IN brief

London forges £2 billion research cluster

University College London's main campus.

Five London-based medical research centers have partnered to become Europe's largest Academic Health Science Centre (AHSC). Uniting University College London (UCL) with four of the capital's most renowned hospitals—Great Ormond Street, Moorfields Eye Hospital, the Royal Free and University College Hospital—this venture aims to position London internationally as a hub of biomedical innovation. The new partnership, called UCL Partners, began life last month with a combined annual budget of around £2 billion. Together, the partners will treat 1.5 million patients a year and employ 3,500 scientists, senior researchers and medical consultants. UCL Partners is based on a model well established in North America, and in Europe, deepening the ties between universities and hospitals to inform academic and clinical research, improve professional education and enhance patient care. Such collaborations give rise to spin-off companies that create new treatments. "The clusters do work: they do attract investment," points out Ernst and Young's London partner, Chad Whitehead. "What investors are looking for is great science and great management teams. If you have that you will get the money." The UCL partnership follows recommendations made in July 2007 by Health Minister Lord Darzi to establish AHSCs as a way to reform the UK's National Health Service and accelerate the transmission of new ideas from bench to bedside. In the UK, the first AHSC was established in October 2007 when Imperial College London joined forces with Hammersmith and St. Mary's hospitals. Integrated governance is the top criterion that AHSCs must meet. For UCL Partners, this will come from its board, which is made up of the heads of its member organizations, operating under the umbrella of the not-for-profit company UCL Partners. Neil Goodwin, Project Director, says UCL Partners studied the governance arrangements of AHSCs in the US, Europe and Singapore, before choosing Harvard as its role model. In part, this is because the aim is to achieve a similar stature, but also because Harvard's governance model rests on partnerships, rather than central control. "Making this work is about more than being the biggest or having the most money, it is about establishing fruitful and effective partnerships," he suggests. UCL partners will concentrate initially on ten research areas chosen for London's existing expertise: the nervous system, children's health, heart disease, transplantation, immunology, ophthalmology, deafness and hearing impairment, dental and oral disease, cancer and women's health. *—Nuala Moran*

Collen claims that the auction for TB-403 "generated a great deal of interest from the pharmaceutical community." And clearly, Roche would not want the PlGF inhibitor in the hands of a competitor.

The critical attribute, and one which is expected to make TB-403 stand out from the anti-VEGF crowd, is that PlGF regulates the onset of angiogenesis in diseased but not healthy tissue. Other advantages include the fact that unlike anti-VEGF products, PlGF antibodies block infiltration of pro-angiogenic macrophages, believed to be the route by which cancer cells develop resistance to VEGF inhibitors.

The *Cell* paper provides evidence that anti-PlGF antibodies do not induce resistance, that they enhance the sensitivity of tumors to anti-VEGF and amplify the antitumor effects of chemotherapy also. Collen claims that TB-403's ability to block the development of blood vessels via mechanisms that exist only in disease states could "alter the landscape" of antiangiogenic therapy.

This contrasts with Avastin, which mops up VEGF before it can engage with its receptors, and multikinase inhibitors, which block various VEGF receptors. Because of the central role of VEGF in the formation of both normal and tumor blood vessels, these modes of action lead to significant, dose-limiting side effects, ranging, in the case of Avastin, from hypertension to fatal gastrointestinal perforations.

A similar, though not as serious, side effect profile has been seen with aflibercept (previously referred to as VEGF-Trap), a fusion protein that binds and neutralizes both VEGF and PlGF. Murray Goldberg, chief financial officer of Tarrytown, New York-based Regeneron, resisted direct comparisons with Avastin when he presented the latest data on the phase 3 compound at the Jefferies 2nd Annual Healthcare Conference in New York in June, saying, "Some observers have tried to take the results and compare them to Avastin. I think that is problematic because of the different study populations, stages of disease and so on."

Aflibercept is in four phase 3 studies in hormone-resistant prostate cancer, non-small cell lung cancer and colorectal and pancreatic cancer, which began in the second half of 2007. At around the same time, Regeneron extended its deal with Paris-based Sanofi-Aventis to include the development of antibodies. The French company invested a further $312 million in Regeneron stock, extending its holding in the company to almost 20%.

Another product in advanced clinical development is New York's ImClone's IMC-1121B, a fully human mAb that targets VEGF receptor-2, the predominant receptor driving angiogenesis. This has FDA special protocol assessment designation for a pivotal 1,100-patient trial in metastatic breast cancer, which began recruitment recently. Further back in its pipeline, ImClone has a preclinical-stage antibody called IMC-18F1 that blocks both PlGF and VEGF.

Other routes to inhibiting VEGF and PlGF are emerging. Sirna Therapeutics, of San Francisco (now owned by Merck), partnered AGN-745 (Sirna-027), a short-interfering-RNA product, with Irvine, California–based Allergan for the treatment of age-related macular degeneration.

In a paper published in *Nature Biotechnology* in July, Judah Folkman, who died in January, and coauthors describe how nanotechnology had been applied to rescue TNP-470, one of the earliest antiangiogenesis agents in the clinic. After ten years in development, the product was dropped because of its short half-life and reversible neurotoxic side effects. The researchers describe improving the properties of TNP-470, by conjugating it to two polymers. Now renamed lodamin, the orally available agent is being developed for chronic use by SynDevRx, located in Cambridge, Massachusetts.

Undoubtedly, the antiangiogenesis field is becoming more crowded, raising the question of how TB-403 will be positioned in relation to Avastin. Although likely to be effective as a single agent, Collen has pitched TB-403 on its additive and possibly synergistic effects, suggesting that co-administration may make it possible to reduce the dose of Avastin, and thus lessen the side effects.

In effect, Collen says PlGF acts as a "biotransistor" activating the VEGF receptor-1, located on the vasculature's endothelium, and amplifying the effect of VEGF in tumor tissues. "Therefore, we believe there could be synergy with Avastin, but also that tumors resistant to Avastin could be sensitive to PlGF inhibitors."

Two weeks before the deal with Roche was signed, Thrombogenics and BioInvent announced TB-403 had successfully completed phase 1 and was moving into a 30-patient phase 1b study in advanced solid tumors. Roche has now taken over clinical development, and Dan Zabrowski, global head of pharma partnering at Roche, promises a very aggressive program in multiple indications with the aim of getting TB-403 to market by 2012.

Zabrowski noted that angiogenesis is associated with many different mechanisms. "[TB-403] could be complementary to Avastin. It's early days, but we think they will work together." The hope is for a different safety profile enabling Avastin and TB-403 to be used sequentially, in combination with other therapies.

Nuala Moran *London*