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# Computational Nanomedicine: Helping Us Get Through COVID-19

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At a time when Universities closed their doors to research during the COVID-19 pandemic out of safety concerns, researchers endured and even thrived. While some faculty and graduate students used this closure time to write review papers, grants, or develop research plans for their specific fields of interest, many academic researchers turned towards computational modeling to solve COVID problems. Although we all knew that computational modelling can be done at home, not requiring access to University research labs, we did not realize how helpful computational modelling would be to find solutions for COVID-19.

3 years after the onset of the COVID-19 pandemic, it is clear that computational modeling significantly helped us get through COVID-19 [1-7]. From using molecular dynamics to understand binding of the SARS-CoV-2 spike protein to the ACE2 receptor of mammalian cells during the virus replication process to optimizing the design of small molecules to bind to the envelop protein of SARS-CoV-2 to stop it from replicating, the field of computational modeling was critical at a time when academic research labs were unavailable [4]. Further, adsorption, distribution, metabolism and excretion (ADME) and quantitative structure-activity relationship (QSAR) computational modeling was also instrumental towards understanding the pharmacological properties of COVID therapies and vaccines [8]. Without such advances in computational modeling made throughout the decades, it is clear that we would not have the COVID-19 solutions that we have today, including COVID prevention, diagnosis, and treatment.

Our personal story includes one of frustration then exultation where upon the onset of COVID-19 in the Fall of 2019 and Spring of 2020, we believed as scientists it was our duty to help the world get through the COVID-19 pandemic. Many researchers did the same, making masks for healthcare workers when there were shortages, developing new more sensitive and easy to use diagnostic kits, and trying to develop vaccines and therapies for COVID-19 [10]. While we had over 20 years of experience in biomaterials and tissue engineering, we had little to no experience in viruses or virology. So, how could we contribute to finding COVID solutions? And, even if we did have ideas, it got worse. Like many Universities, our University research labs were shut down due to COVID safety protocols, despite the fact that many industries kept their labs open enabling their researchers to conduct life saving research.

So, in the early days of COVID-19, we were stuck. We did not know how to help and we had no where to conduct studies anyway. Thankfully, during this critical time in our global health, the scientific community initiated virtual webinars, conferences, and other activities to keep our minds active. We distinctly remember giving several webinars concerning how nanotechnology was trying to provide solutions to COVID-19 through embedding nanoparticles in masks which could release reactive oxygen species to passivate SARS-CoV-2 when trapped in masks to using iron oxide nanoparticles functionalized to attach to SARS-CoV-2 increasing detection sensitivity under an applied magnetic field [6]. Even Moderna and Pfizer were researching nanodimensional liposomes for brand new mRNA based vaccines [9]. After one of these webinars, we had an idea: transition the self-assembled nano materials that we were previously developing for tissue engineering applications into those which can attach, self-assemble

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around, and "blanket" SARS-CoV-2 inhibiting it from entering mammalian cells to replicate [4-8, 10]. Our nanomaterials were similar in size to SARS-CoV-2, so the idea theoretically could work. But what could we functionalize onto our self-assembled materials to attract them to SARS-CoV-2? And where could we experimentally prove this concept?

Computational modeling came to our rescue. We quickly contacted several virologist friends to obtain the amino acid sequence of the envelop protein of SARS-CoV-2 and developed peptide sequences that compliment those regions for attachment [11]. While everyone else was targeting the spike protein in SARS-CoV-2, we targeted the envelop protein since we knew the spike protein would eventually possess more mutations than the envelop protein. Then, as we were still unable to complete research in our academic research labs (going well into 2020), we used molecular dynamics extensively to identify a self-assembled nano material that would strongly attach to SARS-CoV-2, "blanket it", and keep it from replicating. After extensive molecular dynamics simulation, we then completed pharmacological computational modeling (ADME and QSAR) to further validate our self-assembled nanomaterial [8]. We then spun out this molecule commercially and we were able to conduct in vitro and in vivo studies validating the efficacy of this self-assembled nanomaterial towards passivating SARS-CoV-2 (and other viruses) [12].

Looking back at our experience, we are incredibly grateful to the computational modeling community. At a time when we and others needed them most due to experimental lab closures, we were able to quickly and effectively learn computational models that have been developed and optimized over the decades. We would not have developed a therapy or so many other technologies to help fight COVID had it not been for computational nanomedicine.

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