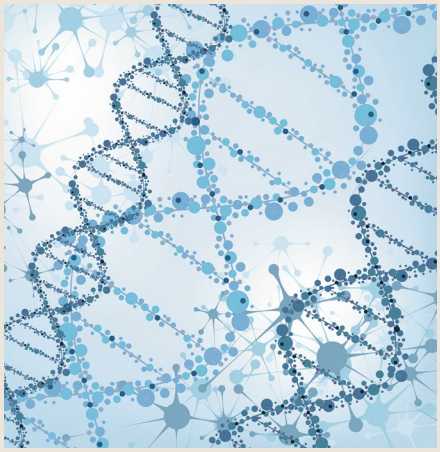
NEWS IN BRIEF

FDA approves SMA gene therapy



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The FDA has approved Novartis's onasemnogene abeparvovec, a gene therapy for children less than 2 years of age with spinal muscular atrophy (SMA).

SMA is a rare genetic disease caused by mutations in the survival motor neuron 1 (*SMN1*) gene, leading to motor neuron death and often fatal muscle weakness. In 2016, the FDA approved Biogen's antisense drug nusinersen for injection four times a year to modulate the splicing of *SMN2* and thereby to boost production of the compensatory protein. Onasemnogene abeparvovec now provides a one-time adeno-associated virus vector-based gene therapy that inserts a functional copy of the *SMN1* gene into motor neurons.

In ongoing and completed trials, patients on onasemnogene abeparvovec showed significant improvements in their ability to reach developmental motor milestones compared with the infantile-onset SMA natural history.

Onasemnogene abeparvovec will cost more than US$2 million, drawing attention as the world's most expensive therapy. Novartis has argued that the gene therapy is cost-effective compared with the standard of care, and will let payers spread payments out over 5 years. The gene therapy has been praised as a worthwhile and welcome advance by some. Others have flagged the price tag as a sign of out-of-control and unsustainable drug pricing. Peak sales could reach $1.8 billion in 2022, show consensus sales forecast data from Clarivate Analytics' Cortellis database.

Novartis bought gene therapy company AveXis for $8.7 billion last year, in part for onasemnogene abeparvovec but also to expand its advanced cell therapy capabilities. Novartis has also licensed the rights to develop and commercialize Spark Therapeutics' gene therapy voretigene neparvovec, for an inherited form of blindness, outside the United States. And in 2017, it secured the first ever approval for a chimeric antigen receptor T cell therapy, tisagenlecleucel for acute lymphoblastic leukaemia.

Asher Mullard

KRAS's undruggability cracks?

KRAS, identified over 30 years ago as a proto-oncogene, is one of the most frequently mutated oncogenes in human cancer. Researchers might at last have overcome this target's druggability challenges, show data that Amgen recently presented at the American Society of Clinical Oncology annual meeting.

Amgen enrolled 35 heavily pretreated patients, with various tumour types, into a small phase I trial of KRAS inhibitor AMG 510. In a cohort of 10 patients with non-small-cell lung cancer (NSCLC), 5 patients experienced a partial response and another 4 had stable disease, they reported. 13 of 19 patients with colorectal cancer achieved stable disease with treatment, but the company has not yet reported any tumour responses in these patients.

Drug hunters have struggled in the past to identify pockets on KRAS that small molecules can bind to tightly to modulate protein activity. Amgen, and others, seem to have cracked the code at last by building on the identification of binding sites on the G12C-mutated form of the protein. G12C, notably, is the most frequent RAS mutation in NSCLC. AMG 510 binds the mutated cysteine irreversibly to lock the protein into an inactive state.

Other companies are also making a move on KRAS. Mirati Therapeutics is recruiting 200 patients into a phase I/II trial of its KRAS-G12C inhibitor MRTX849 in solid tumours, with early proof-of-concept data anticipated later this year. And Wellspring Biosciences and partner Johnson & Johnson recently received an investigational new drug (IND) approval for their small-molecule KRAS-G12C inhibitor ARS-3248.

"Lung cancer aside, the G12C mutation is found in only a small subset of cancers compared with other KRAS mutations and it may be difficult to selectively target other commonly found mutations," cautioned authors of an overview of RAS drug discovery in *Nature Reviews Drug Discovery* in 2014.

Moderna and Merck & Co. are meanwhile set this summer to start a phase I trial of mRNA-5671, an mRNA cancer vaccine that encodes four commonly found KRAS mutations.

Asher Mullard

Understanding how microbiome bugs metabolize drugs

In case drug discovery isn't complicated enough, drug hunters may need to pay closer attention to the emerging field of pharmacomicrobiomics.

In order to systematically understand how the microbiome affects drug activity, and whether variability in the microbiome impacts drug activity and toxicity, researchers at Yale University looked at how 76 different strains of human gut bacteria metabolize 271 orally delivered drugs. Two-thirds of the assayed drugs — spanning drug space and indications — were metabolized by at least one bacterial strain, they report in *Nature*. And each strain metabolized 11–95 different drugs. The group also identified specific metabolites that can come out of these interactions, both in vivo and in vitro, and developed an approach to identify the microbial gene products that drive drug metabolism.

"Depending on the drug and its formulation, we anticipate that such microbiome drug metabolism could play a role in determining intestinal and systemic drug and drug-metabolite exposure," the authors write.

Last year, another group conversely showed in *Nature* that many drugs have unanticipated effects on the microbiome. The group screened 1,000 marketed drugs against 40 strains of human gut bacteria, and found that nearly a quarter of drugs designed to act on human targets slowed the growth of at least one strain of bacteria. This could have implications for toxicity assays and the clinical effects of drugs.

Asher Mullard