# A CRISPR collaboration compilation

**Major biopharma companies are partnering with pioneers of genome-editing technologies to realize the potential of this emerging precision medicine modality.**

Credit: Cavan Images / Alamy Stock Photo

*Biopharma Dealmakers*

Last year saw a landmark approval in precision medicine for the first therapy based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR associated protein 9 (Cas9) genome editing. Little more than a decade after the initial publications on the technology, Casgevy (exagamglogene autotemcel or exa-cel) from Vertex Pharmaceuticals and CRISPR Therapeutics is now marketed for the treatment of sickle cell disease and beta-thalassemia.

The ex vivo cell therapy is created using a CRISPR–Cas9 nuclease to inactivate the gene coding for B cell lymphoma/leukemia 11A (BCL11A), a repressor of the fetal hemoglobin gene, in hematopoietic stem and progenitor cells that have been harvested from patients. Transplantation of modified blood cells back to patients leads to the production of fetal hemoglobin, addressing the deficiencies in adult hemoglobin function that cause the two diseases.

Building on this breakthrough, large biopharma companies have recently entered collaborations with companies that have developed various technologies harnessing CRISPR systems, with the aim of expanding the range of diseases that can be treated as well as addressing challenges for the first-generation platforms such as delivery of the therapeutics.

Exa-cel originated from a collaboration that began in 2015 between Vertex and CRISPR Therapeutics, one of the first companies to be founded to harness CRISPR systems to develop therapies. Since then, the two companies have signed further deals, including one in March 2023 worth up to $330 million to use CRISPR–Cas9 genome editing to develop hypoimmune insulin-producing islet cells for the treatment of patients with type 1 diabetes (see deal snapshot below).

A key issue with the broad applicability of exa-cel for sickle cell disease and beta-thalassemia is the need for patients to undergo bone-marrow ablation—a high-risk process that involves weeks in hospital—to remove dysfunctional blood cells before transplantation of the edited cells. Multiple companies are working on genome-editing therapeutic candidates for disorders such as sickle cell disease that make genome edits in vivo instead, with the aim of avoiding this process.

One such company, Scribe Therapeutics, signed a deal with Sanofi in July 2023 worth up to $1.24 billion (see deal snapshot below). The companies will collaborate to combine Scribe's engineered Cas endonucleases, which have higher activity, specificity

### Vertex licenses genome-editing technology from CRISPR Therapeutics to develop type 1 diabetes therapies

**Deal announced:** 27 March 2023

**Potential deal value:** $330 million

**Deal overview**

- CRISPR Therapeutics, a Switzerland-based company co-founded in 2013 by CRISPR pioneer Emmanuelle Charpentier, agreed to license its CRISPR–Cas9 genome-editing technology to Vertex Pharmaceuticals to develop hypoimmune insulin-producing islet cells for the treatment of patients with type 1 diabetes.
- CRISPR Therapeutics originally established a collaboration with Vertex to use CRISPR–Cas9 genome-editing technology to develop new therapies for genetic diseases including sickle cell disease in 2015. This collaboration resulted in the approval of the pioneering CRISPR-based therapy Casgevy (exagamglogene autotemcel) by the US Food and Drug Administration in 2023.
- Under the terms of the agreement, Vertex will make an upfront payment of $100 million to CRISPR Therapeutics, and potentially up to an additional $230 million in research and development milestone payments. CRISPR Therapeutics will also receive royalties on future products resulting from the collaboration.

### Sanofi partners with Scribe Therapeutics on medicines for sickle cell disease and beyond

**Deal announced:** 17 July 2023

**Potential deal value:** $1,240 million

**Deal overview**

- Sanofi signed a deal with Scribe Therapeutics, a Californian company co-founded by CRISPR pioneer Jennifer Doudna in 2017, to gain an exclusive license to use Scribe's genome-editing technologies for developing in vivo therapies for sickle cell disease and other disorders.
- Scribe's CRISPR X-Editing (XE) genome-editing platform is based on engineering CRISPR systems with higher activity, specificity and deliverability to enable in vivo genetic modification, rather than the ex vivo modification approach used for the first approved CRISPR-based therapy. The companies will collaborate to combine such systems with Sanofi's targeted non-viral delivery technologies.
- Under the terms of the deal, Scribe will receive an upfront payment of $40 million from Sanofi, and is potentially eligible to receive more than $1.2 billion in milestone payments, as well as royalties on product sales. The deal expands on one between the two companies in September 2022, in which Sanofi agreed to pay Scribe $25 million upfront and potentially more than $1 billion in milestones to use Scribe's platform in the development of natural killer (NK) cell therapies for cancer.

**Prevail partners with Scribe on CRISPR-based medicines for neurological and neuromuscular diseases**

**Deal announced:** 16 May 2023

**Potential deal value:** $1,575 million

**Deal overview**

- Prevail Therapeutics entered a collaboration to use Scribe's CRISPR XE genome-editing platform for the development of in vivo CRISPR-based therapies directed against specified targets that cause serious neurological and neuromuscular diseases.
- Prevail is a New-York-based subsidiary of Lilly following its acquisition by the pharma company for $1.04 billion, which was announced in 2020 and completed in 2021. Prevail's most advanced pipeline candidate is a virally delivered gene therapy for patients with Parkinson's disease with acid beta-glucocerebrosidase (*GBA1*) mutations and Gaucher's disease types 1 and 2.
- Under the terms of the agreement, Prevail agreed to pay Scribe $75 million upfront, including an equity investment, and Scribe is eligible to receive more than $1.5 billion in development and commercial milestone payments, as well as royalties on sales of products resulting from the collaboration.

**Lilly buys Beam's rights to Verve's base-editing programs for cardiovascular disease**

**Deal announced:** 31 October 2023

**Potential deal value:** $600 million

**Deal overview**

- Lilly agreed to acquire Beam Therapeutics' opt-in rights to jointly develop and commercialize Verve's programs for cardiovascular disease, including those focused on PCSK9, angiopoietin-related protein 3 (ANGPTL3) and an undisclosed target.
- Beam, a Massachusetts-based company co-founded by base-editing pioneer David Liu in 2017 to develop medicines using base-editing technologies, originally partnered on its technology platform with Verve Therapeutics, another Massachusetts-based company focused on applying genome editing to treat cardiovascular disease, in 2019. It amended this agreement in 2022.
- Under the terms of the deal, Lilly agreed to make a $200 million upfront payment to Beam as well as a $50 million equity investment in the company. Beam is eligible to receive up to $350 million in milestone payments linked to the progression of the therapeutic candidates from Verve's programs. Verve's most advanced candidate, a base-editing therapeutic known as VERVE-101 that targets PCSK9, is in phase 1 development.

and deliverability than Cas9, with Sanofi's non-viral delivery technologies to develop in vivo therapies for sickle cell disease and other disorders.

This was the second major deal signed by Scribe last year, following on from one with Eli Lilly's Prevail Therapeutics in May (see deal snapshot above). Prevail agreed then to pay $75 million upfront, including an equity investment, and more than $1.5 billion in potential milestones to use Scribe's technologies for the development of in vivo therapies directed against targets known to cause serious neurological and neuromuscular diseases.

## Base-editing therapeutics

First-generation genome editors such as exa-cel make double-stranded breaks in DNA. This may raise safety concerns related to off-target effects, particularly for therapeutics that make edits in vivo rather than ex vivo, as with exa-cel. CRISPR-based technologies such as base editing that can make precise changes to genes without creating double-stranded breaks have been developed by companies including Beam Therapeutics.

In October 2023, Lilly signed a deal that could be worth up to $600 million to acquire opt-in rights from Beam to programs for base-editing therapeutics being developed by Verve Therapeutics for cardiovascular disease (see deal snapshot above). Verve's lead candidate, known as VERVE-101, is a base editor in phase 1 trials that targets the gene coding for the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9). VERVE-101 is designed to alter a single base in *PCSK9* to reduce the production of the encoded protein and thereby durably decrease levels of low-density lipoprotein cholesterol, a long-known cardiovascular disease risk factor. In contrast to exa-cel, VERVE-101 makes this alteration in vivo using a lipid nanoparticle delivery vehicle.

Lilly made another deal last year with Verve around a program focused on lipoprotein(a), elevated levels of which also increase the risk of cardiovascular disease independently of low-density lipoprotein cholesterol. In June, Lilly agreed to pay Verve $60 million consisting of an upfront payment and equity investment, and up to $465 million in milestones, as well as royalties on the sales of resultant products.

Multiple companies are now pursuing cardiovascular disease targets such as PCSK9 and lipoprotein(a) with various therapeutic modalities including monoclonal antibodies, antisense oligonucleotides and small interfering RNAs (siRNAs)—some of which are already on the market (*Biopharma Dealmakers* **17**(4), B17–B19; 2023). So, a key question for genome-editing therapeutics aimed at the same targets will be if their potential for a 'one-and-done' treatment will enable them to compete effectively.