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Therapeutic focus - Astra and Rigel throw a JAK into the cytokine-targeting asthma box

Jacob Plieth

AstraZeneca's early-stage alliance with Rigel Pharmaceuticals looks set to tackle asthma using a widely tested pharmacological approach – inhibition of the effects of IL-13 and IL-4 signalling. But where the deal departs from convention is in its use of a small molecule – an inhaled JAK inhibitor, no less – to do what most others are tackling with proteins and monoclonals.

While another novel inhaled therapy has been studied recently, according to *EvaluatePharma* data no other anti-asthma agents use the JAK approach, which is more commonly associated with myelofibrosis and rheumatoid arthritis. And the big race in the IL-13/IL-4 inhibitor class is between monoclonals: Roche's lebrikizumab, currently in a large phase III study, has Novartis and AstraZeneca snapping at its heels.

The mechanisms through which IL-13 and IL-4 regulate immune responses are well documented, and both cytokines are thought to use JAKs (Janus-associated kinases) to initiate signalling. While the Rigel project, R256, specifically inhibits the activity of JAK3 – thus damping down the effects of cytokine-mediated signalling - monoclonal antibodies against the cytokines themselves work to prevent this signal from being generated in the first place.

Leader of the pack

Roche recently started a 1,400-patient phase III trial comparing the effects of three subcutaneous doses of the antibody lebrikizumab in improving the rate of asthma exacerbations over 52 weeks versus placebo. This study is specifically looking at asthmatics who are already on inhaled corticosteroids and a second controller medication, but will not read out until 2017.

Lebrikizumab was originated by Tanox, a company taken over by Genentech in 2007 before the latter was itself acquired by the Swiss pharma giant.

As the table below shows, AstraZeneca already has expertise in this area, and both it and Novartis have similar anti-IL-13 monoclonals in phase II asthma studies. AstraZeneca's tralokinumab was to have completed phase II earlier this year but appears still to be recruiting patients, while Novartis's study of QAX576 reads out in February 2013.

Much earlier in development are three unusual projects, the most advanced of which is pitrakinra, an inhaled recombinant protein in development by the Bayer spinout company Aerovance. The private German biotech Pieris is working on PRS-060, a low-molecular weight protein formulated for pulmonary delivery, while Targepeutics has its Targ-allerg project.

Positive data were reported two years ago from a phase II trial of pitrakinra in 534 eosinophilic asthma patients, but no further development has taken place although plans of entering phase III had been mooted. Development of Targ-allerg depends on a partner taking it forward, given that asthma is not a focus for the privately held Targepeutics.

The area has also been notable for discontinuations; most recently, Pfizer's anrukinzumab, an anti-IL-13 monoclonal, was abandoned after being studied in phase II in patients with persistent asthma, although its development in ulcerative colitis continues. RG1671, an antibody against IL-13 receptor alpha chain that had been originated by Genmab, was discontinued by Roche after phase I studies under a portfolio review.

Asthma interleukin pipeline					
Status	**Product**	**Pharmacological Class**	**Company**	**Routes of Admin.**	**Trial ID**
Phase III	lebrikizumab	Anti-IL-13 MAb	Roche	Injection	NCT01545440
Phase II	QAX576	Anti-IL-13 MAb	Novartis	Injection	NCT01479595
	tralokinumab	Anti-IL-13 MAb	AstraZeneca	Injection	NCT01402986
	SAR156597*	IL-4/IL-13 antibody	Sanofi	Injection	-
	pitrakinra	Recombinant IL-4 & IL-13 antagonist	Aerovance	Inhaled	NCT00801853
Phase I	GSK2434735	Anti-IL-13 MAb	GlaxoSmithKline	Injection	NCT01563042
Pre-clinical	R256	Small-molecule IL-13 inhibitor	AstraZeneca/ Rigel Pharmaceuticals	Inhaled	-
	PRS-060	IL-4 alpha antagonist protein extract	Pieris	Inhaled	-
Research project	Targ-allerg	Recombinant IL-13 antagonist	Targepeutics	Inhaled	-
	IL4 Research Project	Recombinant IL-4 antagonist	Cosmix	-	-
* Phase II is for idiopathic pulmonary fibrosis indication					

The deal with Rigel

R256, the molecule Rigel has licensed to AstraZeneca, has so far only been studied in preclinical models, in which it was shown to prevent allergen-induced airway hyper-responsiveness and inflammation, and reduce inflammation in a chronic asthma model.

Interestingly, Rigel is also developing two other JAK3-inhibitors – R348 and R548 – for non-asthma immunology indications. The JAK3 mechanism is used by Pfizer’s RA project tofacitinib, awaiting US approval, while myelofibrosis agents employing JAK1/2 inhibition include Novartis/Incyte’s marketed ruxolitinib.

AstraZeneca’s $1m signing payment is relatively insignificant, but is in line with the early nature of the project, and Rigel stands to receive a further $8.3m in undisclosed milestones that it says could become due by the end of next year. The alliance is heavily backend-loaded, and the total milestones are worth $100m in addition to undisclosed sales royalties.

An earlier deal with AstraZeneca focuses on Rigel’s oral SYK-inhibitor fostamatinib, which is in phase III studies for treating rheumatoid arthritis.

While in asthma the monoclonal race between Roche, Novartis and AstraZeneca is set to continue, the UK company looks like it is also making an early bet on a related small-molecule approach.

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