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Bristol bets on cytokines again

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The company's deal with Dragonfly shows that disappointments have not eliminated interest in cytokine approaches.

Yesterday's move by Bristol Myers Squibb to license Dragonfly's under-the-radar IL-12 asset will remind investors that there is still mileage in cytokine therapies. This despite 2018, which some had touted as the year of the cytokine, ultimately ending in disappointment for the field.

The torch bearer back then was Nektar's IL-2 project bempegaldesleukin, which could only manage middling efficacy in the Pivot-02 study, notwithstanding a $1.85bn bet on it by Bristol. But there was interest in cytokines beyond IL-2, and IL-12 is one in which Bristol now joins companies including Astrazeneca and Moderna.

Like IL-2, IL-12 is a cytokine that broadly speaking stimulates the growth and activity of T cells. But – also like IL-2 – developing it as a therapy approach has been dogged with complexities around the toxicities associated with broad immune system activation, as well as a relatively short half-life; data so far have been mixed.

Why have some industry players remained interested in such toxic approaches? One obvious reason is that anticancer immunotherapy tends to work only in "hot", or immunogenic tumours, and pro-inflammatory cytokines are thought to be capable of turning cold tumours hot.

If this theory could expand the uses of an anti-PD-1 MAb like Opdivo it explains Bristol's continued fascination with cytokines. Despite the Pivot-02 disappointment the company this year doubled down on bempegaldesleukin.

Harnessing the power

Work on reducing the toxicity of IL-12, meanwhile, has focused on local or intratumoural delivery, controlling *in situ* expression, or targeting the cytokine to the tumour microenvironment. Bristol's deal with Dragonfly, for which it is paying $475m in "near-term up-fronts", concerns DF6002, a monovalent IL-12 Fc fusion protein that aims to extend IL-12's half-life.

A look at the industry pipeline shows an array of projects that similarly seek to harness the therapeutic power of this cytokine while minimising its shortcomings. These include gene therapies as well as another fusion protein.

Perhaps the most closely watched asset is Astrazeneca/Moderna's MEDI1191, which comprises IL-12-encoding mRNA, encapsulated in lipid nanoparticles and delivered by intratumoural injection. A phase I study in

combination with Imfinzi started last year.

Other Immunotherapy combinations include Merck KGaA's fusion protein M9241, which is in the Bavencio combo study Javelin IL-12, while Bristol's "armored" Car-T project JCAR020 combines IL-12 secretion with targeting of the Muc16 antigen. Ziopharm's Ad-RTS-hIL-12 is being studied with Libtayo, though it has been in development for years without scoring a notable success.

Selected oncology projects working on IL-12 signalling			
Project	**Company**	**Class**	**Clinical trial**
Phase II			
Tavo	Oncosec	Electroporation-delivered IL-12 gene therapy	Keynote-695 (Keytruda combo)
Ad-RTS-hIL-12	Ziopharm	Intratumoural IL-12 gene therapy	Libtayo combo
HemaMax	Neumedicines	rhIL-12	NCI study in cutaneous T-cell lymphoma
Phase I			
GEN-1	Celsion	IL-12 gene therapy	Ovation-2
INO-9012	Inovio	Plasmid encoding IL-12 subunit proteins	Libtayo combo
MEDI1191	Astrazeneca/Moderna	IL-12 mRNA therapeutic	Imfinzi combo
DF6002	Dragonfly/BMS	Monovalent IL-12 Fc fusion protein	Dose escalation
M9241	Merck KGaA	IL-12/Ab fusion protein	Javelin IL-12 (Bavencio combo)
JCAR020	BMS (ex Juno)	IL-12 secreting anti-Muc16 Car-T	Muc16-positive tumours
Preclinical			
CA-IL12	Cytonus	IL-12 cell therapy	None
Immunalon	Medac/Provecs Medical	IL-2, IL-12 & 4-1BBL gene therapy	None
RTX-224	Rubius	4-1BBL & IL-12 red blood cell therapy	None
Source: EvaluatePharma & clinicaltrials.gov.			

Ad-RTS-hIL-12's slow progress should remind investors of other IL-12 disappointments, most notably Oncosec's Tavo, which like bempegaldesleukin failed to turn cold melanoma hot, disappointing in an IO combo trial. Like the Nektar project it remains in development.

Not so Regulon's LipoVIL12 and Avrobio's AVR-ONC-01, which are both discontinued. Also out is AM0012, a recombinant human IL-12 that Lilly got along with its $1.6bn purchase of Armo Biosciences; Armo's lead cytokine, the IL-10 project pegilodecakin, also now appears to be going nowhere.

Interestingly, before yesterday Bristol already has a deal with Dragonfly, via a 2017 tie-up signed by the legacy company Celgene, covering rights to develop cell therapies based on NK cells. Judging by Dragonfly's pipeline this is by a long way the private biotech's primary focus.

Indeed, Dragonfly had barely mentioned the existence of DF6002. Having emerged from stealth mode this asset now represents Bristol's latest attempt to deliver on the cytokine promise.