Directions for innovation models and the role of public investment: Notes from hepatitis C

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Public investment in the ‘directionality’ of innovation: The replicon example from hepatitis C

Hepatitis C Virus—From Discovery to Cure
The 2016 Lasker-DeBakey Clinical Medical Research Award

Ralf F. W. Bartenschlager, PhD
Heidelberg University Hospital, Heidelberg, Germany.

Charles M. Rice, PhD
Laboratory of Virology and Infectious Disease and Center for the Study of Hepatitis C, Rockefeller University, New York, New York.

Michael J. Sofia, PhD
Arbutus Biopharma, Dealestown, Pennsylvania.

The 2016 Lasker-DeBakey Clinical Medical Research Award has been presented to Ralf F. W. Bartenschlager, Charles M. Rice, and Michael J. Sofia for the development of a system to study the replication of the virus that causes hepatitis C virus and for use of this system to revolutionize the treatment of this chronic, often lethal disease.

The liver is the largest organ in the human body and is central for metabolism and many other functions. Several viruses specialize in infecting the liver and are called hepatitis viruses. Five such viruses are known, including hepatitis C virus (HCV), which was originally recognized as an agent of posttransfusion non-A, non-B hepatitis. Given that about 6% of patients receiving blood transfusions developed non-A, non-B hepatitis, tremendous efforts were mounted to isolate and molecularly the patient-derived HCV population or cDNA cloning in the laboratory, injected into chimpanzees, which often gave rise to a productive HCV infection, providing the first genetic system for proviral HCV-specific drug targets were essential.

With virtually unlimited quantities of viral RNA, validated as infectious in vivo and expected to be suitable cell lines quickly followed, but that was not the case. The solution came from work in the lab of Ralf Bartenschlager that used another genome cloned from the liver of a chimpanzee. With the aim to isolate rare cell lines, Bartenschlager’s team developed a system called the replicon, which is a cell line that integrates a cDNA molecule of HCV RNA into the genome. The replicon system allowed for the study of viral replication and provided a basis for the development of new treatments for hepatitis C.

NIH funding behind replicon:

- $3.4m USD for Rice Lab, ‘99-’03

- $3.38m USD for APATH, which manufactured and distributed replicon

See also:
APATH LLC website: https://www.apath.com/


Cut and paste. From the hepatitis C genome (top), researchers cut genes for structural proteins and added others to make a replicon (bottom). A productive mutation (S1179G) appeared in region 5A.
Acquisition model of drug development in hepatitis C

Gilead to Buy Pharmasset for $11 Billion to Win in Hepatitis

Merck Agrees to Buy Idenix for $3.85 Billion
Merck Pays Three Times Idenix’s Value Friday in Bid to Expand Hepatitis C Portfolio

Bristol bags hot hep C drug developer Inhibitex for $2.5B
by John Carroll Jan 9, 2012 8:36am

Enanta’s HCV Collaboration Partner AbbVie receives Approval by the European Commission for MAVIRET™
August 2, 2019, 8:51 AM EDT
Pharmasset’s emergence from public investment

- 64 NIH grants, $10.5 million, between 1991-2012
- 49 patents disclosing public funding between 1986-2009
- 7/8ths of base salary paid as Veterans Affairs employee (U.S. public agency for veteran health care)
- 16 grants at $2.46 million, from NIH Small Business Innovation Research program (SBIR)
- Schinazi’s previous company, Triangle Pharmaceuticals, also bought by Gilead Sciences in 2002 for $464 million

Ray Schinazi, founder of Pharmasset

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<thead>
<tr>
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<th>Revenues $b</th>
<th>Net Income $b</th>
<th>Stock buybacks $b (as a % of NI)</th>
<th>Cash dividends $b (as a % of NI)</th>
<th>R&amp;D expenditures $b (as a % of Rev)</th>
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</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>546</td>
<td>86</td>
<td>61 (71%)</td>
<td>68 (79.4%)</td>
<td>82 (15%)</td>
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<td>Johnson &amp; Johnson</td>
<td>668</td>
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<td>65 (49.8%)</td>
<td>82 (12.3%)</td>
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<tr>
<td>Gilead Sciences</td>
<td>142</td>
<td>61</td>
<td>37 (61.2%)</td>
<td>4 (7.1%)</td>
<td>19 (13.7%)</td>
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<tr>
<td>Amgen</td>
<td>176</td>
<td>50</td>
<td>33 (66.8%)</td>
<td>10 (20.8%)</td>
<td>35 (20.2%)</td>
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<tr>
<td>Merck</td>
<td>382</td>
<td>62</td>
<td>32 (51.8%)</td>
<td>45 (72.5%)</td>
<td>75 (19.5%)</td>
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From 2007 to 2016, the 19 pharmaceutical companies included in the S&P 500 Index in January 2017 spent $297 billion repurchasing their own shares, equivalent to 61% of their combined R&D expenditures over this period.

How do we make ‘access’ an ex-ante design feature of evolving innovation models?
THANK YOU

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*Royal Radar Establishment (RRE), National Science Foundation (NSF)*

Source: Mazzucato (2013)
Prodrug approach used in hepatitis C came from publicly funded HIV research

Michael Sofia

Christopher McGuigan

Discovery of a β-α-2,β-2′-α-fluoro-2′-β-C-methyluridine Nucleoside Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus


Pharmasset, Inc., 301-3 College Road East, Princeton, New Jersey 08540

Received July 10, 2003

A = Phosphoramide structure developed thru McGuigan method initially developed via British, Belgian, and European Commission Funding and tested on sofosbuvir in 2005-2008 at Pharmasset

B = Sofosbuvir backbone Developed in 2003 by Pharmasset via VC, NIH, and VA support

Sofosbuvir developed at Pharmasset by Sofia team via bringing together prior backbone with phosphoramide structure in a novel manner.