# IN brief

## 9,000 tumors for stratified medicine

A new collaborative program to ready the UK's National Health Service (NHS) for personalized cancer care is underway. The £5.5 ($8.7) million Stratified Medicine Programme, led by the charity Cancer Research UK in partnership with the National Health Service and London-based AstraZeneca and New York-based Pfizer, aims to develop a standardized national genetic screening service to help tailor oncology treatments for patients. The initiative will store clinical data from 9,000 individuals with breast, bowel, lung, prostate, ovary and skin cancers, along with the molecular diagnosis of their tumors, to develop a multigene panel to guide personalized cancer care across the UK. Genetic stratification allows clinicians to determine which individuals will respond to which treatment, for instance, *KRAS* testing in bowel cancer to see if Amgen's Vectibix (panitumumab) and Imclone's Erbitux (cetuximab) is indicated. Currently, only a minority of NHS patients receive such tests. "The Stratified Medicine Programme will improve genetic testing in the UK," says James Peach, director of the program. "It will also provide hypotheses about the interaction between drug and tumor, which will help companies design better cancer clinical trials." Peach noted that there has been a surge in approvals for drugs with companion diagnostics. So far, there are no other biotech companies involved in the project. *Susan Aldridge*

## Chinese inventors catch up

In 2010 China rose to be the fourth largest filer of patents with the World Intellectual Property Organization, according to a new study published in September by the Institute for Fiscal Studies (IFS). The report from the London-based think tank (http://www.ifs.org.uk/wps/wp1115.pdf) provides evidence that a decade of hefty investments in skills, infrastructure and R&D, has indeed boosted Chinese technological advancement. In 2000 China filed 1.8% of Patent Cooperation Treaty (PCT) patents; in 2010, it filed 7.5%. The authors claim the study counters the current view that China is doing a lot of lower level, incremental R&D and instead shows that Chinese innovation is as technologically advanced as in the West. Rather than count patents as a measure of innovation, the study counted citations from patents to the scientific literature to single out innovations that draw from basic research. With this metric, they found the proportion of patents near the science base to be at least as high as in patents filed by Western investors. "Given what the literature says, we were surprised to find China is more involved in near-science innovation than expected," said study co-author, Helen Miller, senior research economist of the IFS. Past studies took exports or levels of foreign direct investment as an indication of innovation. "Chinese inventors display the capacity to innovate alongside US and European inventors at the technological frontier," the report concludes. Chinese innovation may be growing dramatically, but in number of patents US and European inventors are still far ahead. *Nuala Moran*

**Table 1** Selected US-based clinical trials using anti-CD19 CARs

| Institute | CAR signaling/ co-stimulatory domain | Delivery vector | Indication | Development phase and clinicaltrials.gov number |
|---|---|---|---|---|
| National Cancer Institute | CD3z/CD28 | Retrovirus | Lymphoma, chronic lymphocytic leukemia | Phase 1/2 (NCT00924326) |
| Memorial Sloan-Kettering Center | CD3z/CD28 | Retrovirus | Chronic lymphocytic leukemia, refractory | Phase 1 (NCT01416974) |
| | CD3z/CD28 | Retrovirus | B-cell acute lymphoblastic leukemia, relapsed | Phase 1 (NCT01044069) |
| Baylor College of Medicine | CD3z/CD28 versus CD3z | Retrovirus | B-lineage non-Hodgkin's lymphoma and chronic lymphocytic leukemia | Phase 1 (NCT00586391) |
| | CD3z/CD28 versus CD3z-EBV CTLs | Retrovirus | B-lineage non-Hodgkin's lymphoma and chronic lymphocytic leukemia | Phase 1 (NCT00608270) |
| MD Anderson Cancer Center | CD3z/CD28 | Electroporation/ Sleeping Beauty transposon | Advanced B-cell lymphoma | Phase 1 (NCT00968760) |
| University of Pennsylvania | CD3z/4-1BB | Lentivirus | Refractory B-cell leukemia/ lymphoma | Pilot (NCT00891215/ NCT01029366) |

CARs, chimeric antigen receptors; EBV CTLs, Epstein-Barr Virus-specific cytotoxic T lymphocytes. Source: *Mol. Ther.* **19**, 432, 2011; http://www.clinicaltrials.gov

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"The major difference in our study was that we saw proliferation until the target was gone," says Carl June. "And that really surprised us." According to June, proliferation followed by persistence could explain his study's dramatic results; the three patients initially became violently ill, describing it as the worst flu of their lives, before two patients went into complete remission, the third into partial remission. "We think that was due to a side-effect of killing cells expressing CD19. Clearly, there's 'no pain, no gain' here, when you have 1–2 kg of tumor like these patients had, that's not going to go away easily," says June. The case study presented in *NEJM* showed how little a dose was actually required. "When you look at the number of T cells that the patient received, that's something we would use to treat a few mice," says co-investigator Bruce Levine, a research associate professor of Pathology and Laboratory Medicine at the University of Pennsylvania.

Despite their excitement, all researchers in the field are keen to stress that these are early days, saying it remains to be seen whether these results will hold up in larger patient numbers, whether responses can be sustained over longer time periods, and whether this approach can be translated to other targets and diseases. "If those three things happen, we're going to turn around in ten years time and say this was a real turning point in the field," says David Porter, a professor of medicine and director of Blood and Marrow Transplantation at the Hospital of the University of Pennsylvania, and lead author of the *NEJM* paper.

Last year, there were two reports of serious adverse events in separate clinical trials, one death resulting from a cytokine storm in an anti-CD19/CLL trial by Sadelain's group (*Mol. Ther.* **18**, 666, 2010), another in a trial by Rosenberg's group targeting the HER2-neu antigen in advanced colon cancer (*Blood* **116**, 4099, 2010). However, Sadelain says it is unfair to draw any conclusions from these unrelated adverse events, especially as it is generally accepted that the engineered T cells did not directly cause the cytokine storm. Rosenberg agrees, adding that target selection is crucial. "CD19 is almost ideal because it is only expressed on normal B lymphocytes, and you can do without them," says Rosenberg, chief of surgery at the US National Cancer Institute in Bethesda, Maryland. "However, if you target an antigen that's on normal tissue, you get rid of the cancer but it can cause toxicities, and that's what we ran into."

That said, all researchers agree that there is still much to learn about optimal CARs design, gene delivery methods and dosing. Different groups working on anti-CD19 CARs are exploring different permutations and combinations of co-stimulatory domains and vectors (**Table 1**); one possible explanation touted for the University of Pennsylvania group's results is that they were the first to test the 4-1BB co-stimulatory domain and lentivirus delivery vectors. Added to this, the T cell-engineering process requires a further level of technical complexity to what the US Food and Drug Administration defines as "minimal manipulation" methods, such as stem-cell transplantations.