www.mednous.com

Vol 15, No 3 March 2021

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Editorial

Executive Editor: William Ellington

Editor: Victoria English

Science Editor: Peter Charlish

Associate Editors: Jane Morrison, Rosie Bannister

Contributing Editors: Bruno Pagliara, Tim Farries, Karen Finn

Market Research: Janet Barrie

Production Editor and Art Director: Melissa Sterry

Website Designer: Keith Jay

Publisher: Evernow Publishing Ltd
Registered in England & Wales under the number: 6019186. Registered office: 264 Banbury Road, Oxford, OX2 7DY, UK. VAT registration number: 912 7394 21

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An annual subscription, which includes unlimited access to the website and 10 issues per year of the print publication is:

- Company/Organisation rate of £299 or €360 or $469
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Evernow Publishing Ltd, PO Box 26 BPost Bruxelles Livingstone, Rue Stevin 41-43, 1000 Brussels, Belgium

Tel: +44 (0)20 7704 1015
+32 (0)27 332 889
Email: editor@evernow.eu

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  Quarter page; £100
  Half page; £200
  Full page; £400
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Printer: *MedNous* is printed by Bookbinders of London Ltd, 33-37 Chambers Street, Hertford, Hertfordshire, SG14 1PL, United Kingdom

ISSN 1757-9937 (Print)

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MedNous Editorial Board

Letter from the Editor

One agent, two targets

When Eli Lilly and Co announced in January that it had signed a licensing deal with Merus NV of the Netherlands to research and develop up to three bispecific antibodies for cancer, *MedNous* decided to take another look. As products, bispecifics are not new, but they are also not common. What could be attracting the interest of this US pharma company to the sector?

Under the deal, Lilly has agreed to pay Merus $40 million upfront as well as milestone payments of up to $540 million per project, bringing the potential milestones up to $1.6 billion. The projects will all focus on the development of bispecific molecules that redirect T cells to a cancer as a way of killing cancer cells.

Bispecific antibodies are antibodies that bind to two different types of antigen at the same time. Two bispecifics have been approved by a regulator to treat cancer, and one has been approved for haemophilia. One of the cancer drugs was withdrawn from the market by its developer for commercial reasons. This leaves the other, blinatumomab, as the cancer representative. Blinatumomab was developed by the German company Micromet and is currently marketed to treat four types of leukaemia. Micromet, in the meantime, has become part of Amgen Inc.

Blinatumomab is effective, but it has limitations. One of these is a short half-life which means that it has to be administered to patients by continuous infusion. In a bid to improve on the concept and to expand the uses of the drug, pharma companies have been investigating follow-on products. These include products for haematologic malignancies as well as for solid tumours. There are now about 100 projects in clinical development, many of them originated by small biotech companies. As illustrated by the deal between Lilly and Merus, however, a number of large pharma companies have also entered the fray.

In an article starting on page 6, we interview three companies active in the bispecific antibody space: Merus, Genmab A/S of Denmark and NovalGen Ltd of the UK. Courtesy of our contributing editor, Bruno Pagliara, we also provide a table with a representative sample of products in clinical development. This table shows that there are several products in Phase 3 and one product, developed by Johnson & Johnson, that has been submitted for review to the Food and Drug Administration. Our interviewees argue that the next few years will see a significant expansion in the use of these therapies.

Elsewhere in this issue, Gabriele Campi explains why RNA therapeutics are attracting more interest from investors. Dr Campi is managing partner of AurorA Science in Milan which recently led a Series B financing round for the Dutch company InteRNA Technologies. Also, Peter Charlish reviews antivirals and antibody therapies in development against Covid-19 and Paula Salmikangas and Björn Carlsson write about the challenges of developing gene therapies.

– By Victoria English, 17 March 2021

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European Licensing and Collaboration Briefs

	Licensor/Vendor		Licensee/Acquirer	Product/Company	Comment	Date
DE	Evotec SE	US	Chinook Therapeutics Inc	Precision medicines for chronic kidney diseases	Undisclosed F + A + M + R	Mar-21
BE	Complix NV	CN	I-Mab Biopharma	Protein therapeutics against two intracellular targets	Jointly manage clinical work	Mar-21
CH	Debiopharm International SA	DE	Merck KGaA	Rights to xevinapant for head and neck cancer	Global commercialisation rights, including US	Mar-21
AU	Kazia Therapeutics Ltd	SE	Oasmia Pharmaceutical AB	Rights to Cantrixil for ovarian cancer	F=$4m + M=up to $42m + R	Mar-21
BE	eTheRNA immunotherapies NV	UK	ConserV Bioscience Ltd	Develop mRNA vaccines for infectious diseases	Initial focus will be on HIV	Mar-21
UK	Autifony Therapeutics Ltd	DE	Boehringer Ingelheim GmbH	Investigate ion channel target linked to lysosomal dysfunction	Undisclosed A + M	Mar-21
IE	Perrigo Company Plc	US	Altaris Capital Partners LLC	Sale of Generic Rx Pharmaceuticals business	Deal value is $1.55b	Mar-21
FR	Iktos SAS	US	Pfizer Inc	Use AI for small molecule drug discovery programmes	Financial terms not disclosed	Mar-21
SE	Beactica Therapeutics AB	KR	Oscotec Inc	Cancer drugs targeting lysine-specific demethylase 1	Equity + F + M=up to €149m + R	Mar-21
UK	Oxford Genetics Ltd	CN	WuXi AppTec	Acquisition of CRO with gene therapy technologies	Focus on viral vector manufacture	Mar-21
US	Pandion Therapeutics Inc	US	Merck & Co Inc	Acquisition of company with candidate drugs for autoimmune diseases	Deal value is $1.85b	Feb-21
US	Microsoft Corporation	BE	UCB SA	Use AI to discover new drugs	Financial terms not disclosed	Feb-21
CH	Novartis	US	Bill & Melinda Gates Foundation	Develop *in vivo* gene therapy for sickle cell disease	Grant funding from Gates Foundation	Feb-21
US	Nektar Therapeutics Inc	US	SFJ Pharmaceuticals Inc	Finance and co-develop bempegaldesleukin in cancer	F=up to $150m to support Phase 2/3 study	Feb-21
FR	Cellectis SA	US	Cytovia Therapeutics Inc	Develop gene-edited iPSC-derived natural killer cells	F or equity=$15m + M=up to $760m + R	Feb-21
FR	Institut Pasteur	FR	Sensorion SA	Gene therapy collaboration targeting hearing loss	To investigate GJB2 mutations	Feb-21
UK	Cambridge Quantum Computing	US	Crown Bioscience Inc	Quantum computing for cancer biomarker discovery	JSR Life Sciences is also partner	Feb-21
US	Audax Private Equity	DK	Novo Holdings A/S	Acquisition of Altasciences contract research company	Financial terms not disclosed	Feb-21
UK	Silence Therapeutics Plc	IE	Mallinckrodt Plc	Work on third target in ongoing RNAi collaboration	M=$2m following start of work	Feb-21
US	Illumina Inc	DE	University Hospital Tübingen	Whole genome sequencing for genetic diseases	Investigate polygenic risk score	Feb-21
UK	Exscientia Ltd	UK	Alzheimer's Research UK	Treatments for Alzheimer's disease	NLRP3 inflammasome inhibition	Feb-21
DE	Evotec SE	US	Related Sciences	Joint drug discovery, development for range of therapies	Fees linked to success of assets	Feb-21
NL	Erasmus Medical Center	NL	Pan Cancer T BV	Spin-out to develop T cell receptor T cell therapies	Undisclosed seed funding	Feb-21
US	Vir Biotechnology Inc	UK	GlaxoSmithKline Plc	Therapies for influenza and other respiratory viruses	F=$225m + equity of $120m	Feb-21
UK	GlaxoSmithKline Plc	CH	Sandoz (Novartis)	Acquisition of cephalosporin antibiotics business	Deal value is up to $500m	Feb-21
CH	Debiopharm International SA	KR	Genome & Company	Antibody-drug conjugates for cancer	Financial terms not disclosed	Feb-21
SE	Medivir AB	UK	Ubiquigent Ltd	Rights to ubiquitin specific peptidase 7 programme	Revenue share for any products	Feb-21

(F) front-end fee (M) milestone payments (A) research funding (L) licensing fees (R) royalties on net sales (E) equity investment US

RNA Modulation: Gabriele Campi

Why we should take a second look at RNA technology

As a scientist first, but also as an investor, I have always believed in the potential of RNA molecules as therapeutics. While most current drugs aim to stop disease by modulating existing proteins, RNA molecules operate one step earlier. In the case of RNA interference (RNAi), they modulate the genes involved in different pathological processes. The RNA molecules, small interfering RNA and microRNA, both degrade messenger RNA (mRNA) and prevent it from being translated into proteins.

I am the co-founder of the investment company AurorA Science, which recently led a Series B financing round for the Dutch company InteRNA Technologies, which is developing RNA therapeutics for the treatment of advanced solid tumours. This is an ambitious project, but with a potential for success. This is because the RNA therapy sector, which started with great momentum and slipped into disfavour, is now back with new technology and confident leadership.

Most observers credit the US scientists Craig Mello and Andrew Fire for inspiring the wave of RNA therapeutics research that started at the turn of the last millennium. Messrs Mellow and Fire received the Nobel Prize in Physiology or Medicine in 2006 for describing the role played by double-stranded RNA in silencing genes that code for the production of disease-causing proteins. At the time of the award, a number of small companies were already starting to exploit the RNAi technology, including Sirna Therapeutics.

In 2007, Merck & Co bought Sirna for $1.1 billion in cash. At the time, Merck had an ongoing partnership with Alnylam Pharmaceuticals, a university spin-out with a patent position in RNAi. That same year, Roche reached a deal with Alnylam, paying $331 million upfront for access to its RNAi technology.

But what looked like a new wave of therapeutics ran into difficulties after a number of early clinical programmes were halted by the Food and Drug Administration following adverse events. Developers were seeing off-target effects from the therapies including unexpected innate immune responses and most importantly, problems with delivery of the drugs into the cytoplasm of target cells.

With doubts raised about the drugs' safety and delivery, Roche and Merck started to cut their exposure. Roche was first, with a decision to discontinue RNAi research and early development in 2010. A year later, it sold its RNAi assets to Arrowhead Research Corp. In 2014, Merck sold Sirna to Alnylam for $175 million in cash and equity, plus milestone commitments of up to $105 million per product – roughly 25% of the price it had paid for Sirna in 2007.

Alnylam may have looked like a winner at the time, but it too encountered a setback. In 2016 it discontinued development of revusiran, a siRNA therapeutic for hereditary ATTR amyloidosis with cardiomyopathy, for safety reasons. A review of a Phase 3 study found that more patients died in the treatment arm of the study than those who were on placebo. However, the decision to discontinue revusiran didn't affect another late-stage molecule – patisiran.

Patisiran is also a siRNA but for a different disease: hereditary ATTR amyloidosis with polyneuropathy, an autosomal dominant neurodegenerative disease. In 2018 patisiran (Onpattro) was approved by the FDA. It is delivered to cells by lipid nanoparticles rather than GalNAc (N-Acetylgalactoseamine-siRNA conjugates).

Since the end of 2018, investors have made a cautious return to the RNA therapy space with a targeted funding of existing RNA companies. In parallel, new companies are entering the arena. An unexpected boost to the industry has come from the development and approval of the first mRNA vaccines to treat Covid-19 from Pfizer/BioNTech and Moderna.

I have always believed in the potency of RNA interference and modulation techniques that allow a researcher to target specific messenger RNAs through the use of siRNAs, or multiple targets, with microRNAs. Like every powerful technology however, it needs to be fine-tuned and well controlled. Transcriptomic experiments are crucial, not only to certify the direct effect of the molecule on the target(s), but also to detail what downstream modulation the intervention can exert, in addition to shedding light on potential safety issues and off-target delivery. InteRNA Technologies' lead compound, INT-1B3, which is in clinical development, exploits potential anti-tumoural activity in a miRNA-based fashion. The company intends to revert the reduction of miRNA-193a-3p observed in tumour cells using a miRNA-193a-3p mimic integrated into lipid nanoparticles.

The convincing feature of INT-1B3 stands in its dual mechanism of action that addresses multiple hallmarks of cancer simultaneously. First, it directly targets tumour cells and the tumour microenvironment by modulating multiple signaling pathway components across the PTEN tumour suppressor pathway and the oncogenic PI3K/Akt and Ras/MAPK pathways, resulting in the inhibition of proliferation and migration and induction of cell cycle arrest and apoptosis.

Second, it triggers the immunogenic tumour cell death process as well as the down-regulation of the adenosine-A2A receptor pathway through inhibition of CD39/CD73, leading to a decrease in immunosuppressive FoxP3/Lag3 regulatory T cells and monocytic myeloid-derived suppressor cells. As a result, the immune system is activated, and long-term immunity is triggered by the recruitment of CD8+ effector T cells, leading to decreased metastasis development and improved animal survival.

At AurorA Science we tend to focus on science, working to build a portfolio solidly based on innovative therapies. Our technical committee of scientists from Italfarmaco and Rottapharm Biotech enables us to conduct in-depth scientific due diligence, while our board of directors with Guido Guidi as chairman, and the entrepreneurs Lucio Rovati and Francesco De Santis as members, gives us a structured direction.

This article was written by Gabriele Campi, PhD, co-founder and managing partner of AurorA Science of Milan, Italy.

Bispecific antibody development gains momentum

As a concept, the bispecific antibody has been the object of scientific research for decades, but only recently has the clinical pipeline started to fill up. Cancer is the area of greatest activity. Here, the pipeline consists of several candidate products in Phase 3 and one, a product developed by the Janssen Pharmaceutical Companies of Johnson & Johnson Inc, that is in registration for non-small cell lung cancer at the US Food and Drug Administration.

Developers of bispecific molecules say that the FDA approval of blinatumomab (Blincyto) in 2014 was a threshold event for the sector. This is because it showed that an antibody construct could engage the immune system by creating a link between T cells and cancer cells. Blinatumomab came of age just as the entire field was opening up to immunological approaches to cancer with regulatory approvals for checkpoint inhibitors and reports of striking efficacy data for the new chimeric antigen receptor T cell therapies.

As illustrated in the table on pages 8 and 9, a large number of the bispecific antibodies in clinical development are T cell engagers, following the blinatumomab model. They target a T cell receptor in addition to a number of tumour-associated antigens including CD20 and CD33 on haematological malignancies and the prostate-specific membrane antigen in prostate cancer. Among the bispecific antibodies that do not re-direct T cells, there are compounds that target other antigen pairs, in some cases with the intention of influencing an immune pathway. While many of the new molecules are being pioneered by small biotech companies, a growing number of large pharma companies are investing in the field either on their own, or in partnerships with the smaller companies. The table is a representative sample of the nearly 100 compounds in clinical development.

In this article we interview executives from three companies active in the field, two of which are listed on the Nasdaq market in the US and one that is a recent start-up. The two listed companies, Merus NV and Genmab A/S, have substantial portfolios. The start-up, NovalGen Ltd, is due to bring its first product into clinical studies in the first half of this year.

The view from Merus

Merus is a Dutch biotech with a long-standing interest in bispecific antibodies. It originated in the Netherlands, but now has a management presence in the US. In 2013, the company led a European Union consortium investigating bispecifics for cancer, specifically looking at the role of the Wnt signalling pathway in promoting tumour growth. In the years that followed its portfolio grew and in 2016, Merus signed a licensing deal with Incyte Corp giving the US company rights for up to 11 bispecific antibody research programmes, in exchange for cash and an equity investment.

In January of this year, Merus announced a research collaboration and licensing deal with Eli Lilly and Co for up to three CD3 T cell engager therapies in cancer indications. If all three compounds are developed and commercialised, Merus would be due $1.6 billion in milestone payments. This is in addition to an upfront payment and an equity investment from Lilly.

In an interview, Bill Lundberg, Merus' chief executive, said it was the company's ability to screen through thousands of potential antibodies against a T cell component that made the technology so attractive to Lilly. This is possible because the company's platform uses the IgG format as a starting point. "I think the field is coming to appreciate the importance of the fully human format and the ability to evaluate many of these characteristics before you have to decide which one you take into the clinic," he said.

"In essence, we have a freezer full of more than 10,000 different antibodies and we use robotics and automation to do the molecular biology to clone them into the bispecific format," he added. These are then evaluated in assays for their ability to block or to bind or to change cellular behaviour. "We can tease apart all of these different characteristics across a large panel of characteristics," the executive said.

Merus' lead proprietary product, zenocutuzumab, is a bispecific designed to bind to the HER2 and HER3 receptors on cancer cells to block the interaction of HER3 with its ligand, neuregulin 1 (NRG1). The molecule is being studied in pancreatic, lung and a number of other solid tumours. "With our lead molecule Zeno we use the left arm to grab onto the cancer cell with the commonly-expressed antigen HER2, and we use the right arm to grab onto the cancer signalling mechanism and block that. In a population of molecularly-defined cancer cells that signal through the HER3 antigen by virtue of having this NRG1 fusion, we can potentially disrupt the NRG1 fusion pathway," the executive said. This is a 'dock and block mechanism' where one arm of the antibody anchors onto the cancer cells and the other blocks a cancer pathway.

In a project partnered with Betta Pharmaceuticals Co of China, Merus is taking the 'dock and block' strategy one step further. This is to first block the signalling of the EGFR and cMet antigens in order to inhibit tumour growth and survival. Second, it uses an antibody-dependent cellular cytotoxicity mechanism to increase the cancer cell killing potential of the molecule.

Merus' collaboration with Incyte has also produced an early-clinical stage product. This is a bispecific directed against solid tumours that engages PD-L1 on tumour cells and the T cell co-stimulatory molecule CD137. The concept is to activate immune effector cells in the tumour microenvironment while simultaneously blocking PD-L1 in the same immune cell population.

The view from Genmab

Genmab is an established European biotech with a history of successful partnerships. It was founded in 1999 as a spin-out from Medarex with IP for monoclonal antibody development. Through a 2012 licensing deal with Janssen Biotech, Inc for daratumumab, a monoclonal antibody therapy for multiple myeloma, Genmab saw its technology reach the market. It has been receiving substantial royalty income ever since. The

company now has four technology platforms, one of which is called DuoBody for bispecific antibodies.

On 1 March, Tahamtan Ahmadi, previously head of oncology, took over the new position of chief medical officer, head of experimental medicines. Before joining Genmab, Dr Ahmadi was head of experimental medicine at Janssen, where he led the development of daratumumab. In an interview, he discussed some of the programmes in the current Genmab portfolio.

Genmab's lead programme is epcoritamab, a bispecific antibody that targets CD20 on malignant B cells and CD3 on the surface of T cells. The dual targeting redirects a patient's T cells to engage and eliminate the malignant B cells, a mechanism of action pioneered by the developers of blinatumomab. "I think we will see in the near future the true potential of T cell (re)direction through bispecifics. I think that we are just at the very beginning of an era frankly," Dr Ahmadi said.

Epcoritamab is currently in Phase 3 development for diffuse large B cell lymphoma (DLBCL) under a partnership with AbbVie Inc. The molecule is generated from two conventional IgG antibodies in a process called 'controlled Fab-arm exchange.' This allows the binding arms of two distinct antibodies to be exchanged while still keeping the natural immunoglobulin structure and functions. "The Genmab point of view is that if you stay as close as possible to human biology and if you have a discovery process that allows you to interrogate as many epitope combinations as possible, then you are probably in a very iterative process…. and can get to the best possible construct," Dr Ahmadi said.

Epcoritamab is one of three bispecific projects that Genmab is undertaking with AbbVie under a collaboration that was announced in June 2020. The agreement involved an upfront payment of $750 million with total potential milestone payments of up to $3.15 billion. The two other projects are in Phase 1, one of which is a CD37 directed bispecific for haematologic malignancies, and the other is a bispecific targeting CD3 and the tumour antigen 5T4 for the treatment of solid tumours.

In addition to the new collaboration with AbbVie, Genmab has licensing deals with Janssen for multiple bispecific projects, the most advanced of which, amivantamab, has been submitted for a regulatory review in the US. Amivantamab targets tumours with EGFR and Met mutations for patients with non-small cell lung cancer. "This is something that is only just emerging, which is the idea of using [bispecifics] to target mechanisms of resistance and signal pathways," the executive said.

Also in the solid tumour space, Genmab has two early clinical projects underway with BioNTech SE to investigate ways of activating the immune system without generating toxicity. One combines a checkpoint blockade with the conditional stimulation of T cells. "Both programmes are trying to use bispecifics to address very complex biology in the immuno-oncology space," Dr Ahmadi said.

The view from NovalGen

NovalGen Ltd is a privately-held company launched in 2019 on the basis of new technology from University College London (UCL). The company's founder Amit Nathwani is a UCL professor, clinician, and serial entrepreneur. He previously founded and led the gene therapy company Freeline Therapeutics, now a Nasdaq listed company, where he remains a member of the board of directors. NovalGen received Series A funding from Convergys Capital, the UCL Technology Fund and UCL Business.

In an interview, Prof Nathwani said the reason for founding NovalGen was in large part due to his more than 20 years of experience treating patients with chronic lymphocytic leukaemia (CLL). "What is frustrating about this leukaemia is that even though it is the most common leukaemia in adults, the treatment opportunities, particularly when we think about curative therapies, really do not exist for this population," he said.

The bispecific approach attracted him because of the opportunity it provided to target two different antigens and therefore disrupt multiple pathways. "This is a necessity when you're targeting complex disorders like cancer or even when you get into other conditions such as inflammation," he said.

NovalGen has embraced the synthetic route to bispecific antibody development for which there is a growing number of proponents. The company's molecules are composed of two antibody-derived single chain variable fragments (scFv) linked in tandem, but with no Fc region. "In essence, they are different from antibodies in that they are synthesised essentially as a single peptide that falls on itself to form this bispecific format *in vivo*," the executive said. This means the molecules can be produced in a variety of formats depending on the disease.

NovalGen's lead product, NVG-111, follows in the footsteps of blinatumomab as a synthetic T cell engager but with a much broader mandate. The molecule is starting clinical development in patients with CLL and mantle cell lymphoma in the first half of this year, but there are plans to investigate it in solid tumours as well. "We're confident that we can move from haematological malignancies, which is where we're starting our programme, to solid tumours in a seamless fashion without having to further engineer or modify our lead compound NVG-111 in any way whatsoever," Prof Nathwani commented.

The reason for the confidence is the molecule's target. NVG-111 is directed against ROR1, a member of the receptor tyrosine kinase family. ROR1 is a cell surface antigen that is present on a range of malignancies and cancer initiating stem cells but is absent or expressed at low levels in healthy adult tissues.

NVG-111 has two modes of action: as a T cell engager, it brings T cells into proximity with cancer targets. And it also blocks a signalling pathway, the interaction between Wnt5 and ROR1, to limit tumour proliferation. "The fact is, it is the only T cell engager with a dual mode of action," Prof Nathwani said. Just over the horizon, but not yet built into the lead product, are biological sensors that would enable the company's bispecific molecules to turn on and off in response to cues from the environment.

This article was written by the *MedNous* editor on the basis of a literature search and interviews and data provided by the *MedNous* contributing editor Bruno Pagliara.

Bispecific antibodies in clinical development, March 2021				
Drug name	**Sponsor**	**Target**	**Phase**	**Indication**
Amivantamab	Johnson & Johnson Inc	EGFR/cMet	BLA filed in US	NSCLC
AFM-13	Affimed NV	CD30/CD16	2 pivotal	PTCL-CD30+
Glofitamab	Roche	CD20/CD3	3	NHL
KN046	Alphamab Oncology	PD-L1/CTLA-4	3	NSCLC
Flotetuzumab	MacroGenics Inc	CD123/CD3	2 pivotal	AML
Tebentafusp	Immunocore Ltd	gp100/CD3	3	Uveal Melanoma
Epcoritamab	AbbVie/Genmab	CD20/CD3	3	DLBCL
Mosunetuzumab	Roche	CD20/CD3	3	foll NHL
Teclistamab	Johnson & Johnson Inc	BCMA/CD3	2 pivotal	M. Myeloma
REGN5458	Regeneron/Sanofi	BCMA/CD3	2 pivotal	M. Myeloma
Elranatamab	Pfizer Inc	BCMA/CD3	2 pivotal	M. Myeloma
MP0250	Molecular Partners	VEGF/HGF	2	M. Myeloma
Zenocutuzumab	Merus NV	HER2/HER3	2	Breast
MEDI5752	AstraZeneca Plc	PD-1/CTLA-4	2	Kidney
BI 836880	Boehringer Ingelheim	VEGF/ANG2	2	Anal
NVG-111	NovalGen Ltd	ROR1/CD3	1	CLL + Mantle Cell Lymphoma
Navicixizumab	Oncxerna Therapeutics	DLL4/VEGF	1	Ovary
Cibisatamab	Roche	CEA/CD3	1	Solid tumours
AMG 330	Amgen Inc	CD33/CD3	1	AML
Cevostamab	Roche	FcRH5/CD3	1	M. Myeloma
AMG 596	Amgen Inc	EGFRviii/CD3	1	Glioblastoma
AMG 757	Amgen Inc	DLL3/CD3	1	SCLC
Tidutamab	Xencor Inc	SSTR2/CD3	1	Neuroendocrine
FS118	F-star Therapeutics	LAG3/PD-L1	1	Solid tumours
RG6194	Roche	HER2/CD3	1	Breast
GEM333	GEMoaB/BMS	CD33/CD3	1	AML
AMG 427	Amgen Inc	FLT3/CD3	1	AML
REGN4018	Regeneron/Sanofi	MUC16/CD3	1	Ovary
EMB-01	EpimAb Biotherapeutics	EGFR/cMET	1	Solid tumours
XmAb23104	Xencor Inc	PD-1/ICOS	1	Solid tumours
ATOR-1015	Alligator Bioscience	CTLA-4/OX40	1	Solid tumours

MCLA-145	Merus NV	PD-L1/CD137	1	Solid tumours
TG-1801	TG Therapeutics Inc	CD47/CD19	1	Lymphomas
XmAb22841	Xencor Inc	CTLA-4/LAG3	1	Solid tumours
AMG 160	Amgen Inc	PSMA/CD3	1	Prostate
Hu3F8-BsAb/nivatrotamab	Y-mAbs Therapeutics	G2/CD3	1	Neuroblastoma
GS-1423	Gilead Sciences Inc	CD73/TGFbeta	1	Solid tumours
HPN536	Harpoon Therapeutics	Mesothelin/CD3	1	Solid tumours
JNJ-67571244	Johnson & Johnson	CD33/CD3	1	AML/MDS
BNT-311	BioNTech/Genmab	PD-L1/CD137	1	Solid tumours
GEM3PSCA	GEMoaB/BMS	PSCA/CD3	1	Solid tumours
REGN5678	Regeneron	PSMA/CD28	1	Prostate
AK112	Akesobio	PD-1/VEGF	1	Solid tumours
HX009	Waterstone	PD-1/CD47	1	Solid tumours
AMG 199	Amgen Inc	MUC17/CD3	1	Gastric
BI 905711	Boehringer Ingelheim	TRAILR2/CDH17	1	Gastrointestinal
RG6139	Roche	PD-1/LAG3	1	Solid tumours
AFM24	Affimed NV	EGFR/CD16A	1	Solid tumours
IBI315	Innovent	PD-1 /HER2	1	HER2+ solid tumours
AMG 509	Amgen Inc	STEAP1/CD3	1	Prostate
PF-07062119	Pfizer Inc	GUCY2C/CD3	1	Gastrointestinal
FS120	F-star	CD137/OX40	1	Solid tumours
AMG 910	Amgen Inc	CLDN18.2/CD3	1	Gastrointestinal
ABBV-184	AbbVie Inc	Survivin/CD3	1	AML, NSCLC
SAR442257	Sanofi SA	CD38/CD28/CD3	1	M. Myeloma
Gen-1044	Genmab/AbbVie	5T4/CD3	1	Solid tumours
RG6296	Roche	BCMA/CD16a	1	M. Myeloma
CDX-527	Celldex Therapeutics	PD-L1/CD27	1	Solid tumours
JNJ-75348780	Johnson & Johnson	CD22/CD3	1	Hematologic malign.
RO7293583	Roche	TYRP1/CD3	1	Melanoma -TYRP1+
REGN5668	Regeneron	MUC16/CD28	1	Ovary
REGN7075	Regeneron	EGFR/CD28	1	Solid tumours
M1231	Merck KGaA	EGFR/Mucin 1	1	Solid tumours
TAK-186	Takeda	EGFR/CD3	1	Solid tumours

Covid-19: new treatments in the pipeline

In the battle against Covid-19, health authorities have been using three main strategies to defeat the virus: limiting exposure to the SARS-CoV-2 virus through public health measures; preventing infection with vaccines; and developing treatments based on new or repurposed drugs for people suffering from serious Covid-19 infection.

The combination of public health measures and the deployment of vaccines is starting to pay off. As experience in Israel and elsewhere is showing, Covid-19 vaccines are highly effective at preventing serious illness among individuals of all ages and, equally importantly, evidence is accumulating that the vaccines can prevent person-to-person transmission of the virus. However, there are still some unknowns with vaccines, such the duration of the immunity they induce.

So far, results of the third strategy, developing treatments for Covid-19, have been mixed. The aim of such treatments is twofold: to attack the infection itself with the use of antiviral agents and specific antibodies, and to ameliorate potentially lethal complications of the infection, such as lung inflammation and hyperimmunity. This article reviews the status of a variety of therapies in advanced clinical trials, starting with candidate antiviral agents and moving on to prospective antibody treatments, JAK inhibitors and immunomodulators. It does not, however, explore treatments designed to address so-called 'long Covid'.

One antiviral drug that has attracted a great deal of attention to date is Gilead Sciences' remdesivir (Veklury), which has been approved or authorised for temporary use as a Covid-19 treatment in approximately 50 countries worldwide. Remdesivir is a nucleotide analogue that displays broad-spectrum antiviral activity against a number of emerging viral pathogens, including *in vitro* activity against SARS-CoV-2.

In clinical trials to date the benefit of remdesivir has been modest. The product's US labelling cites three clinical studies. In the double-blind, placebo-controlled ACTT-1 trial, remdesivir appeared to shorten the median time to recovery among subjects with severe Covid-19, but not in those with mild to moderate Covid-19. In the second study, where the primary endpoint was clinical status on day 14, there was no difference between those receiving a five-day course of remdesivir and those receiving a ten-day course. In the third study, a five-day course appeared to increase the chance of improvement at day 14, but the difference was not seen with a ten-day course.[1]

In March 2020, the WHO began a large, international trial (the Solidarity trial) to evaluate the effects of remdesivir (and three other drugs) on in-hospital mortality. The results pointed to remdesivir having little or no effect, as indicated by overall mortality and other endpoints. This led in November 2020 to the WHO issuing a conditional recommendation against the use of remdesivir in hospitalised patients, regardless of disease severity.[2]

These findings notwithstanding, Gilead is carrying out two late-stage clinical trials of remdesivir. One is evaluating its efficacy against Covid-19 in an outpatient setting, while the other is assessing its efficacy in hospitalised Covid-19 patients aged under 18 years. Remdesivir is also one component of the ACTIV-3 study, sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), which is assessing the safety and effectiveness of various drugs in treating Covid-19 in people who have been hospitalised with the infection.

Another possible treatment for Covid-19 is favipiravir (Avigan), originally developed by Fujifilm Toyama Chemical Co Ltd (part of Fujifilm Corp) as an influenza antiviral drug. It was approved in Japan in 2014, for use only when there is an outbreak of novel or re-emerging influenza virus infections in which other antiviral drugs are insufficiently effective. It has never been distributed commercially either in Japan or elsewhere.

In March 2020, Fujifilm initiated a Phase 3 trial of Avigan for patients with Covid-19 in Japan, and a Phase 2 trial was begun in the US in April. The following September the company announced that Avigan had met its primary endpoint in the Japanese trial (time to elimination of detectable SARS-CoV 2 RNA and alleviation of symptoms), and it applied to the Japanese authorities to extend the product's indications to include Covid-19 infections. However, the health ministry postponed a decision on the grounds that the data submitted were insufficient to allow a determination of the drug's effectiveness. In February 2021 Nikkei Asia reported that Fujifilm is to restart clinical trials in April.[3]

In July 2020 Fujifilm partnered with Dr Reddy's Laboratories Ltd and Global Response Aid, a healthcare logistics company, to deploy Avigan outside Japan. Dr Reddy's is currently carrying out a Phase 3 evaluation in Kuwait, which will assess the efficacy of favipiravir as an adjunct to supportive care in patients with moderate to severe Covid-19. A similar Phase 3 study is underway in the UK. In addition, the Canadian company Appili Therapeutics has joined the Avigan global consortium and is carrying out a study in mild to moderate Covid-19 in adult outpatients in Florida. Two further Phase 3 trials of favipiravir are underway in the Russian Federation.

Other companies with a significant position in the antiviral space include Merck & Co Inc and Romark Laboratories LC. Merck's candidate is molnupiravir which, like favipiravir, can be administered orally (remdesivir must be given intravenously). It is being developed in collaboration with Ridgeback Biotherapeutics LP. Molnupiravir is currently the subject of two Phase 2/3 clinical trials, in both the hospital and out-patient settings. The company previously stated that it anticipates initial efficacy data in the first quarter of 2021.

Romark, based in Tampa, Florida, is conducting late stage clinical trials of its candidate NT-300 (nitazoxanide extended-release tablets). Nitazoxanide is an antiparasitic compound originally developed for treating cryptosporidiosis and giardiasis, and is marketed under the name Alinia for those indications. Laboratory studies demonstrated antiviral activity, which led to its development for treating and preventing viral respiratory illnesses caused by a wide range of viruses, including influenza viruses, rhinoviruses and SARS-CoV-2.

Romark is carrying out three pivotal Phase 3 trials of NT-300 in Covid-19, two for the prevention of Covid-19 and other viral respiratory illnesses in high-risk populations and the third as a treatment for mild or moderate Covid-19. The Argentine company Laboratorios Roemmers, a licensee of Romark, is also conducting a Phase 2/3 study of nitazoxanide in adult patients with mild Covid-19.[4]

Antiviral small-molecule drug candidates in advanced clinical trials against Covid-19 are shown in Table 1.

Table 1

Candidate	Originator	Mechanism
ABX464	Abivax*	Modulation of RNA splicing
DAS181	Ansun Biopharma	Removal of sialic acids from the lung surface so virus cannot bind
enisamium iodide	Farmak	Inhibition of viral RNA polymerase
favipiravir	Fujifilm Toyama Chemical	Inhibition of viral RNA-dependent RNA polymerase
molnupiravir	Merck	Induces copying errors during viral RNA replication
nitazoxanide	Romark Laboratories	Blocking maturation of the viral hemagglutinin
PTC299	PTC Therapeutics	Inhibition of dihydroorotate dehydrogenase
remdesivir	Gilead Sciences	Inhibition of viral RNA-dependent RNA polymerase

Table 1: small molecule antivirals against Covid-19. * As *MedNous* went to press, Abivax announced that it was halting the miR-AGE Phase 2b/3 clinical trial in high-risk Covid-19 patients following an independent Data and Safety Monitoring Board recommendation for lack of efficacy.

While many companies are investigating the use of synthetic antivirals against Covid-19, others are evaluating the effectiveness of interferon, which is part of the body's own response to viral infections. Synairgen Plc, a company spun out of Southampton University in the UK, is conducting Phase 3 trials of SNG001 (inhaled interferon beta) in hospitalised Covid-19 patients who require oxygen therapy. The rationale for this is that coronaviruses like SARS-CoV-2 suppress endogenous interferon beta production in the lung, thus helping the virus to evade the innate immune system.

Results of a Phase 2 study published in July 2020 indicated that SNG001 was associated with a more rapid recovery from Covid-19. Dosing has now begun in the SNG001 sub-study of the NIH's ACTIV-2 Phase 2/3 trial in the US, evaluating patients with mild to moderate Covid-19 symptoms not yet requiring hospitalisation. Separately, Synairgen is carrying out Phase 3 trials at three sites in the UK designed to confirm that SNG001 can accelerate the recovery of patients with confirmed SARS-CoV-2 infection receiving oxygen. SNG001 is also being evaluated for use by at-risk patients in the home setting.[5]

JAK inhibitors

One area of investigation that is attracting particular interest is the use of Janus kinase (JAK) inhibitors. JAK inhibitors prevent the phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation, and are used in the treatment of conditions with a significant autoimmune component, such as rheumatoid arthritis. The rationale for their use in the treatment of Covid-19 patients is that they may reduce the inflammation and associated immune disruption observed in patients with severe Covid-19. They may also have a direct antiviral effect.

Three JAK inhibitors are currently undergoing Phase 3 trials in Covid-19 patients: Eli Lilly & Co's baricitinib, Incyte Corp's ruxolitinib and CTI BioPharma Corp's pacritinib. Lilly markets baricitinib in the US and the EU, under the trade name Olumiant, for the treatment of rheumatoid arthritis. In the US it has been granted an Emergency Use Authorization (EUA) for the treatment, in combination with remdesivir, of Covid-19 in hospitalised patients who require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation. Baricitinib is also the subject of a multinational Phase 3 trial (the COV-BARRIER study) in hospitalised Covid-19 patients, due for completion later this year.

In addition, baricitinib is being investigated as part of Oxford University's Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, which aims to identify treatments that may be beneficial for people hospitalised with suspected or confirmed Covid-19. Results so far suggest that baricitinib with remdesivir is superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among Covid-19 patients.[6]

Incyte's ruxolitinib is marketed as Jakafi or Jakavi for the treatment of myelofibrosis, polycythaemia vera and graft-versus-host disease (GvHD). The company is currently recruiting patients with Covid-19-associated acute respiratory distress syndrome into a multicentre Phase 3 study (the RUXCOVID-DEVENT study) to assess the efficacy and safety of ruxolitinib. The 500-patient trial is taking place at 35 sites in the US and one in the Russian Federation.

Lastly, CTI BioPharma is carrying out the Phase 3 PRE-VENT study of pacritinib in hospitalised patients with severe Covid-19. The trial will evaluate whether pacritinib can prevent progression to acute respiratory distress syndrome and mechanical ventilation.

Antibodies

The development of anti-SARS-CoV-2 monoclonal antibodies as potential treatments for Covid-19 was discussed in *MedNous* Vol 14 No 9 (October 2020), and the field continues to see considerable activity. Phase 3 trials continue with a number of products, including GlaxoSmithKline Plc/Vir Biotechnology Inc's VIR-7831 and Regeneron Pharmaceuticals Inc's REGN-COV2, and a number of antibody products that were in early clinical trials in 2020, such as Eli Lilly & Co/AbCellera Biologics Inc's LY-CoV555 and AstraZeneca Plc's AZD7442, have now progressed to Phase 3.

In March 2021 two reports emerged regarding the efficacy of VIR-7831. In the ACTIV-3 trial of various drugs in hospitalised adults with Covid-19, concerns about the magnitude of potential benefit of VIR-7831 led the Data and Safety Monitoring Board to recommend that the VIR-7831

arm of the trial be closed to enrolment.[7] However, in the COMET-ICE trial evaluating VIR-7831 as monotherapy for the early treatment in adults at high risk of hospitalisation, the Independent Data Monitoring Committee recommended enrolment be stopped following an 85% reduction in hospitalisation and death in treated patients. Based on these findings, the companies said they plan to submit an EUA application in the US and elsewhere.[8]

Meanwhile the Korean company Celltrion Healthcare recently announced that the Ministry of Food and Drug Safety has granted a Conditional Marketing Authorisation (CMA) for the emergency use of regdanvimab (CT-P59), the company's anti-Covid-19 monoclonal antibody treatment candidate. The CMA applies to adult patients with moderate symptoms of Covid-19, and to patients with mild symptoms aged 60 years and over or with at least one underlying medical condition. It is based on the interim results of a Phase 2/3 trial of regdanvimab in patients with Covid-19-related mild to moderate symptoms of severe acute respiratory syndrome which showed that treatment significantly reduced the risk of hospitalisation, progression to severe Covid-19 and time to clinical recovery.

A global Phase 3 clinical trial is currently recruiting and expected to enrol 1,172 patients with mild-to-moderate symptoms of Covid-19 and is designed to evaluate the efficacy and safety of regdanvimab. The company recently said that regdanvimab had demonstrated neutralising capability against key emerging mutations, including the UK variant (B.1.1.7) in addition to six variant genome mutations of SARS-CoV-2.

Anti-SARS-CoV-2 antibody products in advanced clinical trials are shown in Table 2.

Among the investigational antibody products not directed against the SARS-CoV-2 virus, granulocyte macrophage colony-stimulating factor (GM-CSF) and its receptor appear to be popular targets. GM-CSF is a cytokine that plays a significant role in lung inflammation and immunological disease. Three products in particular are in advanced clinical trials: Humanigen Inc's lenzilumab and I-Mab Biopharma Co Ltd's TJ003234, both of which target GM-CSF itself, and Kiniksa Pharmaceuticals Corp's mavrilimumab, which targets the GM-CSF receptor.

Humanigen is developing a portfolio of immunology and immuno-oncology monoclonal antibodies. Lenzilumab is being investigated for its ability to prevent and treat cytokine storm hyperinflammation in three situations: in hospitalised patients with confirmed Covid-19 pneumonia, as a prophylactic therapy to mitigate the side-effects of CAR T treatment in patients with B-cell lymphoma, and as an early treatment or potential prophylaxis for acute GvHD following haematopoietic stem-cell transplantation.

In patients with Covid-19, there is a correlation between high levels of GM-CSF on the one hand and disease severity, cytokine storm, and respiratory failure on the other. Humanigen is therefore carrying out a Phase 3 trial in the US and Brazil to evaluate the impact of lenzilumab on ventilator-free survival in hospitalised, hypoxic patients with Covid-19. Lenzilumab is also being investigated as part of NIAID's ACTIV-5/BET study, which is designed to facilitate the discovery of new Covid-19 treatments by repurposing licensed or late-stage-development medicines.

I-Mab Biopharma, based in Shanghai, China, is carrying out a multicentre trial to evaluate the safety and efficacy of its anti-GM-CSF candidate, TJ003234, in subjects with severe Covid-19 receiving supportive care, and to assess its effect on cytokine levels. Kiniksa's monoclonal antibody mavrilimumab in contrast targets GM-CSF receptor alpha rather than GM-CSF itself. The company is carrying out a Phase 2/3 study in the US and several South American countries designed to evaluate the efficacy and safety of mavrilimumab in participants who have tested positive for SARS-CoV-2 and who have evidence of bilateral pneumonia, active or recent fever, and clinical laboratory results indicative of hyperinflammation.

Immunomodulators

While the response of the body to Covid-19 infection is complex and still not fully understood, activation of the innate immune system has been shown to be one of the body's defences against the infection. One possible fruitful area of research is therefore to stimulate the immune system into mounting a greater response to the virus.

A number of companies are carrying out late-stage clinical trials of therapies designed to boost the immune response in Covid-19 patients, including BCG vaccine, which is well known as a profound stimulator of innate immune responses. Serum Institute of India Pvt Ltd (SII) is working with its majority-owned German subsidiary Vakzine Projektmanagement GmbH to explore the use of VPM1002, an improved recombinant BCG vaccine, in mitigating the clinical course of Covid-19 among high-risk elderly patients and high-exposure healthcare professionals.

In one trial, a total of 2,038 adults aged 60 or over are being enrolled across a number of trial sites throughout Germany. Following administration of VPM1002, subjects will be followed for 240 days to determine whether the vaccine can reduce the frequency of respiratory infections and hospital admissions. In a second trial, 1,200 healthcare professionals with high expected exposure to SARS-CoV-2 will receive a single dose of VPM1002 (or placebo) and be followed up for absenteeism from work, adverse events, hospitalisations, and intensive care unit admissions.

SII is also collaborating with the Canadian company Verity Pharmaceuticals Inc and Germany's Max Planck Institute in a trial to evaluate the effectiveness of VPM1002 in preventing Covid-19 infection and reduce its severity

Table 2

Candidate	Originator
AZD7442	AstraZeneca
CT-P59	Celltrion
LY-CoV555 + LY-CoV016	Lilly/AbCellera
REGEN-COV	Regeneron
TY027	Tychan
VIR-7831/GSK4182136	Vir Biotechnology/GlaxoSmithKline

Table 2: anti-SARS-CoV-2 antibodies in advanced trials

in front-line employees. Separately, SII and Verity are planning to distribute Covishield, SII's licensed version of the Oxford/AstraZeneca Covid-19 vaccine, in Canada, subject to regulatory approval.

Other companies carrying out late stage trials of bacterial preparations with immunostimulant properties include Spain's Inmunotek SL and Immodulon Therapeutics Ltd of the UK. Inmunotek, which specialises in allergy and immunology, is evaluating its product Bactek-R (MV130) in subjects with mild pneumonia due to Covid-19 infection. The trial is being carried out in the Dominican Republic and is expected to be completed later this year. Immodulon is working with a number of partners to evaluate whether its candidate, IMM-101, can reduce the incidence of severe respiratory and Covid-19 infections in cancer patients at increased risk of exposure (the COV-IMMUNO trial).

As discussed already, GM-CSF has attracted considerable attention as a possible therapeutic target in Covid-19, and both direct administration of GM-CSF and administration of GM-CSF inhibitors are currently being tested in Covid-19 clinical trials. The Japanese company Nobelpharma Co Ltd is sponsoring a multicentre study to evaluate the efficacy and safety of inhalation administration of sargramostim, a recombinant form of GM-CSF, as an add-on to the standard treatment in Covid-19 patients. Under the trade name Leukine, sargramostim has been used for many years to promote myeloid reconstitution after bone marrow transplantation and to treat neutropenia during chemotherapy.

While stimulation of immunity might be expected to have some therapeutic benefit in the early stages of Covid-19, some of the later pathological changes in the disease are associated with hyperactivity of the immune system, implying that immunosuppressive drug treatment may be beneficial. One such drug that has attracted attention is F Hoffmann-La Roche Ltd's tocilizumab, marketed as Actemra for the treatment of rheumatoid arthritis and certain other conditions. Tocilizumab is a humanised monoclonal antibody against the interleukin-6 receptor (IL-6R): IL-6 is involved in the immune response and there is evidence that it acts as an inflammatory marker for severe Covid-19 infection with poor prognosis. In 2020 Roche reported that the Phase 3 COVACTA trial of tocilizumab had failed to meet its primary endpoint of improved clinical status in hospitalised patients with severe Covid-19 pneumonia. However, the time to hospital discharge or 'ready to discharge' was shorter in patients treated with tocilizumab than in those treated with placebo.

In January 2021, the UK National Institute for Health and Care Excellence (NICE) reported that preliminary evidence from the REMAP-CAP study had suggested that tocilizumab is beneficial in critically ill adults with severe Covid-19 receiving respiratory or cardiovascular organ support. Furthermore, the RECOVERY trial has assessed the efficacy of tocilizumab in adult patients admitted to hospital with Covid-19 with evidence of both hypoxia and systemic inflammation, and preliminary results released in February 2021 concluded that tocilizumab improved survival. The effect was independent of the level of respiratory support and was additional to the benefits of systemic corticosteroids.

Roche, via its Genentech subsidiary, continues to assess the efficacy and safety of tocilizumab in hospitalised participants with Covid-19 pneumonia through the EMPACTA study. The provisional completion date for the study is December 2021. In addition, Roche is collaborating with Gilead to evaluate whether tocilizumab in combination with remdesivir shortens the time to discharge in hospitalised patients with severe Covid-19 pneumonia.

There is clearly no quick fix to the need for specific treatments for Covid-19. Nevertheless, there has been good progress to date: last year the RECOVERY trial showed that dexamethasone reduces mortality in hospitalised patients with Covid-19, and more recently the STOIC study found that inhaled budesonide administered within seven days of the onset of symptoms reduces the need for urgent care and hospitalisation. Given the level of investment into finding new treatments, it is hoped that more drugs will join these two sooner rather than later. In any case, with experts warning that Covid-19 is unlikely to be the last pandemic to hit the planet, any therapeutic advances made now will stand us in good stead in the future.

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This article was written by Peter Charlish, PhD, science editor at *MedNous*, and a former editor at Informa Plc.

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COVID-19 Collaborations			
Partners	**Collaboration Type**	**Comment**	**Date**
Merck & Co Inc and Johnson & Johnson Inc	Merck to support manufacture and supply of J&J vaccine	Merck to use manufacturing facilities in the US	Mar-21
CEPI and partners	Draft plan to cut vaccine development time for future pandemics	Compress development time to 100 days	Mar-21
Valo Therapeutics Ltd and ImmunoScape	Identify peptides for pan coronavirus vaccine	Conserved peptide sequences in SARS-CoV-2 variants which can be targeted	Mar-21
CureVac NV and Novartis AG	Manufacturing agreement for CureVac vaccine	Production of up to 50 mln doses by end 2021	Mar-21
Centre for Process Innovation and UK government	Develop an mRNA vaccine library	Enable mRNA vaccines to be developed against new variants	Mar-21
DNA Script Inc and GE Research	Develop vaccines in response to biothreats	Produce nucleic acid-based vaccines and therapies	Mar-21
EMA and Health Canada	Publish full clinical data for Moderna vaccine authorisation	Build confidence in Covid-19 vaccines	Mar-21
AstraZeneca Plc and COVAX	Supply of Covid-19 vaccine to low and middle-income countries	Vaccine manufacture by AZ and Serum Institute of India	Mar-21
Regulatory agencies from different regions	Align approaches to vaccine regulation	Coalition of Medicines Regulatory Authorities	Feb-21
Group of Seven industrial nations	Cooperate on health response to Covid-19	Strengthen World Health Organization	Feb-21
BioNTech SE and Darmstadt regional government	Increase vaccine production in Germany	Manufacturing site in Marburg	Feb-21
Pfizer/BioNTech and European Commission	Supply additional 200 mln doses of mRNA vaccine to EU	New agreement brings total up to 500 mln doses	Feb-21
EU and COVAX	EU doubles contribution to COVAX to €1 bln	COVAX target is to deliver 1.3 bln vaccine doses by end 2021	Feb-21
EU and World Health Organization	Allocation of €7 mln for vaccination of people in western Balkans	Project includes training health professionals	Feb-21
European Commission and Moderna Inc	Second vaccine supply contract for up to 300 mln doses	150 mln doses in 2021 and option on 150 mln in 2022	Feb-21
US government and Moderna Inc	Delivery of first 100 mln doses by end of Q1	Second 100 mln doses expected by end May	Feb-21
AstraZeneca Plc and IDT Biologika Corp	Letter of intent to raise Covid-19 vaccine production	Expand production site in Dessau, Germany	Feb-21
Evonik Industries AG and BioNTech SE	Additional lipid production in Germany	Lipid supply for mRNA-based Covid-19 vaccine	Feb-21
Technical University of Munich, Johns Hopkins University, Oxford University	Research effectiveness of government pandemic responses	Lockdown policies vary across countries	Feb-21
Intravacc, Bilthoven Biologicals, others	Design multi-purpose vaccine production plant	Produce vaccine candidates in Phases 1 and 2	Feb-21
University of Oxford and others	Expand RECOVERY trial for Covid-19 treatments to Indonesia and Nepal	World's largest clinical trial for Covid-19 treatments	Feb-21
Terms: CEPI=Coalition for Epidemic Preparedness Innovations; COVAX=Covid-19 vaccine global access facility; FIND=Foundation for Innovative New Diagnostics; EMA=European Medicines Agency			

US & European Regulatory Actions

Drug or Device	Comment	Sponsor	Action	Agency	Date
Actemra (tocilizumab)	Systemic sclerosis associated lung disease	Roche Group	NI	FDA	Mar-21
Janssen Covid-19 vaccine	Conditional marketing authorisation - EU	Janssen Pharmaceutica NV	PO	EMA	Mar-21
Hominis Surgical System (device)	Robot-assisted transvaginal hysterectomy	Memic Innovative Surgery Ltd	AP	FDA	Mar-21
Evrysdi (risdiplam)	Small molecule for spinal muscular atrophy	Roche Group	PO	EMA	Feb-21
Jemperli (dostarlimab)	Recurrent or advanced endometrial cancer	GlaxoSmithKline Plc	PO	EMA	Feb-21
Orladeyo (berotralstat)	Prevent recurrent hereditary angioedema attacks	BioCryst Pharmaceuticals Inc	PO	EMA	Feb-21
Cabometyx (cabozantinib)	Monotherapy for advanced renal cell carcinoma	Ipsen SA	NI	EMA	Feb-21
Epidyolex (cannabidiol)	Seizures from tuberous sclerosis complex	GW Pharmaceuticals Plc	NI	EMA	Feb-21
Opdivo (nivolumab)	With cabozantinib for renal cell carcinoma	Bristol-Myers Squibb Co	NI	EMA	Feb-21
Quofenix (delafloxacin)	Community-acquired pneumonia	The Menarini Group	NI	EMA	Feb-21
Sarclisa (isatuximab)	In combination for multiple myeloma	Sanofi SA	NI	EMA	Feb-21
Elebrato Ellipta (fluticasone furoate/ umeclidinium/vilanterol)	New indication for asthma refused	GlaxoSmithKline Plc	NO	EMA	Feb-21
Cosela (trilaciclib)	Reduce bone marrow suppression from chemotherapy	G1 Therapeutics Inc	AP	FDA	Feb-21
Janssen Covid-19 vaccine	Emergency use authorisation for Covid-19	Janssen Biotech Inc	AP	FDA	Feb-21
Libtayo (cemiplimab)	Non-small cell lung cancer with PD-L1 expression	Sanofi SA	AP	FDA	Feb-21
Humira (adalimumab)	Paediatric ulcerative colitis	AbbVie Inc	NI	FDA	Feb-21
Q-Collar (device)	Protect athletes' brains during head impacts	Q30 Sports Science LLC	AP	FDA	Feb-21
Nulibry (fosdenopterin)	Molybdenum cofactor deficiency Type A	Origin Biosciences Inc	AP	FDA	Feb-21
Amondys 45 (casimersen)	Duchenne muscular dystrophy mutation	Sarepta Therapeutics Inc	AP	FDA	Feb-21
Pepaxto (melphalan flufenamide)	Relapsed/refractory multiple myeloma	Oncopeptides AB	AP	FDA	Feb-21
Botox (onabotulinumtoxinA)	Paediatric neurogenic detrusor overactivity	Allergan (AbbVie Inc)	NI	FDA	Feb-21
cPass kit (diagnostic)	Emergency use authorisation for convalescent plasma screening	GenScript USA Inc	AP	FDA	Feb-21
Urine sample type (diagnostic)	Urine sample for diagnosing BK virus in transplant patients	Roche Group	AP	FDA	Feb-21
Evkeeza (evinacumab)	Homozygous familial hypercholesterolaemia	Regeneron Pharmaceuticals Inc	AP	FDA	Feb-21
Bamlanivimab and etesevimab	Emergency use authorisation to treat Covid-19	Eli Lilly and Co	AP	FDA	Feb-21
Entresto (sacubitril/valsartan)	Expanded indication in chronic heart failure	Novartis	NI	FDA	Feb-21

AP=approval (FDA), APL=appeal, CRL=complete response letter, LU=label update, NI=new indication, NO=negative opinion (EMA), PO=positive opinion (EMA), RE=recall, R=restriction, S=suspension, SL=suspension lifted, SR=safety review, SU=safety update, W*=warning, WD=withdrawal [For full information about the drugs, see mednous.com]

J&J vaccine cleared for use

A single dose vaccine developed by Janssen Biotech Inc to prevent Covid-19 has been cleared for emergency use by the US Food and Drug Administration, and given a conditional marketing authorisation by the European Commission, the third vaccine for the coronavirus to be allowed onto the US market.

The two authorisations were based on data from an ongoing Phase 3 placebo-controlled trial being conducted in South Africa, certain countries in South America, Mexico and the US. Trial participants did not have evidence of SARS-CoV-2 infection prior to receiving the vaccine. Among the participants, half received the vaccine while the remainder received a saline placebo. Overall, the vaccine was 67% effective in preventing moderate to severe Covid-19 at least 14 days after vaccination and 66% effective for the same group at least 28 days after vaccination. Amongst people with severe Covid-19, the vaccine was 77% effective at 14 days after administration and 85% effective at 28 days, the FDA said.

Data are not yet available to determine how long the vaccine will provide protection, nor is there evidence that it prevents transmission of SARS-CoV-2 from person to person.

The Janssen Covid-19 vaccine uses an adenovirus type 26 to deliver DNA to the body for the spike protein of the SARS-CoV-2 virus to the body. After being vaccinated, the recipient makes the spike protein which triggers the immune system to recognise any future infection. Janssen Biotech is part of Johnson & Johnson Inc.

DMD drug approved in US

A new treatment for Duchenne muscular dystrophy (DMD) has been approved in the US which uses a technology called exon skipping to bypass a specific genetic mutation in the production of dystrophin, a protein which strengthens muscle fibres and protects them from injury. By skipping the exon, normal amounts of dystrophin protein are produced. DMD is a genetic disorder characterised by dystrophin loss and a progressive deterioration of muscle.

The drug, Amondys 45 (casimersen), is an antisense oligonucleotide developed by Sarepta Therapeutics Inc which binds to exon 45, a piece of DNA that provides information for the production of the dystrophin protein. In 2019, the FDA approved a Sarepta drug that skips exon 53, and in 2016, a drug that skips exon 51, both for DMD. In all three cases, the drugs were shown to increase dystrophin production, which is a marker for clinical benefit in patients with DMD.

Amondys 45 was evaluated in a double-blind, placebo controlled study in which 43 patients were randomised 2:1 to receive either the drug or a placebo. All the patients were male and had a genetically confirmed mutation of the DMD gene that is amenable to exon 45 skipping. In the study, patients who received the drug showed a significantly greater increase in dystrophin protein levels from baseline to week 48 of treatment than those on a placebo.

Amondys 45 received an accelerated approval which means that further clinical data will need to be provided to the FDA to show clinical benefit.

New bone marrow therapy

The US Food and Drug Administration has approved a new small molecule drug for patients with small cell lung cancer who are set to receive chemotherapy but may be at risk of damage to their bone marrow. Cosela (trilaciclib) is to be administered before chemotherapy in order to preserve bone marrow and immune system function.

It inhibits the cyclin-dependent kinase 4/6, an enzyme that plays a role in controlling cell division, in order to prevent myelosuppression. Myelosuppression, or the decrease in bone marrow activity, is one of the most common side effects of chemotherapy and can lead to anaemia, neutropenia and thrombocytopenia.

"For patients with extensive-stage small cell lung cancer, protecting bone marrow function may help make their chemotherapy safer and allow them to complete their course of treatment on time and according to plan," said Albert Deisseroth of the FDA's Center for Drug Evaluation and Research.

The effectiveness of Cosela was evaluated in three studies in which 245 patients were randomly assigned to receive an infusion of Cosela or a placebo before undergoing chemotherapy. The studies compared the two groups for the proportion of patients with severe neutropenia, or an abnormally low white blood cell count, and the duration of this neutropenia during the first cycle of chemotherapy. In all three studies, the patients who received Cosela had a lower chance of having severe neutropenia than those on a placebo. Among patients who had neutropenia, those receiving the drug had the disease for a shorter period of time than those on a placebo. Cosela was developed by G1 Therapeutics Inc of the US.

Spinal muscular atrophy drug recommended

The European Medicines Agency is recommending approval of Evrysdi (risdiplam) to treat spinal muscular atrophy (SMA) – a rare and often fatal disease affecting neurons in the brain and spinal cord that control muscle movement. SMA is caused by mutations in the SMN1 gene that encodes for the survival motor neuron (SMN) protein.

The active ingredient of Evrysdi, risdiplam, acts as an RNA splicing modifier. It works by increasing the expression of a compensatory gene called SMN2 in order to enable the production of normal SMN protein. This is expected to rescue motor neurons and reduce symptoms of the disease. The EMA's positive evaluation, which awaits European Commission approval, is based on the results of two clinical trials, one of which evaluated the drug in patients with infantile-onset SMA and the other in later-onset disease. The first trial showed beneficial effects in the motor development and survival of very young patients at 12 months, compared with the natural course of the disease. The second showed the drug's benefit in later-onset disease compared with a placebo in patients between the ages of two and 25 years. Evrysdi was developed by an alliance that included the Roche Group. It was approved by the US Food and Drug Administration in August 2020.

Initiation of US & European Clinical Trials					
Name of drug or device	**Sponsor**	**Treatment**	**Phase**	**Comment**	**Date**
BT-001 (oncolytic virus)	Transgene + BioInvent International	Targets tumour microenvironment	1/2a	Encodes Treg-depleting antibody + GM-CSF cytokine	Mar-21
MRT5500 (vaccine)	Sanofi + Translate Bio Inc	mRNA vaccine against SARS-CoV-2	1/2	Interim results expected in Q3 2021	Mar-21
COVID-eVax (DNA vaccine)	Takis + Rottapharm Biotech	DNA vaccine to prevent Covid-19	1/2	Vaccine said to have adjuvant properties	Mar-21
NVD-003 (cell therapy)	Novadip Biosciences SA	Autologous cell therapy for bone disease	1	US study to enrol young children	Mar-21
Tilvestamab (antibody)	BerGenBio ASA	Ovarian cancer expressing AXL	1b	Test modulation of AXL expression	Mar-21
VLA15 (vaccine)	Valneva SE + Pfizer Inc	Paediatric study of Lyme disease vaccine	2	Vaccine covers six serotypes in North America + Europe	Mar-21
M1Pram (insulin + amylin analogues)	Adocia SAS	Type 1 diabetes	2	Comparator in study is insulin lispro	Mar-21
NOUS-PEV (vaccine)	Nouscom AG	Melanoma or non-small cell lung cancer	1b	Targets mutations unique to a patient's tumour	Mar-21
SLN360 (RNAi molecule)	Silence Therapeutics Plc	Treat elevated lipoprotein (a) levels	1	Silence gene making disease-specific protein	Feb-21
ImmTOR (gene therapy)	Selecta Biosciences + AskBio	Inhibit the formation of AAV-specific antibodies	1	Develop strategies for repetitive dosing of AAV	Feb-21
Tetanus-epitope targeting platform	Ultimovacs ASA	Relapsed prostate cancer patients	1	Antigens + vaccine adjuvant in same molecule	Feb-21
VTP-300 (vaccine)	Vaccitech Ltd	Chronic hepatitis B infection	1b/2a	With + without low-dose anti-PD-1 antibody	Feb-21
BNT162b2 (vaccine)	BioNTech SE + Pfizer Inc	Evaluate Covid-19 in pregnant women	2/3	Trial sites in nine countries	Feb-21
RGLS4326 (oligonucleotide)	Regulus Therapeutics Inc	Autosomal dominant polycystic kidney disease	1/b	Designed to inhibit miR-17 + target kidney	Feb-21
CAN04 (antibody)	Cantargia AB	Pancreatic cancer	2a	Phase 2a extension of CAN04 + chemotherapy	Feb-21
Valeda (medical device)	LumiThera Inc	Dry, age-related macular degeneration	3	Device approved in EU but not yet in US	Feb-21
TT11X (cell therapy)	Tessa Therapeutics Ltd	Patients with CD30+ lymphoma	1	Allogeneic CD30-CAR Epstein Barr virus specific T cell therapy	Feb-21
Descartes-11 (cell therapy)	Cartesian Therapeutics Inc	Newly diagnosed multiple myeloma	2a	mRNA chimeric antigen receptor T cell therapy	Feb-21
Efgartigimod (antibody fragment)	argenx SE	Inflammatory demyelinating polyneuropathy	2	Molecule designed to reduce disease causing IgG antibodies	Feb-21
Covid-19 vaccine	GSK + Sanofi SA	New Phase 2 study with refined antigen formulation	2	If successful, Phase 3 to start in Q2 2021	Feb-21
ART0380 (small molecule)	Artios Pharma Ltd	Advanced or metastatic solid tumours	1/2a	DNA damage response treatment	Feb-21
IBI310 (antibody)	Innovent Biologics Inc	Advanced hepatocellular carcinoma	3	Anti CTLA-4 antibody with sintilimab injection	Feb-21
GSK3844766A (vaccine)	GlaxoSmithKline Plc	Respiratory syncytial virus	3	Candidate vaccine programme for older adults	Feb-21
INT-1B3 (microRNA)	InteRNA Technologies BV	Advanced solid tumours	1	Mimic of endogenous tumour suppressor miR-193a-3p	Feb-21
NOX-A12 (oligonucleotide)	NOXXON Pharma NV	Newly diagnosed brain cancer	1/2	In combination with radiotherapy	Feb-21
SNG001 (inhaled interferon beta)	Synairgen Plc	Covid-19 outpatients	2/3	Sub-study evaluating patients not yet requiring hospitalisation	Feb-21

Clinical Trials: a round-up of recent advances and setbacks

One of several clinical studies of canakinumab in non-small cell lung cancer has failed to meet its primary endpoint, but other studies in the programme are continuing, **Switzerland**-based **Novartis** announced on 9 March. Canakinumab is a monoclonal antibody designed to neutralise the bioactivity of human interleukin-1beta (IL-1beta). The Phase 3 CANOPY-2 trial, which was evaluating canakinumab in combination with the chemotherapy agent docetaxel, did not meet its primary endpoint of overall survival. The trial was conducted among 237 adults with locally advanced or metastatic non-small cell lung cancer whose disease had progressed while on or after chemotherapy and a checkpoint inhibitor. However Novartis said that two other Phase 3 CANOPY trials are continuing. These are evaluating the drug in first-line and adjuvant settings. "While results from the CANOPY-2 trial are not what we hoped for in patients with advanced or metastatic non-small cell lung cancer who have been treated with other lines of therapy, these data give us valuable insights into IL-1beta inhibition," said John Tsai, chief medical officer at Novartis.

A Phase 3 trial of the checkpoint inhibitor Libtayo (cemiplimab) is to be stopped early after showing an improved overall survival in patients with cervical cancer, reducing the risk of death by 31% compared with chemotherapy, **Regeneron Pharmaceuticals Inc** of the **US** and **France**-based **Sanofi SA** announced on 15 March. The companies plan regulatory submissions in 2021. Libtayo was being tested as a monotherapy in patients previously treated with chemotherapy whose cervical cancer was recurrent or metastatic. The trial is being stopped early on the recommendation of the independent data monitoring committee. Libtayo is a fully-human monoclonal antibody targeting the immune checkpoint receptor PD-1 on T cells. By binding to PD-1, the therapy blocks cancer cells from using the PD-1 pathway to suppress T cell activation.

ViiV Healthcare, the specialist HIV company majority owned by **GlaxoSmithKline Plc** of the **UK**, has reported positive data from a Phase 2a proof-of-concept study of an investigational maturation inhibitor for HIV. The study showed that the antiviral activity of the drug, known as GSK'254, established a relationship between dose and antiviral response, with the 140 mg and 200 mg doses showing the greatest reduction in plasma HIV-1 RNA. Maturation inhibitors are a class of antiretroviral medicines that target the late stage of the HIV viral life cycle. They can prevent the HIV replication process by blocking key enzyme activity at this stage, which results in the formation of immature virus particles. Their mechanism of action is therefore different from other antiretroviral drugs. "Because of HIV's tendency to develop resistance to treatment over time, there is a need to improve the number of treatment options available for people living with HIV," said Christoph Spinner of the Technical University of Munich hospital.

A small molecule drug being developed by **Immunic Inc** has shown evidence of clinical activity in hospitalised patients with moderate Covid-19 disease. Immunic is co-located in **Germany** and the **US**. The finding, from a Phase 2 trial, suggests that the drug, IMU-838, may have application in patients aged over 65 years, as well as preventing long-term Covid-19 symptoms such as fatigue. The analysis of the Phase 2 CALVID-1 trial is based on data from 204 randomised patients and includes top-line clinical efficacy, safety, disease markers and virology data. The primary endpoint of the trial was defined as the proportion of hospitalised patients without any need for invasive ventilation through day 28. As fewer than 1% of the patients required invasive ventilation, it was not possible to evaluate the primary endpoint. For similar reasons, it was not possible to assess two key secondary endpoints. However, the clinical activity of IMU-838 was confirmed using multiple secondary clinical endpoints. These were, time to clinical recovery, time to clinical improvement, treatment benefits for patients over the age of 65 years and viral burden after treatment.

Lynparza (olaparib) has passed an important threshold in a Phase 3 trial of patients with early breast cancer with the result that it will undergo a primary analysis for efficacy earlier than planned. This follows a recommendation by the trial's independent data monitoring committee which concluded that the drug has the potential to achieve a sustainable and clinically relevant treatment effect in patients, according to the sponsors **UK**-based **AstraZeneca Plc** and **Merck & Co Inc** of the **US**. Lynparza is a poly ADP ribose polymerase (PARP) inhibitor that has already been approved for ovarian, breast, pancreatic and prostate cancers. It works by blocking the DNA damage response in cells and tumours harbouring a deficiency in homologous recombination repair, such as mutations in the BRCA1 and/or BRCA2 genes. The Phase 3 trial, called OlympiA, is testing the drug against a placebo as an adjuvant treatment in patients with early breast cancer. It is being given after surgery to prevent the disease from coming back. Patients in the trial have germline BRCA-mutated, HER2-negative early breast cancer. Based on a planned interim analysis, the data monitoring committee concluded that the trial had crossed the superiority boundary for the primary endpoint which is invasive disease-free survival.

An experimental oncolytic virus therapy in clinical development by **Norway**-based **Targovax ASA** has continued to show a survival benefit for patients with malignant pleural mesothelioma 21 months after treatment. At follow-up, half of the patients in the first-line treatment group were still alive and median overall survival had not been reached, the company announced on 23 February. The oncolytic virus, ONCOS-102, was administered in combination with chemotherapy. The Phase 1/2 trial treated 31 patients of whom 20 received ONCOS-102 and chemotherapy and 11 received chemotherapy alone. Patients were assessed on a first-line or later-line treatment basis. Based on current survival data, median overall survival is expected to be 20.5 months or longer.

Antimalarial drug for cancer

A commonly used anti-malarial and pneumonia drug has shown promise in improving the impact of cancer treatments. Scientists from the University of Oxford investigated the potential for atovaquone to improve lung tumour receptiveness to cancer treatments like chemotherapy and radiotherapy. Atovaquone is cheap and has few side effects, and could quickly be adopted into clinical use if required.

Results from a study called ATOM showed that the drug can reduce very low oxygen tumour environments, which has potential to make cancers behave less aggressively and to improve the impact of everyday cancer treatments. Because cancers metabolise lots of oxygen to create the energy needed to divide, grow and spread rapidly, environments around tumour cells are hypoxic (oxygen-starved). Hypoxic tumours behave more aggressively and are more resistant to most treatments, especially radiotherapy which relies on oxygen to attack cancer cells.

The ATOM study administered atovaquone to patients with non-small cell lung cancer before the surgical removal of their tumours. Scans measuring tumour hypoxia found that tumours had 55% less hypoxic volumes than those who didn't receive the drug. Genetic analysis showed that atovaquone successfully disrupted the metabolic pathways of the tumour that are involved in the consumption of oxygen to create energy for tumour cells. The drug successfully reprogrammed the tumour cell metabolism so that more oxygen was present around the tumour, making it more susceptible to treatments.

The potential of atovaquone is now being further investigated in a new trial, ARCADIAN. The ATOM study was published in *Clinical Cancer Research* on 17 February 2021.

New findings about fungi

Scientists have found that fungi have colonised deep parts of the Siljan impact structure, Sweden, which is the largest impact crater in Europe. Siljan is more than 50km in diameter and formed almost 400 million years ago. The study, which was published in *Communications Earth & Environment* on 18 February 2021, found fossil evidence of fungi in newly retrieved bore cores from drillings deep into the crater.

Samples were taken from a 534m to 542m vertical depth from the ground surface, and fine filamentous structures in the vuggy rock were detected. On laboratory inspection, these were found to be the fossilised remains of fungi. The researchers, from the Linnaeus University in Sweden, discovered that the fungi seem to have been fuelling methane and sulfide production in the crater, possibly along with other micro-organisms. This conclusion was reached because of the relative abundance of different isotopes of carbon and sulfur within minerals found in relation to the fungi.

The team says their findings suggest that fungi may be widespread decomposers of organic matter and overlooked symbiotic partners to other, more primitive, micro-organisms, thereby capable of enhancing the production of greenhouse gases in the vast rock-hosted deep biosphere.

Strategy for treating ALS

A particular type of stem cell has been found to have therapeutic benefits for patients with amyotrophic lateral sclerosis (ALS), a disease which currently has no cure. Scientists at Okayama University in Japan investigated the potential of multi-lineage differentiation stress enduring cells (Muse cells), which can recognise damaged sites in the human body, for treating ALS.

Muse cells are a kind of pluripotent stem cell, meaning that they can differentiate into several standard cell types encountered in the human body. They occur in the connective tissues of organs, bone marrow and blood, and were discovered in 2010 by the research group of Dr Mari Dezawa. Muse cells can repair tissue *in vivo*, a property that has been investigated in mouse models with pathologies including muscle degeneration, stroke and spinal cord injury.

ALS is a fatal neurodegenerative disease that affects bodily motion. It results in the gradual loss of motor nerve cells (neurons) that control voluntary muscles. Symptoms at the early stage include stiff muscles, limb weakness and slurred speech. Ultimately, control of the muscles needed for moving, speaking, eating and breathing is lost which leads to paralysis and respiratory failure. Existing treatments for ALS are aimed at improving the symptoms, but there is no cure for the disease.

The study, which was published in *Scientific Reports*, conducted experiments in mice and revealed promising potential therapeutic benefits for ALS patients. Initially, the researchers determined that intravenous injections of Muse cells was the best way to administer them, by comparing that method to intrathecal (into the spinal canal) injections in mice. They found that intravenous injection led to Muse cells appearing in different relevant body areas.

The team then looked at the effect of intravenous administration of Muse cells into G93A mice, an ALS mouse model with mutations in the SOD1 gene. They found that the cells migrated to the spinal cord, a key part of the central nervous system. The Muse cells did not differentiate into neurons, but mainly into astroglial cells. There are beneficial aspects associated with the latter, including stimulating the growth of nervous tissue and modulating inflammatory responses. The researchers' findings also suggested that the injection of Muse cells prevented the shrinking of muscle cells in ALS mice, as well as improving muscle strength compared to the control groups.

The team, which was led by Professor Abe Koji and Associate Professor Yamashita Toru, hope that their findings represent a valuable result in the context of establishing a potential strategy for treating ALS. They say that Muse cells can be a promising cell resource for the treatment of ALS patients.

– *By Rosie Bannister*

Evox completes financing

Less than a year after signing a lucrative licensing deal with Eli Lilly and Co, UK-based Evox Therapeutics Ltd has completed a Series C financing round to advance therapeutics based on exosomes into the clinic. The £69.2 million financing was led by Redmile Group, a US hedge fund, which was joined by the new investors OrbiMed Healthcare Fund Management and the Invus Group LLC. Proceeds of the financing will enable several compounds directed at rare disease to progress towards clinical development as well as support the exosome technology platform. Exosomes are nanometer-sized vesicles that transfer lipids, proteins and nucleic acids from one cell to another, thereby mediating cell to cell communication. In 2007, the Swedish scientist Jan Lötvall and colleagues discovered that exosomes could transfer microRNA to cells and suggested that they could play a role in therapeutics. Subsequent research showed that exosomes can deliver short-interfering RNA to the brain in mice. Evox has taken the science further to show that it is possible to engineer exosomes to contain drugs.

At the preclinical level, Evox has a proprietary programme in urea cycle disorders and a programme partnered with Takeda Pharmaceutical Co Ltd for the lysosomal storage disorder Niemann-Pick disease type C. Earlier projects in discovery address rare diseases and neurological disorders. All of Evox's existing investors participated in the Series C round including Lilly.

Funding for eye treatments

UK-based Oxular Ltd has secured $37 million in venture finance to advance its lead product for diabetic macular oedema (DME) into Phase 2 as well as support earlier stage ophthalmologic products. The venture capital firm Forbion led the financing, which included existing investors IP Group, NeoMed and V-Bio Ventures. Oxular, formerly known as Precision Ocular Ltd, has a portfolio of retinal treatments that are being developed for DME, macular degeneration, retinal vein occlusion, uveitis and certain ocular cancers. The company's lead product, OXU-001, is a sustained release formulation of dexamethasone, a glucocorticoid medication. Both the drug formulation and the delivery procedure are new, and intended to be safer and less invasive than existing methods. OXU-001 is delivered to the eye using a microcatheterisation procedure. An illuminated microcatheter is placed into the suprachoroidal space just under the sclera, or white of the eye, and above the choroid, or vascular tissue. Once placed, OXU-001 is injected to a site alongside the posterior retina, the critical tissues involved in retinal disease. A single administration is intended to provide up to 12 months of treatment. The newest financing round follows capital raising events between 2016 and 2020 which generated nearly £20 million from existing investors for the company. As part of the newest financing, Dmitrij Hristodorov, a principal at Forbion, will join the Oxular board of directors.

European Biotech Financings

	Recipient	Type of Finance	Use of Proceeds	Comment	Date
BE	ExeVir Bio BV	Series A financing closed at €42 mln	Antibody therapies against viral infections	Led by Fund+	Mar-21
UK	Amphista Therapeutics Ltd	$53 mln Series B financing	Synthetic small molecule protein degraders	Co-led by Forbion and Gilde Healthcare	Mar-21
UK	Exscientia Ltd	$30 mln Series C top-up to $100 mln	Expand AI-driven drug discovery	New investor is BlackRock Inc	Mar-21
NL	InteRNA Technologies BV	€2.7 mln clinical innovation credit	Support clinical validation of lead miRNA drug	Dutch government award	Mar-21
UK	Touchlight Genetics Ltd	£42 mln from financing round	Manufacturing capacity for synthetic DNA vector	Led by Bridford Investments Ltd	Mar-21
DK	Bavarian Nordic A/S	DKK 1.148 bln from share placement	Support vaccines for infectious diseases	Danske Bank A/S was a manager	Mar-21
US	Ventyx Biosciences Inc	$114 mln in equity finance	Small molecule drugs for inflammatory diseases	Led by venBio Partners	Mar-21
BE	AgomAb Therapeutics NV	$74 mln Series B financing	Regenerative pathway modulators	Led by Redmile Group	Mar-21
DE	ActiTrexx GmbH	€3.5 mln in Series A financing	Cell therapy against transplant rejection	Led by LBBW Venture Capital GmbH	Mar-21
UK	NeoPhore Ltd	£15.2 mln Series B round	Drugs targeting DNA mismatch repair for cancer	Led by Claris Ventures	Mar-21
UK	Twelve Bio	£3.6 mln for 49% stake in company	Cas12a nucleases for therapeutic gene editing	Investor is Arix Bioscience Plc	Mar-21
CH	Asceneuron SA	$2.2 mln grant	O-GlcNAcase inhibitor for Alzheimer's disease	Alzheimer's Drug Discovery Foundation	Mar-21
DE	InflaRx NV	$75 mln from public share offering	Inhibitors of C5a for inflammatory diseases	Gugenheim Securities was bookrunner	Mar-21
UK	Oxular Ltd	$37 mln in venture finance	Treatment for diabetic macular oedema	Led by Forbion Capital Partners	Mar-21
FR	EG 427 SAS	€12 mln in Series A financing	HSV-1-based vectors for gene therapy	Led by David Lamond and US family offices	Mar-21
BE	Rejuvenate Biomed NV	€3.2 mln Series A financing	Product for acute and chronic sarcopenia	Led by Vesalius Biocapital III	Mar-21
FR	Argobio SAS	€50 mln for new life science fund	Create five biotechs over five years	Initiated by Kurma Partners and Bpifrance	Mar-21
FR	CVasThera	€1.3 mln from first venture round	Preclinical studies of drug for Crohn's disease	Led by venture group OCSEED	Mar-21
UK	Centessa Pharmaceuticals Ltd	$250 mln in Series A financing	New company with assets from 10 smaller entities	Launched by Medicxi	Feb-21
BE	AMR Action Fund	$140 mln investment	Develop two to four new antibiotics by end of decade	Wellcome Trust, BI and EIB	Feb-21
BE	Imcyse SA	€21.3 mln Series B extension	Advance immunotherapy compounds	Pfizer Inc becomes shareholder	Feb-21
UK	AbFero Ltd	Undisclosed grant funding	Iron chelating agent for Parkinson's disease	Grant from Cure Parkinson's	Feb-21
UK	Two new life science funds	Total investment of $215 mln	Invest in new therapeutics and medical technology	Investor is Advent Life Sciences	Feb-21
UK	Acacia Pharma Group Plc	€27 mln from private share placement	Support roll-out of hospital medicines	Degroof Petercam was bookrunner	Feb-21
UK	Vinehealth Digital Ltd	£1 mln in grant funding	Companion app being tested in cancer trial	Grant from Innovate UK	Feb-21
CH	Basilea Pharmaceutica Ltd	CHF 45.75 mln from private share placement	Advance clinical development of oncology drugs	Cantor Fitzgerald was a bookrunner	Feb-21
BE	DeuterOncology NV	Undisclosed early-stage investment	Develop dual MET and RAS pathway inhibitor	Investor is Newton Biocapital I	Feb-21
NO	Nordic Nanovector ASA	NOK 361 mln from private share placement	Prepare confirmatory Phase 3 trial for Betalutin	ABG Sundal Collier was bookrunner	Feb-21
DE	Creative Balloons GmbH	€15 mln in venture financing	Balloons for catheter manufacture	Wellington Partners, MIG Fonds and Salvia	Feb-21

ES	MedLumics SL	€18 mln in venture financing	Real-time ablation catheter for atrial fibrillation	Kurma Partners is new investor	Feb-21
UK	Optibrium Ltd	Undisclosed private equity funding	Advance computer-aided drug discovery	Investor is Kester Capital	Feb-21
UK	Mereo BioPharma Group Plc	$115.1 mln from public share offering	Drugs for oncology and rare diseases	SVB Leerink was bookrunner	Feb-21
UK	Microbiome research project	Undisclosed funding for research	The role of prebiotics in supporting sleep	OpiBiotix Health is a funder	Feb-21
FI	Faron Pharmaceuticals Oy	€15 mln from private share placement	Support precision immunotherapy bexmarilimab	European Investment Council Fund was investor	Feb-21
UK	Evox Therapeutics Ltd	£69.2 mln Series C financing	Advance exosome therapeutics into the clinic	Led by Redmile Group	Feb-21
FR	OSE Immunotherapeutics SA	Loan agreement for up to €25 mln	Expand indications for lead cancer product	European Investment Bank	Feb-21
FR	MedinCell SA	€29.8 mln from private share placement	Controlled-release technology for existing drugs	Bryan, Garnier & Co Ltd was a bookrunner	Feb-21
UK	Quell Therapeutics Ltd	$84 mln from extended Series A round	Treg cell therapy for liver transplantation	Led by Syncona Ltd	Feb-21
FR	Novadiscovery SAS	€2.5 mln in a Series A2 financing	Clinical trial simulation platform	Investor is Sanofi SA	Feb-21
NL	VectorY BV	Undisclosed seed funding at launch	Develop vectorised antibodies for CNS disorders	Investor is Forbion	Feb-21
BE	argenx SE	$1.15 bln from global share offering	Infrastructure for roll-out of first product	J.P. Morgan, Morgan Stanley, BofA were bookrunners	Feb-21
NL	InteRNA Technologies BV	€18.5 mln in Series B financing	microRNA therapeutic for advanced solid tumours	Led by AurorA Science	Feb-21
FR	ErVaccine Technologies SAS	$3 mln in seed funding	Cancer vaccines targeting endogenous retroviruses	Seventure Partners was investor	Feb-21
NL	Pan Cancer T BV	Undisclosed seed funding	T cell therapies for solid tumours	Investors were Swanbridge and Van Herk	Feb-21

Source: Company announcements, Jon Rees Associates Ltd

A new chapter for argenx

In just 12 years, argenx NV has grown from a Dutch start-up into an internationally recognised biopharma enterprise. The company has a portfolio of wholly owned and partnered antibody therapeutics, the first of which has been submitted for review to the US Food and Drug Administration. And on 5 February, it announced gross proceeds of $1.15 billion from a global share offering, managed by J.P. Morgan and three other leading US financial institutions.

With cash and cash equivalents of $2 billion on 31 December 2020, added to receipts from the share offering, argenx is preparing to create infrastructure for a global roll-out of its lead product efgartigimod, once regulatory approval is secured. An FDA authorisation would be followed by a regulatory application in China. Applications are also being prepared for Japan and the EU, with a filing to the European Medicines Agency expected in the second half of 2021.

In preparation for a European roll-out, argenx has appointed Anant Murthy, formerly of Alnylam Pharmaceuticals, as general manager of argenx Europe.

The lead product, efgartigimod, is an antibody fragment designed to reduce disease-causing immunoglobulin G (IgG) antibodies. It binds to the neonatal Fc receptor which is widely expressed throughout the body. Blocking this receptor reduces IgG antibody levels, potentially addressing several autoimmune diseases including myasthenia gravis, a disease of the muscles; pemphigus vulgaris, a disease characterised by blistering of the skin; and immune thrombocytopenia, a bleeding disorder.

Argenx is seeking FDA approval for efgartigimod in generalised myasthenia gravis.

In parallel, the company is investigating cusatuzumab, a CD70 directed monoclonal antibody, in acute myeloid leukaemia. The compound is currently in Phase 2 under a collaboration with Janssen, the pharmaceuticals division of Johnson & Johnson Inc.

Like many other European-based companies, argenx has taken steps to establish a footprint in China. On 6 January, it announced a collaboration with Shanghai-based Zai Lab Ltd to develop and commercialise efgartigimod in mainland China, Hong Kong, Taiwan and Macau. Argenx is to receive $75 million upfront in Zai Lab equity and $100 million in near-term milestone and other payments.

"We are excited to enter a new chapter for argenx as we look towards commercialisation and achieving our mission of reaching patients with debilitating rare diseases," Tim Van Hauwermeiren, the chief executive, said on 8 January, during a presentation of the company's corporate priorities for 2021.

Engitix appoints two new managers

Engitix Therapeutics of the UK has made two new appointments to its management team. Alan Holmes joins the company as senior director, fibrosis, and John Prime has been named director, computational biology. Dr Holmes joins from UCB SA where he was director, drug target identification. He has previously worked at GlaxoSmithKline Plc and at University College London, where he received his PhD in 2007. Dr Prime has more than 10 years of bioinformatics experience.

AZ sees higher revenue

AstraZeneca Plc is expecting total revenue, at constant exchange rates, to increase by a low-teen percentage this year, on the back of continued demand for its drugs for cancer, and respiratory and metabolic diseases. However the forecast doesn't incorporate any revenue or profit projections from the roll-out of its Covid-19 vaccine, developed jointly with Oxford University, nor its proposed acquisition of Alexion Pharmaceuticals Inc, a US specialty pharma company.

The Alexion acquisition was announced in December 2020 and is expected to complete in the third quarter. AstraZeneca is offering to pay $39 billion in a cash and share offer that will be financed partly with an underwritten bridge-financing facility. The acquisition price is high – the company is paying a 45% premium to the share price – but is expected to be immediately earnings accretive.

In 2020, AstraZeneca achieved group revenue of $26.6 billion, up by 9% from a year earlier. This included product sales of $25.9 billion, up by 10%, and collaboration revenue of $727 million, down by 11%. The collaboration revenue included milestone payments from Merck & Co under a co-development deal for the PARP inhibitor Lynparza.

Operating profit for the year was $5.2 billion, up from $2.9 billion in 2019 when the company took a $533 million impairment for a clinical trial failure. This gave an operating margin of 19.4%, up from 12% in 2019.

Sales of oncology drugs increased by 23% from a year earlier to $11.5 billion and represented 43% of group sales. This compared with a share of 38% for biopharmaceuticals and 19% for legacy medicines. The biopharmaceutical segment includes drugs for cardiovascular, renal and metabolic diseases as well as drugs for respiratory and immunological disorders. The acquisition of Alexion will fill out the immunology portfolio with drugs for rare diseases. It will also contribute technology for targeting the complement system of the innate immune system.

Pascal Soriot, the company's chief executive, singled out three products from the current portfolio for mention. Tagrisso, first approved in 2015 for lung cancer, recently received a new indication in the US for early-stage lung cancer on trial data showing a significant disease-free survival benefit. Farxiga, first approved in 2014 for Type 2 diabetes, won a new US indication in 2020 for the treatment of heart failure with reduced ejection fraction. And tezepelumab, a monoclonal antibody targeting an epithelial cytokine, has shown promise in severe asthma, he said.

AstraZeneca's Covid-19 vaccine generated sales of $2 million in 2020. As of early February, the vaccine had received conditional or emergency use authorisations in more than 50 countries. On 15 February, it received an emergency authorisation from the World Health Organization for use around the globe. The company is providing the vaccine at a non-profit basis during the pandemic.

Launch of Centessa

The Medicxi investment group has launched Centessa Pharmaceuticals Ltd, a new pharmaceutical company that brings together a group of diverse assets in order to develop them at scale with oversight from experts in the field. The launch marks a new stage in the Medicxi investment model that focuses on developing new drugs from single assets with a minimum of infrastructure in order to increase productivity and improve the return on investment.

In this case, the assets are being drawn from 10 smaller companies, each with a unique therapeutic focus. On 16 February, the 10 companies were merged into Centessa and the new group was equipped with $250 million in Series A financing. The oversubscribed financing round was led by the US private equity firm General Atlantic, and co-led by Janus Henderson Investors of the UK and Vida Ventures of the US.

"The vision of Centessa is to build a pharmaceutical company with a unique operational framework that aims to reduce some of the key R&D inefficiencies that classical pharmaceutical companies face because of structural constraints," said Francesco De Rubertis, co-founder and partner at Medicxi.

Altogether, the Centessa subsidiaries have four clinical-stage programmes and more than 10 earlier projects spanning oncology, haematology, immunology, inflammation, neuroscience and rare diseases. Six of the companies are from the UK, one is from France, one from Germany and two from the US.

The UK companies include ApcinteX Ltd, with a therapy for haemophilia; Morphogen-IX Ltd, with a treatment for pulmonary arterial hypertension; Z Factor Ltd, which is developing agents to treat alpha-1-antitrypsin deficiency; Capella BioScience Ltd, with monoclonal antibodies for oncology and autoimmune disease; Orexia Therapeutics Ltd, with drugs for neurological disorders; and LockBody Therapeutics, which is developing immuno-oncology drugs.

In France, PegaOne has merged into Centessa to work on monoclonal antibodies for cancer, and in Germany, Pearl River Bio GmbH will work on small molecule drugs for lung cancer. The new subsidiaries from the US are Palladio Biosciences Inc, with a drug for polycystic kidney disease, and Janpix Bio, with drugs for haematological malignancies.

AZ withdraws Imfinzi indication

AstraZeneca Plc has voluntarily withdrawn a bladder cancer indication for its checkpoint inhibitor Imfinzi (durvalumab) in the US, which was given an accelerated approval in 2017 but failed to show the required efficacy in a follow-up study. The Food and Drug Administration awards accelerated approvals to certain drugs, based on surrogate endpoints, but confirmation of clinical benefit needs to be verified in subsequent trials.

The follow-up Phase 3 DANUBE trial of Imfinzi in first-line metastatic bladder cancer did not meet its primary endpoints. AstraZeneca said the withdrawal of the indication in the US does not affect the indication outside the US or other approved indications for the drug both in and outside the US.

Genmab gains traction

Genmab A/S moved a step closer to its goal of becoming a fully integrated biotech in 2020 following a licensing deal with AbbVie Inc which pushed revenue higher and put the Danish company on course to co-develop three bispecific antibody compounds. The agreement, concluded in June, delivered an upfront payment of $750 million, helping to deliver significantly higher revenue for the year.

Total revenue was DKK 10.1 billion ($1.6 billion), up by 88% from DKK 5.4 billion a year earlier. In addition to the payment from AbbVie, revenue was boosted by DKK 4.7 billion in royalty payments, led by the Genmab-discovered antibody therapeutic Darzalex (daratumumab) for multiple myeloma. Darzalex is being commercialised by Janssen Biotech Inc under a partnership that goes back to 2012. Two other Genmab-discovered products, Kesimpta for multiple sclerosis, and Tepezza for thyroid eye disease, were approved for marketing in 2020.

Genmab reported an operating profit of DKK 6.3 billion, more than double the DKK 2.6 billion earned in 2019. The increase was driven by higher revenue, which was partly offset by an increase in operating expenses. On 21 December 2020, cash and cash equivalents amounted to DKK 16.1 billion, up by 47% from the previous year. In addition to its monoclonal antibody therapeutics, Genmab is developing bispecific antibodies and three other antibody structures which are designed to increase the compounds' potency. At the end of 2020, Genmab's partner Janssen submitted regulatory applications in both the US and the EU for the bispecific antibody candidate amivantamab for the treatment of non-small cell lung cancer. The compound received a breakthrough therapy designation, signifying its innovative nature, in March 2020 from the US Food and Drug Administration.

Transformational year for MorphoSys

MorphoSys AG saw a significant rise in revenue and liquidity in 2020 following the launch of its cancer drug Monjuvi (tafasitamab) in the US. Revenue was €327.7 million, up from €71.8 million in 2019. Liquidity at the end of the year amounted to €1.24 billion compared with €357.4 million at the end of 2019. Driving up revenue in the year were €18.5 million in sales of Monjuvi and royalty income of €42.5 million from Tremfya for plaque psoriasis. Tremfya was developed by Janssen Research & Development LLC using MorphoSys' antibody technology. Monjuvi on the other hand is a proprietary product – the company's first wholly-owned product to reach the market. Monjuvi was approved for marketing by the US Food and Drug Administration on 31 July 2020 for the treatment, in combination with lenalidomide, of patients with refractory diffuse large B cell lymphoma. The product is also under review at the European Medicines Agency.

MorphoSys reported earnings before interest and taxes of €27.4 million compared with a loss of €107.9 million a year earlier. "Despite the challenges brought on by the global pandemic, we delivered one of the most successful years as a company," said Jean-Paul Kress, the MorphoSys chief executive.

Non-insulins lift Novo

Novo Nordisk A/S reported a 4% rise in net sales to DKK 126.9 billion (€17.06 billion) in 2020 as demand for its glucagon-like peptide-1 (GLP-1) drugs for diabetes accelerated while sales of traditional insulins declined. Operating profit was DKK 54 billion, up by 3%, giving an operating margin of 42.6%, one of the highest in the industry.

Geographically, just over half of the company's sales were generated by territories outside North America, with a double-digit increase in China, Hong Kong and Taiwan. Sales in the US rose by just 1% as a result of lower prices for insulins. By therapeutic area, insulin sales were still higher by value than sales of the GLP-1 drugs, but the trend was moving in the opposite direction. Insulin sales declined by 5% during the year, while those for GLP-1 drugs rose by 26%.

GLP-1 is a naturally occurring hormone that stimulates the body to secrete insulin when blood sugar levels rise after a meal. It also lowers glucagon secretion from the liver. Novo's three GLP-1 medicines, Victoza (liraglutide), Ozempic and Rybelsus (both semaglutide) mimic the actions of the natural hormone. Both Victoza and Ozempic are taken by injection, while Rybelsus has been approved in an oral formulation. While Victoza was the first of the three GLP-1 drugs to receive a regulatory approval, it has been outflanked by semaglutide which has shown therapeutic potential in obesity, non-alcoholic steatohepatitis and Alzheimer's disease. In December 2020, Novo submitted marketing authorisation applications in the US and EU to use semaglutide to treat obesity. In the same month, it announced plans to start a Phase 3 study with oral semaglutide in 3,700 people with Alzheimer's disease. The study will investigate the efficacy and safety of the once-daily drug compared with a placebo.

This year, Novo expects to face more competition for both its diabetes and biopharmaceutical products, which include drugs for haemophilia and growth disorders. Sales are expected to grow by 1% to 5%.

Exscientia completes financing round

Exscientia Ltd has enlisted the support of one of the world's largest asset managers, BlackRock Inc, to support its expansion in artificial intelligence-driven drug discovery. Funds managed by BlackRock joined the company's Series C investment round in early March, bringing total proceeds to the UK company up to $100 million.

The new capital will support Exscientia's activities in drug design, expand its capabilities in biological analytics, and help it to continue building a proprietary drug pipeline. William Abecassis, head of Innovation Capital at BlackRock, will join the Exscientia board of directors as an observer.

Exscientia is a 2012 spin-out of the University of Dundee. The company was founded by Andrew Hopkins, chair of medicinal informatics at the university, and Exscientia's chief executive officer. Exscientia has collaborations with a number of large pharma companies.

Imcyse extends financing

Imcyse SA has raised an additional €21.3 million in Series B financing in order to advance its pipeline of immunotherapy compounds, and simultaneously brought Pfizer Inc on board as a shareholder. Earlier, Imcyse announced a licensing deal with Pfizer to develop a preclinical asset for rheumatoid arthritis.

The Series B extension included existing investors, such as the Regional Investment Company of Wallonia, Belgium. Pfizer is a new investor and is taking an undisclosed equity stake in the company as part of the licensing agreement. The total size of the Series B round, including funds raised in 2019, is €49 million.

Imcyse is a 2011 spin-out of the Catholic University of Leuven and is currently located in the Belgian city of Liège. It has developed technology for addressing severe autoimmune diseases by creating synthetic peptides called Imotopes. These peptides are designed to block the immune responses causing immune-mediated diseases. Specifically, they generate T cells that are intended to eliminate antigen-presenting cells and autoantigen specific lymphocytes. The company describes its approach as the deletion of specific immune cells involved in an immune reaction rather than immune suppression.

Imcyse has been in a research collaboration with Pfizer since 2017. The new licensing agreement takes this relationship to the next level by increasing Pfizer's financial commitment and establishing a framework for product development and commercialisation. In addition to the equity stake, Pfizer is making an undisclosed upfront payment to the Belgian company. It has also committed to milestone payments of up to $180 million as well as tiered royalty payments for any product brought to the market.

Merck withdraws indication for Keytruda

Merck & Co Inc has voluntarily withdrawn the metastatic small cell lung cancer indication for Keytruda (pembrolizumab) following the results of a Phase 3 study which didn't support the terms of its earlier accelerated approval from the US Food and Drug Administration. The FDA awards accelerated approvals to certain drugs, based on surrogate endpoints, but confirmation of clinical benefit needs to be verified in subsequent trials.

The decision doesn't affect other indications for Keytruda, the company said.

Merck received an accelerated approval for the lung cancer indication in June 2019 based on tumour response rate and durability of response data from two clinical trials. Continued approval was contingent on data establishing superiority of Keytruda, as determined by overall survival. Merck's Phase 3 trial for this indication met one of its dual primary endpoints of progression-free survival but did not reach statistical significance for overall survival.

Round-up of European biopharmaceutical company news

Switzerland-based **Novartis** and the **Bill & Melinda Gates Foundation** of the **US** have announced plans to work together to develop an *in vivo* gene therapy for sickle cell disease, one of the oldest known and most common genetic disorders. The project will pool the Swiss company's drug discovery expertise with the Gates Foundation's charitable healthcare mission. A therapy developed by the collaboration would be distributed to low and middle-income countries. Novartis said it hopes to develop an *in vivo* therapy that could potentially be administered once, directly to the patient, without the need to modify cells in a laboratory. Further details were not provided.

A spin-out from the Erasmus Medical Center in the **Netherlands** has raised seed funding to discover and develop new T cell therapies for solid tumours including triple negative breast cancer. The company, **Pan Cancer T BV**, will be investigating T cell therapies which have been equipped with new receptors enabling them to target specific cancer antigens. The group of therapies is known as T cell receptor (TCR) T cells. Triple negative breast cancers do not have estrogen or progesterone receptors, nor do they make much of the HER2 protein. This makes them particularly difficult to treat. Pan Cancer T will apply its technology to this cancer as well as to glioma and bladder and lung cancers. Its approach consists of two elements. First, it will investigate targets that are exclusively expressed by multiple solid cancers. Second, it will engineer TCRs that recognise the targets and develop treatments that will be able to navigate the tumour micro-environment en route to killing the cancer. An undisclosed amount of seed funding was supplied to the company by Swanbridge Capital and Van Herk Ventures, both of the Netherlands. Pan Cancer T's chief executive is Katrien Reynders-Frederix, a former programme director at Celyad Oncology SA, a Belgian cell therapy company. She earned a master's degree in biomedical science and a postgraduate degree in business administration from the Catholic University of Leuven in Belgium.

UCB SA of **Belgium** and **Microsoft Corp** of the **US** have entered into a multi-year strategic collaboration to use UCB's medicinal capabilities and artificial intelligence from Microsoft to discover new drugs. The collaboration builds on work the two companies have already done as part of the Covid Moonshot project, an international effort to develop an antiviral treatment for Covid-19. Financial terms of the collaboration were not disclosed. Under the agreement, Microsoft will provide AI technology and applied scientists to work with UCB scientists and data specialists to discover new correlations and patterns leading to the discovery of individualised drugs. Under the Moonshot project, UCB has already contributed compound designs for an orally bioavailable anti-viral for Covid-19. The two companies have drafted four strategic objectives for their new collaboration: to provide personalised medicines for patients; increase an understanding of the biological causes of disease; use data to enable a faster discovery of therapeutic molecules and accelerate clinical development. "By amplifying the power of scientific innovation through digital transformation, we hope to have a better understanding of what makes a patient's journey unique so that we can provide personalized and differentiated medicine in a sustainable way," Jean-Christophe Tellier, CEO of UCB, said in a statement on 23 February.

Finland-based **Valo Therapeutics Ltd** has entered into a collaboration with the San Diego, US company **ImmunoScape** to explore the possibility of developing a pan coronavirus vaccine as well as adapt current vaccines to new Covid-19 variants. The objective is to identify novel peptides from conserved proteins beyond the currently identified SARS-CoV-2 spike protein. ImmunoScape has technology that reportedly can characterise a patient's immune profile at ultra-high resolution. This has enabled an analysis of blood cells from Covid-19 convalescent patients with different clinical outcomes, enabling the identification of CD8+ T cell responses relevant to SARS-CoV-2. This information is expected to inform the enhancement of current vaccines as well as the development of new ones.

Belgium-based **Galapagos NV** ended 2020 with a strong balance sheet but a reconfigured pipeline following its decision, together with partner Gilead Sciences Inc, to abandon plans to pursue a US marketing authorisation for Jyseleca (filgotinib), its small molecule drug for rheumatoid arthritis. The Food and Drug Administration turned back the application in August because of concerns about its benefit/risk profile at a dose of 200 mg. The two companies dropped plans for a US filing in December. The same drug was approved in the EU and Japan however. Galapagos ended the year with cash and current financial investments of €5.2 billion and €2.8 billion in deferred revenue. The strong cash position was the result of several successful equity offerings and the company's lucrative partnership with Gilead. This partnership is ongoing, but was restructured toward the end of 2020 to reflect a new strategy for filgotinib. Filgotinib has completed studies in ulcerative colitis and is being reviewed for this indication by the European Medicines Agency. It is also in a Phase 3 programme for Crohn's disease. Galapagos' revenue and other income from continuing operations was €530 million for 2020, down from €886 million in 2019. The company had a net loss of €305 million compared with a net profit of €150 million in 2019. While Galapagos reported positive topline data in December from a Phase 2a study of a small molecule drug for idiopathic pulmonary fibrosis (IPF), a Phase 3 study of another drug for IPF with a different mode of action, ziritaxestat, was stopped early on a recommendation of the independent data monitoring committee. This drug was also being developed in partnership with Gilead. An analyst at the GlobalData consultancy noted that trial designs for IPF studies have historically been very difficult. Given the high clinical unmet need in IPF, the discontinuation of the trial represents a major setback for the disease space, the consultancy noted.

Commentary: Paula Salmikangas and Björn Carlsson

Addressing the challenges of GTMPs

Novel gene therapy medicinal products (GTMPs) are complex medicines, often involving manipulation of the genome of cells to remove unwanted genes or to modify or add therapeutic gene sequences. Such manipulations can be achieved with gene editing techniques like the CRISPR/Cas9 or by using viral vectors. Yet despite the complexity, expectations for these products are high. Gene therapies have the potential to cure severe conditions such as cancer and fundamentally alter the trajectory of many other disabling diseases by engineering the correct functionality of cells or genes. One has only to look at the efficacy of Kymriah and Yescarta, both chimeric antigen receptor (CAR) T cell therapies for B cell malignancies, to see the potential.

In this commentary, we discuss key challenges GTMP developers are facing. In particular, we look at the selection of the virus vectors used in GTMPs, the conduct of preclinical studies and the generation of evidence for a regulatory review.

The pros and cons of different viral vectors

Currently, most gene therapies are based on viral vectors, the most common of which are lentiviruses and adeno-associated viruses (AAV). The selection of the vector is usually made based on the known safety profile and expected persistency of the vector, but also on the packaging capacity of the vector (size of the gene construct) and specific requirements relating to the target tissue and indication. Viral vectors can be used *in vivo*, i.e. by administering them directly to the patient, or *ex vivo*, where (autologous) patient cells are procured, genetically modified *in vitro* and given back to the patient (e.g. Libmeldy from Orchard Therapeutics for treatment of MLD). Many GTMP developers focusing on genetically modified cells are moving from autologous products to allogeneic, off-the-shelf products, which utilize well-characterised cell banks originating from cells of healthy donors. This, however, includes the challenges relating to immunological recognition and rejection of foreign cells, which necessitates removal of the HLA genes from the donor cells using e.g. gene editing.

Lentiviruses (and other retroviruses) are integrating vectors which means that the genetic material which they carry is incorporated directly into the chromosome of the host cell. These vectors are mainly used for indications where the gene expression is expected to be long-term and stable, also in cells with high mitotic index. Lentiviruses are also used to permanently modify the genotype and phenotype of certain cells, like in case of the CAR T cells.

However, the integration event is not controlled (i.e. may happen to any sites in the genome) and it may cause changes into the genome and activate oncogenes. In the worst case, this may lead to uncontrolled growth of cells and development of cancer. Such an event was seen in early clinical studies of X-linked severe immunodeficiency (X-SCID) where a few treated patients suffered from integrational mutagenesis and developed leukaemia.[1] In most of the cases, the treatment was successful and the gene therapy product provided long-lasting therapeutic effect against the X-SCID. Recently, a new leukaemia case emerged in one of the treated patients, 15 years after the administration, and was resolved with anti-leukaemia treatment.[2]

Later studies have identified that the early retroviral vectors contained strong enhancer sequences within viral long terminal repeat (LTR) regions, which contributed to the activation of the cancer-related genes. This led to active development of safer vectors, including self-inactivating gammaretroviral and lentiviral vectors.[3]

However, this example shows the importance of understanding the benefits and risks of novel gene therapy products and addressing these risks during product development. It is important to include genotoxicity studies into the development of integrating vectors and have pharmacovigilance systems in place to monitor the product after it goes to the markets.

AAV vectors have become a popular choice for GTMPs due to their good safety profile and there are already AAV-based products approved in the EU and the US (Luxturna for retinal dystrophy, Zolgensma for SMA). Unlike lentivirus, this vector is not expected to integrate into the host cell genome, but to remain in an episomal form in the cell nucleus. However, wild-type AAVs are known to be capable of integrating into a specific locus in chromosome 19[4] and recently, recombinant AAVs were reported to have been integrated in a dog model[5], which highlights a possible risk for insertional mutagenesis and cancer also for AAVs. However, as of today, there are no genotoxic events reported in humans for authorised AAV-products or for those in clinical studies.

On the other hand, non-integrating vectors are suffering from lower persistency and it is likely that the DNA delivered into the cells by these vectors is likely to get lost at some point. AAVs are also known to be immunogenic, which currently prevents repeated administration of AAV vectors. Many patients have also pre-existing antibodies against wild-type AAVs and most recombinant AAV products require immunosuppressive co-medication to avoid immunogenicity -related safety and efficacy problems.[6]

Establishing the safety of gene therapy targets

Both Kymriah and Yescarta target the CD19 antigen, which is expressed exclusively on B cells, both malignant and non-malignant. Since the CAR T therapy-related B-cell aplasia can be treated by immunoglobulins, CD19 could be used as a target for CAR T immunotherapies for B-cell malignancies.

In other cases, target selection can be fraught with difficulties. For example, a developer may identify a target which is deemed to be tumour specific. But if, on later examination, this target is naturally occurring in the body, there is a risk of directed toxicity against healthy cells. With a conventional drug, a chemical substance, the developer

first finds out if it reacts to receptors in the cardiovascular system *in vitro*. If it does, the developer most likely terminates the project. The next step is safety pharmacology studies in animal models. If there is an adverse reaction in the cardiovascular system or CNS, the developer likewise ends the project. When it comes to modified T cells, these methods do not work. A developer cannot inject human cells carrying a human receptor into animals and have a relevant readout. Consequently, the developer is hampered by the lack of *in vivo* models, in which to generate crucial safety data.

Unfortunately, there is no simple way to circumvent this problem. The safety of such GTMPs boils down to more or less relevant *in vitro* methods or complicated homologous *in vivo* models (animal-derived product in the autologous species). Nowadays, there are high throughput models where developers can test their gene-modified cells against practically every existing protein. The problem is knowing how valid and sensitive these tests are compared to what will happen when the cells are injected into humans. GTMPs are incredibly potent products and if the wrong cells are targeted, the consequences can quickly be lethal.

Kinetics is another challenge. If a conventional drug shows adverse effects, a patient stops taking it. Within a certain amount of time, from hours up to a few months, the drug is washed out from his/her system. CAR T cells are a living drug which means that once activated by the correct receptor, the cells divide and the patient gets a drug response that continues for as long as there are targets. If a patient and caregiver act quickly, some of the adverse effects, for instance the cytokine storm, can be successfully treated. Nevertheless, once active the CAR T cells will continue to destroy the patient's B cells to some degree despite pharmaceutical measures to block this response.

For most gene therapy products, the nonclinical safety programme is often handled on a case-by-case basis. In this case, discussions with regulatory authorities can be expected to include questions about whether relevant safety data can be generated *in vitro*; what type of animal model should be used for safety studies in relation to the intended clinical use and if two species should be used; whether the animal model expresses the receptor that the vector needs in order to enter cells; whether the transgene is pharmacologically active in the chosen animal model; if the expressed protein is active and intact over time; how to address the PK of the expressed transgene including immunogenicity (local and systemic); safety assessment upon administering the vector to vulnerable sites in the body and differences in size of such structures between man and animal; dose-selection and margins of exposure and what duration of time the preclinical study should be in relation to the length of expression of the transgene. It is vital that a developer can justify the choice of the animal model(s) and design of the studies, otherwise the data might be regarded as irrelevant to the non-clinical safety of the product.

Evidence generation for GTMPs

Regulatory decisions for any new medicinal product, be it an application for a clinical trial or for marketing authorisation, are always based on the benefits and risks of the product, determined by all information and data available at the time of the application. This includes information related to manufacturing and quality controls (CMC), pre-clinical studies (pharmacodynamic and -kinetic studies, mode of action, safety) and clinical safety and efficacy studies. In addition, for those risks that are not addressed by data, there should be proper risk mitigation measures in place and controls established through a risk management plan (RMP) and pharmacovigilance (PhV) activities. The overall requirements may vary between products and are highly dependent on the risks of the product and the intended indication.

Many of the gene therapy clinical trials are conducted in patients with rare diseases, where populations are small. This may hamper the CMC development, if based on patient cells, and clinical data generation. Moreover, the durability of the clinical effect and late emerging safety concerns may require a very long follow-up of patients. This can make the pivotal clinical trials lengthy and data generation cumbersome. For all GTMPs an early risk analysis and carefully considered target product profile (TPP) are recommended, to support the design of the product, but also design of all necessary non-clinical and clinical studies to satisfy the regulatory requirements.

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This article was written by Dr Björn Carlsson and Dr Paula Salmikangas of the NDA Group, Upplands Väsby, Sweden. Please address correspondence to paula.salmikangas@ndareg.com.

On the Move

Jon Kratochvil, an experienced scientist and lawyer, has joined **ERS Genomics Ltd** as head of business development and licensing for North America. ERS manages intellectual property for the Crispr-Cas9 gene editing technology co-owned by Emmanuelle Charpentier. Mr Kratochvil comes to ERS from MilliporeSigma where he managed global development for the company's gene editing technologies. He has also worked as a licensing manager for Abbott Diagnostics. Mr Kratochvil is an inventor on more than 40 patents and patent applications, and holds a master's degree in microbiology and immunology and a law degree from Loyola University Chicago School of Law, US.

4D Pharma Plc, which is developing live biotherapeutic products for cancer, has appointed **John Beck** as chief financial officer and a member of the management team. Live biotherapeutics are a class of drug derived from the microbiome. Mr Beck joins the company from Ritter Pharmaceuticals where he was CFO and oversaw the company's merger with Qualigen Therapeutics Inc, an oncology drug developer. He was also CFO of Ardea Biosciences where he completed a $1.2 billion merger with AstraZeneca Plc in 2012. Mr Beck holds a bachelor's degree in accounting from the University of Washington, Seattle and a degree in theology from a Seattle area seminary, US.

Heidelberg Pharma AG has expanded its management team with the appointment of **Mathias Locher** to the newly created position of chief development officer. Simultaneously, it has promoted **András Strassz** to the position of chief medical officer. Heidelberg Pharma is developing antibody conjugate technology for cancer. Dr Locher joins the company from Janssen Pharmaceutical Companies where he directed external innovation at a hub in London, UK. He holds a PhD in biochemistry from the University of Tübingen in Germany. Dr Strassz has been senior medical officer since April 2020 having joined Heidelberg from Affimed NV. He holds both a medical degree and a master's in business administration from the University of Pécs in Hungary.

Jeroen Rovers, formerly managing director of DCprime of the Netherlands, has been named chief medical officer at **Immunicum AB** following the merger of the two companies in December 2020. Dr Rovers joined DCprime as CMO at the end of 2018 before moving up to the position of managing director. Prior to DCprime, he was CMO at the cell therapy company Kiadis Pharma BV which is being acquired by Sanofi SA. Dr Rovers obtained his MD and PhD in medicine from Leiden University in the Netherlands.

Sweden-based **Hansa Biopharma AB** has appointed **Magnus Korsgren** as head of research and development to advance the company's pipeline of drug candidates for rare immunologic diseases. He brings more than 15 years of experience in preclinical and clinical drug development from a variety of companies including Ferring Pharmaceuticals SA, AstraZeneca Plc, BioInvent International AB and Novartis. Dr Korsgren is board certified in clinical pharmacology.

Tahamtan Ahmadi has been appointed to the newly created position of chief medical officer, head of experimental medicines, at the Danish biotechnology company **Genmab A/S**. Dr Ahmadi moves into the role from his current position as head of oncology at Genmab, which he has held since 2017. Based in Genmab's US office, Dr Ahmadi will lead the company's research, discovery, regulatory and medical activities. He is a haematologist and oncologist by training, holds an MD from the University of Cologne, and a PhD in immunology from the University of Freiburg, both in Germany.

NovalGen Ltd of the UK has announced a number of key appointments to its management team as it prepares to bring its first bispecific antibody therapeutic into human trials. The company's founder, **Amit Nathwani**, a professor at University College London, becomes chief executive and member of the board of directors. Prof Nathwani is an entrepreneur in cancer research, immunology and gene therapy. He is also the founder of Freeline Therapeutics Ltd, where he remains on the board. Among the five other new members of the executive team joining Prof Nathwani at NovalGen, are his fellow UCL professor, **Kerry Chester**, who becomes chief scientific officer, and **Natalia Misciattelli**, who joins as chief business officer.

Michael J Parini has been appointed to the newly-created role of president and chief operating officer at UK-based **Freeline Therapeutics Plc**, a developer of gene therapies. The company has also announced the departure of Brian M Silver, its chief financial officer and head of corporate development, who has decided to leave Freeline for a new opportunity. Mr Parini will be based in the US, and will support the chief executive in developing global strategy. He joins Freeline from Vertex Pharmaceuticals Inc, where he worked for five years, after more than a decade at Pfizer Inc.

Immunocore Plc, a UK company developing T cell receptor bispecific immunotherapies, has announced two new appointments. **Ralph Torbay** joins from AstraZeneca Plc as new head of commercial affairs, and **Roy S Herbst** becomes a member of its board of directors. Mr Torbay has a background in strategy, marketing and sales and over the past four years, has launched three oncology drugs. Dr Herbst previously served as a member of Immunocore's scientific advisory board. He is a specialist in lung cancer treatment and research, and is chief of medical oncology at the Yale Cancer Center and Smilow Cancer Hospital in New Haven, US.

Companies and universities in this issue

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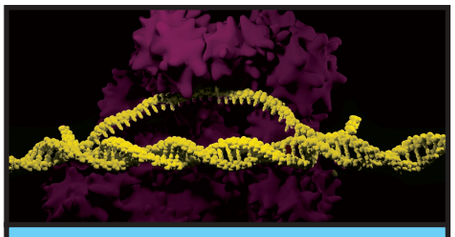

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Angela Columbano
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Amir Hefni
Vice President and Global Commercial Head for Cell & Gene, **Novartis**

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