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Amgen, Arrakis taking the logic of PROTACs to RNA degraders

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After a decades-long lull in innovation, a wave of candidates is advancing through the HSV pipeline that could combat drug resistance, suppress viral reactivation or even clear the virus completely.

While the past decades have seen functional cures for HCV and powerful vaccines for other viruses, only three FDA-approved systemic antivirals have shown clinical benefit in randomized trials for HSV since the discovery of acyclovir in 1974.

"It's ironic that the virus and the drug that set off the antiviral revolution that got the pharmaceutical industry interested in virology hasn't had much progress in almost 45 years," Larry Corey told BioCentury. Corey co-developed acyclovir with Gertrude Elion, who later won the Nobel Prize.

HSV establishes a latent infection in sensory nerve ganglia that persists for life and can periodically reactivate in several areas of the body. Activated virus travels down to nerve endings, where it replicates and sheds, infecting the skin and causing painful blisters.

HSV-1 is commonly associated with oral herpes and HSV-2 with genital herpes, though it is possible for either virus to present in either location (see Figure 1).

HSV can also reactivate in the eye, causing herpes keratitis, a corneal infection that is a major cause of blindness worldwide; other HSV-triggered conditions include encephalitis, pharyngitis and whitlow.

Drug development for HSV was partly hindered by the success of acyclovir, a synthetic nucleoside analogue that reduces genital herpes recurrences by about 70% and transmissibility by about 50%.

"Acyclovir has been so successful, and it's a generic so the cost of goods is so low, that it's been inhibitory towards the development of new drugs," said Corey, who is now a professor at Fred Hutchinson Cancer Research Center.

However, he believes a next-generation therapy that could avoid resistance, reduce outbreaks further, or clear latent virus to reach a functional cure would see substantial sales in the face of a generic.

The HSV pipeline holds close to two dozen therapies that span six modalities and are designed to achieve one or more of those outcomes (see Figure 2).

The most advanced candidates are small molecules. Among these, two are in Phase III testing, and three have converged on the same target: the virus' helicase-primase complex, which unwinds DNA during the replication process.

Other modalities in the pipeline include antibodies, two of which are in Phase II studies, and nanoparticles. But the biggest step changes in care and prevention could come from gene therapies and vaccines in early development.

The pipeline holds four gene therapies intended to completely clear both active and latent virus, an approach that could be curative; the most advanced is in Phase I/II testing.

At least eight companies are developing vaccines to either prevent infection or quell reactivation of the virus; only one of these has entered the clinic.

Unwinding resistance

One reason HSV therapy innovation hasn't taken off is because the virus has not developed widespread resistance to acyclovir, despite almost 50 years of use, said Corey.

But while resistance rates to the three nucleosides approved for HSV are about 1-5% in the general population, they rise to 5-30% in immunocompromised populations, such as transplant patients.

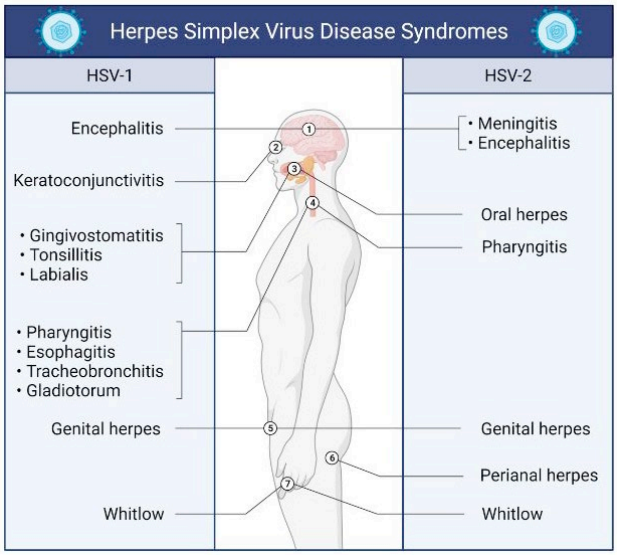
Acyclovir resistance results from mutations in either the virus' thymidine kinase or polymerase. Helicase-primase inhibitors offer a way around this resistance by hitting an orthogonal target.

AiCuris Anti-infective Cures AG believes its Phase III helicase-primase inhibitor pritelivir will both overcome drug resistance and have fewer side effects than current second-line options.

The company discovered the molecule through a phenotypic screen for compounds that interrupt viral replication, and then retrospectively identified the target. "The beauty of such an approach is you let the biology tell you where the Achilles heel is," AiCuris CEO Holger Zimmermann told BioCentury.

Zimmermann said the helicase-primase complex is similar enough between the two HSV types that pritelivir inhibits both, yet the compound is specific enough that it doesn't hit other viruses, including the broader family of herpesviruses.

According to Zimmermann, AiCuris' Phase II trial demonstrated that "efficacy wise, we were better than valacyclovir."



The company is focusing first on immunocompromised patients, "irrespective of where the immunosuppression comes from," Zimmermann said. He added that, "from all the Phase II and preliminary other data, we didn't run into a problem with pritelivir resistance."

Zimmermann declined to say when the company expects results from its Phase III trial, but ClinicalTrials.gov lists the primary study completion date as March 2024.

Maruho Co. Ltd. is testing Amenalief amenamevir, which also targets the complex, in a Phase III trial in Japan. The company declined an interview for this article.

Innovative Molecules GmbH founder and CEO Gerald Kleymann told BioCentury that the frequency of in vitro resistance to the company's preclinical helicase-primase inhibitor IM-250 is less than 1/100,000, compared with about 1/1,000 for acyclovir.

A week after announcing a series A raise of €20 million ($24.3 million) in June, the German biotech reported in Science Translational Medicine that IM-250 reduced the frequency of recurrences, viral shedding and the duration of symptoms in guinea pig models of primary and recurrent genital herpes.

In mice, the brain-to-plasma ratio of IM-250 was higher than pritelivir or Amenalief, and the compound reduced the latent viral load in dorsal root ganglia and spinal cords of HSV-2 infected guinea pigs in a dose-dependent manner. Kleymann expects IM-250 to enter the clinic this year.

Towards a cure

Antivirals block the virus from replicating, which alleviates symptoms, but an ideal treatment would eradicate latent virus from the body to eliminate the possibility of viral reactivation or transmission.

Shanghai BDgene Technology Co. Ltd., Excision BioTherapeutics Inc. and Keith Jerome's lab at Fred Hutch are each taking a gene engineering approach to a potential cure.

BD111 from BDgene, is a gene editing therapy administered via corneal injection, is designed to clear HSV-1 from patients with refractory herpetic viral keratitis. The CRISPR/Cas9 mRNA program, which is in Phase I/II testing, is followed by a preclinical gene editing therapy aimed at clearing HSV-2.

Excision BioTherapeutics is taking a dual-cut gene editing approach to avoid viral escape.

A fundamental challenge to using gene editing to cure infections has been that single cuts in viral genomes cause only small deletions of about 20 or fewer base pairs, which can allow continued viral replication, Excision CEO Daniel Dornbusch told BioCentury.

The company's EBT-104 is a Cas9 dual guide RNA therapy designed to cut out a critical section of the HSV genome large enough to deactivate the virus, and to avoid subsequent mutagenesis that could reactivate it.

"Single cuts have been shown by researchers at Excision as well as other, unaffiliated labs to lead to viral escape. Promiscuous viral promoters can translate the genome inaccurately and make active viral particles," said Dornbusch.

Excision's programs remove hundreds to thousands of base pairs with its dual gRNA method, disabling the virus from making viral particles.

The excised viral fragment is then degraded, said Excision CMO Lisa Danzig. "Measurements using multiple genetic assays demonstrated that excised proviral DNA is no longer detectable after administration with the Excision compounds," she said.

The company is still considering whether it will use an adeno-associated virus (AAV) vector for delivery, or a non-viral vector such as a lipid nanoparticle. It hasn't yet chosen a specific indication, but is considering starting with herpes keratitis due to ease of administration.

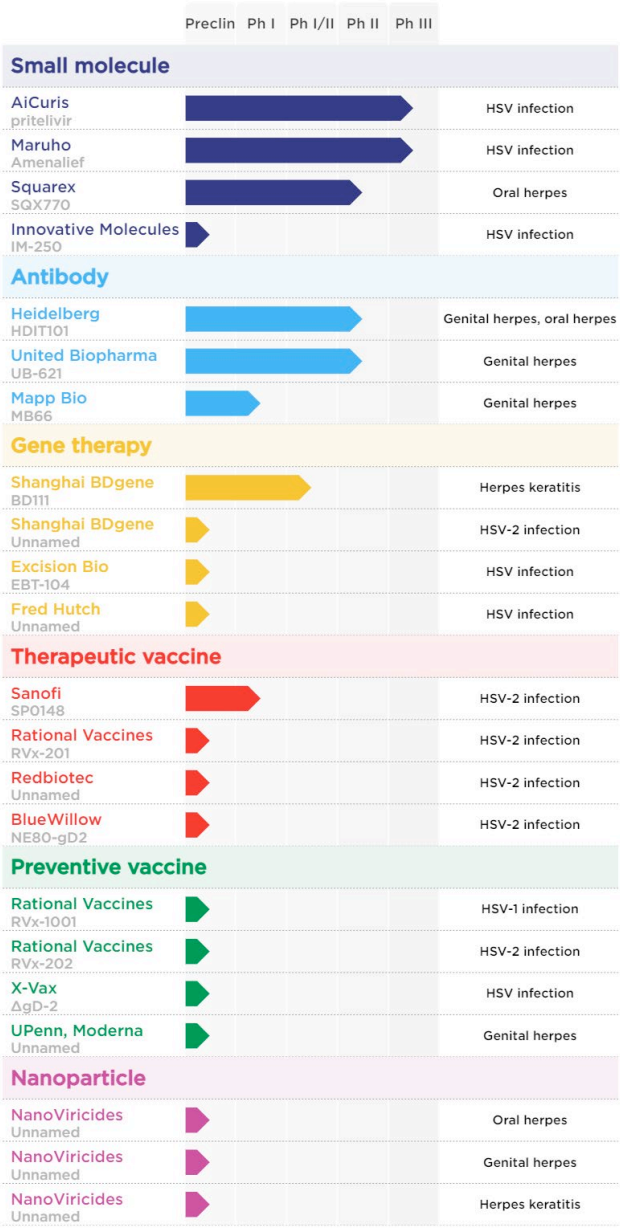
HSV-1 and HSV-2 share about 50% sequence homology, so EBT-104 may target both virus types, depending on how the gRNAS are designed, said Dornbusch.

Keith Jerome, professor at Fred Hutch, is taking a similar dual cut approach, but using a different enzyme.

Jerome's group is using an AAV-delivered meganuclease to mediate gene editing of HSV. His team showed last year in Nature Communications that the method eliminated over 90% of latent virus from the superior cervical ganglia in mice.

"That translates into less virus that wakes up and goes back to the periphery," Jerome told BioCentury. "I hope we can get to where we get rid of all of it."

Herpes simplex virus (HSV) pipeline



Source: BCIQ, ClinicalTrials.gov, company websites

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Jerome said that in a survey his team conducted of why people living with HSV want to be cured, the number one reason was that they don't want to worry about transmitting the virus to someone else, which can occur when an HSV-positive person engages with a sexual partner while actively shedding virus.

Mice aren't typically used to study viral shedding because HSV-1 remains latent in the animals, meaning it doesn't re-activate, travel to the neuronal periphery and shed as it does in humans.

Jerome's lab developed a way to force viral reactivation in mice, enabling it to study whether the therapy also reduced viral shedding.

"The mice shed tremendously less, and the vast majority of them are cured of shedding," he said, adding that he expects to publish a paper soon detailing the results.

The therapy uses a meganuclease from yeast that has some advantages over Cas enzymes, including its smaller size (about 300 amino acids), which enables efficient packaging in AAVs, said Jerome.

"We found AAVs that are good at going to the neurons where herpes lies dormant," he said. "And the meganucleases fit really well, whereas CRISPR/Cas just barely fits, which means you have to cut some corners elsewhere."

The meganuclease cuts the episome, the viral circle of DNA, in two places, causing the DNA to be degraded.

The team is making separate therapies for HSV-1 and HSV-2. Meganucleases require a string of 20 nucleotides as a template, which must be an exact match for efficient cutting.

"There are sequences that are exactly the same between HSV-1 and 2, and if we happened to target those areas, maybe we could make a single enzyme that targets both. The ones that we have in hand need to be tailored, though," he said. "We're equally committed to curing both."

Jerome said the group is actively building relationships with investors and development partners. "I'm hopeful that we can get into our first-in-human trial in the next couple of years."

Vaccines rebooted

A lack of basic molecular understanding of herpesviruses and a dearth of funding have stifled vaccine development for HSV. One trend among new entrants is ridding vaccines of specific viral genes to boost immune responses.

In the 1990s, Corey led vaccine trials that targeted the viral glycoprotein B and glycoprotein D, but weren't successful. "We were never really able to follow up," he said. "It's not that those proteins might not be candidates, they just weren't in the right structure and didn't elicit the right kind of antibodies."

Current options to treat HSV

Company	Therapy	Modality	Indication
Oral			
Generic	Acyclovir	Small molecule	Oral and genital herpes
Generic	Famciclovir	Small molecule	Oral and genital herpes
Generic	Valacyclovir	Small molecule	Oral and genital herpes
Topical			
Anhui Anke	Anterferon	Recombinant IFNA2B	Oral and genital herpes

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Herpes vaccine development took another big hit in 2010 when GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) discontinued development of Simplirix after showing the protein subunit vaccine, which also targeted glycoprotein D, missed the primary endpoint of significantly preventing genital herpes disease.

In 2017, Genocea Biosciences Inc. (NASDAQ:GNCA) made a business decision to cease spending on GEN-003, a therapeutic protein subunit vaccine containing mutant glycoprotein D combined with a large fragment of HSV-2 T cell antigen ICP4 that "looked like it actually worked in controlled clinical trials," but then couldn't raise the funds to push it further, said Corey.

Genocea has since pivoted to neoantigen-based therapies for cancer; in 2020, the company entered a material transfer agreement and exclusive license option with Shionogi & Co. Ltd. (Tokyo:4507) to develop a new HSV-2 vaccine using Genocea's HSV-2 antigens from the GEN-003 program.

At least six other companies have abandoned development of an HSV vaccine after it reached the clinic, according to a 2020 review in vaccine.

"We have a situation in which the small biotech company can't raise enough money to do the program and then the large company decides 'gee, it's not worth the money', and they can it," said Corey.

The handful of companies developing HSV vaccines include Sanofi (Euronext:SAN; NASDAQ:SNY), which has the therapeutic vaccine SP0148 in Phase I testing. Sanofi developed SP0148 in collaboration with Immune Design Corp., which Merck & Co. Inc. (NYSE:MRK) acquired in 2019.

At least four biotechs and one academic institution are also working on HSV vaccines, all of which are preclinical. Two of the biotechs are using gene engineering strategies to increase immunogenicity.

While glycoprotein D has been a primary target for HSV vaccines in the past, X-Vax Technology Inc. is developing a live-attenuated candidate that lacks the target completely.

Deleting glycoprotein D, which is required for viral cell entry, attenuates the vaccine's ability to replicate. X-Vax believes the deletion may also boost protective immune responses by preventing ineffective immunodominant responses against glycoprotein D, as well as unfavorable immune cell modulation mediated by the target.

The company's preventive vaccine candidate, ΔgD-2, induces Fc receptor-activating antibodies that mediate antibody-dependent cell-mediated cytotoxicity (ADCC) as the primary mechanism of protection, veering from the field's historic focus on neutralizing antibodies.

X-Vax exclusively licensed IP covering the vaccine from Albert Einstein College of Medicine, where researchers showed in a 2015 eLife paper and a 2016 JCI Insight paper that ΔgD-2 protected against lethal intravaginal or skin challenges and prevented the virus from establishing latency.

Rational Vaccines Inc. is also developing a live HSV vaccine whose attenuation mechanism doubles as a way to boost immune responses.

The company's lead candidate RVx-201 is a therapeutic vaccine with attenuating mutations in ICP0, a viral protein that controls the balance of HSV latency and replication, and helps the virus evade interferon-mediated immune responses.

University of Pennsylvania professor Harvey Friedman is also developing a vaccine designed to minimize viral immune evasion, using a trivalent antigen approach.

The preventive mRNA vaccine encodes glycoprotein D, glycoprotein C and glycoprotein E; the latter two antigens are immune-evading molecules expressed on the viral envelope.

Glycoprotein C binds a complement protein to inhibit the complement cascade, and glycoprotein E inactivates antibody Fc regions.

"The glycoproteins are on the surface of the virus and expressed on the surface of the cell as the virus replicates, so they're potentially accessible to antibodies induced by vaccination," Friedman told BioCentury. "These antibodies would be lying there waiting for the virus to come along and then bind and block [the glycoproteins'] function so that they can't evade our immune responses."

Friedman's team is collaborating with UPenn professor Drew Weissman and BioNTech SE (NASDAQ:BNTX). Weissman, along with Katalin Kariko, co-created the nucleoside-modified mRNA technology and other mRNA vaccine-related improvements used in the development of COVID-19 vaccines.

Under the 2018 deal terms, UPenn will develop HSV vaccines through IND-enabling studies, and BioNTech is eligible for exclusive worldwide licenses to develop and commercialize the resulting products. UPenn is eligible to receive milestone and royalty payments on vaccines resulting from the collaboration. Financial details are not disclosed.

Friedman said the main advantage of the mRNA technology is durability.

His group published a paper in The Journal of Clinical Investigation in October showing an increase in antigen-specific memory B cells in mice after immunization with the trivalent mRNA vaccine compared with a protein vaccine, with the cells persisting for up to one year. He expects the vaccine to enter the clinic this year.

Friedman said his team is also interested in creating a separate therapeutic vaccine with different antigens.

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