IN brief

Argos attracts unorthodox backers

Dendritic cell immunotherapy specialist Argos Therapeutics closed a \$42.5-million series E round late in August by casting an unusually wide geographical net. Argos attracted venture capitalists from Russia and South Korea to invest alongside existing backers from Europe and the US, an international round that “reflects the globalization of immunotherapy,” says Jeff Abbey, CEO of the Durham, North Carolina-based company. It was not a case of Argos going prospecting but rather that indigenous pharma companies in emerging markets were looking to globalize. Drugmakers Pharmstandard of Moscow and Green Cross of Yonging-Si backed Argos’ phase 3 study of personalized kidney cancer vaccine AGS-003 and secured licenses to commercialize AGS-003 in their home markets. The deal highlights an important new dynamic in funding and partnering in emerging markets, particularly relevant to early-stage biotechs with risky technologies. In countries like Brazil, Russia, India and China, it no longer makes sense to license worldwide rights to a single pharma partner, because they lack the local knowledge and networks of national champions. Even the biggest pharma partner may not have the regulatory expertise to get novel products—like dendritic cell therapies—approved in as timely a way as the local incumbent does.

For biotechs, doing deals in developing markets can bring in cash, validate risky technology and provide a source of expertise. Pharmstandard and its associated biotech operation IBC Generium are also becoming co-development partners with Argos. And this year, Pharmstandard has invested in Protagonist Therapeutics of Menlo Park, California, a specialist in orally available peptides, and Aquinox Pharmaceuticals of Vancouver, British Columbia, Canada, a specialist in the phosphoinositide 3-kinase (PI3K) pathway. All three investments were managed by Inbio Ventures, a Luxembourg-based company headed by Alexandr Shuster, a board member of Pharmstandard.

The Argos deal stands out as the first time Pharmstandard has led a round. Commenting on the investment Shuster says, “Immunotherapy is increasingly recognized as a treatment that will represent a new paradigm in the management of cancer.” Given this, investing in Argos is both a step forward in the globalization of Pharmstandard and in its focus on identifying cell-based therapies, Shuster says. *Nuala Moran*

IN their words

“For too many of our friends and family, life has been cut short or the quality of their life is too often lacking. Art [Levinson] is one of the crazy ones who thinks it doesn’t have to be this way.” Apple CEO Tim Cook about the new startup Calico. (*The Verge*, 18 September 2013)

Monoclonal T-cell receptor drugs pique pharma’s interest

Over a three-week period this summer, Immunocore entered two early-stage partnerships, with GlaxoSmithKline and Genentech, based on its ImmTac monoclonal T-cell receptor (TCR) technology, a bispecific fusion protein, which seeks to capture in one biologic drug both the potency and specificity of a T cell–mediated immune response. The promise of an ImmTac (immune-mobilizing monoclonal TCR against cancer) lies in its ability to co-opt T-cells into attacking a universe of intracellular targets that are inaccessible to monoclonal antibodies (and it may have other serendipitous advantages; see Box 1). Altor Bioscience, of Miramar, Florida, is pursuing a similar approach with its soluble T-cell antigen receptor (STAR) technology, which consists of a single-chain TCR fragment fused to an effector molecule, such as a cytokine. But with only a smattering of human data so far to support the underlying concept, the efficacy of the approach is as yet clinically unvalidated. In addition, safety concerns exist; similar to adoptive T-cell therapy, recombinant TCR approaches rely on the potency of explosive T-cell responses. Indeed, two cancer patients died recently, due to unexpected cross-reactivity between unrelated T-cell epitopes, in trials of a cell-therapy–based implementation of the same technology, under development at Immunocore’s sister firm Adaptimmune (*Sci. Transl. Med.* 5, 197ra103, 2013).

ImmTacs are new reagents consisting of two arms: a high-affinity monoclonal TCR fused to a humanized anti-CD3 single-chain variable antibody fragment (scFv) that engages T-cells. To eradicate neoplasms, the epitope-specific TCRs specifically recognize endogenously processed peptide antigens bound to major histocompatibility complex (MHC) on the tumor cell surface. At the same time, the anti-CD3 fragments activate any CD8⁺ cytotoxic T-cells, regardless of their TCR specificity, redirecting them to kill cancer cells, even those with low surface epitope densities (*Nat. Med.* 18, 980–987, 2012).

As recombinant TCRs are a protein-based therapeutic, they may have a lower level of risk than for cell therapies based on adoptive T-cell transfer. “A soluble T-cell receptor has a finite PK [pharmacokinetic] profile, and you start at a low dose,” says James Noble, who is CEO of both Immunocore and Adaptimmune. Compared with a cell-based therapy, fine tuning of the dosage of a recombinant TCR protein is easier, and administration can be discontinued

Steve Gschmeissner/Science Photo Library

T-lymphocytes (red) recognize antigens on a tumor cell (yellow). Recombinant T-cell receptor therapeutics rely on the potency of these T cell-mediated immune responses to kill cancer cells.

in the event of safety problems.

Even so, caution is warranted as attempts to harness the immune system have, in the past, led to cases of severe toxicity. Whether it is endogenous cells primed by recombinant TCRs or *ex vivo*–activated T-cells reintroduced into the body, “CD8⁺ T-cells are self-replicating critters, so once they go rogue they are difficult to stop,” says Andrew Sewell, distinguished research professor at Cardiff University School of Medicine, in Cardiff, UK. “Most of the time, it’s possible to test for and screen out this danger.” Predicting the likelihood of such serious adverse events remains by no means routine, however, as Nicholas Restifo discusses on p. 999.

Immunocore and Adaptimmune, both of Abingdon, UK, have their roots in Avidex, a UK firm, which Martinsried, Germany–based Medigene acquired in 2006. Two years later, it spun out the TCR technology platform, under the leadership of Avidex’s scientific founder Bent Jakobsen and Noble, its founding CEO. Under the recent deal with S. San Francisco, California–based Genentech, which concerns an undisclosed set of cancer targets, Immunocore is receiving an upfront ‘initiation fee’ of \$10–20 million per program and could receive up to \$300 million more in development and commercial milestones for each molecule, as well as sales royalties. Under the alliance with London-based GlaxoSmithKline, which involves cancer and viral targets, Immunocore could receive up to £142 (\$221) million in preclinical milestones across all programs and up to £200 (\$323)