Building global health with lego vaccines

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Prof Tuck Seng Wong and Dr Kang Lan Tee from the University of Sheffield, explain building global health with LEGO vaccines

The lessons learned from the COVID-19 pandemic emphasise the crucial need for swift responses, whether in vaccine development or manufacturing, and highlight the importance of our readiness for future pandemics. Engaging in a Whac-A-Mole game with emerging diseases, novel pathogens, or new variants is risky. Such a strategy would only leave us vulnerable, resulting in delayed responses that could jeopardise the health and well-being of our global population.

Rather than developing a new vaccine in response to a threat, a more prudent approach is first to explore our existing toolbox, identifying the right tool or combination that is both effective and cost-efficient. With these established tools, we possess knowledge of their manufacturing processes and application strategies to address the challenges at hand effectively. Moreover, these existing tools have undergone design, process optimisation, and regulatory approval, enhancing their reliability and efficacy.

The LEGO vaccine concept

The LEGO vaccine concept is elegantly simple. Just as a box of LEGO bricks spark the imaginative creativity of a Youth Fan of LEGO (YFOL), these building blocks facilitate the rapid construction of new designs.

First and foremost, the LEGO bricks are intuitively designed for user-friendliness, featuring interlocking tubes at the bottom and studs on top for seamless connectivity. Secondly, the same set of bricks allows for an extensive range of diverse constructions, showcasing remarkable flexibility.

Additionally, the set can be expanded by including Nanofigs, Microfigs, Bigfigs, and other pre-fabricated parts. Lastly, the individual bricks and intricate structures are crafted for durability, ensuring sturdiness and stability through using robust materials. Though seemingly simple, the ‘Pick and Build’ philosophy in the LEGO world carries profound lessons that vaccine engineers can draw inspiration from.

Vaccine design

Connectivity (C), flexibility (F), and stability (S) are the essential attributes we seek in a vaccine designed to combat known diseases or unforeseen threats like Disease X. Regarding vaccine design, connectivity empowers the creation of monovalent and multivalent vaccines. Flexibility facilitates a nimble response, allowing for adapting existing vaccines to address new variants or strains of pathogens.

Ultimately, the stability of vaccines streamlines the storage and logistics involved in vaccine distribution and administration. When viewed through the lens of vaccine manufacturing, the triad of C-F-S translates to enhanced manufacturability and sustainability. Here, manufacturability denotes the ease of production, ensuring a more stable supply, while sustainability entails economically sound processes that minimise adverse environmental impacts.

Indeed, numerous existing vaccine platforms, including protein-based, mRNA-based, and viral vector-based approaches, provide the framework for implementing the LEGO's C-F-S triad. To illustrate, let's look at the example of virus-like particles (VLPs), a representative protein-based vaccine platform. These nanoscale structures result from the self-assembly of viral structural proteins, devoid of viral genetic material, making them non- replicative and non-infectious.

VLPs are dispersed nanomaterials, which can be easily manufactured across diverse systems, such as mammals, plants, insects, yeasts, and bacteria. Leveraging VLPs for antigen presentation in vaccines or as carriers for bio- and nanomaterials, such as drugs, quantum dots, and imaging substances, becomes attainable due to their inherent structures and the cavities within them.

In terms of connectivity (C), both single antigen (monovalency) and group of antigens (multivalency) can be seamlessly tethered to the VLP surface, achieved through well-developed techniques such as genetic fusion or bioconjugation (e.g., SpyTag/SpyCatcher and its derivatives). Many viral structural proteins, including those from the Hepatitis B virus (e.g., surface antigen and core antigen) and non-viral proteins like ferritins and lumazine synthase, demonstrate the ability to self-assemble into vesicles.

We have only scratched the surface of the vast biological resources that Nature has provided, suggesting the potential for creating a diverse array of VLP systems of varying sizes for various purposes. By treating the VLP as a 'baseplate', the surface antigen (or 'brick') can be easily replaced to address new diseases or pathogens, underscoring its flexibility (F) as a vaccine platform. Notably, the protein self-assembly inherent in VLPs contributes to their high stability (S), and further stability enhancements can be achieved through protein engineering. If we standardise the design and manufacturing of VLPs, they hold tremendous promise in vaccine applications.

Synthetic biology has surged

Synthetic biology, often known as engineering biology, has tactfully embraced the LEGO concept. In this context, standardised parts, commonly called 'BioBricks,' are ingeniously assembled to construct a biological system not found in Nature but designed to serve a specific function.

Over the past two decades, synthetic biology has experienced a surge, marked by the emergence of numerous synthetic biology startups and the creation of intriguing novel biological systems and tools (e.g., CRISPR-Cas, synthetic cells, synthetic genomes). There is compelling evidence to suggest that a similar level of success can be achieved with LEGO vaccines. In fact, part assembly to create circular RNAs for enhanced protein production has met with great success. mRNA vaccine design will likely move in this same direction – assembly of well-characterised parts or bricks.

A collaborative response to global health threats

Led by the University of Sheffield, the recently inaugurated UK-South East Asia Vaccine Manufacturing Research Hub (UK-SEA Vax Hub) signifies a collaborative response to global health threats between the UK and South East Asia. This initiative is committed to standardizing vaccine manufacturing across three crucial platforms: protein-based, mRNA-based, and viral vector-based approaches. Significantly, within these efforts, a key research priority is the standardisation of VLP systems, adopting an innovative approach inspired by the principles of LEGO.

The essence of engineering lies in the art of simplifying rather than complicating a problem. It is the ability to distil complex challenges into elegantly straightforward solutions. Indeed, the beauty of engineering manifests when a seemingly intricate issue is met with a straightforward and effective strategy. It underscores the transformative power of simplicity in problem-solving, where the most impactful solutions often arise from embracing a clear and straightforward concept.

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