AI-Enabled Protein Design: A Strategic Asset for Global Health and Biosecurity

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The use of artificial intelligence (AI)-enabled protein design tools such as AlphaFold, RoseTTAfold, and RFdiffusion to model proteins and generate new protein structures (referred herein as *AI biodesign*) is fueling a revolution in biology that promises benefits across medicine, sustainability, and beyond (Jumper et al., 2021; Baek et al., 2021; Watson et al., 2023). Specifically, but currently underappreciated, these AI systems for protein design are transformational tools that can be harnessed to create life-saving medical *countermeasures* in a fast-paced manner and could have profound beneficial impacts on global health security. As part of the efforts to ensure the responsible use of AI, maximizing the benefits of AI biodesign and the application of such tools to biosecurity should become a global priority.

Recent health crises like H1N1, H5N1, Ebola, MPox, and COVID-19 have exposed how vulnerable the connected world is to biological threats. To respond more effectively to tomorrow's global health emergencies, countermeasures will need to be created safely and with unprecedented speed. The rapid development and deployment of multiple vaccines during the COVID-19 pandemic shows that it is possible to improve end-to-end efficiencies in existing processes and, by leveraging new innovations such as mRNA vaccines, shorten the time needed to respond to an outbreak. As discussed below, AI biodesign research and tools show similar promise to reduce the latency time for responding to many emergencies. However, maximizing the contribution of AI biodesign to global health security will likely necessitate international collaborations and agreements to support the responsible use of AI in biology, and AI biodesign in particular, to ensure its utility is fully appreciated and that it is positioned as a strategic asset for biosecurity. Moreover, for equitable participation, non-profit organizations and researchers in low- and middle-income countries will require access not only to AI biodesign algorithms but also to training in their use and sufficient computational resources to deploy them, especially in an emergency.

In the not-so-distant future, the authors envision that it will be possible to accelerate responses that disrupt the rise of pandemics via *in silico* analyses: within hours of sequencing a new pathogen of concern, scientists could use AI methods (e.g., AlphaFold, RoseTTAFold) to model the key structures of a pathogen and their counterparts within a host key structure. These insights could be immediately used by teams around the world to guide the rapid development of countermeasures, including tests for diagnostics and surveillance using AI biodesign. Similarly, generative AI-enabled protein design algorithms such as RFdiffusion could be deployed in a matter of hours or days to stabilize antigens, yielding optimized amino acid sequences that are ready to be encoded into a variety of vaccine platforms. These and other AI-enabled tools could also be applied to create protein-based therapeutics that might block infection or facilitate small-molecule drug discovery and synthesis. AI-enabled antibody design tools that are already in development may allow scientists to generate potent synthetic antibodies that could be deployed rapidly and updated continuously, obviating the need to isolate antibodies from convalescent patients, a lengthy process that remains the state of the art today. All of this and more could occur in response to an actual regional outbreak or as part of a preemptive program focused on prototype pathogens. These capabilities align with the aspirational goals set out in the 100 Days Mission, an international call endorsed by the G7 to develop ways of halting outbreaks before they become pandemics (Dzau et al., 2023). Such a goal can only be achieved by embracing radically different and transformational approaches to designing and developing medical countermeasures, such as what is now possible using AI-enabled protein design.

The COVID-19 pandemic highlighted the indispensable role of public institutions and cross-sectoral coordination efforts that prioritize population health over commercial interests. This was exemplified by prescient research on coronavirus antigen stabilization that occurred at the National Institutes of Health Vaccine Research Center and was shared widely across the research community. Other notable examples include the viral vectored

vaccines developed at the University of Oxford, which were licensed to AstraZeneca and Serum Institute of India, and SKYCovione, a protein-based nanoparticle vaccine designed at the University of Washington and licensed royalty free to a developing country manufacturer, SK Biosciences. All three of these breakthroughs were developed and shared freely, leading to some of the earliest and most innovative COVID-19 vaccines. This demonstrates how universities and other non-commercial institutions can rapidly pivot to address new public health crises and to coordinate across sectors to make important contributions to global health security. Such organizations should be supported to maintain cutting-edge research infrastructure, including the most effective AI tools and computational resources for biodesign.

The researchers on the front line of a regional outbreak are also key stakeholders. Promoting broad and equitable access to AI tools for biodesign should be considered essential for building 21st century regional public health resilience, especially in the Global South. Despite the remarkable scientific response seen during the COVID-19 pandemic, global health inequity remains a significant concern. Beyond existing structural deficits in health care education and access, life-saving innovations—including innovative diagnostics, therapeutics, and vaccines—failed to reach many low-income communities. These injustices in expertise and access are not new but deserve fresh thinking from a global perspective. Pandemics can start anywhere, and it is thus in everyone's interest to ensure that all regions, particularly in Africa, have access to AI biodesign tools. It is important for these communities to also maintain a trained workforce that will boost regional responses, enhance global health resilience, and strengthen regional autonomy. Indeed, the distributed and borderless nature of research and development of computational tools for biology offers a unique opportunity for a truly inclusive global response.

With adequate preparation and plans for cooperation, people working in academia, industry, and public sectors around the world could function in coordination to implement fast-paced responses to locally detected biological threats. To achieve an internationally coordinated response that makes efficient use of AI technologies for biodesign, formal efforts should establish clear roles, plans, data, funds, and computing resources to be activated during times of emergency. Such efforts, introduced here as the "International Bioscience Response Reserve (IBRR)," would resemble in some ways the US Civil Reserve Air Fleet, which through contracts ensures that commercial air transport companies will provide air transportation during crises when airlift demand exceeds what the US government

can supply. Similarly, the IBRR could be mobilized within the earliest hours of an outbreak to initiate rapid *in silico* analyses as the first step in a global R&D effort to disrupt a potential pandemic.

As AI capabilities in the life sciences continue to grow, coupling beneficial research with efforts to understand and mitigate risks is crucial. The White House's Executive Order on Safe, Secure, and Trustworthy AI, which directs US agencies to assess how AI technologies might be employed maliciously to create biological threats *and* be harnessed to respond to them, is a step in the right direction. To ensure AI biodesign tools remain beneficial for all, the community has come together around some key principles: a growing list of signatories and supporters from over 30 nations has endorsed a set of specific actions, including controls on DNA manufacturing, an obligation to report concerning research practices, and a commitment to support deliberate efforts to maximize AI applications for the benefit of society (see https://responsiblebiodesign.ai for signatories) (Baker and Church, 2024). The authors urge others, especially those in the global health and biosecurity communities, to recognize the unprecedented potential of AI biodesign to enhance preparedness and response efforts. By enabling rapid development of countermeasures against infectious diseases, AI biodesign delivers new tools to mitigate the risks of biological threats, contributing to a safer and healthier world.

The advent of AI-enabled protein design marks a pivotal moment in the intersection of technology and global health. Embracing these advancements and fostering international collaboration will unlock the full potential of AI biodesign to transform global health security, ensuring a resilient and equitable response to future biological threats.

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