clear if disinfecting surfaces is the optimal approach and, moreover, if it can be improved. Indeed, in many cases the chemicals used might cause ‘microscopic surface wetness’, meaning that even though it appears to be dry, a surface might remain covered with a resilient thin liquid film and tiny microdroplets that are invisible to the naked eye; this phenomenon likely impacts virus survival. The survival of microorganisms on drying surfaces and amid microscopic surface wetness is a main focus of the Kashtan lab, which recently showed that bacteria can survive in such microscopic wetness for as long as several days. Kashtan is now readying to investigate the next part of the mystery: how viruses like COVID-19 are able to survive and remain stable on surfaces, in particular those that have been disinfected. He plans to use bacteriophages — bacterial viruses that are easier and safer to work with — that are structurally similar to COVID-19. These lab models are enveloped, tail-less RNA phages, meaning that in the past they have been suggested as ideal for studying the stability in the environment (e.g. in aerosols and on surfaces) of similarly enveloped human viruses such as influenza A (subtype H1N1). Using the lab models, Kashtan plans to test their stability and survival on several surface types (e.g., plastic stainless steel, glass and cardboard) and in several situations: following disinfection using the recommended protocol for COVID-19; and under various realistic environmental conditions. Based on his findings, he envisages that he will then be able to work towards modified disinfection and post-treatment approaches (e.g. washing with a specific substance) that can reduce COVID-19 survival on surfaces. Says Kashtan: “I consider it my moral and professional duty as a microbiology researcher to contribute to the research required to confront this global crisis.”



## 7. ADDRESSING THE SOCIAL AND SOCIETAL IMPLICATIONS OF THE DISEASE

### Israel's health policy actions to cope with COVID-19 pandemic

*Shuli Brammli, Hebrew University-Hadassah Braun School of Public Health and Community Medicine, Faculty of Medicine*

In December 2019 the first cases of a novel Corona Virus Disease 2019 (COVID-19) were identified in the province of Wuhan in China. That was the beginning of a pandemic not seen in decades. With the outbreak of the pandemic, the scientific world launched into a marathon to deepen its understanding of the disease's epidemiology and development. One fact was clear from the start: the virus' fatality rate depends on the ability of healthcare systems to treat the severely ill, especially those needing ventilators.

Israel reacted swiftly — and faster than other European countries and the US — with many policy measures to contain the contagion and the pace of spread of the disease. The objective of this study is to survey Israel's health policy during the containment phase of the COVID-19 pandemic and provide expert opinions on the rationale and objectives of the policy measures implemented, their sociopolitical contexts, and the various elements that facilitated or hampered the implementation of such measures.

The COVID-19 pandemic requires cooperation among the global healthcare community. Sharing timely and reliable information is critical, and examples of successful policy approaches to cope with the epidemic are likely to help in reducing the spread worldwide and enhance the ability to fight the disease. This case study of the Israeli healthcare system may be useful to countries debating how to contain the current contagion and spread of the disease, as well as providing an example of preparedness and coping measures for future pandemics.

### Social distancing in health and cognitive deterioration: A view from the brain

*Prof. Shahar Arzy, Faculty of Medicine*

The discourse around the COVID-19 pandemic is dominated by public health requirements, which call mainly for "social distancing". With the progress of time, and in view of the severity of the steps taken, it has become clear that the implications of social distancing on individuals and society should be seriously considered. This is even more true with respect to older adults and patients with health disorders, who are more prone to be adversely affected by the disease.

Not much is known about the neurocognitive systems managing social relations. This is of much importance for healthy individuals, and more so for those with cognitive deterioration in whom these systems may already be disturbed on the one hand, and who are requested to remain in strict isolation on the other. The overarching goals of the current research undertaken by the

Arzy group are (1) to understand the brain-based constraints of social distancing, and, consequently (2) to derive the best strategies to adapt to these constraints using newly developed designated tools.

In a recent study, the group deconstructed social distance into three different components: personality traits, egocentric relationships (emotional proximity) and patterns of relations with others. Using fMRI, they showed how a linear combination of these three factors represents overall social distance. In the first part of the new study, they will use their existing datasets to compose a brain-based model of social distance sub-components. They will then apply optimization processes related to perturbations of each of the subcomponents and their combinations to provide a model for effective social relations. The group will test its model on large-scale behavioral data collected over the internet from hundreds of participants, including older adults and people with cognitive deterioration, using a modified version of the group's existing artificial intelligence (AI) based system Clara ([www.claramind.com](http://www.claramind.com)), a tool designed to collect data about the patient's own social world and to run tests.

Where possible, the Arzy group will also test a subset of their subjects under fMRI. Based on their model, they will be able to provide individuals with specific recommendations regarding management of relations with people in their social network that are to be maintained during this crisis. These recommendations will be provided to participants using a designated App and web-based tool, that will also remind both participants and their social network to communicate according to the parameters provided. These recommendations may be particularly useful for seniors who lack an immediate available support network. Results may be updated by participants and optimized accordingly across time, and will be generalized using a recurrent neural network-based model.

### **Mental wellbeing of migrant careworkers in Israel during COVID-19: Vulnerabilities of migrant careworkers and their employers**

*Prof. Yehuda Neumark, Hebrew University-Hadassah Braun School of Public Health and Community Medicine*

There are approximately 67,000 migrant careworkers in Israel, most of whom originated in Southeast Asian countries. Migrant careworkers work and live with populations extremely vulnerable to the novel coronavirus (COVID-19), including the elderly and people with pre-existing conditions. Migrant careworkers are the first-line defense in protecting the elderly against COVID-19. Careworkers are responsible for their employer's home and personal hygiene, errands in the public sphere, and implementing national guidelines. This is especially true during the current pandemic when children and grandchildren are being advised not to visit their parents and grandparents. Careworkers are simultaneously responsible for their own health, their employer's health, and are worried about the health of the family they have left 'at home'.

The Neumark team recently conducted the largest study to date of mental distress among careworkers in Israel, and found that nearly 40% of careworkers experience high levels of mental distress *prior to the current outbreak*. Since the COVID-19 outbreak in Israel, migrant careworkers have been the target of increased racism and stigma. Added stressors related to personal, familial, and employer safety, may exasperate careworkers' mental health, placing them and their employers at risk.

The team will undertake a quick-response survey with four major aims: 1) assess psychosocial status and mental wellbeing of migrant careworkers in Israel during the ongoing COVID-19 pandemic; 2) determine risk-factors and protective-factors associated with mental distress, anxiety, and depression; 3) examine how careworkers organize their lives in order to cope with pandemic conditions; 4) determine careworker knowledge of the outbreak and necessary precautions to prevent transmission. This study will ask about stressors, outbreak knowledge, access to personal protective equipment, and connection with their families concerning the outbreak.

The information generated from this research will serve as the basis for developing a national strategy for addressing the unique threats being faced by migrant careworkers in Israel under pandemic conditions, and help safeguard the health and wellbeing of Israel's elderly and others being cared for by migrant careworkers.

The Neumark team will employ a similar mixed-methods survey methodology to that used in our recently-completed survey. Data will be gathered from an online quantitative survey (self-administered questionnaire including the Hopkins Symptoms Checklist-25) and from qualitative in-depth interviews conducted with a sub-sample of respondents. Data from the different sources will be triangulated using a convergence model. The data will undergo rapid analysis and interpretation using standard software. Conclusions and recommendations will be immediately distributed to the relevant governmental and non-governmental agencies.

They anticipate that the information generated from this study will help safeguard the health of tens of thousands of elderly Israelis and others in need of home care, and of their careworkers who are at particular risk during the ongoing and growing COVID-19 pandemic.

### **Smoking behaviours and quit attempts during COVID-19**

*Dr. Yael Bar-Zeev and Prof. Yehuda Neumark, Hebrew University Hadassah Braun School of Public Health and Community Medicine*

Smoking has been suggested to increase the risk of infection with the coronavirus, and increase the severity of the disease among those infected, including a higher death rate. Preliminary data from China suggest that there was a higher death rate among males and it has been hypothesized that this is due to the higher smoking rates among males in China (~50%) compared to women (~2%). In addition, clinical data that has been published since the onset of

the pandemic suggests that smokers may have a higher rate of severe disease. There is scientific basis for this hypothesis as smoking impairs the immune response, increases the rate and severity of other respiratory infections, and is a known risk factor for most of the comorbidities that have been associated with a severe COVID-19 infection such as chronic lung disease, cardiovascular disease, cancer and diabetes. One possible biological mechanism that was implied as important is that smoking upregulates the Angiotensin Converting Enzyme 2 Receptor (ACE2) which is thought to be a potential adhesion site for the coronaviruses.

Smoking is one of the most important risk factors for morbidity and mortality worldwide, responsible, in non-pandemic days, for 18% of deaths in Israel each year. Much of the current healthcare burden is attributed to smoking-related disease. Motivating people to quit smoking at this time may help reduce the imminent and longer-term burden on the healthcare system.

Data regarding the possible association between smoking and the risk and severity of infection, has been communicated to the public through social media and the regular press, urging smokers to seize the opportunity to quit smoking. It is unclear how people respond to this information and what the effect on people's smoking behaviour is. Understanding people's responses and behaviour regarding their smoking under the ongoing and growing pandemic reality is crucial to designing better messaging and support to help them achieve smoking cessation, which in turn will alleviate some of the healthcare burden of the COVID-19 pandemic.

Using social media recruitment, Bar-Zeev and Neumark will utilize a mixed-methods approach, using both a survey and qualitative interviews with smokers, to better understand:

- 1) Attitudes towards smoking and their possible association to COVID-19 infection and severity of infection;
- 2) Motivation to quit, quit attempts, and severity of withdrawal symptoms;
- 3) Anxiety, negative mood and urge to smoke (including frequency and severity of urges to smoke);
- 4) Changes in smoking behaviour including smoke-free homes rules (due to quarantine and social distancing instructions).

To ensure the immediate relevance of the research findings, the data collection and analysis will be expedited (upon IRB approval) and the conclusions and recommendations will be shared with relevant governmental and non-governmental agencies for implementation.

## Community responses and initiatives for underprivileged and vulnerable populations during the COVID-19 pandemic

*Dr. Yael Bar-Zeev, Dr. Milca Dunchin and Prof. Yehuda Neumark, School of Public Health and Community Medicine*

Certain populations – such as minority groups, the elderly, people with physical and/or mental disability, lower socio-economic status, lower education level, marginalized groups due to sexual orientation and/or religion – suffer from health inequities. Any state of emergency, and even more a health emergency, such as the COVID-19 pandemic, is likely to deepen these social disadvantages and health inequities. For example, less educated persons and those from a lower socio-economic status, may be at greater risk of losing their jobs and not having the financial reserves to keep them secure during uncertain times. Local municipalities and communities are instrumental to coping with these situations and providing support that could alleviate, at least partially, the detrimental effects of emergency situations, including the COVID-19 pandemic. Learning how communities respond, determining which initiatives have been effective, and understanding the mechanisms underpinning the "successes" during this unfolding crisis, are key to building support systems that could reduce social disadvantages and health inequities, now and in the future.

In Israel, there are 255 local municipalities. In 2017, 24% of the population in Israel resided in municipalities in the lowest socio-economic cluster (level 1-2/10), and only 1.3% of the population resided in municipalities in the highest socio-economic cluster (9-10/10). Fifty-two municipalities in Israel are currently part of the World Health Organization's global Healthy Cities Network. Initiated in 1986, the network aims to promote health via a "whole system" approach, integrating multidisciplinary actions, community participation, partnership, empowerment and equity.

The proposed research will map the national and local-level responses and initiatives that were implemented during the COVID-19 pandemic to support socially disadvantaged groups. This will be done using mixed-methods of both survey and qualitative interviews of key personnel in local municipalities in Israel.

It will also assess the response of the population to these initiatives using mixed-methods. Participants will be sampled from various socially disadvantaged sub-populations such as those described above. In addition, it will assess the differences in initiatives and population responses between local municipalities that are part of the Healthy Cities Network and those that are not, between Arab and Jewish local municipalities, and between municipalities according to their socio-economic cluster.

To ensure the immediate relevance of the research findings, the data collection and analysis will be expedited (upon IRB approval) and the conclusions and recommendations will be shared with relevant governmental and non-governmental agencies and the Healthy Cities Network for implementation.

## A Simulation Model of the Spatial Contagion of the Coronavirus in Israeli Cities

*Prof. Daniel Felsenstein and Dr. Yair Grinberger, Department of Geography, Faculty of Social Sciences*

Prof. Daniel Felsenstein and Dr. Yair Grinberger have developed a micro-simulation model for simulating the resilience of cities to major disasters. At the heart of the model are programmable 'agents' whose behavior is determined by a series of decision rules. The model can relate to real-world urban contexts or to hypothetical urban spaces.

This model is highly suited for simulating the spatial contagion effects of the coronavirus in Israeli cities. For simulations over the short term (up to 4 months), the pair are addressing the following questions relating to any given city:

- How many are likely to be affected by the coronavirus epidemic over the time period?
- How many fatalities can be expected over the time period?
- When would the epidemic reach its peak and what is the nature of this peak (flat vs. steep)?
- What is the anticipated time till the effects of the epidemic dissipate?

This would represent the baseline outcome variables of the simulation, without intervention. It is also possible to run the simulations under different policy (intervention) scenarios and then compare the outcomes with the baseline.

The simulation capabilities of the model are derived from a series of (estimated) parameters that can be easily adjusted to increase model stability and robustness. Some of the key parameters relating to the spread of coronavirus within an urban area relate to the:

- Probability of infection as a function of age and health status (studying scenarios with differing intensity of infection).
- Probability of death and/or time to recovery (risk over time, function of age and health status).
- Time until visible symptoms appear/diagnosis (random, normal distribution), and more.

The simulation model results can help policy makers facilitate a comparison of the outcomes discussed above (rate of infection and death, time and extent of peak, time till dissipation) and more easily assess the utility and efficiency of possible interventions.

## **Saving for Retirement and Emergencies and use of Robo-Advisors**

*Prof. Orly Sade, the Jerusalem Business School (with Prof. Olivia S. Mitchell, and Dr. Abigail Hurwitz)*

Past research has demonstrated that many people have only a vague concept of life expectancy and the risk they face at older ages, as well as only a vague concept about funding that they might need for emergencies or uncertain periods. This implies that people are likely to under-save for retirement and for needed emergency funds.

Pandemics and financial crises can affect perceptions about life expectancy and longevity risk. This project proposes to use experimental surveys during this crisis to investigate alternative ways to describe both life expectancy and longevity risk, and to assess how these alternatives might raise peoples' awareness of possible retirement and emergency fund shortfalls. The project will also evaluate whether providing this information can promote interest in saving, and/or demand for longevity insurance products. The results obtained during the crisis would be compared to those pre and post crisis in order to better understand and recommend needed actions in the areas of savings and insurance.

Another study (with Daniel Ben-David), deals with Robo-Advisor Adoption, Willingness to Pay, and Trust—An Experimental Investigation. The current coronavirus crisis is one of health but also of finance. This crisis may affect a change in people's trust in different services. The literature shows that for many individuals, managing long-term savings is a challenge. Hence, many individuals seek the advice of an advisor. Along with 'human' advising services, in recent years we have observed the rise of a variety of robo-advisor options. Robo-advisors are applications for financial investment planning, based on algorithms that provide advice or invest the client's assets, autonomously, according to the client's specific financial situation, risk aversion profile, and investment goals. The Sade lab will compare readiness to adopt and willingness to pay for (as a proxy for trust) financial advice provided three ways - algorithm, human, and a hybrid of algorithm and human – via an online experiment. The goal is to conduct the experiment during the current financial crisis and to compare the obtained results to data we collected before the financial crisis. This will enable a better understanding of the effect of the financial crisis on the willingness to adopt robo/algorithm advisors in financial contexts.

## **The effects of social Isolation on the body's basic regulatory physiological processes and COVID-19 susceptibility**

*Dr. Shir Atzil, Department of Psychology, Faculty of Social Sciences*

Dr. Atzil's lab explores the role of social bonding on the individual's regulation of its basic physiological processes. This automatic regulating process by the body is known as allostasis and is defined as the ongoing process of optimizing the body's internal milieu such as heart rate, glucose levels, microbiome, and hormones. Using research in the fields of biology, neuroscience,

developmental and social psychology, the lab has shown the importance of social interaction in the regulation of such basic physiological processes throughout the lifespan. Moreover, positive social interaction and social support have been shown to act as moderators of many forms of ill-health. For Dr. Atzil, the current Coronavirus pandemic represents a unique opportunity to study the adverse effects of social isolation, and how it compromises the basic regulatory processes of allostasis. She and her team are also planning to measure the impact of different levels of social isolation on COVID-19 susceptibility. The team has developed the infrastructure to collect data with subjects without any physical contact, and is ready to start recruiting subjects.

### **Cognitive-psychological aspects of the pandemic and new ways to improve wellbeing in times of crisis**

*Prof. Ran Hassin, Department of Psychology, Faculty of Social Sciences*

Prof. Hassin is involved in two major Corona-related projects. Both seek to elucidate the cognitive-psychological aspects of the pandemic, and lead to suggested new ways for improving wellbeing in such difficult times. The implications of the Corona era's impact on individuals, and on the nature of societies, is a big mystery — a complete unknown. In the two projects that Prof. Hassin is leading, and working in conjunction with colleagues from top universities in the US, he is trying to examine two crucial aspects of the mystery: Firstly, how people process information, what information they choose to process, and how their predictions lead to actions; Second, how the crisis affects the way we treat minorities and other marginalized groups.

### **Improved food security through the decentralization of food manufacturing**

*Prof. Oded Shoseyov and Prof. Ido Braslavsky, Robert H. Smith Faculty of Agriculture, Food, and Environment and the Center for Nanoscience and Nanotechnology*

Food security in a pandemic situation includes challenges in distributing food to the public. A solution being pursued by Profs. Shoseyov and Braslavsky is the development of a 3D printing system that will enable the production from raw materials of foods with a long shelf life at the customer end.

3D food printing offers the opportunity to personalize food according to the needs and preferences of the customer. Cellulose that can be consumed as non-caloric fibers has rheological properties that are suitable for printing and it also has the ability to stabilize and serve as a binder of food. Profs. Shoseyov and Braslavsky are developing a platform for food printing that is based on cellulose and unique *in situ* thermal processing of the printed food. The textures of the printed food are influenced by printed materials and local processes such as heating. Thus the printing method includes heating during printing for fine control of the texture and chemical reactions. This ability to print food directly from basic, raw, known ingredients will allow for low-calorie, gluten-free, tailored meals and open new gastronomical experience. The



3D printing will also allow for a change in food distribution with the raw ingredients disseminated but the final preparation of the food conducted at the customer end. This digital control of ingredients and texture opens a new horizon for the personalization of food, including adaptations that meet customer restrictions, needs, and preferences. Preparation on demand, moreover, will mean fewer additives and the use of a variety of protein sources.

In the short term, Profs. Shoseyov and Braslavsky are working on a meat-replacement hamburger based on cellulose that is being co-developed with a spin out company from our labs, SavorEat. They are developing and characterizing non-uniform heating sources for cooking and grilling food in thin layers, and plan to develop a unique extrusion process of cellulose and protein mixes to obtain the desirable texture with a controlled level of ingredients. Their long-term plan is for a versatile platform that will allow for the production of different foods using the same system, thus allowing for food production at the customer end.

### **Autonomous, portable living units for coronavirus patients (individuals, families, and communities) during the pandemic**

*Prof. Amotz Agnon with respective teams, Fredy & Nadine Herrmann Institute of Earth Sciences, Faculty of Science*

Autonomous, smart, portable emergency lodgings (ASPELs) offer portable solutions to the spread of a pandemic such as Covid-19. Prof. Agnon will develop autonomous, portable living units for individuals, families, and communities stricken by the Coronavirus. The units will be technologically advanced, meaning that they can be deployed quickly, have no infrastructure requirement and can be mobilized according to changing needs. Each unit will have the capacity to generate energy (solar), produce potable water (via condensation), and recycle waste (without sewage installations).

In addition to requiring no external energy, water, sewage, and communication fittings, these smart accommodation units will allow for remote health monitoring, thus alleviating the stress levels in the patients living in them. The portable units can be deployed and relocated swiftly and according to changing needs — and they can be readily removed when the situation returns to normal.

Emergency situations addressed by ASPELs are not limited to epidemics, and include earthquakes, toxic (including nuclear) contaminations, and damage to water and energy supply systems. The lodgings, if properly designed, are an affordable choice for countries anticipating emergency situations since they can also be used for tourism and “green” electric power generation during non-emergency periods.

Prof. Agnon’s approach is an adaptation of a remedy devised for uprooted communities in the aftermath of a catastrophic earthquake, and it clearly has advantages specific for epidemics. For

instance, the units can be readily disinfected by moderate heat pulses, and by opening the roof to sunshine when weather conditions allow. During the present Covid-19 crisis, infected patients have been placed in isolation in luxury hotels in central areas, with various transit-related hazards (internal such as elevators, and external when moving from permanent dwelling into isolation). While this solution is still being tested and may be optimal for central urban areas with available hotels, ASPELs are suitable elsewhere. Moreover, they offer a straightforward method for regular disinfecting of infected quarantine and infirmaries — by temporarily evacuating patients into nearby ASPELs.

The ASPELs have further advantages: they allow the authorities to address the changing needs of the population, especially in light of the poor predictions of the spreading trajectories of the epidemic (within the country and between countries); they alleviate the need to factor in long-term effects on the local environment and the limitations set by adherence to regulations; and they allow social distancing of emergency teams, thus preventing the spread of the disease.

Timeline: Within 9 months, Prof. Agnon and his team will have selected a workable configuration and assembled a quasi-prototype. They will use an available platform — an adapted shipping container — and using available components, will develop a crude design. This setup would be deployed during the next outbreak of Covid-19, projected for winter 2021, providing a testing stage for the next phase.

### **Social Acceptance of Technological Innovations among Senior Citizens Facing COVID-19**

*Prof. Elyakim Kislev, Federmann School of Public Policy and Government, Faculty of Social Sciences*

The social distancing required for the COVID-19 pandemic is causing severe social isolation and loneliness among elders. Even before the outbreak, 42% of people over 75 years-old in Israel felt lonely in 2015 (according to the SHARE database). Loneliness, in turn, is frequently the source of secondary problems such as anxiety, depression, cardiovascular disease, dementia, and other physical and mental health problems.

However, new technological innovations may tackle these problems, while allowing senior citizens to stay protected, as long as they are willing to accept these technological means. For example, huge leaps in technology have created impressive robots that can be used in ways unimaginable only a few years ago. It is now clear that technology and robots can help with menial household tasks and chores, providing answers for manual and physical needs such as cleaning and cooking. But, robotics has moved toward the development of socially intelligent and socially assistive robots. Such robots have been used for several years in mental healthcare as companions, play partners, and coaches. Alternatively, augmented and virtual reality (AR/VR)

devices can also enrich the lives of seniors living alone. Furthermore, using advanced technology similar to the voice-activated systems of Apple's Siri and Amazon's Alexa, artificially intelligent devices can hold conversations with users and respond positively to human touch. Thus, given the expected advances in robotics, AI, humanoid robots, and AR/VR, the emotional and social needs of seniors can be satisfied, at least partly.

The proposed research, therefore, asks whether technology can indeed meet some of the social and emotional needs of seniors who feel isolated. While the idea of replacing human interactions with technology might seem far from mainstream, it is a possibility that should be considered carefully. In particular, the main questions are whether seniors are ready and willing to adopt such new innovations, what obstacles they face, and what can smooth their acceptance.

Indeed, the research plan is already set, and ethics approval has already been received. The research will first review the most up-to-date and studied social tech-innovations in the field. In parallel, a purpose-designed six-step questionnaire will be delivered to seniors. In addition, the questionnaire will be supplemented with open-ended interviews. All surveys will be conducted online, yet in a simple and easy to comprehend manner, adjusted to seniors. The research is low-risk/high-gain because it is based on several research papers on the subject and a book published by UC Press in 2019.