Evaluate Vantage

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Therapeutic focus – Astra goes ROR fishing and hooks Orca

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AstraZeneca’s deal with Orca Pharmaceuticals, announced today, is the sixth separate big pharma partnership in a very early-stage immunological approach known as ROR modulation.

Only two candidates have entered the clinic but interest from Astra, Johnson & Johnson, Merck & Co and Pfizer suggest more may be coming within months. The hope is to create a molecule that can more directly target inflammatory response in diseases like rheumatoid arthritis without making patients vulnerable to infection because of immunosuppression (see table).

I am Orca, hear me ROR

Astra's deal with privately held Orca is worth up to $122.5m and covers the development of inhibitors of retinoic acid–related orphan nuclear receptor (ROR)-gamma. This nuclear receptor has been shown to convert a type of immune cell called CD-4 positive T cells into T helper 17 cells, which produce the inflammatory cytokine interleukin 17 (IL-17). Excessive activity of ROR-gamma has been implicated in autoimmune conditions.

This collaboration becomes the fifth active partnership researching this family of receptors, joining J&J’s tie-up with German group Phenex, Merck’s with Lycera, Pfizer’s with KaroBio, and Amgen's with Teijin. A sixth collaboration between Bristol-Myers Squibb and Exelixis ended in 2013 and the project has been shelved.

In autoimmune disorders, targeted medications have been effective at throttling back the body’s immune response to reduce symptoms, but that has tended to come at the cost of increased risk of infections. For example, one of the most widely used drugs in this space is Humira, and its label includes a black box warning about risks from tuberculosis as well as fungal and other opportunistic infections.

The scientific rationale here is to target a specific pathway that generates inflammation rather than to turn off immune responses broadly. On the flip side, some researchers also have been looking at activating this pathway to create a cancer-fighting response. Merck partner Lycera, for example, has separate programmes for autoimmune disease and oncology.

Selected projects in retinoic acid–related orphan nuclear receptor research			
Status	**Company**	**Product**	**Therapeutic Subcategory**
Phase I	Japan Tobacco/Torii Pharmaceutical	JTE-151	Immunosuppressants
	University of California, San Diego	ROR1 Modulator Research Project/UC-961 (Cirmtuzumab)	Other cytostatics
Pre-clinical	Innovimmune Biotherapeutics	INV-17	Immunosuppressants
	PheneX Pharmaceuticals/J&J	ROR gamma t Program	Immunosuppressants
	Lycera/Merck & Co	ROR Gamma Agonist	Immunosuppressants
	Vitae Pharmaceuticals	VTP-43742	Immunosuppressants
	Kancera	KAN0439834	Other cytostatics
	Arrien Pharmaceuticals	ARN-6039	MS Therapies
Research project	GENFIT	TGFTX1	Immunosuppressants
	Lycera/Merck & Co	ROR Gamma t Antagonist	Immunosuppressants
	Pfizer/Karo Bio	ROR-Gamma Project	Immunostimulants
	Amgen/Teijin	ROR Gamma Research Program	Immunosuppressants

Toe in the water

The most advanced autoimmune-related ROR project is Japan Tobacco's JTE-151, which the group reported as being in the clinic as of April 2014. Other projects are nearing the clinic, however.

For example, Vitae Pharmaceuticals plans to file an investigational new drug application in the first half of 2015 so VTP-43742 can begin phase I. The Pennsylvania-based group raised $37.8m in January, so it has a decent war chest to support its clinical efforts, but it has active work ongoing with two other unrelated candidates. Thus it may be hoping for some partnership dollars to support its nascent efforts.

In cancer, the University of California, San Diego project UC-961 (cirmtuzumab) has also been in phase I trials in chronic lymphocytic leukaemia, with 56 patients expected to be enrolled in a dose-escalation trial due to finish in August 2016.

A number of others have published preclinical data on their candidates: Innovimmune presented mouse data in rheumatoid arthritis at the 2014 American College of Rheumatology; Merck partner Lycera has generated data in anti-tumour models, and specifically, breast cancer models; and Kancera in preclinical leukaemia models.

Further back in the pipeline, work is underway to identify molecules eligible for preclinical development work. Phenex had stated it wanted to designate a candidate by the end of 2013, although none has emerged yet; its recent sale of its liver-disease assets to Gilead Sciences leaves the ROR programme as its only disclosed work, suggesting that it may be able to divert resources to it.

Through its project with German group Bicoll to identify potential ROR ligands in plant metabolites, French company Genfit has been able to assemble a programme it calls TGFTX1 to identify candidate molecules for inflammatory disease. Arrien Pharmaceuticals has been aiming its project ARN-6039 at multiple sclerosis and psoriasis; it has disclosed little about the project beyond patent filings. Pfizer, meanwhile, took over the development work of its ROR-gamma collaboration with Karo Bio at the beginning of 2015, suggesting that it had seen enough to progress it beyond the current stage.

Given the early state of the research it is difficult to say whether this approach will pay dividends in either immunology or oncology. What can be said is that the number of partnerships forged shows that big pharma likes what it has seen so far, and will be eager to see some more candidates enter the clinic to better judge its promise.

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