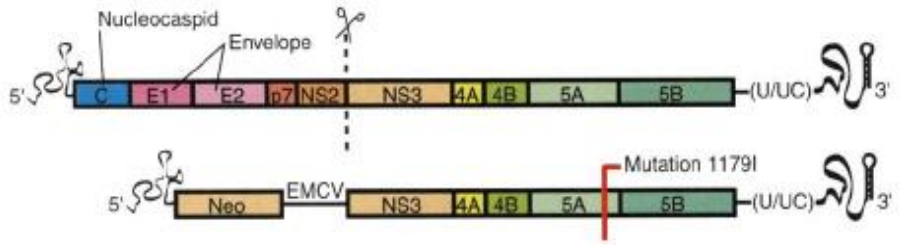
UCL IIPP Institute for Innovation and Public Purpose

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

Victor Roy, MD PhD
IIPP Research Fellow
Resident Physician, Boston Medical Center

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



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 (S1179I) appeared in region 5A.

NIH funding behind replicon:

- **$3.4m USD for Rice Lab, '99-'03**
- **$3.38m USD for APATH, which manufactured and distributed replicon**

VIEWPOINT

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, Doylestown, 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 o
cDNA cloning in the laboratory. Injec
thetic, naked genome RNA into the l
zees gave rise to a productive HCV in
vided the first genetic system for prov
HCV-specific drug targets were essenti

With virtually unlimited quanti
nome RNA, validated as infectious in
expected that finding a suitable cel
would quickly follow, but that was n
solution came from work in the lat
Bartenschlager that used another
genome cloned from the liver of a chr
patient. With the aim to isolate rare ce
bust HCV replication, "selectable mini
replicons were engineered. These repl

Bartenschlager, R.F.W., Rice, C.M., Sofia M J. 2016. "Hepatitis C Virus—From Discovery to Cure: the 2016 Lasker-DeBakey Clinical Medical Research Award." *JAMA.* 316(12):1254–55.
See also:
NIH Reporter Tool, https://projectreporter.nih.gov/reporter.cfm
APATH LLC website: https://www.apath.com/

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

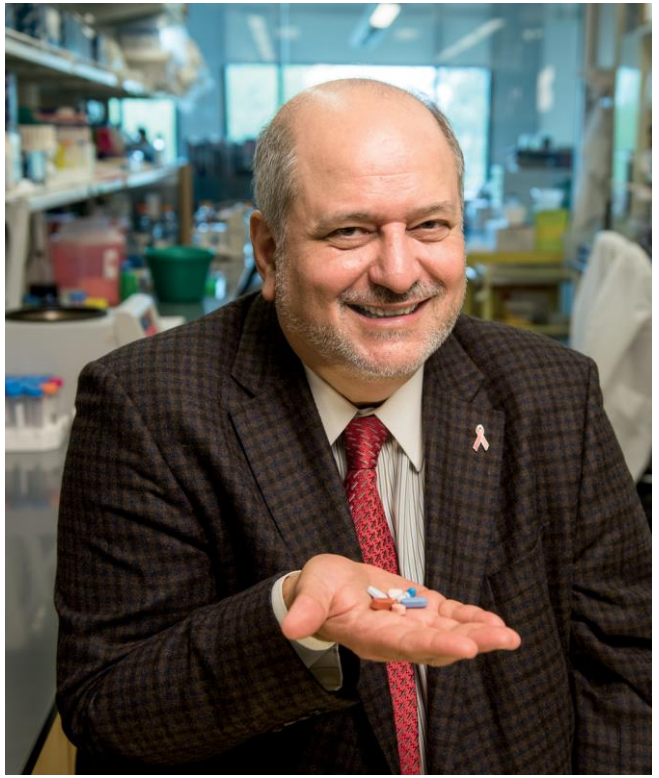
Enanta's HCV Collaboration Partner AbbVie receives Approval by the European Commission for MAVIRET™

August 2, 2019, 8:51 AM EDT

IIPP

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

Cohen, J. 2015. "King of the Pills." *Science* 348(6235):622–25.

Knowledge Ecology International. 2014. "Hepatitis Timeline." https://www.keionline.org/hcv

IIPP

A financialised pharmaceutical sector

	Revenues $b	Net Income $b	Stock buybacks $b (as a % of NI)	Cash dividends $b (as a % of NI)	R&D expenditures $b (as a % of Rev)
Pfizer	546	86	61 (71%)	68 (79.4%)	82 (15%)
Johnson & Johnson	668	131	45 (34%)	65 (49.8%)	82 (12.3%)
Gilead Sciences	142	61	37 (61.2%)	4 (7.1%)	19 (13.7%)
Amgen	176	50	33 (66.8%)	10 (20.8%)	35 (20.2%)
Merck	382	62	32 (51.8%)	45 (72.5%)	75 (19.5%)

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.**

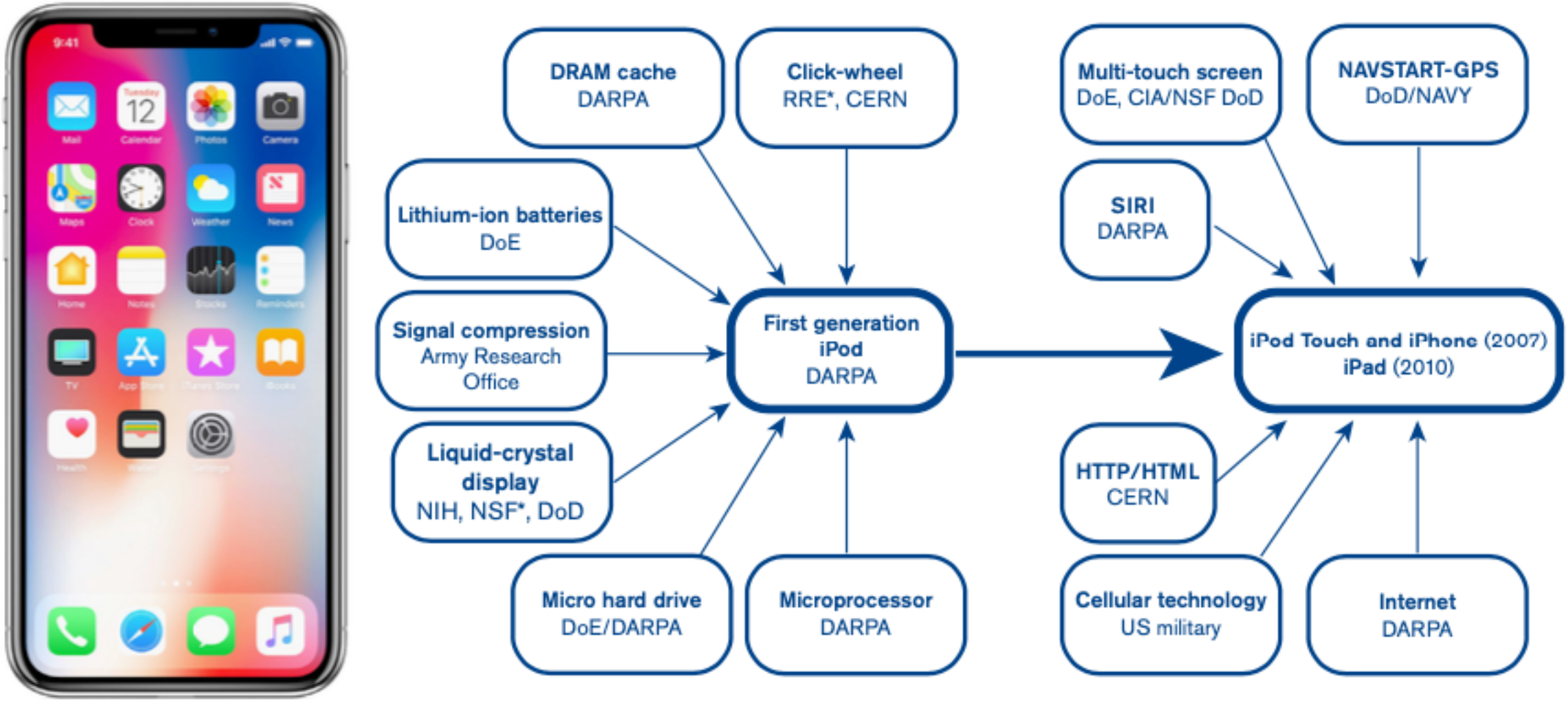
Tulum, Ö, Lazonick W, 2018. "Financialized Corporations in a National Innovation System: the U.S. Pharmaceutical Industry." *International Journal of Political Economy* 47(3-4):281–316.

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

UCL IIPP Institute for Innovation and Public Purpose

THANK YOU

Follow me
@victorroy



*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

(20) McGuigan, C.; Cahard, D.; Sheeka, H. M.; De Clercq, E.; Balzarini, J. Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite. *J. Med. Chem.* **1996**, *39*, 1748–1753.

(21) McGuigan, C.; Sutton, P. W.; Cahard, D.; Turner, K.; O'Leary, G.; Wang, Y.; Gumbleton, M.; De Clercq, E.; Balzarini, J. Synthesis, Anti-Human Immunodeficiency Virus Activity and Esterase Lability of Some Novel Carboxylic Ester-Modified Phosphoramidate Derivatives of Stavudine (d4T). *Antiviral Chem. Chemother.* **1998**, *9*, 473–479.

(22) Saboulard, D.; Naesens, L.; Cahard, D.; Salgado, A.; Pathirana, R.; Velazquez, S.; McGuigan, C.; De Clercq, E.; Balzarini, J. Characterization of the Activation Pathway of Phosphoramidate Triester Prodrugs of Stavudine and Zidovudine. *Mol. Pharmacol.* **1999**, *56*, 693–704.

(23) Perrone, P.; Daverio, F.; Valente, R.; Rajyaguru, S.; Martin, J. A.; Lévêque, V.; Le Pogam, S.; Najera, I.; Klumpp, K.; Smith, D. B.; McGruigan, C. First Example of Phosphoramidate Approach Applied to a 4′-Substituted Purine Nucleotide (4′-Azidoadenosine): Conversion of an Inactive Nucleotide to a Submicromolar Compound versus Hepatitis C Virus. *J. Med. Chem.* **2007**, *50*, 55463–5470.

(24) McGuigan, C.; Kelleher, M. R.; Perrone, P.; Mulready, S.; Luoni, G.; Daverio., F.; Rajyaguru, S.; Le Pogam., S.; Najer, I.; Martin, J. A.; Klumpp, K.; Smith, D. B. The Application of Phosphoramidate ProTide Technology to the Potent Anti-HCV Compound 4′-Azidocytidine (R1479). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4250–4254.

Christopher McGuigan

7202 *J. Med. Chem.* **2010**, *53*, 7202–7218
DOI: 10.1021/jm100863x

Journal of Medicinal Chemistry Article

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

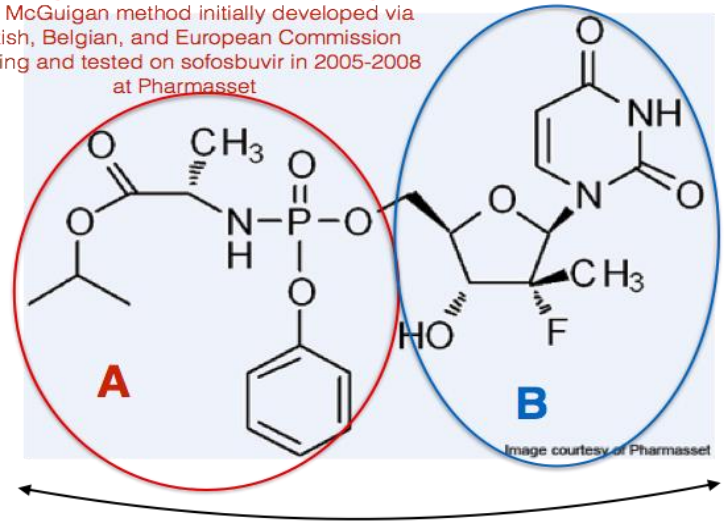
Michael J. Sofia,* Donghui Bao, Wonsuk Chang, Jinfa Du, Dhanapalan Nagarathnam, Suguna Rachakonda, P. Ganapati Reddy, Bruce S. Ross, Peiyuan Wang, Hai-Ren Zhang, Shalini Bansal, Christine Espiritu, Meg Keilman, Angela M. Lam, Holly M. Micolochick Steuer, Congrong Niu, Michael J. Otto, and Phillip A. Furman

Pharmasset, Inc., 303A College Road East, Princeton, New Jersey 08540

Received July 10, 2010

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

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



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

IIPP