HCV cache: the list

By Michael J. Haas, Senior Writer

Researchers at **The Scripps Research Institute** have used a cell-based model of HCV infection to identify compounds on the market or in development for other indications that could be repurposed to treat HCV.¹ But if repurposing the molecules is not feasible, the scaffolds of those compounds could serve as the basis of new HCV therapies.

Standard therapy for HCV infection includes a 48-week course of pegylated interferon- α (PEG-INF- α) and ribavirin for HCV genotype 1 or a 24-week course of the two drugs for genotypes 2 and 3. The regimen only works in 50%–60% of patients and causes a host of side effects.

Because of these shortcomings, Scripps researchers set about looking for new therapeutics that might be able to treat HCV. The group screened 446 compounds from a clinical collection at the **NIH**. The researchers used a human cell-based model of HCV infection that was developed at Scripps in 2005 and reproduces the virus' entire life cycle.²

The group found 33 compounds that had low micromolar to sub-micromolar activity against HCV. Of those, 26 are marketed, approved or in clinical development to treat a range of indications outside HCV (see **Table 1, "HCV cache"**).

The team selected the 12 molecules with the best therapeutic indices and studied their modes of action. Most were inhibitors of viral entry, viral RNA replication or virion assembly.

The results were published in the *Proceedings of the National Academy of Sciences*. The group was led by Francis Chisari, professor of immunology and microbial science, who also headed the Scripps team that had developed the HCV infection model.

"We are very much interested in exploring any opportunities to repurpose existing drugs for HCV infection, and we routinely screen our entire compound collection" for potential hits, said Andrew Spaltenstein, VP of hepatitis C drug discovery at **GlaxoSmithKline plc**. However, he cautioned that repurposing may be complicated by differences in dosing.

Spaltenstein noted that the anti-HCV potencies for most of the compounds identified in the *PNAS* study were in the micromolar range, whereas the drugs' potencies against targets in their approved indications were greater by several orders of magnitude.

"This means that the required plasma concentrations for efficacy against HCV would massively exceed the exposures found safe and

effective for the original purpose" and could lead to undesirable on- and off-target effects, Spaltenstein said.

Indeed, one of the most clinically advanced new HCV therapies in development, the small molecule HCV NS3 protease inhibitor telaprevir (VX-950; MP-424), has an *in vitro* activity against HCV activity of 354 nM (ref. 3)—greater by several orders of magnitude than most of the compounds identified by the Scripps team. Partners **Vertex Pharmaceuticals Inc.**, **Mitsubishi Tanabe Pharma Corp.** and **Johnson & Johnson** have telaprevir in Phase III testing to treat HCV infection.

In the *PNAS* paper, the Scripps team did raise the dosing issue specifically, saying more information than *in vitro* potency was "necessary before concluding that these compounds can be used to treat HCV infection *in vivo*."

Issues beyond dosage

Repurposing specific compounds for HCV might involve additional challenges such as drug delivery and resistance.

According to Spaltenstein, some of the drugs identified in the *PNAS* article may not come with appropriate routes of administration for HCV. A case in point, he said, was salmeterol, an adrenergic receptor β_2 (ADRB2) agonist that was among the hits. GSK markets Advair, an inhaled combination of salmeterol and fluticasone, to treat asthma and chronic obstructive pulmonary disease (COPD).

"Because Advair was optimized and developed as an inhaled agent, the pharmacokinetic properties of salmeterol are not favorable for use as a systemic agent and would likely have to be re-engineered" to target HCV in the liver, Spaltenstein told *SciBX*.

Drug resistance also could be a barrier to repurposing. Spaltenstein noted that drugs in widespread use for other indications have probably been taken by many HCV carriers. As a result, those patients might already harbor drug-resistant HCV. "Such HCV patients would then not respond to the repurposed drug to treat their infection," he said.

Similarly, an antiviral repurposed to treat HCV could induce drug resistance in its approved indication. For example, the *PNAS* study found that **Pfizer Inc.**'s HIV protease inhibitor Viracept nelfinavir had anti-HCV activity. "But if nelfinavir were administered to an HCV patient who was unknowingly co-infected with HIV, then there would be a high likelihood for nelfinavir-resistant HIV to emerge—eliminating an important HIV treatment option for this patient," said Spaltenstein.

He added that GSK would remain open to the possibility of repurposing its drugs, but "at least after an initial analysis, I think chances are low that, in the end, the GSK drugs mentioned in the *PNAS* article will be suitable for repurposing for HCV."

Concurrent with its acquisition of **Genelabs Technologies Inc.** in January 2009, GSK created an R&D unit that focuses on the discovery and early preclinical development of therapies to treat HCV infection. "We are poised to progress multiple assets into preclinical and clinical

"At least after an initial analysis, I think chances are low that, in the end, the GSK drugs mentioned in the *PNAS* article will be suitable for repurposing for HCV."

**—Andrew Spaltenstein,
GlaxoSmithKline plc**

development in 2010,” Spaltenstein said, but he declined to disclose specific compounds or targets.

Finding a mechanism

Repurposing hurdles aside, Spaltenstein said the screening study described in the *PNAS* paper could be a starting point for identifying

new HCV targets and developing new anti-HCV scaffolds, much as cyclosporine did for HCV in the 1990s.

Long known as an immunosuppressant, cyclosporine’s anti-HCV activity prompted many companies to discover “potent drugs that lack the immunosuppressive action of cyclosporine but retain its anti-HCV activity,” Spaltenstein noted.

Table 1. HCV cache. A cell-based screen of over 400 molecules identified 26 compounds with low micromolar to submicromolar activity against HCV that are marketed, approved or in clinical development for other indications. Results were reported in the *Proceedings of the National Academy of Sciences*.

Product name	Mechanism	Company	Status/Indication
AcipHex rabeprazole	Proton pump inhibitor	Eisai Co. Ltd./Johnson & Johnson	Marketed for gastric ulcers and gastroesophageal reflux disease (GERD)
Alinia nitazoxanide	Pyruvate ferredoxin oxidoreductase inhibitor	Romark Laboratories L.C.	Marketed for diarrhea associated with <i>Cryptosporidium</i> or <i>Giardia</i> infection; Phase III to treat <i>Clostridium difficile</i> -associated disease (CDAD); Phase II for HCV infection and Crohn’s disease
Astepro/Optivar azelastine	Histamine H1 receptor (HRH1) antagonist	Meda AB	Marketed as Astepro for allergic rhinitis; marketed as Optivar for allergic conjunctivitis
Clarinet/Aerius desloratadine	HRH1 antagonist	Merck & Co. Inc.	Marketed for rhinitis and chronic idiopathic urticaria (CIU)
Corlux mifepristone	Progesterone receptor and cortisol receptor GR-2 antagonist	Concept Therapeutics Inc.	Phase III for depression and Cushing’s disease
Fareston toremifene	Nonsteroidal selective estrogen receptor modulator (SERM)	GTx Inc./Ipsen Group/Orion Corp.	Marketed for breast cancer; in registration to reduce fractures in men with prostate cancer; Phase III to prevent prostate cancer
Gleevec/Glivec imatinib	BCR-ABL tyrosine kinase inhibitor	Novartis AG	Marketed for acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST) and hematological malignancies
Haldol haloperidol	Butyrophenone antipsychotic	Johnson & Johnson	Marketed for schizophrenia and Tourette syndrome
Mycobutin rifabutin	Antibiotic	Pfizer Inc.	Marketed to prevent disseminated <i>Mycobacterium avium</i> complex (MAC) disease
Rimcazole	σ -1 Receptor agonist	Modern Biosciences plc	In-licensed by Modern for cancer
Serevent salmeterol	Adrenergic receptor β_2 (ADRB2) agonist	GlaxoSmithKline plc	Marketed for asthma and chronic obstructive pulmonary disease (COPD)
Silenor doxepin	HRH1 antagonist	Somaxon Pharmaceuticals Inc.	In registration for insomnia; available as a generic to treat depression
Staccato prochlorperazine	Dopamine D2 receptor antagonist	Alexza Pharmaceuticals Inc.	Phase II with Alexza’s proprietary Staccato system inhaler to treat migraine; available as a generic to treat nausea and vertigo
Viracept nelfinavir	HIV protease inhibitor	Pfizer/Roche	Marketed for HIV/AIDS
Amiodarone	Antiarrhythmic agent	Generic	Fibrillation and tachycardia
Benproperine ^A	Information not available	Information not available	Cough
Calcipotriol	Information not available	Generic	Psoriasis
Carvedilol	Adrenergic receptor β_1 (ADRB1) and ADRB2 antagonist	Generic	Heart failure, hypertension and myocardial infarction (MI)
Cyproheptadine	Serotonin (5-HT ₁) receptor antagonist	Generic	Allergy and hay fever
Fluphenazine	Phenothiazine antipsychotic	Generic	Schizophrenia and bipolar mania
Ketotifen	Second-generation H1 antihistamine/mast cell stabilizer	Generic	Allergic conjunctivitis, asthma and itchy eyes
Lacidipine ^A	Calcium channel blocker	Information not available	Hypertension
Lofepamine	Tricyclic antidepressant	Generic	Anxiety, depression and other neurological indications
Paroxetine	Selective serotonin reuptake inhibitor (SSRI)	Generic	Anxiety, depression and other neurological indications
Pizotiline ^A	Serotonin (5-HT ₁ , 5-HT _{2A} , 5-HT _{2C}) receptor antagonist	Information not available	Migraine
Trifluoperazine	Phenothiazine antipsychotic	Generic	Schizophrenia

^AMay not be currently available on the market.

Cyclosporine's activity against HCV was first observed in post-transplant patients who experienced exacerbations in their HCV infections when they stopped taking the drug as immunosuppressive therapy.⁴⁻⁶

Debiopharm S.A.'s Debio 025, a nonimmunosuppressive cyclosporine that targets cyclophilin, is in Phase II testing to treat HCV infection. At least two other companies have cyclophilin inhibitors in the clinic to treat HCV: **Novartis AG**'s NIM811 is in Phase II testing and **Scynexis Inc.**'s SCY-635 has completed Phase I testing.

In addition, Spaltenstein thinks working out the mechanisms by which each compound in the *PNAS* article exerts its anti-HCV activity will be the key to finding "new anti-HCV targets and/or molecular drug scaffolds."

Indeed, on the heels of the work published in *PNAS* "additional studies by Dr. Chisari and his group revealed target molecules and mechanisms of antiviral actions for some of the compounds," said Linda Pullan, CEO of **Viriome Inc.**, an antiviral company founded in 2007 by Chisari and Vincent Zurawski, president and CEO of neurology company **Varinel Inc.**

Pullan said that Scripps has filed provisional patents covering the findings of the *PNAS* paper and of the follow-on studies. Viriome has an exclusive option to license the IP.

The Scripps team was unavailable for comment.

Haas, M.J. *SciBX* 3(1); doi:10.1038/scibx.2010.3

Published online Jan. 7, 2010

REFERENCES

1. Gastaminza, P. *et al. Proc. Natl. Acad. Sci. USA*; published online Dec. 7, 2009; doi:10.1073/pnas.0912966107
Contact: Francis V. Chisari, The Scripps Research Institute, La Jolla, Calif. e-mail: fchisari@scripps.edu
2. Zhong, J. *et al. Proc. Natl. Acad. Sci. USA* **102**, 9294–9299 (2005)
3. Perni, R. *et al. Antimicrob. Agents Chemother.* **50**, 899–909 (2006)
4. Kanamori, H. *et al. Am. J. Med. Sci.* **303**, 109–111 (1992)
5. Gruber, A. *et al. J. Intern. Med.* **234**, 223–225 (1993)
6. Akiyama, H. *et al. Bone Marrow Transplant.* **20**, 993–995 (1997)

COMPANIES AND INSTITUTIONS MENTIONED

Debiopharm S.A., Lausanne, Switzerland
Genelabs Technologies Inc. (NASDAQ:GNLB), Redwood City, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508), Osaka, Japan
National Institutes of Health, Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
The Scripps Research Institute, La Jolla, Calif.
Scynexis Inc., Research Triangle Park, N.C.
Varinel Inc., West Chester, Pa.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.
Viriome Inc., Newbury Park, Calif.