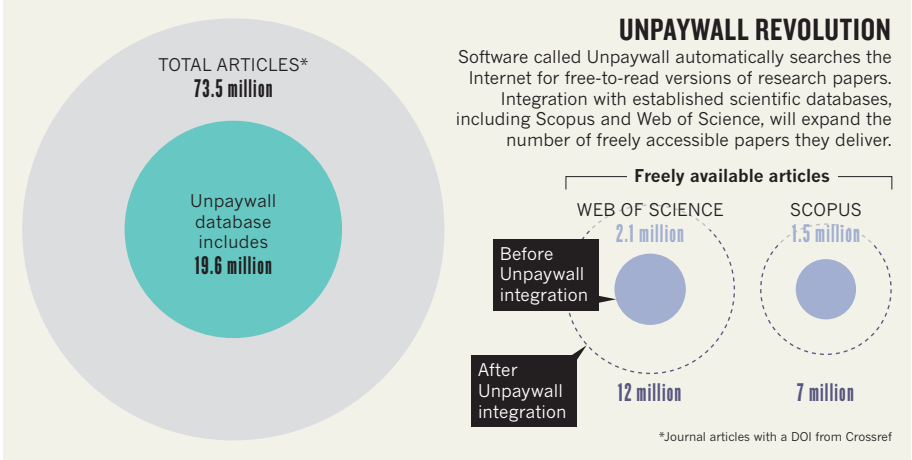
Unpaywall consists of a database that includes a list of almost 20 million freely available scholarly articles. Most researchers access it using a free browser plug-in that was released in 2017. In June 2017, Unpaywall was integrated into a popular science search engine called Web of Science, which is operated by Clarivate Analytics. Dimensions, a service run by Digital Science that launched this year, used Unpaywall from the start. These companies, and now Elsevier, pay a subscription fee for a feed of Unpaywall's database that is updated weekly. Impactstory also offers free access to the Unpaywall database (updated twice a year for non-subscribers).

Since its launch, Unpaywall's technology has also been integrated into many university-library discovery systems, so that users can easily find freely available versions of research papers in institutional repositories. These archives, which are operated by universities, funders and others, host the lion's share of articles in Unpaywall's database, but were difficult to search systematically in the past.

Scientists using Scopus can filter their results to find freely available papers, but the database links to only about 1.5 million papers published in fully open-access journals. Once Unpaywall's integration is complete in November 2018, searches carried out on Scopus for free-to-read literature will also find articles on publisher platforms, even if the journal publishes a mix of open-access and paywalled articles.

This will boost the number of freely available articles in Scopus to 7 million, which is still around 13 million articles fewer than are listed in Unpaywall's database (See 'Unpaywall revolution'). This gap exists because Scopus will not initially link to articles posted in repositories.



SOURCE: CROSSREF/UNPAYWALL/IMPACTSTORY/ELSEVIER/CLARIVATE ANALYTICS

NEW FRONTIERS

Large citation databases such as Scopus and Web of Science list the majority of all research articles. By integrating their records with Unpaywall data, researchers can systematically measure the proportion of the literature that is freely available — a feat that wasn't previously possible. The US National Institute of Mental Health (NIMH), which has an overall budget of around US$1.5 billion, is working with Impactstory to develop a bespoke tool that uses Unpaywall. The agency's goal is to determine the extent to which researchers working at NIMH laboratories in Bethesda, Maryland, and nearby Rockville are making their papers, data and source code freely available.

For Priem, making Unpaywall a go-to tool for researchers is just the start. Last month, Impactstory secured an $850,000 grant to create a search engine aimed at non-scientists. It will also use artificial intelligence to summarize journal articles in its database in plain language, so that non-specialists can understand them. "20 million articles are free for everyone to read but might as well be closed if there is no way for any average person to access it," he says. "We're not yet finished." ■

DRUG DEVELOPMENT

Gene-silencing drug approved

US government okays first RNA-interference drug — after a 20-year wait.

BY HEIDI LEDFORD

US regulators have approved the first therapy based on RNA interference (RNAi), a technique that can be used to silence specific genes linked to disease. The drug, patisiran, targets a rare condition that can impair heart and nerve function.

The approval, announced by the US Food and Drug Administration on 10 August, is a landmark for a field that has struggled for nearly two decades to prove its worth in the clinic. Researchers first discovered RNAi 20 years ago (A. Fire *et al. Nature* **391**, 806–811; 1998), sparking hopes of a revolutionary new approach to medicine. Since then, however, a series of setbacks has lessened those expectations.

"This approval is key for the RNAi field," says James Cardia, head of business development at RXi Pharmaceuticals in Marlborough, Massachusetts, which is developing RNAi treatments. "This is transformational."

Patisiran works by silencing the gene that underlies a rare disease called hereditary transthyretin amyloidosis. In that illness, mutated forms of the protein transthyretin accumulate in the body, sometimes impairing heart and nerve function.

The drug's approval means that pharmacology textbooks will need to be rewritten, says Ricardo Titze-de-Almeida, who studies RNAi at the University of Brasilia. "We are inaugurating a new pharmacological group," he says. "We will have many more such drugs in the coming years."

This was the hope when Alnylam, the company in Cambridge, Massachusetts, that developed patisiran, launched in 2002. Four years later, the Nobel Prize in Physiology or Medicine was awarded to two RNAi pioneers: Andrew Fire of Stanford University School of Medicine in California and Craig Mello of the University of Massachusetts Medical School in Worcester.

But to make RNAi into medicine, developers would first need to determine how to deliver delicate molecules of RNA safely to their target organs. They needed a way to shield the RNA from degradation in the bloodstream, prevent it from being filtered out by the kidneys, and allow it to exit blood vessels and spread through tissues. "That proved to be a substantially harder problem than we anticipated," says Douglas Fambrough, chief executive of Dicerna, an RNAi-focused company in Cambridge, Massachusetts.

As researchers grappled with the delivery puzzle, investors began to lose confidence. In 2008, analyst Edward Tenthoff of investment bank Piper Jaffray in New York City advised his clients to stop buying Alnylam stock. "We saw the promise in the technology, but the delivery was lacking," he says. ▶

By 2010, large pharmaceutical companies were also losing their appetite for RNAi, severing collaborations and ending internal research programmes. "By and large, big pharma left RNAi for dead," says Fambrough. Safety concerns dealt the field another blow in 2016, when Alnylam abandoned one of its leading RNAi programmes after finding a possible link to patient deaths in a clinical trial (see 'Ups and downs').

But gradually, some RNAi companies began to iron out the kinks in their delivery systems. Alnylam experimented with a number of delivery routes and target organs, encasing some of its RNA molecules in fatty nanoparticles or chemically modifying the RNAs to help them survive the perilous journey through the bloodstream.

RNAs protected in this way and injected into the bloodstream tended to accumulate in the kidneys and liver. This led the company to look at transthyretin, which is produced mainly in the liver. In a clinical trial in 225 people with hereditary transthyretin amyloidosis who showed signs of nerve damage, average walking speed significantly improved in those who received the treatment (D. Adams *et al. N. Engl. J. Med.* **379**, 11–21; 2018). Walking speed declined in the placebo group.

UPS AND DOWNS

The biotech firm Alnylam faced several setbacks before winning US government approval for its first RNA-interference drug.

SOURCE: NASDAQ

In the future, Alnylam and others will be able to move beyond the liver, says company co-founder Thomas Tuschl, a biochemist at Rockefeller University in New York City. Quark Pharmaceuticals of Fremont, California is testing RNAi therapies that target proteins in the kidneys and the eye. Alnylam is developing ways to target the brain and spinal cord, and Arrowhead Pharmaceuticals of Pasadena, California, is working on an inhalable RNAi treatment for cystic fibrosis.

"I've never been more optimistic about the future of RNAi," says Fambrough. "All of those tear-your-hair-out days were worth it to get to today."

Advances in RNA delivery might also benefit researchers who are developing gene-editing therapies based on the popular technique CRISPR–Cas9. That system uses a DNA-cutting protein called Cas9, which is guided to the desired site in the genome by an RNA molecule.

Like RNAi before it, CRISPR–Cas9 has become a common tool in genetics laboratories. But it might still face a difficult and lengthy path to the clinic. Much like ordinary drugs, RNAi therapies will break down over time; a gene edit, however, is intended to be permanent, which amplifies safety concerns.

"I hope they can do it more quickly than we did it, but I would not expect it to be so smooth," says Fambrough. "I wish them the best of luck." ■

POLICY

Outrage over changes to EPA chemical assessments

Critics say US environment agency's revisions favour industry over academic research.

BY JEFF TOLLEFSON

The US Environmental Protection Agency is making major changes to the way in which it evaluates chemicals for environmental and public-health effects. The latest push includes changes to chemical-safety guidelines that place greater weight on industry-sponsored research, among other things, and is a part of efforts by US President Donald Trump's administration to reshape how the agency uses science to make decisions.

The Environmental Protection Agency (EPA) issued its chemical-assessment guidance in May, and is soliciting public comments until 16 August. The guidance contains changes dictating the kind of data that studies must include in order to be considered in the EPA's decision-making process. Researchers and environmental and public-health advocates say that the guidelines provide a non-peer-reviewed alternative to the EPA's main system for conducting chemical reviews and calculating acceptable exposure limits. The agency is required by law to do these evaluations, but the guidance defines how officials conduct them. At stake are tens of thousands of chemicals destined for public use and governed by the 1976 Toxic Substances Control Act (TSCA).

The guidance dovetails with a rule proposed in April by then-EPA administrator Scott Pruitt, which, if finalized and implemented, would reduce the role of published scientific studies in decision-making across the agency. The changes also coincide with attacks on the EPA's core chemical-assessment programme, known as the Integrated Risk Information System (IRIS), by industry and Republican politicians over the past year.

In a statement to *Nature*, the EPA says the changes are meant to provide clear criteria to help determine the quality of the research used to evaluate chemicals — and that the guidance is a work in progress that can be revised in response to new information. But scientists say the process laid out by the EPA is at odds with established, peer-reviewed procedures for such assessments.

Jennifer Sass, a senior scientist at the Natural Resources Defense Council, an advocacy group based in New York City, suspects that the goals are to promote science from industry and change the calculations that the EPA uses to develop regulations and estimate safe exposure limits for chemicals.

MEETING THE REQUIREMENTS

The guidelines introduce many data reporting requirements — including statistical analyses that measure whether a study correctly identifies the presence of an effect — that are standard for industry-funded research. But because such criteria vary among peer-reviewed journals, many academic studies would be disqualified, says Tracey Woodruff, who led the development of a chemical-evaluation process at the University of California, San Francisco. "Only industry studies will survive."

The changes represent a major shift because they create a new system for chemical-risk assessments under TSCA. Unlike