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Short Communication

Creating an Antiviral Arsenal for Epidemic Preparedness

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Therapeutic Discovery and Advancement of Hidden Microbiome (Microbial) Chemistry with Breakthrough Technology + Antiviral, Dublin, Ohio, United States

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At this point, the coronavirus (SARS-CoV-2 or COVID-19) needs no introduction. As the global medical community struggles to prepare and treat the coronavirus crisis, scientists are racing to find some way to treat, prevent and/or slow down the spread of infection or mitigate its virulence.

We all want to do our part - whether it is social distancing, renewed hygiene practices, lockdown, or helping the local economy. Some individuals are in the unique position of being a scientist or being able to support discovery science and are trying to figure out how else they can help.

As a global community, we are feeling the devastating effects of this virus on our hospitals, medical staff, and medical supply chain. In addition, the ripple effect has untold consequences.

What if… we already had an arsenal of antivirals ready to test on various emerging viruses? What if, at the first emergence of Ebola virus, Hantavirus, coronaviruses, respiratory syncytial virus, human parainfluenza viruses 1 and 3, influenza viruses A and B and adenoviruses, we were able to start testing the bioactive molecules in this arsenal? What if we were able to eliminate the threat of disease even before it had a chance to flourish around the globe? Would our World look much safer?

Bill Gates in his 2015 Ted Talk addressing our global readiness for a pandemic, states that, "we have the benefits of all the science and technology… We have advances in biology that should dramatically change the turnaround time to look at a pathogen and be able to make drugs and vaccines that fit for that pathogen... And we need preparedness". In this presentation, he makes a strong case for investment in R&D efforts to achieve this next level.

In fact, a resource for new, diverse antiviral treatments *is already* within arm's reach. There is substantial mounting scientific evidence showing that untapped antiviral opportunities exist in natural products, i.e. microbes [1-3] and the most abundant source of microbes exists in aquatic environments [4-9]. In the aquatic microbiome, there is constant interaction between bacteria and viruses. Since the development of visualization technologies 30 years ago [10], it has become increasingly clear that viruses are dominant players in the aquatic microbiome, outnumbering their bacterial counterparts typically by tenfold [11]. Therefore, one would expect that some chemical mediation naturally exists by which aquatic bacteria fend off an attack by viruses.

The aquatic environment has been a rich source of potent biologically active chemistry. In recent years it has become increasingly clear that microorganisms, either free-living or in symbiosis with higher organisms, are the primary source of these metabolites [12]. Although the screening of aquatic microbiomes for these agents has been quite limited, there are several diverse types of natural products with differing mechanisms of antiviral action [13]. Some specific examples are described below and shown in table 1.

Modified nucleosides. The commonly used antiviral drugs, Ara-A, acyclovir, remdesivir and vidarabine, although produced by chemical synthesis, owe their origin to the discovery of modified nucleosides, which are usually produced by functional enzyme clusters in sponges and/or their associated symbiotic microorganisms [14]. These drugs interfere with the synthesis of viral DNA inside host cells.
Carbohydrate binding proteins (lectins): Cyanovirin-N (CV-N) is a unique 101 amino acid lectin discovered from the cyanobacterium *Nostoc ellipsosporum* [15]. CV-N has been the subject of intensive research within NIH owing to its potent and specific antiviral activity [16]. CV-N binds to specific envelope glycoproteins which effectively prevents the propagation of HIV and influenza viruses.
Polysaccharides. Naviculan, isolated from the diatom *Navicula directa*, is a high molecular weight sulfated polysaccharide that inhibits the propagation of enveloped viruses, by blocking adherence and penetration of the virus into host cells [17].
Macrolides. Macrolactin A was discovered through fermentation of an unidentified deep-sea bacterium [18]. It inhibits the proliferation of HIV in host cells by an unknown mechanism. This family of compounds has subsequently been isolated from several other microbial sources; the compound has been produced by total chemical synthesis [19].
Protease inhibitors. Numerous protease inhibitors have been successful in the treatment of Human Immunodeficiency Virus (HIF), Human cytomegalovirus (HCMV) and severe acute respiratory syndrome (SARS). A potent peptidic inhibitor of HIV-1 protease of bacterial origin, ATBI has been found in an extremophilic *Bacillus* sp; inhibitors of the cytomegalovirus protease have been described from bacterial (*Streptomyces*) and fungal (*Cytonaema*) origins; and there is potential for microbial protease inhibitors to be effective in SARS-CoV-2 treatment. There is a vast diversity of proteases in aquatic microbiomes that have been found to be a rich source of protease inhibitors as well [20].

Table 1

Given the diverse range of microbes with antiviral activity, the possibilities of untapped antiviral therapies need thorough exploring. The current challenge lies with scale and speed. A diverse, relevant source of microbes that can be rapidly sorted by chemistry and screened to discover active compounds is ideal to meet the challenge. The current crisis is highlighting the need to execute scaled searching, sorting, and testing novel antivirals compounds. Biosortia technologies for exploring the hidden chemistry of unculturable microbes and microbiomes are at scale and ready to deploy.

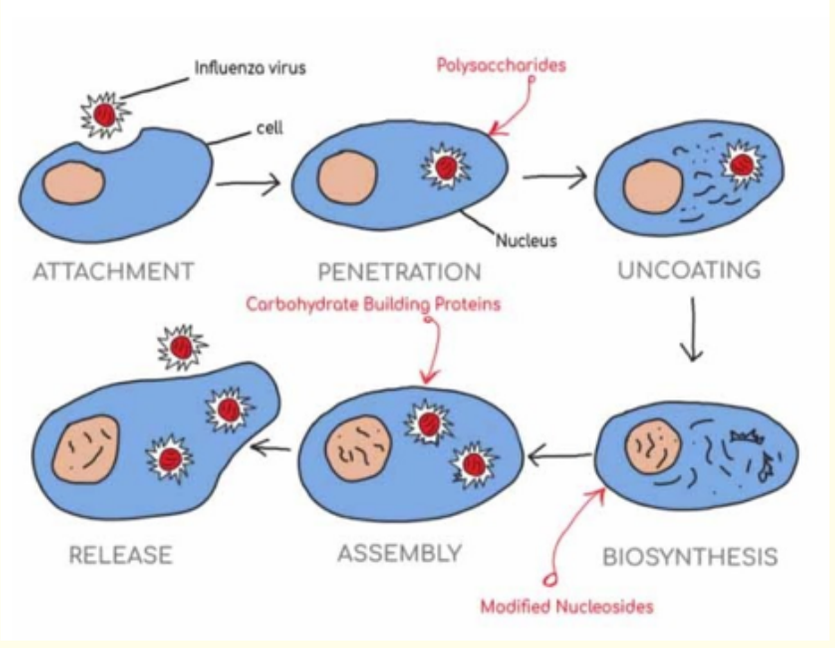

Figure 1: *Life cycle of virus and various points of action for antiviral compounds.*

Biosortia has a platform technology that makes the process of obtaining and discovering multiple new therapeutic starting points faster and more efficient (Figure 2). Biosortia's proprietary technology allows nearly limitless access to uncharted aquatic microorganisms. The execution of the technology enables deep microbiome mining for the hidden chemistry and genomics, allowing efficient sorting, searching, and screening. In short, Biosortia Pharmaceuticals can harvest 20 million liters of aquatic habitat, mine the microbiome for bioactive compounds and, test them for antiviral properties. Today, this technology can be implemented at scale to screen for viable antivirals that can change the course of viral epidemic outbreaks.

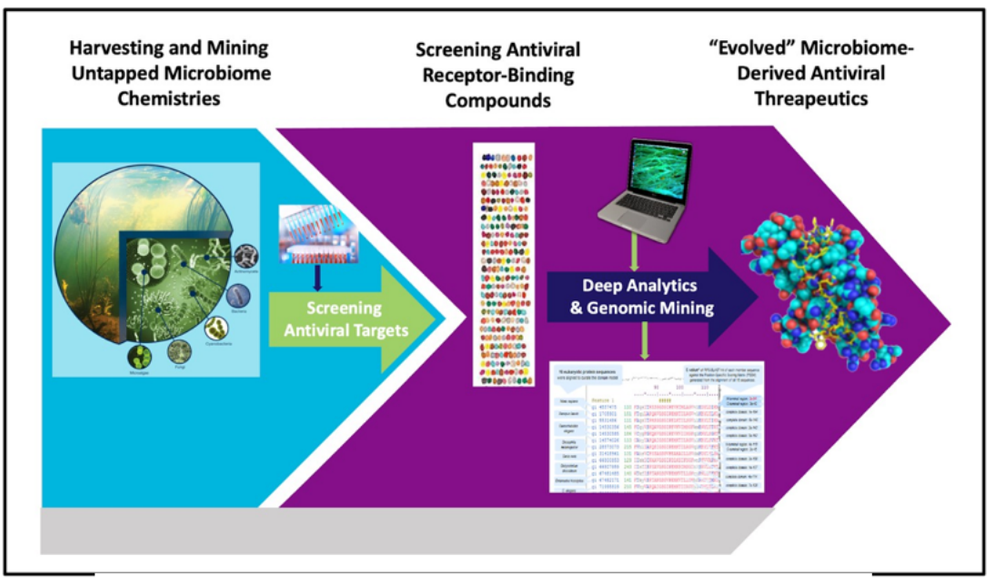

Figure 2: *Exploring the aquatic microbiome for hidden defense chemistry and genomics for antiviral activities.*

Biosortia Pharmaceuticals has successfully proven and established the following:

- Inventories of diverse aquatic microbiome,
- Proprietary methods to acquire a vast quantity of the microbiome while preserving quality (extreme microbiome harvesting),
- Validated rapid and effective sorting capability that is readily available off the shelf,
- High throughput screening for drug discovery (See figure 3),
- Laboratories ready to do necessary preclinical and clinical studies.

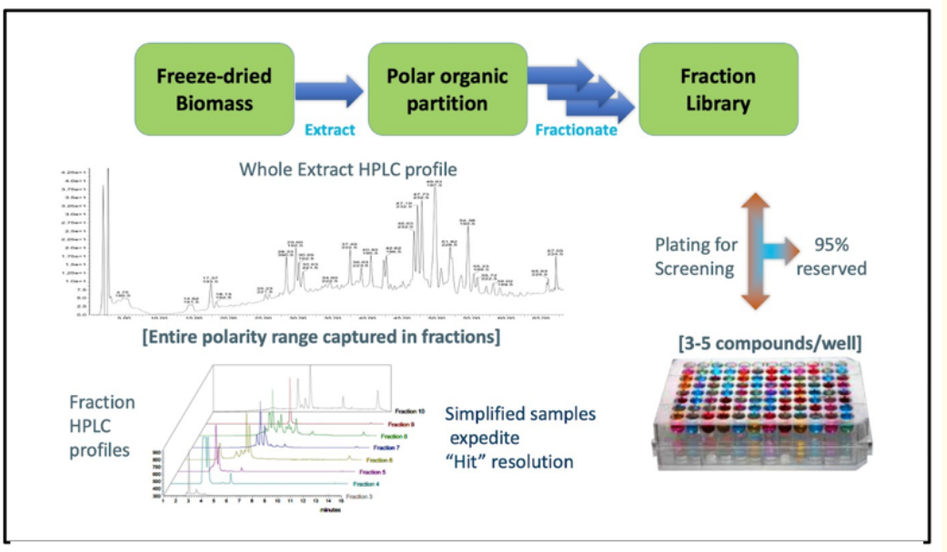

Figure 3: *Microbiome chemistry. Deep chemical exploration requires sizable quantity and high-quality biomass. Subsequently, a series of extractions and fractionations permit access to off-peak molecules for direct exploration of antiviral activities.*

Extreme microbiome harvesting concepts had validation by peer-review [4]. Biosortia received nearly $10 million of initial funding to support technology development through ARPA-E, DARPA, U.S. AFRL, and the State of Ohio. These collaborations supported the advancement of the technology to recover whole microbiomes from the richest habitats on earth. Additionally, investment of $11 million was received by angel investors for scaling and proving the validity of the technology breakthrough. It is typical that companies with breakthrough technologies in any industry, and especially pharmaceuticals, struggle with finding execution funding. The current public health crisis may put a spotlight on innovation opportunities such as Biosortia's extreme microbiome mining technologies.

COVID-19 has created a pandemic, economic disaster, and untold human suffering that has engulfed most of the globe. History has demonstrated that new viral threats will continue emerging. Today, humanity has an opportunity to prepare by having a reserve of accessible antiviral compounds at its disposal to activate when necessary. Biosortia's ability to access microbial chemistry and offer potential therapeutics positions, both commercial and federal agencies, with the arsenal to improve the treatment, prevention, and/or mitigate the impact of contagions. The cost of obtaining next-generation antiviral compounds is a fraction of the costs of a single hour of shutting down the world's economies.

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