IN brief

GSK slashes internal R&D

GSK's Stevenage, London site houses a cluster of CEDDs.

Job cuts at its Centres of Excellence for Drug Discovery (CEDD) in the US, UK and Italy, accompanied by an expansion of research in China, are raising questions about where GlaxoSmithKline (GSK) is going next in its bid to boost R&D productivity. Although it acknowledges 350 of 16,000 R&D jobs have been cut, the London-based company has recently announced it remains committed to the CEDD model and considers it to have been successful. GSK's head of drug discovery Patrick Vallance says: "In line with scientific developments, some realignment has taken place to focus our efforts where the science has created most opportunity and, as a result, reducing activity in other therapy areas." CEDDs are specialized units designed to be as nimble as biotechs but as well-resourced as pharma. Outgoing CEO J.P. Garnier said recently it's too soon to tell if CEDDs have borne fruit, given they have been in existence for seven years and the drug development cycle lasts for ten. But in July, GSK said it considered the model successful in terms of increasing productivity and strengthening the pipeline. Newly appointed CEO, Andrew Witty, is a supporter of the 'small-is-beautiful' model of biotechs. Inspired by a visit to GSK subsidiary Domantis, in Cambridge, UK, Witty has suggested that the optimum size for a CEDD may be as few as 35 staff. GSK has now formed even smaller units within CEDDs with a focus on accountability for single disease areas. "The small unit entrepreneurial culture we create will be supported by the depth and infrastructure of big pharma—the best of both worlds," Vallance adds. According to Martyn Postle, director of the consultancy Cambridge Biotech and Healthcare, the CEDD structure is becoming more and more flexible. As long as the CEDDs stick to their budgets and deliver on productivity targets they are given complete autonomy. "The heads of CEDDs can make them as integrated, or not, as they like; there will be people who are heads of CEDDs with very few internal resources." GSK will also seek to improve productivity by taking programs out of the CEDDs and entrusting them to spin-offs. The company has set up a new venture capital fund, though it has not said what the investment brief will be, nor how it will sit alongside GSK's long-running SR One fund. GSK is reported to have invited regulators and payers to critique drugs in development and to be prioritizing its pipeline accordingly. This move could be viewed as a nod to value-based pricing, a movement to fix reimbursement according to the benefits of a drug, which is gathering pace in Europe. *–Nuala Moran*

Box 1 KRAS kits and homebrews

The emergence of *KRAS* as a cancer biomarker presents both a challenge and an opportunity for companies selling drugs that target epidermal growth factor receptor (EGFR). But for firms developing KRAS diagnostics, it represents an obvious new market in which to win business. Even here, though, the outlook isn't entirely straightforward. Molecular diagnostics companies like DxS will have to compete against 'homebrewed' tests developed by clinical laboratories and against laboratory-developed tests, which are offered as a service by firms. A plethora of firms are offering *KRAS* testing, among them Cambridge, Massachusetts–based Genzyme Genetics and Caris Diagnostics, of Irving, Texas. "The FDA regulates products and not services," says Peter Collins. "It is a very challenging process to develop an assay that works the same everywhere." In Europe, DxS has obtained the CE mark, which indicates conformity with European health and safety requirements, for its TheraScreen realtime PCR-based K-Ras mutation test, and it is pursuing a premarket approval application in the US. "We don't believe there is anyone else with a CE-marked test in Europe," says Collins. The company recently entered a marketing alliance with Roche Molecular Diagnostics of Basel for territories outside the US, Canada, Mexico and Hong Kong.

However, cost factors could hamper adoption of the kit. "At present the cost of the test is so expensive I prefer to do it on my own," says Pierre Laurent-Puig, whose laboratory is currently genotyping around 30 tumors each week. "From a biological point of view, this target is one of the simplest tests we can perform in molecular biology, because we only have seven mutations to detect." The *KRAS* biomarker is useful in eliminating people who would not benefit from anti-EGFR therapy, but it does not positively identify the 60% of colorectal patients with wild-type *KRAS* tumors who will actually respond to Erbitux. "*KRAS* is not the end of the story. We have to find other markers, which add more information," says Laurent-Puig. His laboratory is also investigating the connection between markers such as BRAF, NRAS and p10 and Erbitux treatment outcomes.

Cancer genomics firm Genomic Health, of Redwood City, California, is in discussions with Bristol-Myers Squibb and ImClone on the development of a commercial assay that would pinpoint gene expression profiles linked to disease control. Increased expression of the genes encoding epiregulin and amphiregulin—both EGFR ligands—correlates with increased likelihood of response to Erbitux, says Genomic Health chief scientific officer Joffre Baker.

Meanwhile, KRAS testing is beginning to emerge in other oncology indications, outside of colorectal cancer. Around 15–30% of patients with non-small cell lung carcinoma (NSCLC) have tumors with *KRAS* mutations, and these are resistant to small-molecule drugs that inhibit EGFR tyrosine kinase activity, such as Tarceva (erlotinib) and Iressa (gefitinib), the former marketed by S. San Francisco, California–based Genentech and Melville, New York–based OSI Pharmaceuticals, and the latter by London-based AstraZeneca. New York–based Memorial Sloan-Kettering Cancer Center has been using an in-house *KRAS* assay to screen NSCLCs for several years. "We use the mutation test to guide treatment decisions and to prioritize the order of treatment," says oncologist William Pao. "Not a lot of centers around the country are doing that yet." *CS*

KRAS genes respond. Amgen's Vectibix, used in advanced colorectal cancer at present, is currently lagging behind these two products, but remains a long-term threat to Erbitux. Analysts are divided on how stratifying patients according to their *KRAS* genotype will affect Erbitux sales. Sale declines in second- and third-line settings will be slight, says Markus Metzger, a Cologne, Germany-based analyst at Bank Vontobel. "I feel this will be more than compensated for by use in the first-line setting." However, London-based Morgan Stanley analyst Andrew Baum, drawing on an in-house survey of opinion leaders in colorectal cancer, predicts that adoption of Erbitux in the key first-line setting will be slower and more limited than the current consensus forecast suggests. In a research note published on July 2, he suggests that Erbitux will gain only a 12% market share for first-line treatment, well below the 20% consensus estimate. Merck is positioning Erbitux as a potentially curative therapy for patients with wild-type *KRAS* tumors, because a positive response to the drug can reduce metastases to a point where resection or surgery becomes feasible. This is one area where Erbitux may differentiate itself from Avastin, as the latter can cause hemorrhage and wound-healing complications. "The higher response rate [for Erbitux] does correlate with a high resection rate," Kisker says. The challenge for Merck, and its US counterparts Bristol-Myers Squibb and ImClone, will be to boost the category of those eligible for surgery— estimates indicate that it currently constitutes 15–30% of the patient population.

Cormac Sheridan *Dublin*