Evaluate Vantage

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Novartis pushes on with iscalimab after transplant disappointment

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The autoimmune target CD40 has yielded few hits despite years of research, but a few companies are keeping the faith.

A scan of the varied indications in which antibodies against CD40 are being investigated gives the distinct impression that this remains an elusive target. Not that work in this area is new – researchers have been putting anti-CD40 projects into the clinic for more than 20 years.

Novartis was the latest to suffer a setback, saying last week that a trial of iscalimab in kidney transplant patients had been abandoned. The company is pushing on in a number of other settings, however, alongside a list of other developers keeping the faith with this mechanism.

CD40 is thought to be involved in chronic immune activation, and the interaction of CD40 and its ligand – CD40L or CD154 – can trigger the overstimulation of immune cells, leading to immune response cascades and inflammation. CD40 expression is known to be elevated in diseases like ulcerative colitis, rheumatoid arthritis and systemic lupus erythematosus (SLE).

Thus researchers have been working on ways to block or interrupt this pathway, largely with monoclonal antibodies, although other technologies have emerged more recently. For example, the Japanese company Napajen last year reported encouraging early results with an oligonucleotide, NJA-730a, although a promised move into phase 2 has yet to be confirmed.

Agonists of CD40 are being explored in oncology, an area not considered here.

Anti-CD40 & anti-CD40L projects in recent development			
Project	**Company**	**Description**	**Trial details**
Phase 3			
Dapirolizumab pegol	UCB/Biogen	Anti-CD40L pegylated FAb	Phoenycs Go in SLE, first data due H1 2024
Phase 2			
Iscalimab (CFZ533)	Novartis/Xoma	Anti-CD40 MAb	Cirrus-1 in kidney transplant discontinued; see table below for other studies
ABBV-323 (ravagalimab)	Abbvie	Anti-CD40 MAb	Possibly abandoned in ulcerative colitis; presumed abandoned in Sjögren's syndrome
Bleselumab	Astellas Pharma	Anti-CD40 MAb	Abandoned this year after trials in transplant rejection and psoriasis
HZN-4920 (VIB4920 or dazodalibep)	Horizon	Anti-CD40L-Tn3 fusion protein	Acquired with Viela. Trials ongoing in Sjögren's Syndrome, ph2b; kidney transplant rejection, ph2; RA, ph2
BI 655064	Boehringer Ingelheim (Abbvie had option)	Anti-CD40 MAb	Presumed recently abandoned; two SLE trials recently completed
SAR441344	Sanofi (from Immunext)	Anti-CD40L MAb	Ph2 ongoing in Sjögren's Syndrome and MS
AT-1501	Eledon Pharmaceuticals	Anti-CD40L MAb	Ph2 islet cell transplantation; ph2 ALS; ph1/2 in kidney transplant due to start
BMS-986004 (letolizumab)	Bristol Myers Squibb	Anti-CD40L MAb	Only ongoing trial is academic sponsored, GvHD
Phase 1			
NJA-730a	Napajen Pharma	Anti-CD40-oligonucleotide (conjugated with beta-glucan delivery technology)	Company plans to start ph2 GvHD trial in 2021 after positive ph1 results
KPL-404	Kiniksa Pharmaceuticals	Anti-CD40 MAb	Ph1 in healthy adults completed; RA study to start imminently
Source: Evaluate Pharma, company statements.			

This field of research is not new: Biogen abandoned two antibodies – ruplizumab (BG9588) and Idec-131 – around 20 years ago after a thrombosis signal was seen in SLE and Crohn's disease. In the past couple of decades Bristol Myers Squibb has also scrapped a couple of projects, BMS-224819 and more recently BMS-986090.

And those terminations are still coming. Astellas confirmed earlier this year that bleselumab had been canned, while an asset that Boehringer highlighted at an R&D day a couple of years ago has also presumably been abandoned, as it no longer features in the company's pipeline.

Thrombosis is a major concern for this mechanism, and it was speculated that lack of such a signal persuaded UCB and Biogen to push on with dapirolizumab, despite that project failing to hit the primary endpoint of a phase 2 SLE trial. Lupus is a notoriously tough setting, of course, and decent tolerability and evidence of control of disease activity presumably provided enough encouragement.

Pushing on

Dapirolizumab is now the most advanced CD40-targeted agent in the clinic although results from the phase 3 SLE trial, Phoenycs Go, are some way off. The history of this asset and partnership provide a neat illustration of just how long it has taken CD40 research to progress. Back in 2004, Biogen initially struck a deal to explore

CD40L projects with Celltech, a company subsequently acquired by UCB. Dapirolizumab first went into the clinic in 2010.

This long history is not deterring all work, however. Horizon is a new arrival, thanks to the acquisition of Viela this year. Dazodalibep, or HZN-4920, is a fusion protein that binds CD40L, and is in three phase 2 trials, with Sjögren's syndrome the largest at 174 enrolees being sought; results are due next year.

Active mid-stage projects includes Sanofi's SAR441344, which was licensed from Immunext back in 2017 but has recently been pushed into a proof-of-concept multiple sclerosis trial. Immunext claims the antibody was engineered to avoid thromboembolic concerns; data should emerge next year in the lead Sjögren's setting.

Eledon Pharmaceuticals, meanwhile, was forged last year from the failed company Novus Therapeutics and the private group Anelixis, which was focused purely on CD40 ligand biology. Its lead asset, AT-1501, is poised to begin a kidney transplant trial in Canada before the end of the year; the company is also investigating ALS, islet cell transplantation and IgA nephropathy.

Kiniksa has eyes on a bigger prize with KPL-404, an antibody described as an inhibitor of CD40-CD40L interaction. The company plans to start a phase 2 proof of concept trial in RA in the fourth quarter; phase 1 data in healthy volunteers were released earlier this year.

And Novartis still has skin in the CD40 game, the table below shows. As with many other developers, a major focus is Sjögren's, an autoimmune condition that affects parts of the body that produce fluids. But, unless a viable project emerges from the clutch of compounds currently in the clinic, it will become harder to justify ongoing efforts against this target.

Novartis's iscalimab programme		
Condition	**Status (primary completion)**	**Trial ID**
Sjögren's syndrome (ph2)	Recruiting (Mar 2022)	NCT03905525
Sjögren's syndrome (ph2)	Recruiting (Feb 2024)	NCT04541589
Liver transplant rejection (ph2)	Recruiting (Jul 2022)	NCT03781414
Lupus nephritis (ph2)	Recruiting (Sep 2022)	NCT03610516
Hidradenitis suppurativa (ph2)	Recruiting (Sep 2022)	NCT03827798
SLE (ph2)	Recruiting (Oct 2024)	NCT03656562
Type 1 diabetes (ph2)	Recruiting (Jun 2027)	NCT04129528
Kidney transplant rejection (ph2)	Terminated Sep 2021	NCT03663335
Kidney transplantation (ph1/2)	Completed	NCT02217410
Rheumatoid arthritis (ph1)	Completed	NCT02089087
Primary Sjögren's syndrome (ph2)	Completed	NCT02291029
Myasthenia gravis, generalised (ph2)	Completed	NCT02565576
Graves' disease (ph2)	Completed	NCT02713256
Source: clinicaltrials.gov.		

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