$60M Wellcome Leap Program jointly funded with CEPI
R3: RNA Readiness and Response

We need a global network of 'living' biofoundries.
Distributed, multi-product, RNA-based manufacturing capabilities will provide increased access to diverse biologics and sustainable pandemic response.

In one of the greatest scientific accomplishments of our generation, mRNA technology has demonstrated the ability to change the timeline for developing and delivering a new vaccine from years to months. And the entire world was witness to that demonstration. The development of an mRNA-based vaccine for COVID-19 took just 63 days from release of the virus sequence to first dosing in humans, leading to accelerated clinical trials and ultimately billions of doses manufactured. The new mRNA vaccines have demonstrated efficacies in the high 90s, with minimal side effects, and have been manufactured by two different RNA technology firms to date, with others adding further production capacity.

The scale of this on-going achievement was made possible because, unlike the established existing vaccine manufacturing techniques, RNA technology shifts the most difficult and complex parts of manufacturing — the key proteins needed for a vaccine — to the natural bioreactor that is the human body. This shift meant the mRNA vaccine could deliver the instructions for how to make the antigen, or spike protein, needed to train our immune systems rather than the antigen itself. The development of lipid nanoparticles (LNPs) ensured that instructions would arrive intact to our cells – a critical element of the mRNA vaccine delivery and effectiveness. Importantly, this RNA-based approach holds promise for treatments beyond vaccines and infectious diseases to diverse biologics as treatments for cancer, metabolic disorders, cardiovascular conditions, and autoimmune diseases.[i]

Given this vaccine breakthrough, it would be reasonable to expect a wave of activity to discover, develop, and deliver new RNA-based biologics – a diversity of organizations; academic, small biotech, private and public research centers around the world flooding clinical facilities with novel, investigational products. All these products could then be tested against diseases that cause millions of deaths per year; thus providing access to these new products, while also securing protection against the next pandemic.

While we see continued and increasing global investments to scale existing mRNA manufacturing capabilities, such investments alone will not be enough to increase the number, diversity, affordability, and pace of discovery for these new biologic treatments, or to provide continuing access to agile, state-of-the-art manufacturing processes likely needed for rapid response to another pandemic.

What's holding us back?

The discovery and development of RNA-based products is still subject to the same, existing limitations chronically afflicting biologics: difficult access to current good manufacturing practices (cGMP) material for clinical trials as well as long and large investments (4-8 years[ii] and $300-$500 million dollars[iii]) in bespoke, manufacturing processes at dedicated facilities. This limits innovation and creates prohibitive production costs.

Today, RNA scientists trying to develop an innovative product are limited to using laboratory-grade materials in pre-clinical studies. Outside of one of the few biopharma corporations investing in cGMP for RNA-based biologics, most researchers have limited or no access to the know-how and resources required to develop a small-scale manufacturing process required for clinical trials. And even within those corporate environments, lacking a product with an expected net present value nearing a billion dollars, it would be challenging to get priority in the large-scale manufacturing strategy of the company.

R3 seeks to change the dynamics and costs of biologics development and production, addressing the limitations of current manufacturing by establishing RNA as a versatile, deployable, standardized, multi-product platform technology, that: 1) in non-emergency times provides developers and researchers with access to cGMP-formulated RNA for the development and production of a diversity of viable RNA-based products, and 2) in emergency times shifts to needed products at speeds & quantities sufficient to mount a globally coordinated, regionally focused response to a pandemic.

The opportunity for R3.

The limitations in today's RNA-based production bears similarities with the limitations faced by the semiconductor industry at the end of the 1970s. In the twenty years following the invention of the first integrated circuit in the late 1950s, the design of semiconductor-based products was almost exclusively confined to a handful of large, vertically integrated companies that could afford the investments required by customized ISO-certified manufacturing processes. Designing a new semiconductor-based product was limited to employees within those companies and often came with adjustment and refinements to manufacturing processes. As one measure of how access to manufacturing constrained innovation, on average there were only 3 to 4 new semiconductor start-ups created globally each year during the decades between 1958 and 1978.[iv]

Then, in the decade after 1978, the number of new start-ups more than tripled – tens to dozens of new semiconductor start-ups. What happened to accelerate the number, diversity, and pace of semiconductor innovation?

Two related developments changed the rules of the game for the semiconductor industry. The first was the publication in 1978 of "*Introduction to VLSI Systems*"[v] by Mead & Conway, outlining the elements of Very Large Scale Integration (VLSI) for the design of semiconductor circuits. Mead & Conway decoupled the *design* of a circuit from the *fabrication* of a circuit using digital design, simulation, and verification tools. These tools also captured and characterized different, specific fabrication processes using high-level, parametric descriptions for those processes. The decoupling of design from fabrication and the parametric abstraction of fabrication processes made it possible for a greater number and diversity of people to design integrated circuits (in the decade following publication, 1,000 to 10,000 times more people[vi], ranging from students to experienced chip designers). Just as importantly, the decoupling and parametric abstraction enabled any of these designs to be fabricated at any of a multiplicity of fabrication sites at scale and seamlessly.

The resulting demand for fabrication services from chip designers created the market space for a second breakthrough. In 1987, the first "pure-play" foundry was stood up – a semiconductor company exclusively manufacturing third-party designs, without developing or marketing their own products. With the availability of pure-play foundries, it became possible for a new type of company to emerge – fabless semiconductors companies. These companies designed and delivered chips as their products – notable examples include Broadcom and Nvidia – but had no fabrication facilities of their own.

Vertically integrated companies with captive fabrication facilities thrived alongside the new fabless companies as both types of companies delivered a greater number and diversity of semiconductor products, growing the semiconductor industry at a compound annual growth rate of more than 10% over the last 40 years.[vii]

Since then, continued process improvements, the emergence of different lines for different classes of products, and optimization of production load balancing, has led to new speed and vibrancy in the ecosystem, further fueling additional breakthroughs. Indeed, whenever an industry has succeeded in raising the level of abstraction to allow more innovators to participate and reduce the barriers to product delivery, seemingly explosive growth of innovation has been the result. We need this type of technological advance for RNA-based products.

Program goals.

The R3 program has two goals: one, to increase exponentially the number of biologic products that can be designed, developed, and produced every year, reducing their costs and increasing equitable access; and two, to create a self-sustaining network of manufacturing facilities providing globally distributed, state-of-the-art surge capacity to meet future pandemic needs.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over three (3) years (with a potential additional one-year option) in one or more of the following thrust areas, to either develop the platform, develop products, or demonstrate the platform implementation.

Proposers should clearly relate work in these thrust areas to one or more of the program goals, but are not required to provide both platform technologies and end-to-end demonstrations. Synergies among performers will be facilitated by Wellcome Leap.

Thrust Area 1: Establish the RNA 'Living' Biofoundry

We seek the development of standardized process elements to achieve formulated RNA products starting from digital sequence input. Each module will be characterized by Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) sufficient to grant, in a Quality-by-Design (QbD) framework[viii], computationally supervised Continued Process Verification (CPV[ix]) and continuous manufacturing.[x]

Manufacturing processes proposed must be suitable for multi-design runs of heterogeneous RNA-based products, including vaccines, monoclonal antibodies, therapeutic biologics, and diagnostics. Convergence with high-volume manufacturing technologies for non-health related products, such as pesticides, fragrances, and flavors, will also be considered, to the extent that cGMP-grade processes could be made compatible with current cost of goods for such products when made using spare capacity.

Development of innovative fill-to-finish technologies, although essential to complete the product delivery chain, are not of interest in this initial call.

1.A) Development of software tools for RNA products supporting:

1.A.i) ***In silico* RNA product design** predicting the pharmacodynamic profile of RNA-based products sufficient to achieve 'first-pass' fabrication success. Particularly for coding-RNA

products, we expect a reliable prediction of *a) potency:* amount of the translated biologic and timing of the translation, and *b) reactogenicity:* the quantitative extent of innate-immunity response induced by the RNA-based product. We are particularly interested in approaches based on knowledge-networks as a bases for multi-level functional simulation modules;[xi]

1.A.ii) **Manufacturability verification** accurately predicting compliance of the product design with prescribed CQA and CPP ranges of the available manufacturing processes. Approaches based on the development of "digital twins", possibly leveraging hybrid combinations of physics-based simulations & data-driven learning from digital sensors, are of interest; and

1.A.iii) **Simulation of animal to human translation.** For RNA-based products designed and specified using the previous two modules, we expect a 50%[xii] increase over current industry averages of the accuracy of reactogenicity and potency/immunogenicity prediction from pre-clinical to clinical settings, as demonstrated by a retrospective assessment across appropriate products.[xiii]

1.B) Development of cGMP processes to deliver formulated RNA satisfying the following requirements:

1.B.i) Fully or largely automated implementation, through robotics or other technologies, ensuring real-time product quality and performance monitoring through high-density digital sensors and computerized control;

1.B.ii) Capable of delivering multiple product designs in parallel, for an overall throughput of at least ~50 grams of formulated RNA[xiv] per day. Of particular interest are systems limited in size, not to exceed an overall capacity of 10 liters;

1.B.iii) Demonstrated against a range of RNA lengths from ~100 to above ~10,000 nucleotides, and against mRNA with diverse UTRs[xv], modified nucleosides and sequence/codon optimizations[xvi], suitable for combinations of different products; and

1.B.iv) Each formulation module should ensure thermostability, efficient encapsulation or carriage, tropism, enhanced or specific tissue-targeting and endosomal release, effective *in vivo* – and, possibly, needle-free – delivery. We are particularly interested in advances in broadly applicable formulations – with their respective analytical tools – based on improved lipid or inorganic nanoparticles, polymers / biopolymers[xvii] and programmable nanomaterials, including graphene[xviii].

1.C) Establishment of a Third-Party Foundry Service Broker.
Organization(s) serving in the intermediary role between the plurality of product designers accessing the foundry services and the plurality of manufacturers offering foundry services, to define suitable brokering processes, protections, certifications, and infrastructure.

Thrust Area 2: Increasing the diversity, number, and pace of biologics development

Applications to generate clinical proof-of-principle towards one or multiple RNA-based products, or to one product across multiple indications, in the areas shown below. All products must be capable of production in the RNA biofoundry and thus will simultaneously and continuously inform process development in Thrust Area 1.

2.A) Enabling ≥100-fold dose reduction.
Self-amplifying[xix] or alternative strategies – including, but not limited to, trans-amplifying[xx] and

endless[xxi] RNA – achieving non-reactogenic, effective dosage in humans at ≤1 μg formulated RNA.

2.B) Pandemic preparedness breadth.
Demonstrate tolerability and immunogenicity of an RNA-based vaccine against a non-viral target. We are particularly interested in bacterial pathogens characterized as priority anti-microbial-resistance targets.

2.C) RNA-mAbs and accessibility.
Optimization of mRNA-based monoclonal antibody constructs increasing tissue-targeted antibody expression and prolonged bioavailability, demonstrating protective / therapeutic effects in humans. Demonstrate manufacturability of an RNA-based Monoclonal Antibody (mAb) for <1-10 US$ / dose.

2.D) Alternative delivery mechanisms.
Tissue-targeting strategies and needle-free delivery technologies for multiple RNA-based products. We are particularly interested in delivery strategies alternative to intravenous infusion and intramuscular injection, including oral, mucosal[xxii] and transdermal.

Thrust Area 3: Sustainable production under steady-state non-emergency conditions, providing immediate surge capacity to address emergency pandemic needs

As the iterative loop between Thrust Area 1 (process) and Thrust Area 2 (applications) reaches sufficient maturity to support sustainable capacity, an at-scale demonstration of an RNA 'living' biofoundry is to be constructed. A biofoundry capable of producing the requisite diversity of viable RNA-based products in non-emergency times, and can relocate and shift to needed products at speeds & quantities sufficient to mount a globally coordinated, regionally focused response to future pandemics in emergencies. Thus, the biofoundry should deliver on one or both of the following objectives:

3.A) Demonstration of agile capacity balancing
Demonstrate the compatibility of the production platform, within cGMP standardized procedures, to:
- Manufacture at least two RNA products simultaneously, possibly belonging to the same product class (e.g., two different RNA-based vaccines)
- Manufacture RNA-products belonging to different classes sequentially (e.g., an RNA-based vaccine one day, an RNA-based monoclonal antibody the next day, and an miRNA the third day) without requiring re-validation at product change over; and

3.B) RNA Foundry Integration and Deployment
Integrate a largely automated (limited- to no-human intervention), end-to-end RNA foundry (from digital input of the sequence template to formulated RNA output) implementing a standardized cGMP process in a closed, easily deployable manufacturing unit (e.g., a 40-foot intermodal ISO container), including one or more formulation modules. Deployment demonstration:
- produce a cGMP-grade formulated batch of an RNA-based product, in a first location;
- ship container to a different continent;
- produce a second batch of the for same product in the new location;
- demonstrate equivalence of the two batches.

Program Demonstrations. Each year, the program will demonstrate biofoundry processes developed in Thrust Area 1, by manufacturing diverse RNA products and modalities advanced in Thrust Area 2.

By year 2, a regional 'living' biofoundry will be demonstrated, capable of economically sustainable operations and suitable as part of a global network delivering 20B doses per month of vaccine in a global outbreak event.

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