Replicor, Inc.
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Replicor: leading the fight against hepatitis B and D

By applying its unique nucleic acid polymer technology, Replicor is developing a breakthrough therapeutic approach to clear hepatitis B surface antigen from infected patients—a critical step in achieving a functional cure for the disease.

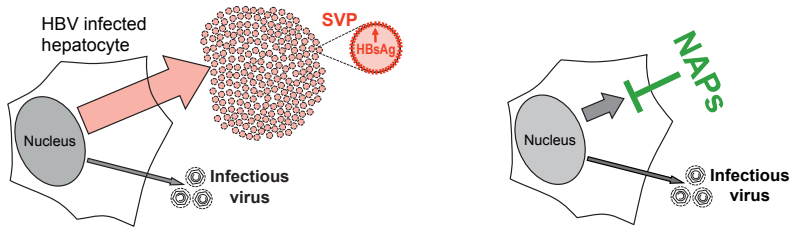
Over 80% of those who contract hepatitis B virus (HBV) recover from the disease, but some 350 million people worldwide are not able to control the virus and develop chronic infection that can seriously damage the liver—over 750,000 people die from complications every year. Furthermore, 15–20 million of these patients are co-infected with hepatitis D virus (HDV), the most deadly form of hepatitis, which can be contracted only by those already infected with HBV; 80% of HDV patients will develop cirrhosis within 10 years. Unfortunately, there are no treatments for HDV, and approved therapies for HBV rarely provide a functional cure, even after many years of therapy. Having worked out why existing therapies fail, Replicor, a privately held clinical-stage biopharmaceutical company located in Montreal, Canada, is developing the first effective treatment to restore immune control in people with HBV and HBV–HDV infection.

HBV continually produces and releases into circulation subviral particles, small non-infectious particles packed with the HBV surface antigen (HBsAg). The particles are the most abundant viral component in the blood of infected patients, and the HBsAg they carry suppresses immune responses to the virus, enabling infection to persist in the liver. Additionally, HDV needs HBsAg to infect liver cells. The longer the surface antigen is in a patient's blood, the more the person's immune system is damaged. Eliminating HBsAg therefore allows the immune system to recover and regain control of the infection (**Fig. 1**).

Unfortunately, existing therapies for HBV, such as interferons and polymerase inhibitors, target the virus but do not interfere with the mechanism underlying the synthesis and release of subviral particles; HBsAg continues to be produced and released, continually impeding the immune system. As a result, these therapies are only marginally effective at restoring immune control of infection.

Replicor has come up with a clever solution, using its nucleic acid polymer (NAP) technology to develop the first class of novel therapeutic agents aimed at eliminating HBsAg from the blood—a key step in achieving a functional cure for HBV and HBV–HDV patients. "HBV infection can be described as a chronic immunological disorder as well as a viral infection," explained Replicor CSO Andrew Vaillant. "Removing HBsAg is key to restoring the immune system, which is crucial for successful treatment."

NAPs are oligonucleotides designed to be amphipathic (that is, they contain both hydrophilic and hydrophobic parts). This enables them to bind with high affinity to exposed amphipathic protein structures, which are rare in normal human biology but commonly found at the surface of many enveloped viruses. This targeting action results in broad-spectrum antiviral effects with minimal side effects.



Subviral particles (SVP)
- >10,000 for every virus
- Primary source of HBsAg
- HBsAg suppresses immune response
- HBsAg in the blood permits chronic infection

SVP elimination by NAPs
- NAPs selectively block release of SVPs
- Effective clearance of HBsAg from the blood
- Allows restoration of immune response with immunotherapy

Figure 1: Clearance of subviral particles by NAPs. The elimination of NAPs allows restoration of the immune system with immunotherapy.

Replicor has discovered that in HBV infection, NAPs do not target the HBV per se but instead interfere with the assembly of subviral particles in infected cells, preventing the release of HBsAg into the blood. Studies have shown that NAPs reduce amounts of circulating surface antigen to undetectable levels over 20 weeks of treatment[1]. "Administering NAPs is like throwing a wrench in the conveyor belt of subviral particle production," explained Vaillant, who discovered the technology. "The body is always working to clear circulating subviral particles, so treatment with NAPs is akin to turning off the faucet and letting the water dry up."

For some patients the removal of HBsAg is enough to allow their immune system to completely suppress and establish control of their HBV infection. For others, additional immunotherapy is needed to restore the immune system's ability to quash infection. Results from phase 2 clinical trials in patients with chronic HBV or HBV–HDV infection have shown that NAP therapy can dramatically improve patient response to immunotherapy[1]. "NAP therapy results in the removal of circulating HBsAg, which is a critical step in allowing the immune system to do its job," said Vaillant. "So the only way immunotherapies are going to work in HBV or HBV–HDV is when used in combination with NAPs."

What sets NAPs further apart from other oligonucleotide-based drugs is that their antiviral functionality is dependent on the overall polymer chemistry, not the specific sequence of nucleotides. Whereas sequence-dependent aptamers, antisense oligonucleotides and short interfering RNA have been associated with significant toxicities and viral resistance, Replicor is able to engineer antiviral NAPs that have no inflammatory or off-target effects, rendering them safe, well tolerated and highly unlikely to trigger resistance.

Partnering this groundbreaking therapy

Replicor is looking for collaborators—from angel investors and venture capitalists to large pharmaceutical and bioscience companies—that can help move this NAP technology quickly through the approval process necessary for it to become the new backbone for combination therapy in HBV and HBV–HDV infection. The company is also open to licensing opportunities.

The first NAP to enter the approval process will be Replicor's lead first-in-class surface-antigen-release inhibitor, REP2139. This NAP is currently in phase 2 development for the treatment of HBV and HBV–HDV infections in combination with immunotherapy and HBV polymerase inhibitors. A second candidate, REP2165, is in early clinical development.

"There is a clear and urgent need to develop new effective treatments for hepatitis B and D," said Vaillant. "By taking the brakes off the immune system, our NAP therapy opens the way for a cure. We are looking to partner with anyone who can help deliver this groundbreaking therapy to the 350 million patients who desperately need it."

1. Al-Mahtab, M. *et al. PLOS One* **11**, e0156667 (2016).

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