More than one way to stop HCV

By Tracey Baas, Senior Editor

A French team led by Epixis S.A. has developed an HCV vaccine that triggers both a T cell response and broadly neutralizing antibodies in macaques.¹ Because of the ability to elicit both types of immune responses, the vaccine could have advantages over other HCV vaccines in development

that focus only on T cell responses or that elicit neutralizing antibodies that do not attack the multiple genotypes of HCV.

Six companies have HCV vaccines in early stage clinical trials (see Table 1, “HCV vaccines in clinical development”).

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—Michael Houghton,
University of Alberta

HCV is difficult to neutralize because there are at least six distinct genotypes with more than 50 known subtypes. Genotypes 1a, 1b, 2b and 3a are the most common in the U.S., but even in a single infected individual, the virus is not homogeneous.

Epixis’ vaccine has three components based on HCV genotype 1a: an adenovirus vector that produces HCV envelope protein E1 (E1) and E2, which elicit T cell responses, and two virus-like particles (VLPs) that present those proteins to the immune system and trigger antibody responses (see Figure 1, “Virus-like particles for HCV vaccine regimen”).

The company first immunized macaques with the adenovirus vector to prime the immune system, followed by a boost with the two VLPs. This regimen provided T cell responses and antibody production against both HCV envelope proteins.

Next they showed cross-neutralization activity of the antibodies by using two types of *in vitro* assays based either on HCV pseudoparticles or cell culture-adapted HCV. Whereas HCV pseudoparticles mimic the early infection steps of HCV, making them useful for evaluating antibodies that neutralize virus entry, cell culture-adapted HCV goes through all stages of the virus’ life cycle, allowing the evaluation of which life cycle stages are affected by the antibodies.

With the nonreplicating HCV pseudoparticles, sera from macaques showed 50%–70% neutralization toward the genotype

1a strain of HCV. Importantly, the vaccine also showed 10%–65% neutralization of 5 other genotypes of HCV.

With a cell culture-adapted HCV, the team showed that the macaque sera had >80% cross-neutralization against a non-type 1a strain of HCV.

Data were published in *Science Translational Medicine*.

The team included researchers from the University of Lyon, the French Alternative Energies and Atomic Energy Commission (CEA), Pierre and Marie Curie University, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), the Pasteur Institute and Pitié-Salpêtrière Hospital.

“Our work shows the prime-boost regime is effective in neutralizing HCV,” said Charlotte Dalba, CEO of Epixis and co-corresponding author on the paper. “It also suggests that theoretically the strategy could be applied to any enveloped virus. The VLP can be redesigned to present the envelope proteins of your virus of interest rather than the envelope proteins of HCV.”

“Historically, the HCV field in general has predicted that vaccines would only elicit genotype-specific neutralizing antibodies,” said Michael Houghton, a virologist at the University of Alberta. “We now know that this is not the case, and as such, this study represents a significant breakthrough in the field and offers much encouragement for the successful development of an HCV vaccine in the future.”

Houghton co-discovered HCV in 1989 and later developed an

Figure 1. Virus-like particles for HCV vaccine regimen. The virus-like particle (VLP) is made up of multiple copies of gag protein from the Moloney murine leukemia virus (MLV) and envelope proteins from HCV. Gag self-assembles into a shell, resembling the conformation of native virus, and incorporates and displays HCV envelope protein E1 (E1) and E2 at the surface.

In their vaccine regimen, Garrone *et al.* incorporated a double boost step, using VLP-E1E2, which displayed genotype 1a E1 and E2, and VLP-E1G, which displayed a recombinant form of genotype 1a E1.

Table 1. HCV vaccines in clinical development.

Company	Product	Description	Status
Chrontech Pharma AB ^A (SSE:C TEC)	ChronVac-C	DNA vaccine against HCV delivered using the Medpulsar electroporation platform from Inovio Pharmaceuticals Inc. (NYSE-A:INO)	Phase IIB
GlobeImmune Inc.	Tarmogen immunotherapy (GI-5005)	Whole, heat-killed, recombinant <i>Saccharomyces cerevisiae</i> yeast engineered to express a fusion protein of HCV non-structural protein 3 (NS3) and HCV core protein	Phase II
Intercell AG ^B (VSE:ICLL; OTCQX:INRL)	IC41	Vaccine containing five HCV peptides and poly-L-arginine	Phase II
Transgene S.A. ^A (Euronext:TNG)	MVA-HCV (TG4040)	Recombinant modified vaccinia Ankara (MVA) virus containing nucleotide sequences encoding immunogenic NS3, NS4 and NS5B	Phase II
Okairos AG	HCV vaccine	Vaccine composed of two non-cross-reacting, replication-defective adenovirus vectors (chimpanzee-derived serotype 3 (AdCh3) and the rare human serotype 6 (Ad6)) that encode NS3, NS4 and NS5	Phase I

^AChrontech and Transgene are combining their products in a Phase I trial. ^BIntercell is testing its vaccine with the small molecule nitazoxanide from **Romark Laboratories L.C.** in a Phase II trial.

HCV E1E2 vaccine candidate when he worked at Chiron Corp. (now part of **Novartis AG**).

Novartis had planned to run a Phase II trial to assess the vaccine's protective efficacy, but Houghton told *SciBX* that work faltered after his departure in 2007 and development was suspended due to financial and other considerations.²

Staying neutral(izing)

A major limitation to the study was the modest amount of cross-neutralization of other viral types that were not genotype 1a.

Houghton wanted to see more evidence for cross-neutralization. "Although Dalba's team has shown strong antibody

testing."

Most children have had mild infections with adenovirus by the time they start school. If patients have pre-existing antibodies to adenovirus, the immune system will fight the adenovirus vector and the vector will not be able to generate the HCV envelope proteins.

"The adenovirus priming vector used in our studies could be replaced by any of the HCV vaccine candidates being developed by our competitors that induce T cell responses," said Dalba. "That would make those companies potential collaborators rather than competitors."

Epixis said it has no plans for challenge studies at this time and its next steps are toxicology studies and clinical studies. Dalba said the company has been acquired by an undisclosed U.S. drug developer. "They will make that information public by the beginning of September," she said.

The HCV prime-boost regimen is patented and licensed by Epixis.

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cross-neutralization against one type of cell culture–adapted HCV, chimeric cell culture–adapted HCVs expressing envelope proteins from seven major genotypes of HCV are now available.³ It would be appropriate to show that the prime-boost regimen elicits neutralizing antibodies against the seven chimeric HCVs."

"We think that, together, the two types of *in vitro* assays used—based either on HCV pseudoparticles or cell culture–adapted HCV—provide ample evidence for heterologous cross-neutralization," said Dalba. "However, the chimeric cell culture–adapted HCV to further test for cross-neutralization could be an interesting, although not indispensable, addition."

Animal models for possible challenge studies include chimpanzees, severe combined immuno-deficiency (SCID) mice with humanized chimeric livers and a newly developed immune competent mouse model.⁴

"If they do test efficacy in chimpanzees, the efficacy should be obtained using a priming vector that is applicable for use in man," suggested Houghton. "Most humans have been exposed to the adenovirus that Epixis used as the priming vector, so I think they need to select a vector that does not have herd immunity for clinical