BIOBUSINESS BRIEFS

TARGET WATCH

Novel drug targets in 2021

In 2021, regulatory agencies in the United States, European Union and Japan licensed 59 novel drugs in total, of which 50 have well-established mechanism-of-action (MoA) targets for their approved indication (*Nat. Rev. Drug Discov.* **16**, 19–34; 2017). Continuing the annual series, here we briefly summarize the 14 novel MoA targets (TABLE 1) — that is, the targets that had not previously been modulated by an approved drug — based on analysis of the drug labels and primary literature on the new drugs.

Six targets are blocked by monoclonal antibodies (mAbs). The first target in TABLE 1 is the Spike protein of SARS-CoV-2, for which multiple mAbs have been developed for the treatment and prevention of COVID-19. Other targets include three cytokines involved in inflammatory diseases (TSLP, IL-17F and IL-13), a cytokine involved in dyslipidaemia (ANGPTL3), and the neonatal Fc receptor, which is targeted by efgartigimod alfa to reduce circulating immunoglobulin G.

Three targets are inhibited by small molecules. One is another viral target: the cytomegalovirus kinase UL97. The other two are the anticancer drug targets KRAS, a GTPase that for many years was considered 'undruggable', and the transcription factor HIF2α. The antibody–drug conjugate tisotumab vedotin, which targets tissue factor on tumour cell surfaces to deliver a microtubule inhibitor, was also approved for a cancer indication.

Two of the drugs are replacement therapies for rare diseases. Pabinafusp alfa harnesses transferrin receptor protein 1 to deliver the enzyme iduronate-2-sulfatase across the blood–brain barrier to treat Hunter syndrome, while fosdenopterin is a cyclic pyranopterin monophosphate that activates molybdenum cofactor biosynthesis to treat molybdenum cofactor deficiency type A.

Two peptidic drugs were also approved for rare diseases. Vosoritide is a positive regulator of natriuretic peptide receptor 2 that results in endochondral bone growth and received approval for achrondroplasia. Pegcetacoplan is a cyclic peptide inhibitor of complement protein C3 conjugated to polyethylene glycol, which was approved for the treatment of paroxysmal nocturnal haemoglobinuria.

Overall, from a therapeutic standpoint, 9 of the 14 novel targets (64%) are for drugs that treat rare diseases of various types.

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Competing interests

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Table 1 | **Drugs with novel mechanism of action targets approved in 2021**

Drug	Properties	Mechanism of action target (gene name)	Target class	Indication	Agency
Regdanvimab[a], sotrovimab, casirivimab, imdevimab	mAb	SARS-CoV-2 Spike protein (S)[b]	Viral protein	COVID-19	EMA, PMDA
Evinacumab[c]	mAb	Angiopoietin-related protein 3 (*ANGPTL3*)	Cytokine	Homozygous familial hypercholesterolaemia	FDA, EMA
Tezepelumab	mAb	Thymic stromal lymphopoietin (*TSLP*)	Cytokine	Severe asthma	FDA
Bimekizumab	mAb	Interleukin-17F (*IL17F*)	Cytokine	Psoriasis	EMA
Tralokinumab	mAb	Interleukin-13 (*IL13*)	Cytokine	Atopic dermatitis	FDA, EMA
Efgartigimod alfa[c]	mAb	Neonatal Fc receptor (*FCGRT*)	Transcytosis receptor	Myasthenia gravis	FDA
Maribavir[c]	Small-molecule inhibitor	CMV serine/threonine protein kinase UL97 (*UL97*)	Enzyme	Post-transplant CMV infection/disease	FDA
Sotorasib[c]	Small-molecule inhibitor	GTPase KRas (*KRAS*)	Enzyme	Non-small-cell lung cancer	FDA, EMA
Belzutifan[c]	Small-molecule inhibitor	Hypoxia-inducible factor 2 alpha (*HIF2α*)	Transcription factor	von Hippel–Lindau disease	FDA
Tisotumab vedotin	ADC	Tissue factor (*TF*)	Tumour-associated antigen	Cervical cancer	FDA
Pabinafusp alfa[c]	Fusion protein	Transferrin receptor protein 1 (*TFRC*)	Transcytosis receptor	Hunter syndrome	PMDA
Fosdenopterin[c]	Synthetic substrate	Molybdenum cofactor biosynthesis protein 1 (*MOCS1*)	Enzyme	Molybdenum cofactor deficiency type A	FDA
Vosoritide[c]	Peptide	Natriuretic peptide receptor 2 (*NPR2*)	Enzyme	Achondroplasia	FDA, EMA
Pegcetacoplan[c]	Peptide	Complement C3 (*C3*)	Macroglobulin	PNH	FDA, EMA

ADC, antibody–drug conjugate; EMA, European Medicines Agency; CMV, cytomegalovirus; FDA, Food and Drug Administration; mAb, monoclonal antibody; PMDA, Japanese Pharmaceutical and Medical Devices Agency; PNH, paroxysmal nocturnal haemoglobinuria. [a]Not approved by PMDA. [b]Only mAbs that have received full regulatory approval are shown; further mAbs have been granted emergency use authorizations. [c]Orphan drugs.