AstraZeneca is already in phase 2 trials with another OX40 agonist, albeit a murine antibody, which it in-licensed from AgonOx, of Portland, Oregon. A phase 1 trial underlined its promise. "Approximately half of subjects treated in that phase 1 had tumor regression," says Ed Bradley, head of MedImmune's oncology innovative medicines unit. The company will need to develop a humanized version of the drug for future development, however.

Several other stimulatory co-receptor agonists are in early clinical development, including antibodies that target glucocorticoid-induced tumor-necrosis-factor-receptor-related protein (GITR), which, in a preclinical study, compared favorably with antibodies targeting CTLA-4, PD-1 and OX40. "The truth was the anti-GITR antibody was the most potent of all of those," says Jedd Wolchok, medical oncologist at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. GITR was first identified as a regulatory T-cell marker. Shimon Sakaguchi, of the University of Osaka, Japan, later demonstrated its involvement in breaking immunological tolerance by suppressing regulatory T-cell activity (*Nat. Immunol.* **3**, 135–142, 2002). Anti-GITR therapy also appears to result in the loss of the Forkhead box P3 (FoxP3) transcription factor, a hallmark for the regulatory T-cell lineage. This suggests a certain "plasticity" in T-cell lineage commitment, says Wolchok, and raises the possibility of *in vivo* reprogramming of regulatory T-cells.

A phase 1 trial of an anti-GITR antibody is ongoing at MSKCC, but it is proceeding slowly, as a single-ascending dose study. "We need to be quite thoughtful about how we dose these agents," Wolchok says. Targeting any stimulatory co-receptor recalls the disastrous phase 1 trial of TGN1412, a CD28 agonist that caused life-threatening autoimmune reactions in six healthy volunteers (*Nat. Biotechnol.* **24**, 475–476, 2006). However, several observers note that the cytokine storm unleashed by activating CD28 is unlikely to occur with other co-receptor targets. "There are not many mechanisms for that kind of toxic disaster," says Bradley. "CD28 is constitutively expressed on all T cells," Liu says. In contrast, "OX40 is not expressed on resting T-cells."

How best to deploy drugs that target co-receptors is still a work in progress. "I think it's very clear to everyone that combinations are going to be the future. Even though Yervoy helps some people with melanoma, it doesn't help the majority with melanoma," says Wolchok, who was principal investigator on one of the drug's registration trials. Only 10–15% of melanoma patients respond to Yervoy. In early trials of BMS's anti-PD-1 antibody nivolumab, responses ranged from 18–24%, across different cancer indications.

MSKCC and Yale University School of Medicine, in New Haven, Connecticut, are jointly conducting a closely watched, combination trial of Yervoy and nivolumab in patients with advanced melanoma. MedImmune will also shortly begin a combination trial of tremelimumab, a CTLA-4 inhibitor it in-licensed from Pfizer, of New York, and its OX40 agonist. "The preclinical data were spectacular, so we have great expectations for that," Bradley says. 4-Antibody may develop bispecific antibodies that would hit two targets simultaneously.

A major issue with this approach is toxicity. As single agents raise substantial toxicity concerns—Yervoy is associated with enterocolitis, for example—combination therapies could, in theory, be even more problematic. "I bet in the long run it doesn't play out in that way," says Bradley, suggesting that once the major clinical research questions are answered, combinations will be better mimics of the immune system than single agents. "We'll get the first big clue when we get the first ipilimumab–PD-1 [inhibitor] data," he says. Moreover, the development of treatment algorithms has helped to minimize the risks from Yervoy and other therapies. "What the drug engineers are not able to engineer out, the clinicians are able to deal with very effectively," Bradley says.

Numerous combination trials of co-receptor modulators paired with other forms of therapy, including chemotherapy, radiation, cancer vaccines and small-molecule drugs, are also under way. Hints of synergies are emerging. For example, Wolchok and colleagues reported an abscopal effect (regression from irradiation on nonirradiated tissue) in a patient with metastatic melanoma, who received Yervoy and a dose of radiation localized to a single tumor. Several tumors distal to the site of radiation regressed, because radiation released tumor antigens to which a derepressed immune system could respond. "You turn that tumor into a site of endogenous vaccination," Wolchok says. MSKCC is now conducting a larger study, in collaboration with Stanford University, of Stanford, California, and the University of Chicago, in Chicago. By the end of this year, the potential of combination therapies will be a lot clearer as the first trials start to report data. By then it will be evident if cancer immunotherapy will finally be ready for take-off.

Cormac Sheridan, ***Dublin***

IN brief

Biotech bonanza hits UK

Three new UK venture funds are bringing a total £350 ($543) million to support long-term investments in early-stage companies. The largest is £200 million from Syncona Partners, launched by the Investments Division of the London-based biomedical charity Wellcome Trust. Meanwhile the Welsh Life Sciences Fund has £100 ($155) million, with £50 ($77.5) million of it coming from the Welsh government, and the balance raised by Arthurian Life Sciences, a company set up by biotech veteran Chris Evans to bid for the contract to manage the fund. Completing the trio, venture capital investor Sinclair Dunlop, co-founder and managing partner of Rock Spring Ventures, of Bethesda, Maryland, is returning to his native Scotland to launch a European fund.

Syncona will be operating as an independent entity. Its investment philosophy is not only different from that of the Investments Division of the Wellcome Trust, which spends over £20 ($31) million in later-stage companies, but also from conventional venture capital funds, explains Martin Murphy, CEO. "The key difference is that ours is an evergreen fund that can take a long-term view and support technologies all the way through to market," Murphy says. Syncona is prepared to invest for 10–12 years, if necessary. The approach also is distinct from the Wellcome Trust's philanthropic grant programs, such as Seeding Drug Discovery, in that there must be potential for commercial returns. "We will look for unmet medical needs, but there has to be a market," Murphy says. Syncona's first investment in Cambridge EpiGenetix, a Cambridge University startup that aims to commercialize tools and techniques for detecting nucleotide modification, exemplifies the fund's intentions. Following the seed funding, Murphy says Syncona expects to invest in a Series A and subsequent investment rounds.

The Welsh Life Sciences Fund also wants to make large, long-term investments. "The plan is to invest in 10–12 good companies and then stay with them, rather than randomly trying to put money into as many firms as possible," says Martin Walton, a director of Arthurian Life Sciences. Rock Spring Ventures' fund is inspired by the need for more sector-specific financial backing, with the life sciences sector in Scotland and other parts of the UK representing what it describes as "underventured" markets. It plans to form syndicates with other early-stage investors, including funders from outside the UK. To date, Rock Spring Ventures EU has received commitments for £25 ($387.7) million of a proposed £50 ($77.5) million, from investors, including the universities of Aberdeen, Edinburgh and Glasgow, and the EU's European Investment Fund. *Nuala Moran*