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Public funding for transformative drugs: the case of sofosbuvir

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The approval of sofosbuvir (Sovaldi) in 2013 transformed chronic hepatitis C virus (HCV) care, but its high cost was criticized in part because of reports of substantial public involvement in its development. We developed a methodology to assess the public’s contribution through the National Institutes of Health (NIH) in developing sofosbuvir. Using key terms from the timeline of sofosbuvir, we identified articles in PubMed; linked them to federal funding using the NIH RePORTER; reviewed the title, organization, and investigator of each resulting award for relatedness; and converted related awards to 2018 US dollars. Of 6043 unique awards, we identified 29 that were directly (US$7.7 million) and 110 that were indirectly (US$53.2 million) related awards made to major academic institutions and companies engaged in the development of the drug. These findings indicate that public funding had a key role in developing sofosbuvir, with an estimated US$60.9 million provided in NIH funding.

Introduction

In current debates in the USA over the high prices of brand-name prescription drugs, a common argument used to support such prices is that they are needed to fund drug discovery and development [1]. Although manufacturers and venture capitalists invest substantial resources in drug development, many of the most transformative drugs that have emerged in the past few decades (those that are both innovative and have a groundbreaking effect on patient care) were discovered and developed, in part, based on funding from the NIH and other public sources to academic medical centers, government laboratories, and start-up companies [2].

One of the most transformative drugs over the past decade was sofosbuvir (Sovaldi), approved in 2013 as the first in a class of direct-acting antivirals that offered a highly effective and well-tolerated potential cure for patients with chronic HCV. However, controversy arose when its manufacturer launched the drug at a list price of US$84,000 per course of therapy, or ~US$1000 per pill [3]. During its first year on the market, sofosbuvir cost the US healthcare system nearly US$8 billion in list price expenditures [4]. Although prices have since fallen in the ensuring years with the introduction of other direct-acting antivirals, Medicaid (the state- and federal-supported health insurance program for low-income patients) spent a reported ~US$12 billion on HCV drugs from 2014 to 2017, which amounted to 5% of the total spending of the program for all outpatient prescriptions during that period [5].

Some US public and private payors responded to these high prices by restricting access for patients [4]. Patient advocates and others seeking broader availability of these drugs pointed out that this class of drugs was based, in part, on discoveries made by academic and government institutions over the course of many decades, and that sofosbuvir itself was synthesized by scientists based at a start-up company that received public support for this work through the NIH. This raised the question whether such an investment might mean that the public was ‘paying twice’ for their treatments [6].

Estimates of the amount of federal funding that directly contributed to development of sofosbuvir have ranged from US $244,504 to US$1 million to US$9 million to over US$62.4 million [4,7–9]. These estimates indicate the lack of clarity surrounding whether and to what extent federal funding was linked to the development of the drug. Thus, we sought to develop a methodology for rigorously assessing NIH contributions towards developing transformative drugs and to apply it to the case of sofosbuvir.

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Analytical approach

Key term identification

We first identified key persons, organizations, and other terms important to the development of sofosbuvir. We used the Drugs@FDA database to identify the approval date, manufacturer, and mechanism of action of sofosbuvir. We then reviewed the Approved Drug Products with Therapeutic Equivalence Evaluations resource that lists patent and exclusivity information for US Food and Drug Administration (FDA)-approved drug products to identify important patents associated with sofosbuvir (Appendix S1 in the supplemental information online). We searched the US Patent and Trademark Office database to review these patents, collecting all available information about the assignees and inventors, which served as a starting point for identifying individuals and organizations in later development. Finally, we further identified the institutions and individuals involved with the early development of the drug from company filings with the Securities and Exchange Commission, primary investigators listed on NIH awards, and other published reports and articles.

Public funding identification

We used these key terms to conduct searches in the Public Library of Medicine (PubMed) database to find published articles and combined terms (e.g., inventors’ names) with ‘hepatitis C’ to narrow the results (Appendix S2 in the supplemental information online). For each resulting article, we linked its unique PubMed identification number (PMID) with data in the National Institute of Health (NIH) Report Portfolio Online Reporting Tool Expenditures and Results (RePORTER) Tool. We linked them by navigating to the ‘Advanced Search’ function on the NIH RePORTER homepage, selecting the ‘Search Publications’ tab, pasting the PMIDs into the blank text box, and conducting the search. The RePORTER is an electronic tool that allows the public to access information about federal awards from the NIH as far back as 1980 [10]. The information in the RePORTER is managed by the NIH Office of Extramural Research and Integrates information from electronic Research Administration (eRA) databases, Medline, PubMed Central, NIH Intramural Database, and iEdison [10]. The awards we linked through the RePORTER were downloaded in full, duplicates deleted, and their content reviewed for relatedness to the development of sofosbuvir.

Public funding evaluation

For all awards distributed up to and including 2013, we evaluated the title, contact primary investigator (investigator), and organization to determine whether any of these were related to the development of sofosbuvir. Each category was scored 1 if related or 0 if not for each award. We ultimately only included awards distributed up to and including 2007 because that was the year sofosbuvir was discovered. A project title was considered related if the research: described or addressed the management and/or control of HCV; the development of sofosbuvir (or a closely related drug analog) or the mechanism of action of sofosbuvir; and/or included ‘HCV’ or ‘hepatitis’ and was related to drug development for this condition. A Cohen’s kappa statistic was calculated to quantify the level of agreement between title reviewers (R.E.B. and F.A.T.), and disagreements were resolved by a third author (A.S.K.). The kappa statistic was used to measure agreement [11]. This analysis was performed using STATA version 15.0 (College Station, Texas, Stata Corporation, 2017). A kappa statistic was calculated only for the title category because it was most subjective.

An investigator was considered related if the person was a patent-listed inventor, founder, and/or affiliate of an organization involved with the development of sofosbuvir, or another key contributor based on our research (Appendix S3 in the supplemental information online). An organization was considered related if such a key investigator was affiliated with it or the organization was affiliated with a major milestone of development, like drug discovery. These included: Apath, Avid Therapeutics, Centers for Disease Control and Prevention, Emory University, Georgia State University, Gilead Sciences, Idenix Pharmaceuticals, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Disease (NIAID), Pharmasset, Rockefeller University, Scripps Research Institute, Triangle Pharmaceuticals, University of Alabama, University of Georgia, the Veterans Affairs Health System, and Washington University (Appendix S4 in the supplemental information online).

Scores from each category for each award were summed. The higher an award score, the more likely that award was related to the development of sofosbuvir. For all awards scoring a total of 2 or more, we reviewed the abstract of the award. Based on the score and award abstract, we determined whether it was ‘directly related,’ ‘indirectly related,’ or neither. For example, awards distributed to Pharmasset supporting HCV drug development were classified as directly related, whereas awards supporting research for drugs similar to sofosbuvir and by the same researchers but for a different disease were classified as indirectly related. Disagreements on categorizing the awards were resolved by consensus among authors. Finally, the dollar amounts of awards classified as directly or indirectly related were converted to 2018 US dollars using the US Bureau of Labor Statistics consumer price index [12].

Findings

We identified 48 key terms, of which the largest subset was the list of patent-listed inventors (Appendices S1 and S2 in the supplemental information online). The PMIDs associated with published articles that resulted from the key terms searched linked to 50 575 unique NIH awards through the NIH RePORTER. Of those, 42 530 were awards for subprojects, which we removed because they were already accounted for in the core project awards. A total of 8045 core project awards remained, of which 2002 were distributed after 2013 and excluded. We reviewed the remaining 6043 awards for relatedness to the development of sofosbuvir. The kappa-statistic calculation indicated reasonable agreement between reviewers for award title category (Cohen’s kappa = 0.64) [13]. We identified 29 directly related awards, 110 indirectly related awards, and 5904 awards not likely related to the drug’s development during the relevant timeline of its development (Tables 1 and 2; Figs 1 and 2).

Period I: before 1998

Non-A, non-B hepatitis (later renamed hepatitis C) was first identified during the mid-1970s; by 1989, the virus was cloned and sequenced [14,15]. Some of this work was led by Michael Houghton at the Chiron Corporation through a collaboration with the Centers for Disease Control and Prevention (CDC) [16]. In 1990, the first blood test for HCV was developed to
TABLE 1

| Project title | Agency       | Project number | Contact principal investigator | Organization name | Fiscal Year | Fiscal year total cost | 2018 US$ |
|---------------|--------------|----------------|---------------------------------|-------------------|-------------|------------------------|----------|
| Non-carbohydrate Approaches to Anti-AIDS Nucleosides | NIAID | 5R01AI028731-05 | Dennis Liotta | Emory University | 1993 | US$164 257 | US$285 440 |
|               |              | 5R01AI028731-06 |                                 |                   | 1994 | US$192 418 | US$326 029 |
|               |              | 5R01AI028731-07 |                                 |                   | 1995 | US$200 114 | US$329 725 |
|               |              | 2R01AI028731-08 |                                 |                   | 1997 | US$208 475 | US$326 165 |
|               |              | 5R01AI028731-09 |                                 |                   | 1998 | US$199 336 | US$307 084 |
|               |              | 5R01AI028731-10 |                                 |                   | 1999 | US$205 317 | US$309 463 |
|               |              | 5R01AI028731-11 |                                 |                   | 2000 | US$211 475 | US$308 379 |
|               |              | 5R01AI028731-12 |                                 |                   | 2001 | US$217 820 | US$308 843 |
| Nucleosides with Dual Anti-HIV and HBV Activity | NIAID | 1R01AI041980-01 | Raymond Schinazi | Emory University | 1997 | US$154 642 | US$241 942 |
|               |              | 5R01AI041980-02 |                                 |                   | 1998 | US$205 182 | US$316 090 |
|               |              | 5R01AI041980-03 |                                 |                   | 1999 | US$164 061 | US$247 280 |
|               |              | 2R37AI041980-04 |                                 |                   | 2000 | US$192 000 | US$279 980 |
|               |              | 5R37AI041980-05 |                                 |                   | 2001 | US$192 000 | US$272 333 |
|               |              | 5R37AI041980-06 |                                 |                   | 2002 | US$194 177 | US$271 835 |
|               |              | 3R37AI041980-05S1 |                                 |                   | 2002 | US$24 884 | US$34 733 |
|               |              | 3R37AI041980-07 |                                 |                   | 2003 | US$195 507 | US$266 811 |
|               |              | 3R37AI041980-08S1 |                                 |                   | 2004 | US$72 723 | US$96 672 |
|               |              | 5R37AI041980-08 |                                 |                   | 2004 | US$192 000 | US$255 228 |
|               |              | 4R37AI041980-09 |                                 |                   | 2005 | US$225 925 | US$290 483 |
|               |              | 5R37AI041980-10 |                                 |                   | 2006 | US$220 615 | US$274 792 |
|               |              |                   |                                 |                   | 2007 | US$214 217 | US$259 486 |
| Hepatitis C: Models for Replication | NIAID | 1U01AI041424-01 | Curt Hagedorn | Emory University | 1996 | US$200 000 | US$320 085 |
| New Treatment Strategies for Hepatitis C | NCI | 1R41CA077818-01 | Curt Hagedorn | Avid Therapeutics | 1998 | US$100 000 | US$154 053 |
| Modified Nucleosides for Hepatitis C Virus | NIAID | 1R43AI052686-01 | Lieven J. Stuyver | Pharmasset, Inc. | 2002 | US$162 200 | US$226 401 |
| Novel Class of Compounds for Treatment of HCV Infections | NIAID | 1R43AI056720-01 | W. Kyzysztof Pankiewicz | Pharmasset, Inc. | 2003 | US$175 000 | US$238 825 |
| Dioxolane Nucleosides as Antiviral Agents | NIAID | 1R43AI056794-01 | Jinfu Du | Pharmasset, Inc. | 2003 | US$175 260 | US$239 179 |
| 2'-and/or 4'-C-Modified Nucleosides as Anti-HCV Agents | NIDDK | 1R01DK066922-01 | Jinfu Du | Pharmasset, Inc. | 2004 | US$189 277 | US$251 608 |
|               |              | 5R01DK066922-02 | Jinfu Du | Pharmasset, Inc. | 2005 | US$194 954 | US$250 662 |
|               |              | 5R01DK066922-03 | Jinfu Du | Pharmasset, Inc. | 2006 | US$338 736 | US$421 920 |

* Award listed in the NIH RePORTER for the total amount of US$. The cover page indicates the total costs requested for the proposed period of support (2003–2006) to be US$722 957.

routinely screen patients [17]. In 1991, the first medication to treat chronic HCV was approved by the FDA, but it produced very low sustained virological response rates [17].

During the latter half of the 1990s, other therapies for chronic HCV were approved that demonstrated improved response rates, and a process for cloning the virus was developed independently by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) and Washington University School of Medicine that allowed in vivo study of the virus [18,19]. Investigators also characterized how HCV cells replicate in a specific hepatoma cell line that allowed for in vitro studies of HCV RNA replication [20]. By the late 1990s, researchers understood more about HCV and sequenced a key protein, NSSB, that sofosbuvir would later target [20].

During this time, several investigators at Emory University were studying HCV and HIV, including Curt Hagedorn, Director of Hepatology at Emory from 1993 to 2003 [21]. The related HIV work culminated in the development of emtricitabine (Emtriva), later licensed to Triangle Pharmaceuticals, and led by chemistry professor Dennis Liotta, virologist Raymond Schinazi (also affiliated with Atlanta Veteran Affairs Medical Center; University of Georgia; Georgia State University), and researcher Woo-Baeg Choi [22–28]. Both emtricitabine and what would later be discovered as sofosbuvir work through similar mechanisms, and other HCV research at different institutions began receiving federal awards during this period.

In the years leading up to and including 1997, we identified six directly related NIH awards (US$1.8 million) and 28 indirectly related awards (US$11.4 million) (Tables 1 and 2). The six directly related awards went to Emory University, with either Liotta, Schinazi, or Hagedorn as investigators, between 1993 and 1997 (Table 1). For example, one of the awards to Emory in 1996 was titled ‘Hepatitis C—Models for Replication,’ with Hagedorn as the primary investigator, which supported research to study the viral replication of HCV and medications directly targeting the HCV RNA-dependent RNA polymerase (Table 1 and Appendix S5 in the supplemental information online). Of the 28 indirectly related awards, 11 went to the
University of Georgia for anti-HIV research between 1993 and 1997 (US$3.5 million); eight went to Washington University studies of anti-HCV drugs and vaccines and to better understand flavivirus replication (HCV is a flavivirus) (US$3.2 million); eight went to Scripps Research Institute to understand the pathogenesis of HCV (US$4.4 million); and one went to Triangle Pharmaceuticals for nucleoside drug research (US$133 240) (Table 2).

**Period II: 1998 and after**

In 1998, Schinazi and colleagues, including Liotta, Jean-Pierre Sommodassi (of the University of Alabama at Birmingham), and Chung Chu (of the University of Georgia), founded Pharmasset, a start-up company focused in large part on developing oral drugs for HCV [29–31]. That same year, Schinazi and Sommodassi started another drug company, called Idenix Pharmaceuticals, with similar aims to Pharmasset, likely leveraging their university experience at least in part [32,33]. A challenge for oral HCV drugs was their bioavailability, and the team at Pharmasset pursued prodrug formulations to enhance the utility of this approach [34].

Other important research central to the development of the drug focused on developing an HCV cell culture system and growing the virus in vitro. One company, Avid Therapeutics
| Project Title | Agency | Project number | Contact principle investigator | Organization name | Fiscal year total cost | 2018 US% |
|---------------|--------|----------------|-------------------------------|-------------------|-----------------------|---------|
| Synthesis and Biotransformation of Anti-HIV Prodrugs | NIAID | 5R01AI025899-07 | Chung K. Chu | University of Georgia | US$252,551 | US$5438,874 |
| | | 2R01AI025899-08 | | | US$218,198 | US$369,710 |
| | | 5R01AI025899-09 | | | US$249,344 | US$410,840 |
| | | 5R01AI025899-10 | | | US$235,986 | US$377,678 |
| | | 3R01AI025899-10S1 | | | US$24,507 | US$39,222 |
| | | 5R01AI025899-11 | | | US$272,387 | US$426,158 |
| | | 3R01AI025899-11S1 | | | US$75,450 | US$116,233 |
| | | 5R01AI025899-12 | | | US$253,895 | US$391,134 |
| | | 5R01AI025899-13 | | | US$343,217 | US$517,312 |
| | | 5R01AI025899-14 | | | US$353,514 | US$515,304 |
| | | 2R37AI025899-15A1 | | | US$366,482 | US$519,628 |
| | | 5R37AI025899-16 | | | US$371,422 | US$518,436 |
| | | 5R37AI025899-17 | | | US$382,566 | US$522,092 |
| | | 5R37AI025899-18 | | | US$394,042 | US$523,805 |
| | | 5R37AI025899-19 | | | US$405,867 | US$521,844 |
| | | 4R37AI025899-20 | | | US$503,323 | US$626,924 |
| | | 5R37AI025899-21 | | | US$491,584 | US$595,466 |
| Synthesis and (Biological) Evaluation of Anti-HIV Nucleosides | NIAID | 5R01AI032351-02 | Chung K. Chu | University of Georgia | US$173,665 | US$301,789 |
| | | 5R01AI032351-03 | | | US$181,600 | US$307,699 |
| | | 5R01AI032351-04 | | | US$187,724 | US$309,310 |
| | | 5R01AI032351-05 | | | US$191,374 | US$306,260 |
| | | 5R01AI032351-06 | | | US$184,769 | US$289,077 |
| | | 5R01AI032351-07 | | | US$275,462 | US$424,359 |
| | | 2R01AI032351-08A1 | | | US$239,594 | US$361,127 |
| | | 5R01AI032351-09 | | | US$234,898 | US$342,535 |
| | | 5R01AI032351-10 | | | US$241,696 | US$342,697 |
| | | 2R01AI032351-11 | | | US$306,294 | US$427,530 |
| | | 5R01AI032351-12 | | | US$303,947 | US$414,800 |
| | | 5R01AI032351-13 | | | US$313,063 | US$416,158 |
| | | 5R01AI032351-14 | | | US$322,455 | US$414,979 |
| Proteolytic Control of Flavivirus Replication | NIAID | 5R01AI031501-03 | Charles Rice | Washington University | US$178,820 | US$310,747 |
| | | 5R01AI031501-04 | | | US$178,334 | US$302,165 |
| | | 5R01AI031501-05 | | | US$185,368 | US$305,427 |
| Hepatitis C Virus-Developing Antivirals and Vaccines | NCI | 5R01CA057973-02 | Charles Rice | Washington University | US$273,694 | US$475,615 |
| | | 5R01CA057973-03 | | | US$278,900 | US$472,562 |
| | | 5R01CA057973-04 | | | US$297,719 | US$490,546 |
| | | 2R01CA057973-05 | | | US$270,224 | US$432,473 |
| | | 5R01CA057973-06 | | | US$323,448 | US$506,044 |
| | | 5R01CA057973-07 | | | US$303,203 | US$467,094 |
| | | 5R01CA057973-08 | | | US$314,595 | US$474,171 |
| | | 5R01CA057973-09 | | | US$262,940 | US$383,426 |
| | | 7R01CA057973-10 | | Rockefeller University | US$63,500 | US$92,597 |
| | | 2R01CA057973-11 | | | US$385,488 | US$526,080 |
| | | 5R01CA057973-12 | | | US$395,975 | US$526,374 |
| | | 5R01CA057973-13 | | | US$396,857 | US$510,258 |
| | | 5R01CA057973-14 | | | US$387,818 | US$483,054 |
| | | 5R01CA057973-15 | | | US$376,571 | US$456,149 |
| Pathogenesis of Liver Disease in Hepatitis | NIAID | 2R01AI020001-10 | Francis Vincent Chisari | Scripps Research Institute | US$377,751 | US$656,442 |
| | | 5R01AI020001-11 | | | US$387,918 | US$657,280 |
| | | 5R01AI020001-12 | | | US$389,046 | US$641,025 |
| | | 5R01AI020001-13 | | | US$411,437 | US$658,475 |
| | | 5R01AI020001-14 | | | US$430,173 | US$673,018 |
| | | 2R01AI020001-15 | | | US$466,772 | US$719,078 |
| | | 5R01AI020001-16 | | | US$427,991 | US$645,087 |
| | | 5R01AI020001-17 | | | US$459,678 | US$670,316 |
| | | 5R01AI020001-18 | | | US$471,489 | US$668,516 |
| | | 5R01AI020001-19 | | | US$511,845 | US$714,441 |
| | | 2R01AI020001-20 | | | US$320,175 | US$436,947 |
| | | 5R01AI020001-21 | | | US$556,979 | US$740,399 |
| | | 5R01AI020001-22 | | | US$570,762 | US$733,857 |
| | | 5R01AI020001-23 | | | US$571,211 | US$711,484 |
| | | 5R01AI020001-24 | | | US$568,508 | US$688,646 |
TABLE 2 (Continued)

| Project Title | Agency | Project number | Contact principle investigator | Organization name | Fiscal year | Fiscal year total cost | 2018 US% |
|---------------|--------|----------------|--------------------------------|-------------------|-------------|-----------------------|---------|
| Hepatitis C Virus | NCI | 5R01CA058000-02 | Claudio Pasquinelli | Scripps Research Institute | 1993 | US$218 762 | US$380 157 |
| Disease Pathogenesis (in Pathogenic Mice) | NCI | 5R01CA058000-03 | | | 1994 | US$223 753 | US$379 122 |
| Hepatitis C Virus Immunobiology and Pathogenesis | NCI | 1R01CA076403-01 | Francis Vincent Chisari | Scripps Research Institute | 1998 | US$374 924 | US$577 583 |
| Modified Purine Nucleosides as Antiviral Agents | NIAID | 1R43AI040775-01 | Phillip Furman | Triangle Pharmaceuticals | 1997 | US$85 163 | US$133 240 |
| Hepatitis C: Studies of Immunity and Pathogenesis | NIAID | 7U19AI04034-06 | Charles Rice | Rockefeller University | 2000 | US$680 907 | US$992 910 |
| Replications | NIAID | 5U19AI04034-07 | | | 2001 | US$762 360 | US$1 080 936 |
| Characterization of the Hepatitis C NSSa Kinase Complex | NIAID | SF32AI051820-01 | Timothy L. Tellinghuisen | Rockefeller University | 2002 | US$38 320 | US$53 487 |
| Immune Complexes: Origin and Effects in HCV Infection | NIAID | 5F32AI051820-02 | | | 2003 | US$46 420 | US$63 349 |
| Cellular Genes that Control HCV Replication | NCI | 5R01AI06561-01 | Lynn Dustin | Rockefeller University | 2003 | US$48 928 | US$65 040 |
| Functional Analysis of Hepatitis C Virus Glycoproteins | NIAID | 1R01AI050798-01A1 | Jane A. McKeating | Rockefeller University | 2004 | US$337 000 | US$447 978 |
| Analysis of Hepatitis C Virus Tropism in the Liver | NIDDK | 1F32DK070497-01 | Andrew J. Syder | Rockefeller University | 2005 | US$48 296 | US$62 097 |
| Characterization of the HCV NSSa Protein | NIAID | 5F32DK070497-02 | | | 2006 | US$50 428 | US$62 812 |
| Novel Role of NS2 in HCV Infection | NIAID | 5F32DK070497-03 | Timothy L. Tellinghuisen | Scripps Research Institute | 2007 | US$52 898 | US$64 077 |
| Characterization of the HCV p7 Protein Identification and Characterization of Cellular Factors Involved in HCV Entry | NIAID | 1K22AI067645-01 | | | 2006 | US$157 840 | US$196 601 |
| | NIAID | 5K22AI067645-02 | | | 2007 | US$108 000 | US$130 823 |
| | NIAID | 1F32AI069693-01A1 | Cynthia de la Fuente | Rockefeller University | 2007 | US$46 826 | US$56 721 |
| | NIDDK | 1F32DK081193-01A1 | Christopher T. Jones | Rockefeller University | 2007 | US$51 278 | US$62 114 |
| | NIAID | 1R01AI072613-01 | Charles Rice | Rockefeller University | 2007 | US$422 500 | US$511 783 |

(founded in 1994), aimed to develop assays for evaluating compounds for HBV and HCV [35,36]. Another start-up, Apath LLC, was founded by NIH grantee Charles Rice (Rockefeller University and Washington University) that focused on licensing technologies to pharmaceutical companies to develop products to treat HCV. Rice and his team were also working on developing technology to culture HCV, and were successful [37–39]. In 2005, other teams also grew HCV in the laboratory, including researchers...
at the National Institute of Diabetes and Digestive and Kidney Diseases, Rockefeller University, Scripps Research Institute, and probably others [14,40–42].

Meanwhile, research was ongoing at the recently incorporated Pharmasset. During the early 2000s, the compound PSI-6130 was synthesized; controversy emerged regarding who synthesized it—whether Jeremy Clark, a researcher at Pharmasset, or other researchers at Idenix [43]. Important derivatives emerged from it, including PSI-7851 and its diastereomer PSI-7977 [44,45]. Michael Sofia is reported to have synthesized PSI-7977 in 2007, which was later named sofosbuvir based on his name [46].

Pharmasset began animal toxicity studies of PSI-7851 in May 2008 and Phase I studies in March 2009 [47,48]. In 2010, Pharmasset announced it would be rapidly advancing PSI-7977, initiating Phase II clinical studies, because of its favorable safety profile [31,49]. In 2011, Pharmasset announced the success of PSI-7977: all patients were cured of their disease, including the ten patients who had not used interferon [4]. The company then initiated Phase III trials of PSI-7977; it was acquired by Gilead shortly thereafter in January 2012 for US$11.2 billion dollars, with 4% (US$440 million) paid directly to Schinazi [4,31,50–52]. Gilead supported several additional Phase III studies and submitted a new drug application to the FDA for sofosbuvir, which was approved on December 6, 2013 [53].

We identified 23 directly related awards made by the US federal government during this period (totaling US$5.8 million) and 82 indirectly related awards (totaling US$41.7 million) (Tables 1 and 2). Of the directly related awards, one went to Hagedorn at Avid Therapeutics for work to develop an HCV assay in 1998 (US$154 053), crucial because an assay would allow for further analysis of the viral lifecycle and drug development; six went to Pharmasset, with Du or Stuyver as the primary investigator, between 2003 and 2006 focusing on HCV and antiviral research (US$1.6 million); 16 awards went to Emory, with Liotta or Schinazi as the primary investigator, between 1998 and 2007, for their continued anti-HIV and HBV research (US$4.4 million) (Table 1).

We also identified 82 indirectly related awards (US$41.7 million) that appear to have supported important research to develop novel HCV drugs at varying organizations between 1998 and 2007 (Table 2). Nineteen awards supported Chu at the University of Georgia to continue research on anti-HIV nucleosides between 1998 and 2007 (US$8.5 million). Three awards funded Rice at Washington University to research antivirals and vaccines for HCV between 1998 and 2000 (US$1.3 million). Fifteen awards supported Rice at Rockefeller to conduct basic science research on HCV between 2000 and 2007 (US$1.2 million). Another 15 awards went to Rockefeller University to conduct basic science research on HCV, supporting investigators who collaborated with Rice (US$3.6 million). Three awards went to Apath to develop an HCV screening assay between 2000 and 2002 (US$1.1 million). Finally, 27 federal awards supported investigators at the Scripps Research Institute to conduct research on the biology of HCV (US $15.8 million).

**Discussion**

The discovery of the medication ultimately marketed as sofosbuvir originated in several academic centers as early as the 1990s, continued at the start-up Pharmasset, and was later commercialized by Gilead Sciences. During this time, we identified 29 directly related and 110 indirectly related awards from NIH that supported key milestones in the development of sofosbuvir, with a combined estimated total of at least US$60.9 million dollars of support after adjusting for inflation.

Research during Period I (before 1998) focused heavily on virology related to HIV/AIDS, whereas research in Period II (after 1998) focused more specifically on HCV, including both understanding the disease and possible drug therapies. The awards we identified were crucial to the development of sofosbuvir. For example, Rice and Sofia were awarded the Lasker-DeBakey Clinical Research Award in 2016, sometimes referred to as ‘America’s Nobel Prize’, for their work in replicating HCV and developing drugs to target it, which were both key milestones in the development of sofosbuvir [54]. Even though none of the academic researchers are listed on any of the key drug patents and neither could we identify licensing agreements or royalties received by any institution attributable to sofosbuvir specifically, publicly funded research underlay the development of sofosbuvir, as it has with other transformative drugs [2,55,56].

There is a widespread belief that the pharmaceutical industry is the most important source of innovation that leads to the development of prescription drugs, a perception that is effectively disseminated by the industry and used to justify high US drug prices [57]. A US Government investigation found that Pharmasset spent US$62.4 million (US$70 million after adjusting for inflation) developing sofosbuvir [4]. Although most of these funds originated from early-phase private investors, the start-up also received direct support from the Federal Government. Six highly related awards were directed to Pharmasset between 2002 and 2006, including four R01 awards and two R43 awards [58]. The NIH estimates that it has invested > US$1 billion dollars in small businesses (e.g., R43 awards), including Pharmasset, to commercialize research [59]. This policy has been criticized as NIH’s ‘socialization of risk with privatization of gains’ in drug development [60].

Precisely estimating specific federal funding remains difficult, and it is more challenging when funding amounts do not appear for related awards in the NIH RePORTER. One award still lists a nominal funding amount of US$1, which is clearly incorrect. To shed more light on what the Federal Government invested in Pharmasset, we submitted a Freedom of Information Act Request to the NIH about this US$1 award in 2006. The cover page and subsequent progress report of the award for the year in question that we received in response to the request indicated the award amount for that year amounted to US$338 736. Thus, it remains difficult to estimate NIH funding when award amounts are misstated or not readily accessible. Recent legislation introduced aims to improve transparency related to Government research funding, but is limited to drugs developed for Coronavirus 2019 (COVID-19) [62]. However, once better infrastructure is developed to adequately track Government investment, this tool could be used for other drugs.

The amount of public and investment we identified supporting the evolution of sofosbuvir was small compared with the $11.2 billion acquisition cost that Pharmasset was paid by Gilead in 2012 (<1%), but was similar in size to the amount that Pharmasset reported investing in the development of the drug [4,49,50]. This case highlights an opportunity for policymakers to consider
whether a manufacturer should be obligated to consider public contributions that lead to the development of transformative drugs when establishing a price. Pharmasset expected the 12-week HCV treatment with sofosbuvir to cost US$36 000 in the USA, but Gilead ultimately set the price at US$84 000 per course of treatment [4]. The pricing strategy of Gilead allowed them to recoup US $10.3 billion in sales during the first full year that sofosbuvir was on the market [4]. Another recent proposal aims to ensure drugs developed with Federal funding are affordable and accessible by preventing companies from exclusively licensing such drugs used to treat or prevent COVID-19 [63,64]. Although the proposal only covers drugs developed in the context of COVID-19, it could be expanded to include other drugs, such as transformative drugs or those essential to the public health. In the case of sofosbuvir, much of its development relied on public funding of Pharmasset, and patients and payors could have benefited from limitations on pricing of the resulting drug product.

Finally, our estimate should be interpreted as only one component of public’s contribution to the development of sofosbuvir, although it is higher than the value identified in other reports. Our finding might be an underestimate in part because we focused on applied and not basic science research. We did not include other NIH awards related to virology generally, HCV vaccine development, and clinical trials that contributed to the improved understanding of HCV and other novel medications to treat it. For example, we did not consider NIH awards to Emory’s Center for AIDS research that supported the Virology Core led by Schinazi or the Drug Discovery Core led by Liotta, which received nearly US $2.5 million during the years the amounts were reported.

This estimate also does not capture additional public spending on HCV drugs through Government-funded insurance programs [4] or tax incentives awarded to Pharmasset for the research and development costs they incurred. There are also other costs that patients incurred, such as copays and out-of-pocket costs, for their HCV care, which can limit access. Thus, considering key public funding for developing sofosbuvir plus the additional spending by payors and patients, it is evident the public is a major contributor to the development of sofosbuvir.

Limitations

There are limitations related both to the methodology used here and to data from the NIH RePORTER. First, by identifying articles through PubMed using key terms, we were only able to identify awards that resulted in a publication. Thus, while academics are incentivized to publish their work, researchers at start-up or spin-off companies might not have the same incentive, meaning that the costly failures in basic and translational research are not considered by this method. Second, the search terms selected might have unnecessarily limited the resulting articles in PubMed, which in turn would limit the awards linked through the NIH RePORTER. Third, the award titles and abstract provided in the NIH RePORTER were sometimes vague, making relatedness classifications difficult, or the amount of the award was not provided or was clearly mistated (e.g. as one dollar). Fourth, of the different agencies that provide data on awards to the NIH RePORTER, those agencies provided data during different time periods; for example, the VA, Schinazi’s main employer for most of this period, provided data only from 2009 onwards, meaning that we could not account for much financial support from the VA in our estimate [10].

Concluding remarks

Public funding had a key role in the development of sofosbuvir, with an estimated US$60.9 million federal dollars contributed to its evolution. Our methodology and results can contribute to the discussion about the extent to which US taxpayers are ‘paying twice’ for many transformative drugs. When considering that public contributions have a key role in drug development for life-saving medications, policymakers should ensure that patients and payors are able to access it at a fair and reasonable price.

Conflict of interest

REB serves as a clinical consultant to Alosa Health for work unrelated to this publication.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:**https://doi.org/10.1016/j.drudis.2020.09.024.**

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