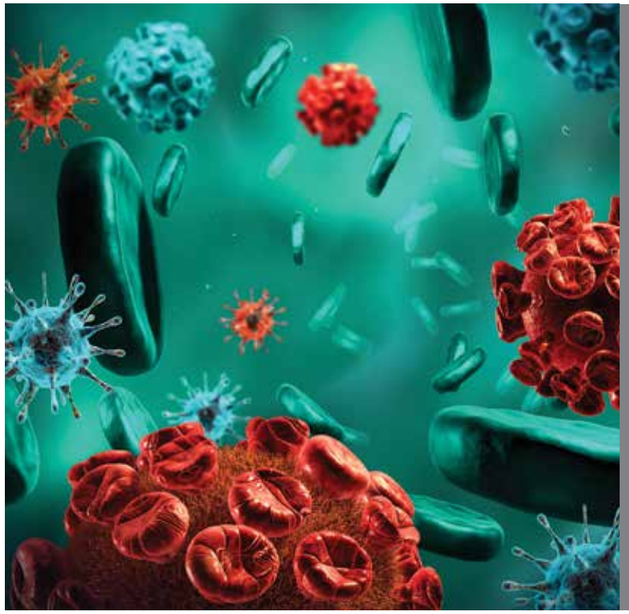
Gates Foundation Plots A Fresh Metric For Market Access: Lives Saved



In Vivo visits Gates Medical Research Institute CEO Dr. Penny Heaton to review its first pipeline of drugs and vaccines to attack four of the world's biggest killers: TB, malaria, enteric diseases and other conditions affecting maternal, newborn and child health.

BY WILLIAM LOONEY

As a drug developer, Gates Medical Research Institute will apply to the FDA for an IND just like any biotech. Last month, it launched its first clinical trial, in South Africa, for a booster vaccine against TB; it is also exploring novel options like applying monoclonal antibodies as a seasonal treatment for malaria when it is most virulent.

CEO Penny Heaton hopes to have 20 product candidates in the pipeline by 2023, with half of these in trials.

So what? The MRI is testing an unusual proposition: can generous, hassle-free financing be combined with a business mindset to treat life-threatening conditions whose persistence is historically associated with market failure? Watch and wait - its an early portent for global market access in the next decade.

What it means to be a drug company has begun to change in recent years, as societal expectations of performance extend beyond investor returns and NGOs and governments claim medicines as a universal public good, accessible to all. Adjacent industries are entering the drugs business while non-commercial actors like patient advocates and philanthropies fund their own R&D programs for medicines to address conditions with high unmet need. Perhaps the most prominent of these emerging players is the Bill and Melinda Gates Foundation, which last year established its own non-profit biotechnology enterprise, the Gates Medical Research Institute (MRI), to develop drugs and vaccines targeting major neglected diseases of poverty like tuberculosis (TB) and malaria.

The Gates MRI initiative is representative of a strategic shift among major private health donors from passive funding to hands-on doing. Interest is high in using the integrative, results-oriented practices of translational medicine to better manage disease etiology in vulnerable populations and increase the speed in which new treatments reach patients on the ground.

What is unique about the Gates MRI is its focus on learnings from the private-sector – including big pharma and biotechs – in moving drugs and vaccines from proof of principle to clinical proof of concept, followed by clinical trials, and ending with registration and uptake in the marketplace. Every Gates MRI project is evaluated on a simple, two-word metric of performance: lives saved. The charge looks simple – deceptively so. The fact is Gates MRI was launched out of the awareness that it is not enough to develop a new life-saving technology; you also have to create the expertise to execute around it, with the organization, logistics, information, policy and partnering skills to ensure that the drug or vaccine can be delivered safely to the market. And, most important, be widely used.

True to form, the Foundation has invested heavily in the money (more than $100 million annually over the next 15 years) and the talent (recruiting top experts in clinical operations and project management, as well as in new fields like quantitative science modeling and AI) to achieve this vision of moving new treatments seamlessly from bench to bedside. Leading the effort is Dr. Penny Heaton, a 55 year-old physician with one of the more distinctive backgrounds in medicine and public health, as an infectious disease expert in academia and the US government and more recently as a vaccine developer at Merck & Co., Novartis AG and the start-up biotech Novavax Inc. As the CEO of Gates MRI, Heaton is also intimately familiar with the working culture of the Seattle-based Foundation, where she helped develop the group's current strategy targeting major diseases with a disproportionate impact on vulnerable populations, especially women, infants and young children.

Heaton thus brings to her new assignment a diverse set of career experiences touching virtually every aspect of the health care landscape. It began with an early introduction to tuberculosis – the world's most deadly infectious disease – when her father, a minister in rural Kentucky, contracted it two years before Heaton was born. "I spent my first years in a household under siege, as my father's eventual recovery left him in constant fear the bacillus might return and infect us all. The one positive was it drew me into the mystery of how something so small could wreak such havoc on human civilization. Even before high school, I knew I wanted to devote my life to the study and treatment of infectious diseases."

Pathogens Pointed The Way

Indeed, Heaton's fascination with bugs led her to the University of Louisville Medical School, where she received an MD in pediatric medicine, followed by an additional research fellowship in infectious diseases funded by a local charity. But, coming as it did just as large-scale health maintenance organizations were depersonalizing the physician-patient relationship, Heaton began to question whether a license to practice medicine was enough to make a difference in people's lives. Looking for opportunities outside Kentucky after the death of her mother, Heaton obtained a position at the federal Centers for Disease Control and Prevention (CDC) in Atlanta where she was assigned to the Epidemic Intelligence Service, specializing in the investigation of foodborne and diarrheal disease outbreaks around the world.

DR. PENNY HEATON, CEO
GATES MEDICAL
RESEARCH INSTITUTE

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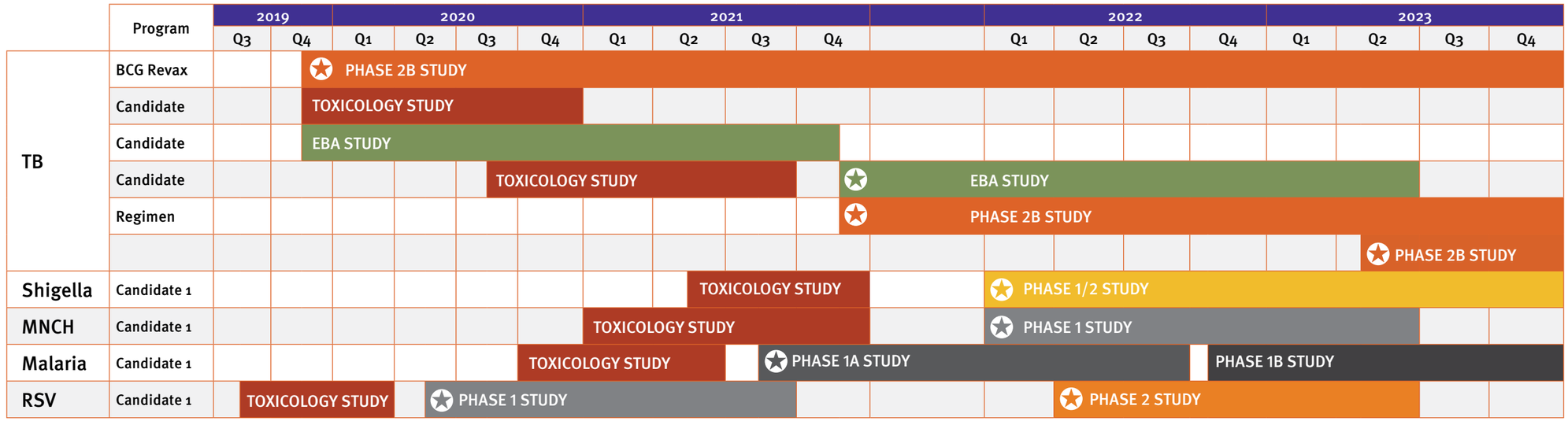
"Working at the CDC gave me a first-hand look at how hard it is to control the spread of pathogens, even in countries with advanced health infrastructure like the US. The inequities in global health also became glaringly obvious, with the prime example being diarrheal disease, which kills more than 500,000 children a year and is almost entirely preventable. More important, it showed me that progress against endemic infectious diseases could benefit from the active involvement of stakeholders outside government, such as the private sector. At the CDC, we knew that simple, remedial measures like boiling water and hand washing could lower the incidence of disease. But I wanted so much more, such as the ability to introduce vaccines and other innovative technologies to prevent these conditions – a goal that publicly-funded efforts could never achieve on their own."

Industry's Calling Card: The Rotavirus Vaccine

It may have been serendipitous but recruiters for big pharmaceutical firms began contacting Heaton as the science advanced on new vaccines for major killers, including for her own specialty in pediatric diarrheal disease. Merck &

MARKET ACCESS: Innovation

Exhibit 1
Gates MRI Drug/Vaccine Pipeline 2019-2023



First Subject In

SOURCE: Gates Medical Research Institute

Co. Inc.proved the most persistent, with a vaccine for the rotavirus in final stages of testing that reflected years of struggle to perfect a liquid formulation suitable for children. "I took the job as head of Merck's rotavirus vaccine development team, taking the candidate through late-state testing as well as dealing with the safety surveillance fallout due to some adverse side effects from a competitor's FDA-approved vaccine. It was a formidable but instructive learning experience – at the time, Merck researchers were best in the world in this field." Heaton followed her time at Merck with a stint at a small Maryland-based biotech, Novavax Inc., where she managed a broad portfolio covering vaccine strategy and early-stage development, and then migrated to the biggest of big pharma, Novartis AG, where she led clinical research for the company's vaccines portfolio.

Of her time in the private-sector, Heaton said it was the ultimate broadening experience. "I learned how to operate in complex, tightly-focused organizations, large and small, prioritizing among a portfolio of drug candidates and marching them through the pipeline to a discernable end – a product that works for patients. Combined with my earlier roles in academic medicine and government service, it put me in the best possible position to lead this new hybrid institution inspired by Bill Gate's vision combining public service and private know-how to generate great medicines for the greatest unmet medical needs."

Heaton's attention turned to the Gates Foundation after she was approached in 2013 by Dr. Trevor Mundel, President of the Foundation's Global Health Division, to discuss a reorganization adding a specific product development component to the group's baseline strategies to fight disease.

Shortly after, Heaton joined the Foundation with the charge to apply her experience in industry to lay out an approach to vaccine development in resource-constrained settings. "A lot of what I did was introduce the processes used in private industry, starting with that living document called the target product profile, laying out all the upfront work necessary to conduct the clinical trials and everything thereafter, especially the regulatory protocols and manufacturing/distribution logistics that are critical to vaccines but weren't really part of the Foundation skill set at the time."

Opportunity Knocks: Origins Of Gates MRI

Thus, when Bill Gates decided in 2017 to create a new unit of the Foundation to develop new drugs and vaccines – just like big pharma, but with a broader access footprint – Heaton was the logical choice to run it. It would work in the manner of a nimble biotech start-up, focused on products to prevent, treat, and cure the diseases of the poor. It would open a new chapter in the Foundation's evolution from a grant-making philanthropy to a hands-on enterprise guided by a business plan relevant to conditions on the ground.

The Gates MRI was launched in January 2018 with a $270m grant from the Foundation, an office in the Cambridge MA biotech hub, and Heaton as CEO. Backed by a staff now totaling 65 professionals from diverse backgrounds in science, clinical practice and commercial operations, the group reports to a board chaired by the Foundation's global health lead Mundel, and which also includes the Foundation CEO, Dr. Sue Desmond-Hellmann, herself a drug industry veteran as the physician oncologist behind Genentech's breakthrough drug for breast cancer, Herceptin.

In addition to the Cambridge HQ, there is a satellite office in Seattle WA, at the University of Washington campus.

Running a non-profit that emulates the mindset of a for-profit enterprise has been a liberating experience for Heaton. "Six weeks in, I felt like a bird let out of the cage, fighting infectious disease while reaping the psychic benefits of giving something back to a world consumed by want. Moreover, I no longer had to worry about finding the financial resources to justify a business plan and the marketing logistics around it, activities that in the private-sector took three quarters of my time. We had the funding to do what we needed to do."

From the start, Gates MRI has observed this simple work rule: the Foundation sets the strategy; MRI executes it. The Foundation has written a broadly framed, 15-year business plan for the Gates MRI stipulating activities on two levels: the first to develop and then introduce to market with partners individual products like drugs and vaccines, geared to combatting pressing threats to patients and public health in low income settings; the second to focus on long-term investments in improving the clinical development process itself, resulting in a more rapid and efficient translation of gains in science to success in the field. Above and beyond the $270m received so far, the Foundation anticipates the Gates MRI will require an operating budget of at least $100 million a year going forward, depending on the pace of progress in the group's portfolio.

Focus On Four Diseases

The strategy is for Gates MRI to develop products to accelerate progress in ending four pervasive conditions that together pose the greatest threat to global health. These are:

- tuberculosis;
- malaria;
- enteric and diarrheal disease, particularly in children under age five; and
- other conditions that lead to adverse maternal, newborn and child health outcomes (MNCH).

Global health statistics bear this out. The TB bacillus is present in one quarter of the world's population, with 10 million new cases a year and 1.3 million deaths reported by the World Health Organization in 2018. It is a leading co-morbidity factor in deaths from HIV, with more than 250,000 deaths linked to TB in 2018. Malaria accounts for nearly 500,000 deaths annually, out of a case burden now totaling more than 200 million in 87 countries, mostly in Africa. The third priority, enteric diseases like shigella, one of the leading causes of diarrhea in infants and young children, kills more than 2,000 children under age five die every day. Added to this are other diseases affecting nursing mothers and young children. One, respiratory syncytial virus (RSV) is the current focus of Gates MRI activities for this vulnerable public health cohort. The big takeaway is all four of these disease areas are preventable – and the technology and expertise already exist to make their eradication feasible, with an equally big payoff in terms of fighting poverty and advancing the Foundation's operative premise that "all lives have equal value."

Shortening The Time From Idea To Impact

Getting organization and process in line with this objective dominated the Gates MRI's first year. "I had to build a group that could turn an abundance of ideas from many quarters into a few specific solutions, aiming to apply the Foundation strategy to projects showing a measurable outcome," Heaton tells *In Vivo*. "In practical terms, my charge is to invoke the principles of translational medicine, pursuing development of new drugs and vaccines with partners that we either contract with ourselves or leverage through the Foundation, progressing to clinical proof of concept and then working with others to pursue market access for the product, including manufacturing and distribution at scale."

The Gates MRI does not expect to do all the heavy lifting, all the time; in many cases, a partner will take the lead in conducting a clinical trial or other milestones required to move the asset into the market. There are plans to work with CROs on the conduct of clinical trials. In fact, one of Heaton's priorities is to find local companies in low-income countries that can manage commercialization, which has the added advantage of transferring know-how to stimulate the growth of a strong market for life sciences investment.

The vehicle to make all this happen

is the product development team (PDT), which Heaton introduced based on her experience in the private sector. The model is integrated and cross-functional; each PDT operates with a single end goal in mind, to deliver a product that is both clinically useful and accessible to low/middle income patients in resource-constrained settings. The process itself focuses on a product development plan that sets out, step by step, how a potential asset will move from pre-clinical review and testing to a completed proof of concept addressing the target population, at which point a joint Portfolio Steering Committee decides whether to move ahead on adaptive phase two or three trials that can be conducted through a partner or, in some cases, by MRI itself. "In doing so," said Heaton, "we are probably a bit more rigorous than a private enterprise might be on access issues like ensuring that the asset fits the needs of the relevant patient community and can be administered successfully in the context of conditions on the ground. We want to be sure it represents the safest and most efficient approach to getting the right therapy to the right patient."

Every PDT is co-led by a physician or PhD scientist with experience in clinical development and a project manager able to coordinate the mix of talent, resources and logistics required by the Gates MRI's translational approach to medicine. Team members include MRI staff grouped into eight zones of expertise: clinical development, project and portfolio management; clinical operations; translational discovery; biomarkers and assay development; regulatory affairs; quantitative sciences; quality assurance; and chemistry, manufacturing and controls. There is also a group that manages business development through partnering.

Importantly, Gates MRI's translational discovery group strives to put all this expertise together, working with the Foundation's extensive list of partners to provide a steady flow of clinical-stage development candidates for the PDTs. "The Foundation funds upstream partner work in the MRI's four priority disease areas, so our discovery team works with these partners to keep tabs on how their projects are progressing and suggest ways to accelerate them into clinical trials and eventually to commercialization," Heaton said.

We Do Drugs ... And Vaccines Too

The bottom line is, yes, the Gates MRI will apply for an IND from the FDA or equivalent agency just like a big pharma or biotech. "We interface with the regulatory agencies, we draft the protocols, we conduct the studies with investigators at each site, using contract research organizations (CROs) to monitor and collect the data which we then report back to the FDA – our business model positions Gates MRI to act as a full-service enterprise."

To guide its work, the Gates MRI adheres to a few principles of public policy developed by the Foundation. Promoting access to products through donations is not part of the MRI agenda – the belief is something that is free is not necessarily the best way to ensure full uptake of a product. Incentives are present, even in a resource-constrained setting. To Heaton and her team, access involves commitments on making products available to low-income countries at an affordable price, which in turn involves negotiations on volumes and timing as well as price.

It follows that a company involved in producing drugs or vaccines is entitled to earn a profit from their investment, although how much profit is always an appropriate topic for discussion. Heaton said, "Over the years, the Foundation has formed a consistent position on how we approach access to health and medicines, and transparency is a key part of our thinking." Thus, Gates MRI supports open sharing of data, clinical studies and other active learnings as well as relevant price information. While the Gates MRI has no plans to consult cost-effectiveness evaluation bodies like the Boston-based Institute for Clinical Evaluation and Research (ICER), evidence is an important tool of its access agenda. What is distinctive is Gates MRI applies different measures of acceptability than the private-sector. "We are willing to fund development of drugs or vaccines that are 'market failures' but they must be affordable and have a significant impact on metrics like disability adjusted life years (DALY)."

Heaton continued, "When we negotiate access for our products, we look at the target population and the potential demand based on need. With that, we establish prices that are affordable to that target within a given time frame. The cost of goods, including manufacturing costs, is part of every consideration. Overall, affordability depends on circumstances that are unique to each product, so we don't think about maximizing profit margin in the same way as a commercial business might. What's important to remember is that, evidence and profits aside, the bottom-line metric for us consists of two simple words: lives saved."

Power From Partnering: MRI's Force Multiplier

The practical expression of MRI's commitment to translational medicine is the desire to work with partners – this is not just a "do it yourself" operation. The net is broad, including, in addition to partners already involved in Foundation-level initiatives, representatives from academia; industry, from big pharma to biotech start-ups; non-profits and NGOs; and CROs and manufacturers. Many are based in low- and middle -income countries, where MRI's disease areas of interest are most prevalent.

The model MRI intends to build on is the Foundation's 2012 launch of the TB Drug Accelerator project, working with the biopharma industry to address a longstanding drought in new drugs to attack the world's biggest infectious disease. The impetus was the arrival that same year of J&J's bedaquiline (Sirturo), the first new treatment for TB in 50 years. To help jump start more R&D, the Foundation organized the Accelerator, which in seven years has morphed to 18 organizations committed to obtaining market approval for a new generation of drugs and vaccines to fight TB. Eight, including J&J, are from big pharma and biotech; the other 10 are leading academic and research institutions. Among other things, members pledged to open their compound libraries to screen for candidates that could activate against the TB bacillus, work that has now produced a large pipeline of possible drugs.

The plan is for Gates MRI to assume the task of neutral broker in taking this bounty forward. "We intend to prove researchers' estimation that a shorter, safer and simpler TB drug regimen is going to require two or three separate drugs used in combination," Heaton noted. "Chances of something as novel as that coming out of the labs of one company is very low. So we are excited about being selected to manage this next phase, in which the Gates MRI will coordinate with four company members of the Accelerator plus the Foundation to identify the first new investigational TB drug regimens for TB, taking forward the most promising regimens regardless of which company they come from. It offers us a great opportunity to notch some new gains against TB, which despite its prevalence remains a truly neglected disease."

In June, MRI announced its first outside partnership, a drug development collaboration with Spero Therapeutics Inc., a Cambridge MA-based biotech active in treatments for multi-drug resistant bacterial infections and rare diseases. Spero has granted Gates MRI a license to develop and commercialize one of the company's candidate antimicrobial drugs, SPR720, for treatment of lung infections caused by the *mycobacterium tuberculosis*, the principal causative agent of TB. The Gates MRI will fund and conduct preclinical and clinical studies on SPR720 to advance it to FDA approval for use in low- and middle-income countries where the disease is endemic. A phase one trial on safety and tolerability of SPR720 has already been conducted by Spero, with a report on top-line data from the trial due out before the end of this year. The candidate has also been designated by the FDA as a Qualified Infectious Disease Product (QIDP), giving it rights to accelerated review time and a longer period of market exclusivity.

"Spero was focusing on SPR720 because of its effect on rare microbial conditions outside TB, but we saw synergies because the drug works by a different mechanism than existing products for TB, where the drug armamentarium has really not changed for decades," Heaton told *In Vivo*. "It was a logical choice for them to be our first partner from private industry and it fits nicely within the remit of the Accelerator initiative."

Heaton expects a significant number of partnerships to be contracted in 2020,

GATES MRI CEO PENNY HEATON SPEAKS...

ON PROGRESS IN GLOBAL HEALTH ...

"When I look back and think about what things were like in 2000, the big multilateral donor institutions we take for granted today did not exist. There was no GAVI for vaccines; no Global Fund for AIDS, TB and malaria; no PEPFAR to prevent the spread of HIV in Africa; the Bill and Melinda Gates Foundation was in its infancy. This concerted institutional response has cut child mortality from infectious disease by more than half, from 10 million deaths annually to less than six million.Deaths from malaria have also been cut by half, new cases of TB are declining by an average of 3% a year, and 80% of sub-Saharan Africans diagnosed with HIV are now on life-saving anti-retroviral drugs."

... AND THE CHALLENGES THAT REMAIN

"Too many people – especially women, infants and children – continue to die of diseases that are largely preventable. I worry about maintaining our progress in improving health status, for two reasons. One is that, from a technological and logistical perspective, what we have left to do is really hard. Having clocked so many "wins," the complexities involved in delivering health solutions on the ground – that "last mile" to the patient – are daunting. The second is basic public health interventions still need more support from private-sector players like big pharma and biotech. They have the product development know-how to help us succeed. But, as investor pressure on the bottom line intensifies, keeping them involved has become tougher than ever."

WHY SHE'S AN OPTIMIST AT HEART ...

We are at a special time in history, with new science that has enormous potential in saving and extending lives. The tools are within our grasp to confront the pathogenic and immunologic roots of infectious diseases that have plagued humankind since the dawn of civilization. Insights derived from the oncology and rare disease space are capable of being translated into interventions with even broader impact on the neglected diseases of poverty that kill millions – *if* we get the access and affordability issues right.

WITH A CLEAR VISION ON THE FUTURE ...

I can envision a time when the potential of every woman, man and child is unleashed by good evidence and unbiased information. Can we use the cloud and the cell phone to overcome the absence of a traditional health data collection and retrieval infrastructure in low income communities? I think we can – and it's a logical step from there to introduce, without the barriers imposed by legacy systems, the latest real world evidence (RWE) technologies to inform our clinical trials and support development of a new generation of vaccines to improve health standards in communities where the unmet medical need is greatest.

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divided between 1:1 deals and collective arrangements involving multiple organizations, with the TB Accelerator being the obvious precedent. All are geared to fighting the four diseases identified by the Foundation as strategic priorities. It's unconfirmed, but GSK, Otsuka, J&J/Janssen, Evotec, the TB Alliance and Institut Pasteur are said to be in active negotiations with the Gates MRI.

Culture: Five Mantras To Motivate

Scoping the disease landscape, building a drug pipeline and cementing external opportunities demand a responsive and disciplined internal culture geared to the Bill and Melinda Gates philosophy of constantly extending the boundaries of what's possible in the pursuit of saving lives. Heaton has put her stamp on the work environment through the delineation of five mantras: (1) innovation; (2) collaboration; (3) courage; (4) rigor; and (5) urgency. "We had some situations where we had to rely on these workplace principles very soon after MRI was established, confided Heaton. "There was one drug we were asked to take into clinical trials in our first six months as an organization, and we were excited about it. But as we were conducting due diligence on the drug we noted a few toxicity issues; ultimately, we had to inform the Foundation board not to proceed unless there was further evaluation."

"It wasn't the best message – the desire to quickly demonstrate our *bona fides* and get something out to patients was strong.But reviewing the evidence against our mantras on courage, rigor and urgency helped us clarify, come together as a team and render the right decision to ask for the delay."

Gates MRI achieved its most important strategic milestone earlier in the summer, when it agreed on a pipeline of candidate drugs and vaccines in the four priority diseases areas (*see Exhibit 1*). On malaria, where the overall goal is to find products that contribute to its ultimate eradication, work is commencing with the Foundation and other partners to develop a vaccine with greater efficacy and durability than the RTS,S vaccine, which is now being introduced for pediatric use in three countries in Africa – Ghana, Kenya and Malawi.

> *"We are a window on emerging country markets of the future, with their enormous untapped demand for better health and well-being, including access to good medicines and vaccines. I wish biopharma CEOs had a better appreciation of that latent desire for a better tomorrow. It's universal among todays poor."*

The Potential Of Monoclonal Antibodies In Malaria

Gates MRI is coordinating an active learning program based on the clinical history of RTS,S. According to Heaton, "We've already learned a lot from RTS,S about the immune response to malaria. What's really exciting us now is how monoclonal antibodies – a treatment platform first identified 30 years ago – could work as an effective and powerful bridge in treatment until a more durable vaccine with longer efficacy in patients can be brought forward. So rather than administer a long-acting but less efficacious vaccine to induce that antibody response, we could focus on a more impactful seasonal approach, giving the antibody before the rainy season when carrier mosquitos proliferate and prevent malaria until the dry season when the threat of infection diminishes. Right now, we know the antibody approach works in animal tests, so the goal is to do human studies, including children, the most vulnerable victims of the disease."

The plan calls for toxicology studies to begin on a selected candidate in late 2020, followed by a phase 1(a) study in third quarter 2021 and a Phase Ib to commence in late 2022, continuing to the end of 2023. At that point, a decision will be made to proceed with human trials leading to full development and eventual commercialization. Another payoff from this effort could involve finding ways to reduce the cost of manufacturing monoclonals so they become more affordable to low income countries. On its own, the Foundation has been considering this for some time.

A Wider Template For TB Vaccines

The pipeline is also primed for new therapeutic options – both drugs and vaccines – to help fight TB. The most important is last month's start of Gates MRI's first sponsored clinical trial on the Bacillus Calmette-Guerin (BCG) vaccine, which was first tested in humans in 1921 and has long been vetted as a potential prophylactic against TB when given to infants. The trial, funded by the Foundation, will see if a booster dose of BCG given when those infants become adolescents and young adults can confer lifetime immunity against TB. The trial will be conducted in South Africa. Heaton said, "This trial is big for us, as it provides the opportunity to demonstrate that the MRI partnering model is as proficient as industry or government in driving so many moving parts to a successful, timely conclusion. We've worked with investigators in designing the study, sites have been selected, recruitment is on schedule, and the necessary regulatory submissions are complete. Training for investigators and nurses has been conducted at each trial site and a final investigator group meeting was held in September – so we are good to go."

The collaboration with Spero Therapeutics, MRI's first in-licensing deal with a non-Foundation partner, is moving forward as well. A research plan for drug candidate SPR720 has been agreed, beginning with conducting the toxicology study that will enable the asset to commence with human clinical trials. Spero will manage the toxicity work and then MRI and Spero will work together to conduct a phase II trial focused on identifying how SPR720 influences bacterial activity and to show it has efficacy in humans.

Focus On Shigella

The third priority, enteric and diarrheal diseases, is perhaps the closest to Heaton's heart. She was instrumental in putting top of this list a vaccine against shigella. "I saw shigella's impact up front when I worked in Kenya for the CDC." The gastrointestinal disease is resistant to conventional antibiotics and kills about 100,000 people a year, mostly infants and young children. The vaccine program is being conducted in collaboration with the Institute Pasteur in Paris. "Our target is a very interesting conjugate vaccine with a unique chemistry that we anticipate will be highly efficacious compared to the vaccines developed in the 1990s. These were fairly effective in adults but were useless in treating children under age three. Hence the goal of our work with the Institute is a vaccine that will be proactive with this very vulnerable patient cohort."

To start, the MRI is working on a manufacturing blueprint for the vaccine, chiefly in building out the chemistry to make a conjugate vaccine against the four strains of shigella that represent the majority of cases among infants and young children. The Pasteur Institute has perfected the chemistry on two; Gates MRI has the assignment for the two others. The MRI expects it will take about two years to initiate the human trial phase, which requires the four strains to be incorporated into a quadrivalent or tetravalent prototype vaccine suitable for testing.

On a broader front, MRI is interested in learning more about the immunology behind shigella, where there is currently no reference point for evaluating an antibody that might counter the strains of bacteria that induce disease. "I am convinced we need to evaluate immunologic factors as a potential avenue in curing enteric conditions, using the same tools and approaches that researchers have applied in fighting cancer," Heaton told *In Vivo*.

A Better And Faster Head Start

Finally, the MRI is beginning to act on a fourth overarching priority driven by the Foundation's research agenda – maternal, newborn and child health (MNCH). In February 2018, the Foundation authorized a funding stream to support work in this high-profile demographic. In response, Gates MRI has decided to focus on treatments for respiratory distress, in particular the respiratory syncytial virus (RSV) which is a key factor behind the deaths of approximately one million premature infants annually, mostly in low income countries. While rich countries have access to the lung intubation tubes and ventilators that help babies with RSV struggle for every breath, these are absent in many parts of the world – a better intervention against RSV is needed.

In response, Gates MRI is supporting a partnership that is working on a drug composed of a dry powder surfactant to be given to infants born prematurely i.e. before they can develop the disease. Much of the work so far is centered on the right particle size to dispense the alveolar surfactant powder in the right amount to the right part of a premature infant's tiny lungs. Preclinical data based on studies involving sheep have been positive; Gates MRI and partners are hopeful a human trial can commence by early 2021.

How Heaton Measures Success

Putting all this together, how does the MRI intend to mark its progress over the normal four year planning cycle? Heaton responded immediately in stressing that hers is an assignment that is going to take many years to reach fruition. Despite that, Heaton is confident about really moving the needle in four years – and in four areas.

First is advancing the pipeline portfolio with solid, well-executed clinical trials that largely meet their intended end points. To put a number on it, Heaton hopes by 2023 to have 20 product candidates in various stages of the pipeline. And at least half of these will be at the clinical trial phase.

Second is establishing an internal culture that will attract – and retain – the best talent, in all parts of the organization. MRI will only succeed if it has the right mix of people who are curious and embrace diversity of opinion and cross-functional thinking as the driver of innovation.

Third, and related to these other two, is getting the process right in the pursuit of our disease priorities. "Process can be boring, but if we are to meet the many objectives set forth by the Foundation we must be very efficient about executing. I intend to spend time ensuring our quality controls are working as intended and that all our partners have the shared data they need to help us succeed as a team. Process is vital in coping with an environment of maximum uncertainty – what's ever been predictable about public health, or science itself?"

Heaton's fourth, and final, goal is certifying MRI as a good partner – the partner of choice. "I'd like to convince *In Vivo* readers in big pharma that working with us is a reputation enhancer, particularly among millennials, soon to be the biggest demographic in employment. And we are a window on emerging country markets of the future, with their enormous untapped demand for better health and well-being, including access to good medicines and vaccines. I personally wish biopharma CEOs had a better appreciation of that latent desire for a healthier tomorrow. It's universal among today's poor."

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