**Overview.** Most vaccines require a series of injections over several months to years, making full vaccination difficult for those without easy access to health care. Drug delivery technologies currently exist for a range of pharmaceutical products, but after more than 20 years of research effort, no controlled-release technology has been able to reduce the number of doses down to a single injection. Langer Lab at Massachusetts Institute of Technology (MIT), with funding from the Bill & Melinda Gates Foundation (BMGF), has invented a new single injection (SI) platform technology that enables one injection to deliver multiple pulsed doses of a vaccine, on a schedule that mimics the licensed vaccine regimen. Particles for Humanity (PFH) is preparing this technology for transfer out of the academic setting. This development plan describes a strategic roadmap for how to roll out the various applications of this technology over time, the rationale for the first product selection, the path to regulatory approval for this first product, and resources needed, both financial and human.

**Large Unmet Need for Single Injection Vaccines.** Vaccination prevents 2-3 million deaths (World Health Organization (WHO, 2019) every year, but 19 million children are under-vaccinated (WHO and UNICEF, 2018). The need for multiple injections to produce effective immunity has been a major obstacle in immunization, including for polio eradication.[1] It is expensive and inconvenient for patients to travel to clinics from rural locations to receive a series of vaccinations, which can result in poor patient compliance with vaccine schedules, especially for vaccines whose delivery is outside routinely administered childhood immunization schedules. Vaccination series also puts a burden on the vaccine supply infrastructure and health care workers who administer them. Each vaccine dose also has costs associated with administration, including supply infrastructure, waste disposal, and health care worker time that single injection vaccination could reduce.

**Promising Single Injection Platform Technology with Encouraging Early Data at MIT.** To achieve protective and long-lasting immunity for many vaccines it is necessary to present antigens at multiple times to enhance maturation of the immune response. Drug delivery technologies currently exist for a range of pharmaceutical products, but after more than 20 years of research effort (Cleland, 1999), they have not resulted in any approved vaccines because it has not been possible to produce an immunologic response equivalent to multiple doses. ***(See Appendix: SI Platform Competition)***. SI technology eliminates multiple injections by encapsulating a vaccine within engineered particles whose degradation kinetics can be manipulated to mimic vaccine schedules. The SI capsules are micro-molded from poly(lactic-co-glycolic acid) (PLGA) polymers. Micro-molding avoids harsh solvents used with many PLGA-microparticle fabrication methods. By “tuning” the particles to release the vaccine at different times, the SI technology has the potential to turn any vaccine with multiple injections

[1] Source: Dave Robinson, Deputy Director, Vaccine Development. Members of the Functional Leadership Team are Orin Levine, Anita Zaidi, and Jay Wenger.

into a single injection that delivers vaccine within the body at the desired schedule. PLGA polymers are already approved for clinical use in humans by the Food and Drug Administration (FDA) and other regulatory authorities and have long been used in injectable drug delivery systems. In mice studies, MIT has demonstrated the ability to mimic a bolus at 7, 14 or 30 days using a model drug, and the ability to induce an immune response similar to two boluses, using a model vaccine. This work was published in Science in September 2017 (McHugh, et al., 2017).

**Strategic roadmap.** To prioritize candidate vaccines, PFH retained Health Advances, a strategy consulting firm for the healthcare industry, to conduct a rigorous, data-driven process. The process included stakeholder interviews, as well as interviews with experts inside and outside BMGF. Priority was put on improving already approved vaccines, especially those where the SI technology could not only eliminate subsequent injections but could also eliminate doctor's visits because they were outside the routine immunization schedule for infants and children. After excluding live/attenuated vaccines because of technical complexity, as well as vaccines that are already single administration or delivered via the oral or nasal routes, more than 50 vaccines were screened for technical compatibility and potential for greatest impact. The most important technical criteria were low antigen mass, high stability, and a dosing regimen that was completed in weeks or months rather than years. This screen yielded ten vaccines for deeper analysis and resulted in these vaccines for first product selection: HPV, meningococcus A/C/W/Y, malaria, inactivated polio virus (IPV) and rabies. ***(See Exhibit A for Health Advances' detailed analysis).***

The first product selected has two roles: 1) a development candidate to improve an important vaccine and 2) a model drug to build out the technology platform, converting the lab scale process developed at MIT into a commercially viable process for producing a wide range of improved vaccines over time. The strategic roadmap of the SI program focuses initially on building out the technology platform with the first product before rolling out other product opportunities. These include reformulating one or more of the remaining top 4 vaccines (i.e., HPV, IPV, meningococcus ACWY, and malaria), other BMGF strategic priorities (e.g., *T. solium*), vaccines with high commercial potential that could provide funding for vaccine development for low resource settings (e.g., Hepatitis B and HPV), and minimizing the number of injections during routine immunization. Over time, the SI technology could be used to formulate vaccines in development for initial regulatory approval as a single injection (e.g., HIV). Over the longer term, the SI technology could be used to create single injection combination vaccines – putting different vaccines together that may have differing dosing regimens.

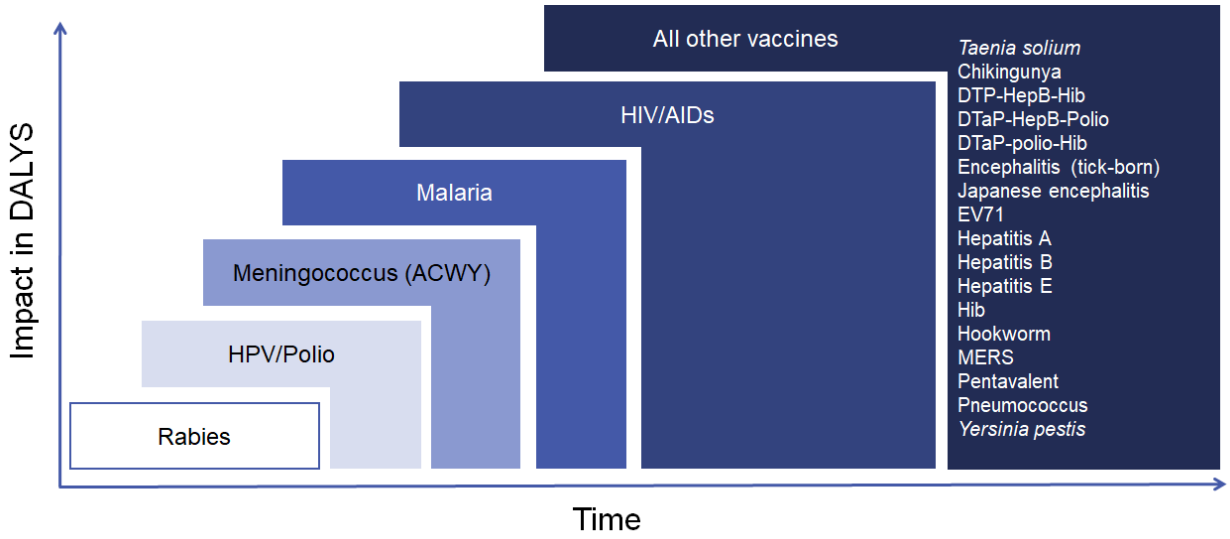


**Figure 1. SI Program Strategic Roadmap**

**First product for development: SI-rabies vaccine.** The rabies vaccine was found to be an ideal fit as both a first product candidate and a model antigen for proving the technical feasibility of the SI platform. It is relatively heat-stable and elicits a strong immunologic response relative to the mass of antigen administered and requires a series of doses that are all administered within 30 days. In addition, it has a well-defined antibody level as an acceptable correlate of human immunity that has been validated and used in licensing studies, enabling quick assessment of immunologically defined effectiveness, which will speed development. The rabies vaccine has a long scientific and regulatory history, so the non-clinical research, clinical development, and regulatory pathways have already been established independently.

Today's marketed rabies vaccines are highly effective when administered post-exposure according to the recommended regimen (Wilde, 2007), however, they require injections on at least four separate days over a period of weeks. This dosing regimen poses a significant barrier for access especially in remote, resource poor settings (Shim, Hompson, Cleaveland, & Galvani, 2009). Rabies is 100% fatal once symptoms develop and is an important health issue in Asia and Africa (WHO, 2018). Children between 5-14 years old are the most frequent victims of rabies, and rabies deaths globally are rarely reported (WHO, 2019). Over the past few years, global momentum has built to prioritize rabies as a disease for investment. Rabies prophylaxis was added to GAVI's investment strategy and to WHO's list of vaccines for stockpiling (WHO, 2018) (GAVI, 2019) (Abela-Ridder, Martin, Gongal, & Engels, 2016). Rabies has also been designated a neglected tropical disease by FDA, and it is eligible for the priority review voucher program (FDA, 2018). Across the globe it is estimated that 3.7 [1.6–10.4] million Disability-

Adjusted Life Years (DALYs) are lost due to rabies, with over 95% lost in Africa (36.2%) and Asia (59.9%) and less than 0.5% (11,950 DALYs) in the Americas (Hampson, et al., 2015). An SI-rabies vaccine would help address a major health challenge in low- and middle-income countries (LMICs), and simultaneously lay a strong foundation for the technology platform that can be applied across a wide variety of vaccines.

**Path to regulatory approval.** Vaccine development often takes 10-15 years and >$300 million. Our development plan describes 5 stages (See Figure 2 for a high-level Gantt chart).

- ***Planning Stage.*** We have recently completed the Planning Stage and Non-Clinical Development Stage is ready to begin once funded.
- ***Non-Clinical Development Stage.*** The first 2 years of non-clinical development will focus on identifying a commercially viable manufacturing process for the platform. Achieving this milestone will involve transferring and reproducing the MIT process, as well as setting up a dedicated lab with formulation, process, and analytical capabilities to generate and characterize intermediates and finished product. We will focus on assessing the scalability of the MIT process steps and identifying commercially viable alternatives for those that are limiting or impractical. The process and formulation development required for this program is extremely specialized work requiring highly skilled engineers that are not easily found at contract research organizations. As a result, PFH will build this capability in-house and outsource more standard safety and efficacy studies, as well as the manufacturing of test articles for these studies. Creating a commercially viable process will require technical innovations that optimize for cost, since affordability is a critical success factor in low resource settings. Attention will be paid to selecting economical materials, reducing unnecessary components or features, and eliminating process steps that will add cost. In addition, price targets will be set during the development of a target product profile (TPP) that will be informed by stakeholder interviews to understand the key drivers of the cost of multiple injections to the health system as a whole. Once the commercially viable process has been demonstrated in animals using a model compound, the next two years will focus on establishing efficacy in animals using the rabies antigen before beginning preclinical toxicology of the SI-rabies vaccine.
- ***Clinical Development Stage***. After filing an Investigational New Drug Application (IND) with FDA, proof of concept in humans of the SI-rabies vaccine will be demonstrated in a Phase 1 study of 40-100 healthy adults or other regulatory authority. Afterwards, a Phase 2 study in 125-400 healthy humans and a Phase 3 study in 800-1200 healthy humans will further explore the safety and efficacy of SI-rabies vaccine while process development and manufacturing scale-up work is conducted in parallel. The clinical program for the SI-rabies vaccine will be accelerated because well-defined antibody levels are an acceptable correlate of human immunity that have been validated and used

in licensing studies, enabling quick assessment of immunologically defined effectiveness.

- ***Regulatory Review and Approval.*** Upon successful completion of human studies, the data will be presented to one of the regulatory bodies (US, EU and India) that is eligible for the WHO pre-qualification process, which is designed to give United Nations (UN) procurement agencies confidence that products are safe, effective, and manufactured under acceptable quality standards.

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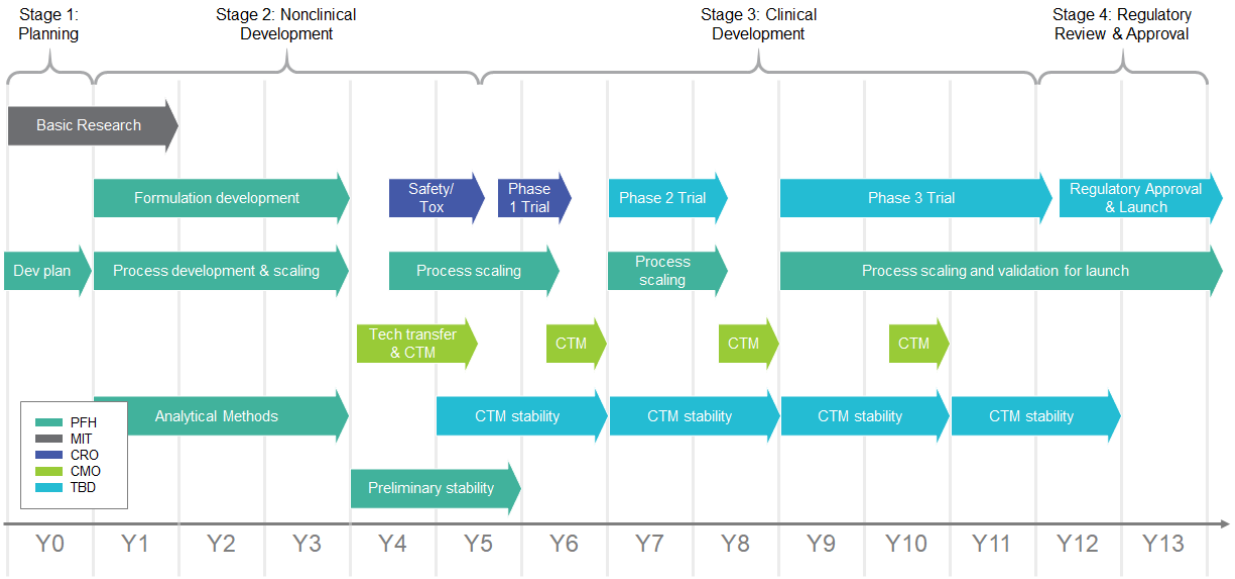


**Figure 2: High-Level Gantt Chart**

**Resources needed.** To be successful, the SI program will require significant funding from multiple sources, and it will need to recruit and retain talented employees with skill sets across a wide variety of disciplines. With BMGF as the lead investor, potential funding sources include government grants, philanthropic investors, corporate partners, social impact investors, and collaborative partnerships. We expect that BMGF will provide all of the funding needs during the first two years of development. Other sources of capital will become available afterwards, eventually reaching 50% of total funding sources until human proof of concept has been achieved. Three divisions at the National Institute of Health (NIH) have expressed interest in funding the rabies vaccine/SI platform and have encouraged us to submit a grant application for Small Business Innovation Research (SBIR) funding – National Center for Advancing Translational Sciences (NCATS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Biomedical Imaging and Bioengineering (NIBIB). In addition, we have spoken with GHIT, a global health fund based in Japan, who has confirmed that the SI

technology is a good fit and has encouraged us to submit an Intent to Apply at their upcoming request for proposals. Later stage clinical development will likely be funded by a corporate partner in India, where rabies is a significant public health problem and a commercial opportunity.

Particles for Humanity's management team has significant experience in recruiting and retaining top talent for ambitious development programs involving innovative process technology. Our President and CEO, Sherri Oberg, brings 25 years of experience as founding CEO of private and public life sciences companies. She has extensive experience in partnering, clinical, and regulatory activities, and broad financing experience having raised over $400 million across multiple market cycles and a wide variety of transactions. Don Chickering, PhD, Chief Technical Officer, brings over 20 years of development experience in drug delivery, medical devices, and pharmaceuticals. He has an extensive background translating innovative, lab-scale microencapsulation concepts into commercially viable processes that meet all the regulatory requirements for approval. He also has a proven track record of creating novel formulations that add significant benefit to approved drugs and taking these formulations through all stages of preclinical and clinical development.

This team benefits from the expertise of world-renowned scientists, advisors, and investors who serve on the board directors. Dr. Langer is one of 10 Institute Professors at MIT; he has won the National Medal of Science, National Medal of Technology and Innovation, the Queen Elizabeth Prize for Engineering, holds over 1350 current and pending patents, and has started over 30 companies with his innovative technologies. Ana Jaklenec, PhD, is a research scientist at MIT's Langer Lab and inventor of the SI technology. Dr. Boris Nikolic is the Managing Director of Biomatics Capital, and former chief advisor for science and technology to Bill Gates. Dan Hartman represents BMGF's interests as a board observer. He has significant global health, drug development and entrepreneurial experience, including CEO and senior level roles at Pfizer and Esperion.

# 1 Appendix: Competitive Technologies in Development

**Table 1. Competitive Technologies for SI-R Product**

| Technology Description | Developer | Objective(s) | Stage of Development | Comments |
|---|---|---|---|---|
| Protein-based vaccine | CPL Biologicals | Reduce number of doses | Phase III clinical | Currently 3-vist regimen, likely not cost effective |
| PIKA adjuvanted rabies vaccine | Yisheng Biopharma | Reduce number of doses | Phase II clinical | Currently 3-visit regimen |
| RNA vaccine | CureVac | Reduce number of doses, increase protection duration | Phase I clinical | |
| Adenovirus vector vaccine (Wang, et al., 2018) | Wistar Institute/ Jenner Institute | Reduce number of doses, enhance stability, decrease cost | Preclinical non-human primate POC shown for PrEP | |
| Intradermal dosing of commercial vaccines | Multiple | Reduce number of doses and volume of vaccine doses | Phase I-III clinical | Trials studying minimum dosing regimens for ID dosed vaccine |
| Recombinant rabies vaccine with membrane-anchored molecular adjuvant (Plummer & McGettigan, 2019) | Thomas Jefferson University | Improve speed of immune response | Preclinical | |

(Fooks, Banyard, & Ertl, 2018)

**Table 2. SI Platform Competition**

| Technology Description | Developer | Objective | Stage of Development | Comments |
|---|---|---|---|---|
| Pulsed release platform | Orbis Biosciences | Develop controlled/pulsed release platform for various indications | Clinical | H1N1 animal vaccine in preclinical development |
| Virus like particles (VLPS) | GeoVax (Fleming, 2018) | Adaptable platform for single vaccination prevention of emerging disease | Pre-Clinical | Single Vaccination for Ebola, Zika, LASV. |
| Messenger RNA platform | BioNtech in collaboration with UPENN, among many others (BioNTechAG, 2018) | RNA platform that could have multiple technologies and potentially become single dose vaccines for infectious diseases | Discovery | |

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