IN brief

Shutdown by auction

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Bids under seal

On December 8, sphingosine 1 phosphate receptor (S1P1) agonists, including preclinical and toxicology data, came under the hammer in a sealed bid auction. The small molecules on offer were generated by Lexington, Massachusetts–based EPIX Pharmaceuticals in collaboration with Amgen of Thousand Oaks, California. Earlier, EPIX was forced to shut down operations due to lack of funds. Rather than enter a formal bankruptcy proceeding, the company assigned the S1P1 agonists along with its other assets to Joseph Finn Jr., managing partner at accounting firm Finn, Warnke & Gayton, of Wellesley Hills, Massachusetts, to be offered in a bidding sale. The procedure, available in Massachusetts and other states including California, is well regarded by troubled biotechs and their creditors because it enables companies to quickly wind down operations. For instance, Source Precision Medicine of Boulder, Colorado, and Woburn, Massachusetts–based Prospect Therapeutics went through such auctions in the last few years. The process of assigning assets, finding a buyer, vetting creditors and distributing the proceeds can be wrapped up in six months, whereas chapter 7 bankruptcies typically take a year or longer. Finn requests sealed bids, which is faster than an open auction where bidders go back and forth trying to top one another as seen in chapter 7 cases. Typically 50 to 60 companies sign confidentiality agreements with about 10% of those actually making a bid. It is difficult to know whether the one-shot bid process results in higher values. Bids sometimes come in within $100,000 of each other suggesting that's the true value of the asset, although other times Finn said the creditors "catch lightning in a bottle" with one bid substantially higher than the rest. Perhaps more important than speed, the assignment process allows company founders to see where the assets they slaved to develop are headed. "I try to make the process of winding up the company one that gives them closure of their life's work," Finn said. *Brian Orelli*

IN their words

"Our portfolio has had seven NDA submissions since 2008, with five approved and two still pending, That should be a success, except it has taken twice as long to get there as it used to five or six years ago. The math with the FDA just doesn't work anymore for us in terms of a venture fund lifecycle." Scale Venture Partners' Kate Mitchell on why their investment firm is retreating from healthcare. (*Forbes*, 8 November 2011)

GlaxoSmithKline malaria vaccine phase 3 trial heralded

London-based GlaxoSmithKline (GSK) released one-year follow-up data from a phase 3 trial of its malaria vaccine RTS,S (Mosquirix) triggering talk that the world's first vaccine against a protozoan disease could be tantalizingly close to market. It's taken several decades to get to this unprecedented achievement: the protective effect is the highest ever achieved for an malaria vaccine in clinical development (*N. Engl. J. Med.* **365**, 1863–1875, 2011). No one doubts that the RTS,S shot represents a tremendous scientific breakthrough, but opinions remain mixed as to its public-health impact owing to its inability to provide more complete protection against infection.

"After over four decades of malaria vaccine research, we have reached a new stage," says Vasee Moorthy, who works on malaria vaccines at the World Health Organization (WHO) in Geneva. Vaccination with RTS,S showed a 54% reduction in clinical malaria cases, and a 47% reduction in severe malaria cases, in 6,000 children aged 5–17 months compared with controls. More data from this large-scale trial, conducted on 15,460 children in total, across 11 sites in seven African countries will emerge over the next 3 years, and barring any major setbacks, the vaccine could be licensed for use in Africa as early as 2015. "Scientifically, this is startling. Few believed that with one protein of a very complex parasite you would be able to make a vaccine that protects at the level that this does," says Melinda Moree, CEO of Washington, DC–based BIO Ventures for Global Health, and former director of the PATH Malaria Vaccine Initiative (MVI).

Recent efforts to control malaria—including the introduction of insecticide-treated bed nets and drugs such as artemisinin (see p. 1072)—have helped control the disease. Yet despite their success, nearly 800,000 people continue to die of the disease each year, most of them children in Africa under 5 years of age. Since the 1970s, several vaccine candidates have come and gone, thwarted by a parasite that is no ordinary foe. The *Plasmodium* parasite that causes malaria has around 5,000 genes, far more complex than a virus or bacterium, and it is unusual in having three stages in its life cycle, changing its form as it progresses through liver (or pre-erythrocytic) and blood stages in humans, as well as in a third stage that occurs in the mosquito gut. "To be frank, it's very hard to make a vaccine that is 90% or 100% effective against any of these stages, as we've discovered," says Adrian Hill, director of the Jenner Institute in Oxford, UK.

Over the past decade, the field has received some much-needed impetus, mainly from WHO's roll back malaria campaign, and PATH MVI, a global program established through the Bill & Melinda Gates Foundation of Seattle. The Malaria Vaccine Technology Roadmap, drawn up in 2006 by WHO and associated stakeholders, sets an intermediate goal for developing a first-generation vaccine by 2015 that is at least 50% effective against severe disease and death,

John-Michael Maas/AP Photo/

A first-generation malaria vaccine that is at least 50% effective could be licensed for use in Africa by 2015.

and lasts longer than one year. The long-term goal, to be reached by 2025, is to have a vaccine that is at least 80% effective against clinical disease and lasts longer than four years.

RTS,S is the most successful first-generation vaccine candidate so far. It targets the parasite associated with the highest malaria mortality, *Plasmodium falciparum*. More specifically, it targets the sporozoite stage, which is injected into people by mosquitoes and invades the liver cells. The vaccine's technology dates back to a paper published in this journal around 25 years ago (*Biotechnology* **6**, 1065, 1988) and was developed initially at the Walter Reed Army Institute for Research in Washington, DC, which entered into a partnership with GSK (then Smith Kline) in 1984. Since 2001, RTS,S has been developed through a public-private partnership between GSK and PATH MVI, with $200 million in support from the Gates Foundation.

According to Joe Cohen, vice president, R&D advisor to the malaria vaccine project at GSK, the vaccine's success lies in the potent immune response induced by its main constituents. RTS,S is a fusion protein corresponding to amino acids 207 to 395 of the circumsporozoite protein and hepatitis B surface antigen (RTS), co-expressed in *Saccharomyces cerevisiae* with unfused hepatitis B surface antigen (S). These two polypeptides spontaneously associate to form RTS,S viral-like particles, which are then added to a proprietary adjuvant system AS01 that favors activation of T helper 1 cells, which in turns boosts $CD8^+$ T-cell responses. AS01 is a liposome-based formulation with the immunostimulants 3-*O*-desacyl-4′-monophosphoryl lipid A and the *Quillaja saponaria* fraction 21 (Qs21), which was originally licensed in 1999 from Framingham, Massachusetts–based Aquila (now Agenus of Lexington, Massachusetts). According to Cohen, the adjuvant is the "special ingredient" that boosts the magnitude and the quality of the immune response against the parasite. "The peak antibody response is very high," he says. "It wanes over the months that follow but then reaches a plateau that can be anywhere from 15- to 30-fold higher than the response that we see in the control group of people, or children living in a malaria-endemic region."

Key upcoming results in the phase 3 trial (**Table 1**) will be data from the 6- to 12-week age group, as this corresponds with the age at which infants receive their routine vaccinations under WHO's Expanded Programme on Immunization. In the *New England Journal of Medicine* paper, the vaccine's reported efficacy against severe malaria in the 5- to 17-month age group was 47%, but the efficacy dropped to just under 35% when both groups were included. One explanation is that the vaccine's benefit in the younger age group is even smaller than 35%; therefore, all eyes will be on the first set of vaccine efficacy data for clinical and severe malaria in 6- to 12-week-old infants, which are due towards the end of 2012.

So even if the results hold, it remains unclear how RTS,S would be deployed. "It would be really easy if you had a 95% efficacious vaccine, you'd switch to the vaccine and roll it out. But we don't have that, so it becomes a really complicated policy discussion." says Moree. "Most people will bet on Mosquirix (RTS,S) being licensed in some form, but I don't think many people would expect it to be widely used unless there's some improvement in making it more effective, and more cost-effective," Hill notes.

Overall efficacy could be boosted by adding a liver-stage component, which would reduce the chances of a person becoming infected, or a blood-stage component, which would reduce disease severity and death during infection. As yet no candidate other than RTS,S has demonstrated proof of concept. Leading the way is the so-called prime boost approach, in which the antigen selected for a vaccine is administered through two different delivery systems to maximize the immune response. "In the last 3 years, things are looking much more effective, and the big change has been the adoption of adenoviral vectors," says Hill, adding that adenoviruses induce significantly better $CD8^+$ T-cell responses than other vaccine delivery technologies.

GSK is hoping to induce a more powerful immune response in RTS,S by substituting the first of the three regular doses of its vaccine with an adenovirus vector expressing the circumsporozoite protein (Ad35.CS), developed by Crucell of Leiden, The Netherlands (now part of New Brunswick, New Jersey–based Johnson & Johnson). Cohen says this protocol significantly increased the cell-mediated immune response to the antigen in preclinical models, and soon GSK and Crucell will begin a clinical trial under a US Food and Drug Administration investigational new drug application to evaluate efficacy under the controlled setting of the human challenge model.

The US Naval Medical Research Center in Bethesda, Maryland, has a liver-and-blood stage prime-boost approach in phase 2, but here the priming vector is plasmid DNA, and a human adenovirus (Ad5) is used to boost the immune response. Hill's group at Oxford, in conjunction with the Basel-based company Okairos, has got as far as testing their candidate in infants in Africa. Their approach uses chimpanzee adenoviruses encoding the thrombospondin-related adhesion protein (TRAP) pre-erythrocytic antigen to prime an immune response, which is then boosted by another viral vector, modified vaccinia virus Ankara (MVA), which encodes the same TRAP insert.

Blood-stage vaccine candidates have fared rather modestly over the years. The most

Table 1 Selected vaccine candidates against *Plasmodium falciparum* in clinical development

Developer	Life cycle stage targeted	Vaccine	Phase	Location	ClinicalTrials.gov identifier
GlaxoSmithKline	Pre-erythrocytic	RTS,S/AS01	3	Multiple African sites	NCT00866619
University of Oxford		AdCh63 ME-TRAP and MVA ME-TRAP	1	Gambia/Kenya	NCT01373879/NCT01379430
Crucell/GlaxoSmithKline		Ad35.CS/RTS,S	1/2a	USA	NCT01366534
Crucell		Ad35.CS.01/Ad26.CS.01	1/2a	USA	NCT01397227
Sanaria		PfSPZ	1	USA	NCT01441167
Walter Reed Army Institute of Research	Blood	FMP2.1/AS02A	2	Mali	NCT00460525
Statens Serum Institut (Copenhagen)		GMZ2	2b	Multiple sites in Africa	N/A[a]
US Naval Medical Research Center	Pre-erythrocytic + blood	DNA-Ad	1/2a	USA	NCT00870987
Johns Hopkins University (Baltimore)	Mosquito	Pfs25-EPA/Alhydrogel	1	USA	NCT01434381

N/A, not available.
[a]Trial as described on GMZ2 website http://www.amanet-trust.org/gmz2/node/62
Source: ClinicalTrials.gov; PATH Malaria Vaccine Initiative website.

recent example, published in September (*N. Engl. J. Med.* **365**, 1004, 2011), was a field trial of a vaccine based on the apical membrane region antigen 1 from *P. falciparum* in 400 Malian children. The study results suggest the vaccine might prevent only around one in five malaria infections from progressing to symptomatic disease, though there are signs that its efficacy might vary by strain.

Ashley Birkett, CSO of PATH MVI, says that MVI's refocusing of its portfolio at the end of the last decade is beginning to bear fruit with "very promising programs" that are progressing into the clinical stages. "Vaccines with higher levels of clinical efficacy than RTS,S, and also vaccines that block the cycle of transmission, really now form the basis of our portfolio," he says.

One possible candidate for higher efficacy is the liver-stage vaccine PfSPZ being developed by Rockville, Maryland–headquartered Sanaria, which delivers whole, live, attenuated, nonreplicating sporozoites harvested from the salivary glands of irradiated mosquitoes. In controlled trials, irradiated sporozoites delivered by mosquito bite to a small number of humans in a controlled setting induced levels of protective efficacy exceeding 90% (*J. Infect. Dis.* **185**, 1155, 2002). However, working out a vaccine administration method that doesn't involve a mosquito bite is a big challenge, says Stephen Hoffman, chief executive and scientific officer at Sanaria. An early-stage clinical trial on 80 humans published in September (*Science* **334**, 475, 2011) showed the vaccine to be safe but the immune response and protection levels after subcutaneous administration were disappointingly low. "It wasn't the optimal way [of] administering it and we didn't get optimal responses, so we went back to the lab, to the nonhuman primate studies, figured out how to inoculate it and have now gone back into a clinical trial," says Hoffman.

The first data from the follow-up trial is expected in the fall next year, and a series of 11 trials over the next 12–15 months will investigate the optimal route of administration. "Our goal is to get a high level of protection, and we'll keep pushing until we get 80–90% protection for a long period of time," says Hoffman. "If we have that, then I think we can make enormous progress on the morbidity, mortality and transmission of malaria worldwide."

Simon Franz *London*

Interest groups jostle to influence PDUFA V

A finalized package of formal recommendations for the Prescription Drug User Fee Act V (PDUFA V)—the first came in 1992—is headed to US Congress this January. Its contents reflect many rounds of negotiations involving the US Food and Drug Administration (FDA), industry, medical groups, patient and consumer representatives and the general public.

"Please, stick with the main recommendations" seems to be the unofficial and near-universal plea—one that seemed to be shared among many of the major stakeholders who met late in October at the latest in a series of FDA-convened public sessions on PDUFA V. The looming question is, what will Congress do between January and September, when authority under PDUFA IV, formally known as the Food and Drug Administration Amendments Act of 2007 (FDAAA), expires?

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Upgrading drug approval.

With 2012 being a presidential election year, all kinds of things might happen. One concern is that Congress will not meet its September deadline for reauthorizing PDUFA V. Such a mishap would stop the flow of resources from user fees and thus might force FDA to cut staff, a demoralizing and disruptive move even if short term. Another concern is that members of Congress might once again, as happened with FDAAA, expand FDA mandates, adding regulatory responsibilities without resources to support those activities.

"Even the threat of downsizing would be devastating to FDA," says Andrew Emmett, managing director of science and regulatory affairs at the Biotechnology Industry Organization (BIO) in Washington, DC, alluding to what might happen if Congress fails to meet the September reauthorization deadline. "BIO supports PDUFA V." In that same vein, BIO president Jim Greenwood lauds the PDUFA (and FDAAA) series, pointing to its aggregate success in helping to bring more than 1,200 new medicines to market since 1992, many of them moving through regulatory reviews more rapidly than in the era before PDUFA.

The singular PDUFA innovation was to institute user fees. This extra revenue was directed to the FDA, allowing it to hire more professional staff. In turn, agency staff was subjected to tighter product review deadlines as well as higher performance standards, all directed at keeping reviews moving at a brisk pace. Since 2005, agency performance standards in terms of meeting review deadlines have hovered at 90% or higher, except for five quarters during 2008 and 2009, according to Theresa Mullin, director of the FDA Office of Planning and Informatics. Even when the agency missed deadlines, it often led to better discussions between companies and agency officials, sometimes accelerating overall product licensure times, she says.

Although many stakeholders embrace the concept of PDUFA V, they are far from unanimous about its details. Some disagreements epitomize a central FDA dilemma over product review stringency versus speed of reviews. For example, several organizations representing patients, including the Friends of Cancer Research, National Health Council and National Organization for Rare Disorders (NORD), claim FDA errs on the side of caution, not recognizing that many patients with chronic disorders or life-threatening cancers are 'risk tolerant' and apt to seek access to experimental treatments. Meanwhile, organizations such as the National Consumers League (NCL) say FDA is too focused on expediting drug approvals while neglecting its duties to protect consumers.

Additionally, several organizations raise concerns over conflicts of interest among outside experts who serve on FDA advisory panels. However, NORD vice president for public policy, Diane Dorman, says that the current conflict-of-interest provisions at FDA already suffer from being "out of balance," and thus too likely to disqualify experts who tend to be in short supply when called upon to review candidate products for treating patients with rare disorders. "We support eliminating provisions that apply only to FDA," she says.

Some consumer advocates rail against direct-to-consumer advertising, calling it misleading to the public. NCL executive director Sally Greenberg is calling for additional user fees to PDUFA V to support FDA reviews of such advertising materials before they are aired or published.

Jeffrey L Fox *Washington, DC*