IN brief

European R&D buoyant

The economic downturn had less effect than expected on biopharma companies in Europe, according to the newly released EU Industrial R&D investment Scorecard published by the European Commission. The report, which included data on industrial research spending for fiscal year 2009, ranked 400 EU-based companies and 1,000 firms based elsewhere. Many cash-strapped firms scaled back research in 2009, with R&D investments across all sectors worldwide down 1.9%. The biopharma group, however, consolidated its position as top R&D investor, with a 5.3% increase in 2008 in global R&D spending and a 2% hike in Europe alone. Swiss drug giant Roche of Basel ranked second among all sectors for R&D investment. John Shortmoor, pharma analyst at Datamonitor, is not surprised at the findings. "To sustain a presence—especially in a time when a significant number of marketed products are losing patent protection—requires constant product innovation and continued R&D investment." For biotech in particular, European firms increased their investment budget by 7.9% in 2009, outperforming their US counterparts, whose R&D spending dropped by 1.6%. "We cannot afford not to invest in R&D and risk losing our market position," says Nickie Inger Spile, vice president at Danish biotech Novozymes. The Bagsvaerd-based firm ranked number 10 for R&D spending among global biotechs. *Emma Dorey*

EU mAb biosimilars path

European regulators laid out the rules for copying biotech's blockbuster monoclonal antibody (mAb) therapies, paving the way for biosimilars developers to access the $36.4 billion market. The draft guidelines, published by the European Medicines Agency (EMA) in November, outline the process biosimilars developers must follow to gain approval for a mAb once a patent on the pioneer drug has expired. The studies and tests needed for approval are "less demanding than expected," comments Huub Schellekens at the departments of Pharmaceutical Sciences and Innovation Studies at Utrecht University, The Netherlands. The EMA will require *in vitro* pharmacokinetic and phamacodynamic studies to demonstrate that a biosimilar mAb is functionally equivalent to a reference mAb. In some cases, *in vivo* nonclinical studies may also be necessary. "The need for these studies should be decided on a case-by case basis," the guideline states. Factors that may warrant the need for such studies are, for instance, processing and formulation differences or insufficient evidence that a biosimilar is as safe and effective as the branded product. The EMA is willing to accept a drug's adverse event profile as proof of biosimilarity, and data from one clinical trial could be sufficient for approval in two different indications if the mechanism of action is the same. "This really opens the door [to biosimilars]," Schellekens points out. The guideline is available for public comment until May 31. *Gunjan Sinha*

plasmid (*BMC Biol.* **5**, 1–11, 2007). LA513 encodes the tetracycline-repressible transcription activator (tTA), a protein whose high-level expression is deleterious to cellular development, probably due to transcriptional 'squelching' and/or interference with ubiquitin-dependent proteolysis (*Nat. Biotechnol.* **23**, 453–456, 2005). When expressed, the tTA protein binds to the tetO operator sequence (upstream of tTA) and drives expression of tTA from a nearby minimal promoter, which in turn binds to tetO, creating a positive feedback system. Because tetracycline binds tTA, preventing the activator from interacting with tetO, batches of transgenic mosquitoes can be grown in the presence of the antibiotic (whereas in its absence, transgenic mosquito larvae die). The resultant transgenic *Aedes* eggs are collected for hatching at a trial site, and the smaller male pupae sorted from females and on maturity released into the field, where breeding with wild-type female mosquitoes results in sterile mating.

Field tests in Grand Cayman were conducted in two stages. The first set of small-scale releases assessed whether transgenic males could survive in the wild and mate with wild females. The presence of transgenic larvae showed that the transgenic males did survive and were capable of finding mates. These results formed the basis for a second trial, which began last year, to test the effect of the transgenic mosquitoes on suppressing the wild population. Adult mosquitoes as well as eggs were monitored using adult traps and ovitraps (black jars containing water and a paddle leading inside, on which mosquitoes lay eggs), respectively. Offspring from transgenic males also carried a fluorescent marker, allowing the transgenic larvae to be easily distinguished from wild counterparts.

According to Alphey's ASTMH presentation, results from the large release showed up to an 80% reduction in the numbers of wild mosquitoes ~11 weeks after the release. This reduction in the population was sustained for a further ~7 weeks until the end of the trial. It is possible that the approach could be even more effective in suppressing wild mosquitoes because in this case the study site was not isolated and surrounding areas contained high densities of wild mosquitoes.

William Black, a collaborator on the Gates project, was impressed by the results; the Cayman Islands trial "went very, very well," he says. David M. Brown, project manager at the department of microbiology and molecular genetics at the University of California, Irvine, agrees that the results enjoyed a very positive reception at the meeting. "There were [even] a few comments of gratitude," he says, as the Cayman Islands trial is an important step in pushing GM insect technology against dengue fever forward.

Alphey says preparatory work for the Grand Cayman trial was extensive and meticulous. Elected political representatives were informed and flyers were distributed. MRCU officials were educated and went on foot to answer questions the locals had about the trials. All vehicles and equipment carried phone numbers and clear labels, so any concerned observers could contact the authorities. There was good awareness, he says, "that the project was testing a new genetic method to control dengue using sterile males, that males don't bite, that not all species of mosquitoes would be controlled."

Even so, some commentators have questioned whether publicity about the trial could have been better handled. For example, many only became aware of the trial's existence after the Cayman Islands government posted a YouTube video announcing the trial (http://www.youtube.com/watch?v=tv6JsC2MQYI)—hardly the traditional forum for publicizing an environmental release of a transgenic organism.

Bart Knols, managing director at K&S Consulting in The Netherlands, says that because the material is now public but has not yet passed through peer review, the trial sponsors have potentially opened themselves up for criticism. According to Knols, public information connected with transgenic insect release trials, at a global and local level, needs to be managed carefully—if not for Oxitec's sake, he says, then for others, because if bad press did occur, it "may not affect Oxitec itself, it may affect other groups around the world who are working on [GM] insects. And then no one can take advantage of all these new tools that have been developed."

David Andow, McKnight University professor of insect ecology, at the University of Minnesota in St. Paul, also feels that Oxitec could have done a better job making the research community aware of its work. It is not clear whether the Cayman Islands evaluated the trials according to international standards such as the guidelines laid out in the Cartagena protocol, he says. "Communication would have gone a long way in making it clear to people like me whether or not [Cayman Islands officials] did that," he says.

Oxitec is continuing talks with the Malaysian government, which is considering releasing transgenic mosquitoes to address its local dengue problem. By comparison, Oxitec has "been good about publicizing the work they're doing in Malaysia," says Andow. "They essentially leapfrogged that [step] in the Cayman Islands." Now, Knols says, the Malaysian