IN brief

GSK picks six cancer research centers

GSK's Axel Hoos.

GlaxoSmithKline (GSK) has launched a collaborative research network with six leading cancer research centers. The Oncology Clinical and Translational Consortium (OCTC), announced in December, partners the London-based pharma with three renowned clinical research centers in Europe—the Gustave Roussy Institute in Villejuif, France; Netherlands Cancer Institute in Amsterdam; and Vall d'Hebron Institute of Oncology in Barcelona, Spain—and three in North America: the Princess Margaret Cancer Centre, University Health Network, Toronto; the University of Texas MD Anderson Cancer Center, Houston; and the Memorial Sloan-Kettering Cancer Center, New York. "GSK has chosen institutes that it can trust," says Ferran Prat, vice president Strategic Industry Ventures at MD Anderson Cancer Center. OCTC will tap into the academics' expertise to identify prospective novel drug combinations and single agents as anticancer therapeutics, including kinase inhibitors, epigenome modulating compounds and immunotherapies. The company will open up data from its early-stage oncology pipeline, including agents in phase 1 and 2, to the external researchers. What makes the OCTC different from other pharma-academia collaborations is that the company is giving academics the opportunity to work with current pipeline products rather than compounds that have been shelved. This is a risky move on GSK's part. Even when confidentiality agreements are in place, data leakage is possible. But Axel Hoos, vice president, oncology R&D at GSK, explains that companies have always shared pipeline information with collaborators, and the benefits of open collaborations override the risks. For the academics involved, GSK has promised total freedom to publish the outcomes of their research, whether positive or negative. Before signing up, academics need to prepare themselves, too. "Academic institutions should assure themselves that there is a mutual interest in the project, a good understanding by the industry partner of the way academia works and a clear vision of the intended outcomes," says Angela Kukula, director of enterprise at the Institute of Cancer Research, London. *Suzanne Elvidge*

to prove a negative, but I think the risks are really low, given the biology of the target of vedolizumab," says Ulrich von Andrian, professor of microbiology and immunology at Harvard Medical School, in Boston, who has worked as a consultant to Takeda. "If the risk was anywhere similar to natalizumab, there should have seen several cases."

But Entyvio's development program did suffer some fallout from the Tysabri crisis. Entyvio was subjected to a clinical hold from January 2006 to July 2007, as regulators grappled with understanding the risk factors that gave rise to PML. Osaka, Japan–based Takeda gained ownership of Entyvio—a humanized version of a murine antibody, anti-Act-1, first described back in 1984—through its $8.8-billion acquisition of Cambridge, Massachusetts–based Millennium Pharmaceuticals in 2008. The company has long sought to differentiate the drug from Tysabri, a dual inhibitor of α4β7 integrin and α4β1 integrin, on the basis of its selectivity for α4β7 integrin, which mediates lymphocyte migration to the gastrointestinal (GI) tract (*J. Pharmacol. Exp. Ther.* **330**, 864–875, 2009). "The gut specificity of this pathway has been known since the early 1990s," says Asit Parikh, Takeda's vice president of general medicine.

Entyvio's gut activity results from binding α4β7 integrin selectively—it binds the heterodimer and prevents it from binding MAdCAM-1 (its ligand, mucosal vascular addressin cell adhesion molecule-1), mainly expressed in the gut, and fibronectin, an extracellular matrix glycoprotein. Tysabri has a broader effect, as it binds α4 integrin common to both the α4β7 and α4β1 integrins. As a result, Tysabri disrupts α4β7 integrin binding to MAdCAM-1 and prevents lymphocyte migration to the GI, but it also disrupts lymphocyte migration to the CNS, by blocking α4β1integrin binding to vascular cell adhesion molecule-1—and potentially introducing the PML risk.

Several lines of evidence support Takeda's position that Entyvio does not present a major PML risk. In contrast with Tysabri, Entyvio lacks efficacy in an experimental autoimmune encephalomyelitis model in Rhesus monkeys (Macaca mulatta) (*J. Immunol.* **190**, 1961–1973, 2013). Also, unlike Entyvio, Tysabri induces peripheral blood lymphocytosis (an increased cell count), as lymphocytes that are prevented from migrating into the gut or CNS accumulate in the blood. Entyvio has less impact on lymphocyte trafficking as its target, α4β7 integrin, is present on about 3% of lymphocytes, whereas α4β1 integrin is found on about 30% of lymphocytes. "It's the major mechanism for T-cell trafficking throughout the body," says Feagan.

In terms of Entyvio's efficacy, the data in ulcerative colitis look clear-cut. Feagan was principal investigator on a combined phase 3 induction-and-maintenance trial of Entyvio in ulcerative colitis, which recently reported six-week response rates of 47.1% and 25.5% for patients on Entyvio and on placebo, respectively (*N. Engl. J. Med.* **369**, 699–710, 2013). After 52 weeks, 41.8% of patients who continued to take Entyvio every 8 weeks and 44.8% of patients who continued to take Entyvio every 4 weeks were in

Table 1 Selected leukocyte trafficking modulators for inflammatory bowel disease

Drug	Description	Developer	Target	Indication	Clinical status
Tysabri	Humanized IgG4 mAb	Biogen Idec (Cambridge, Massachusetts)	α4β1 integrin, α4β7 integrin	Multiple sclerosis, Crohn's disease	Approved (FDA)
Entyvio	Humanized IgG1 mAb	Takeda	α4β7 integrin	Crohn's disease	Registration (in US)
AMG-181	Fully human IgG2 mAb	AstraZeneca (London)/Amgen (Thousand Oaks, California)	α4β7 integrin	Crohn's disease, ulcerative colitis	Phase 2
Etrolizumab (rhuMAb β-7, RG7413)	Humanized IgG1 mAb	Genentech (S. San Francisco, California)	α4β7 integrin, αEβ7 integrin	Ulcerative colitis	Phase 2
EMD 5257 (DI176E6)	Humanized IgG2 mAb	Merck Serono (Darmstadt, Germany)	αv family integrins	Metastatic colon cancer, metastatic prostate cancer	Phase 2
PF-00547659	Fully human IgG2k mAb	Pfizer	MAdCAM-1	Crohn's disease, ulcerative colitis	Phase 2
GLPG0974	Oral small molecule	Galapagos	Free fatty acid receptor 2	Ulcerative colitis	Phase 2
AJM300	Oral small-molecule prodrug	Ajinomoto Pharmaceuticals	α4 integrin	Ulcerative colitis, Crohn's disease	Phase 2

mAb, monoclonal antibody. Sources: Company websites; PubMed