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Public funding for transformative drugs: the case of sofosbuvir

Rachel E. Barenie, Jerry Avorn, Frazer A. Tessema and Aaron S. Kesselheim

Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA 02120, USA

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.

Corresponding author: 881 Madison Ave. Room 573, Memphis, TN 38163. Barenie, R.E. (rbarenie@bwh.harvard.edu)

1359-6446/
https://doi.org/10.1016/j.drudis.2020.09.024

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

Directly related awards to the development of sofosbuvir

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$272 233
		5R37AI041980-06			2002	US$194 177	US$271 035
		3R37AI041980-05S1			2002	US$24 884	US$34 733
		5R37AI041980-07			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	Jinfa Du	Pharmasset, Inc.	2003	US$175 260	US$239 179
2′-and/or 4′-C-Modified Nucleosides as Anti-HCV Agents	NIDDK	1R01DK066922-01	Jinfa Du	Pharmasset, Inc.	2004	US$189 277	US$251 608
		5R01DK066922-02			2005	US$194 954	US$250 662
		5R01DK066922-03			2006	US$338 736[a]	US$421 920
						US$5 382 572	US$7 710 626

[a] Award listed in the NIH RePORTER for the total amount of US$1. 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, NS5B, 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

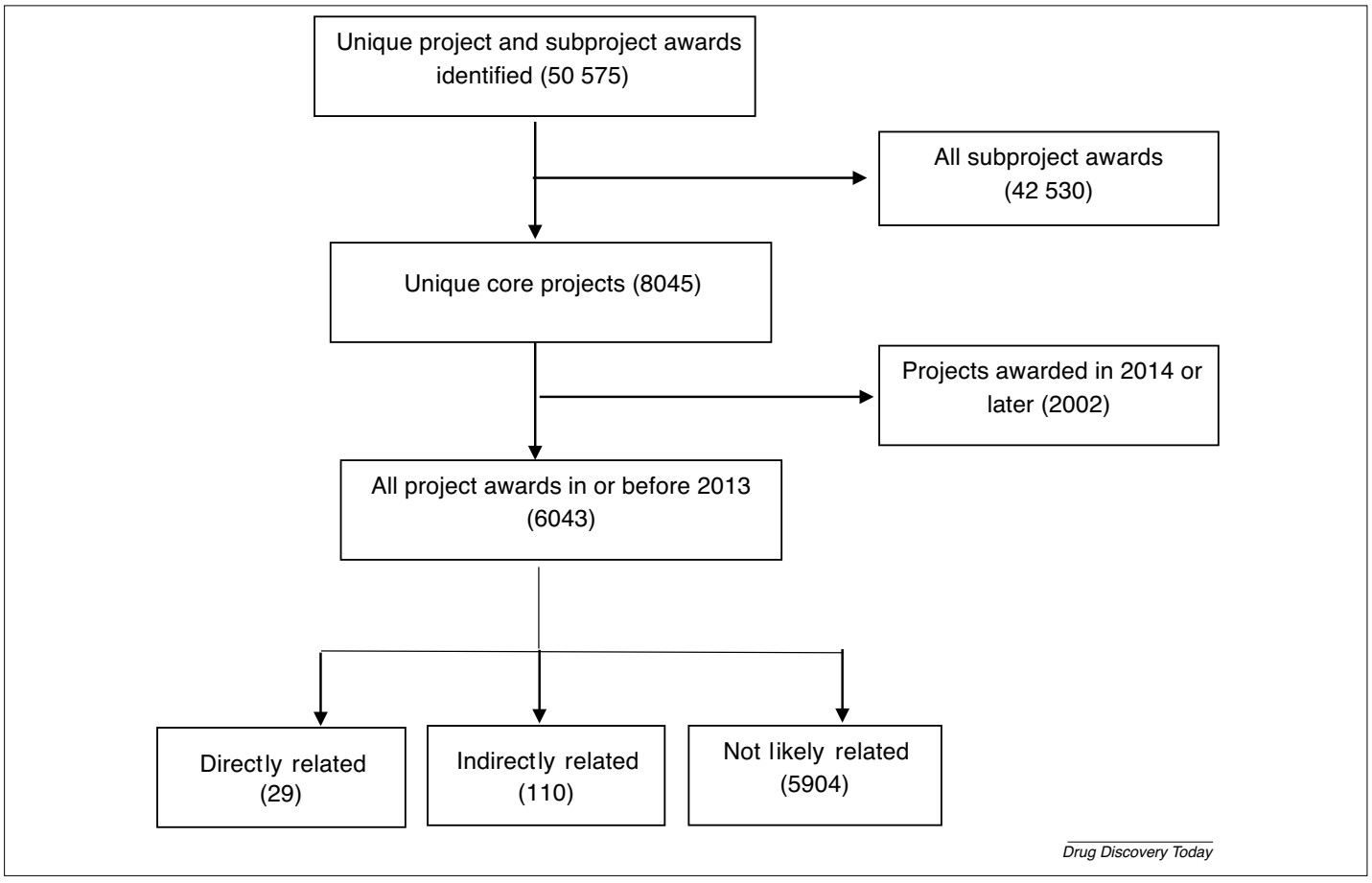

FIGURE 1

Categorization of NIH RePORTER award results.

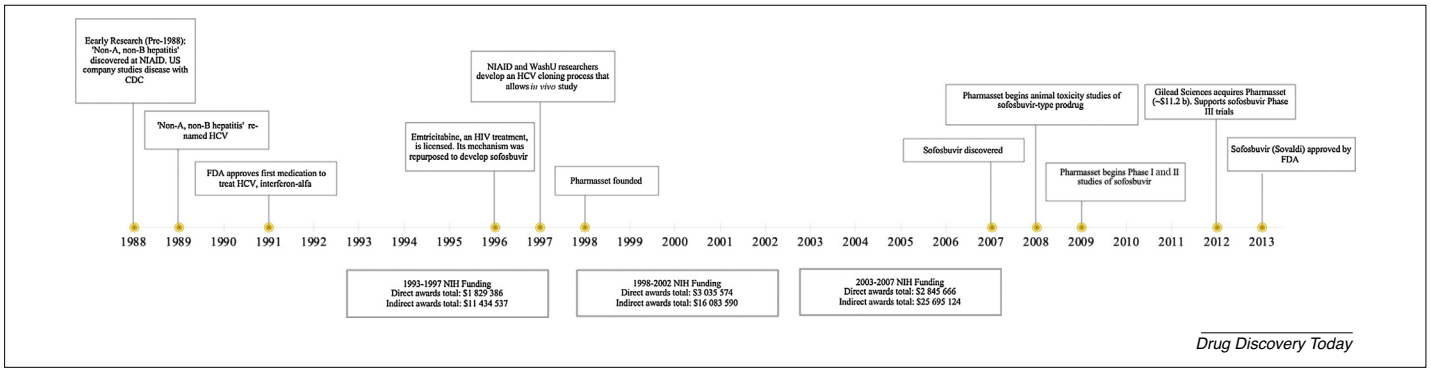

FIGURE 2

Timeline of key milestones and awards in the development of sofosbuvir.

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

TABLE 2

Indirectly related awards to the development of sofosbuvir

Project Title	Agency	Project number	Contact principle investigator	Organization name	Fiscal year	Fiscal year total cost	2018 US%
Synthesis and Biotransformation of Anti-HIV Prodrugs	NIAID	5R01AI025899-07	Chung K. Chu	University of Georgia	1993	US$252 551	US$438 874
		2R01AI025899-08			1994	US$218 198	US$369 710
		5R01AI025899-09			1995	US$249 344	US$410 840
		5R01AI025899-10			1996	US$235 986	US$377 678
		3R01AI025899-10S1			1996	US$24 507	US$39 222
		5R01AI025899-11			1997	US$272 387	US$426 158
		3R01AI025899-11S1			1998	US$75 450	US$116 233
		2R01AI025899-12			1998	US$253 895	US$391 134
		5R01AI025899-13			1999	US$343 217	US$517 312
		5R01AI025899-14			2000	US$353 514	US$515 504
		2R37AI025899-15A1			2001	US$366 482	US$519 628
		5R37AI025899-16			2002	US$371 422	US$518 436
		5R37AI025899-17			2003	US$382 566	US$522 092
		5R37AI025899-18			2004	US$394 042	US$523 805
		5R37AI025899-19			2005	US$405 867	US$521 844
		4R37AI025899-20			2006	US$503 323	US$626 924
		5R37AI025899-21			2007	US$491 584	US$595 466
Synthesis and (Biological) Evaluation of Anti-HIV Nucleosides	NIAID	5R01AI032351-02	Chung K. Chu	University of Georgia	1993	US$173 665	US$301 789
		5R01AI032351-03			1994	US$181 600	US$307 699
		5R01AI032351-04			1995	US$187 724	US$309 310
		2R01AI032351-05			1996	US$191 374	US$306 260
		5R01AI032351-06			1997	US$184 769	US$289 077
		5R01AI032351-07			1998	US$275 462	US$424 359
		2R01AI032351-08A1			1999	US$239 594	US$361 127
		5R01AI032351-09			2000	US$234 898	US$342 535
		5R01AI032351-10			2001	US$241 696	US$342 697
		2R01AI032351-11			2002	US$306 294	US$427 530
		5R01AI032351-12			2003	US$303 947	US$414 800
		5R01AI032351-13			2004	US$313 063	US$416 158
		5R01AI032351-14			2005	US$322 455	US$414 597
Proteolytic Control of Flavivirus Replication	NIAID	5R01AI031501-03	Charles Rice	Washington University	1993	US$178 820	US$310 747
		5R01AI031501-04			1994	US$178 334	US$302 165
		5R01AI031501-05			1995	US$185 368	US$305 427
Hepatitis C Virus-Developing Antivirals and Vaccines	NCI	5R01CA057973-02	Charles Rice	Washington University	1993	US$273 694	US$475 615
		5R01CA057973-03			1994	US$278 900	US$472 562
		5R01CA057973-04			1995	US$297 719	US$490 546
		2R01CA057973-05			1996	US$270 224	US$432 473
		5R01CA057973-06			1997	US$323 448	US$506 044
		5R01CA057973-07			1998	US$303 203	US$467 094
		5R01CA057973-08			1999	US$314 595	US$474 171
		5R01CA057973-09			2000	US$262 940	US$383 426
		7R01CA057973-10		Rockefeller University	2000	US$63 500	US$92 597
		2R01CA057973-11			2003	US$385 488	US$526 080
		5R01CA057973-12			2004	US$395 975	US$526 374
		5R01CA057973-13			2005	US$396 857	US$510 258
		5R01CA057973-14			2006	US$387 818	US$483 054
		5R01CA057973-15			2007	US$376 571	US$456 149
Pathogenesis of Liver Disease in Hepatitis	NIAID	2R01AI020001-10	Francis Vincent Chisari	Scripps Research Institute	1993	US$377 751	US$656 442
		5R01AI020001-11			1994	US$387 918	US$657 280
		5R01AI020001-12			1995	US$389 046	US$641 025
		5R01AI020001-13			1996	US$411 437	US$658 475
		5R01AI020001-14			1997	US$430 173	US$673 018
		2R01AI020001-15			1998	US$466 772	US$719 078
		5R01AI020001-16			1999	US$427 991	US$645 087
		5R01AI020001-17			2000	US$459 678	US$670 316
		5R01AI020001-18			2001	US$471 489	US$668 516
		5R01AI020001-19			2002	US$511 845	US$714 441
		2R01AI020001-20			2003	US$320 175	US$436 947
		5R01AI020001-21			2004	US$556 979	US$740 399
		5R01AI020001-22			2005	US$570 762	US$733 857
		5R01AI020001-23			2006	US$571 211	US$711 484
		5R01AI020001-24			2007	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 Disease Pathogenesis (in Pathogenic Mice)	NCI	5R01CA058000-02	Claudio Pasquinelli	Scripps Research Institute	1993	US$218 762	US$380 157
		5R01CA058000-03			1994	US$223 753	US$379 122
		5R01CA058000-04			1995	US$232 801	US$383 582
Hepatitis C Virus Immunobiology and Pathogenesis	NCI	1R01CA076403-01	Francis Vincent Chisari	Scripps Research Institute	1998	US$374 924	US$577 583
		5R01CA076403-02			1999	US$318 343	US$479 821
		5R01CA076403-03			2000	US$417 683	US$609 077
		5R01CA076403-04			2001	US$429 161	US$608 450
		5R01CA076403-05			2002	US$466 687	US$651 408
		2R01CA076403-06A1			2003	US$518 621	US$707 768
		5R01CA076403-07			2004	US$531 431	US$706 438
		5R01CA076403-08			2005	US$544 625	US$700 252
		5R01CA076403-09			2006	US$545 094	US$678 953
		5R01CA076403-10			2007	US$542 558	US$657 212
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	7U19AI040034-06	Charles Rice	Rockefeller University	2000	US$680 907	US$992 910
		5U19AI040034-07			2001	US$762 360	US$1 080 936
		5U19AI040034-08			2002	US$701 031	US$978 509
		5U19AI040034-09			2003	US$759 817	US$1 036 931
		5U19AI040034-10			2004	US$777 103	US$1 033 012
		2U19AI040034-11			2005	US$848 905	US$1 091 480
		5U19AI040034-12			2006	US$789 280	US$983 103
		5U19AI040034-13			2007	US$789 384	US$956 198
Antiviral Screening Assays Based on HCV Replications	NIAID	1R43AI049604-01	Paul David Olivo	Apath LLC	2001	US$99 395	US$140 930
		2R44AI049604-02			2002	US$429 325	US$599 258
		5R44AI049604-03			2003	US$320 675	US$437 629
Characterization of the Hepatitis C NS5a Kinase Complex	NIAID	1F32AI051820-01	Timothy L. Tellinghuisen	Rockefeller University	2002	US$38 320	US$53 487
		5F32AI051820-02			2003	US$46 420	US$63 349
		5F32AI051820-03			2004	US$48 928	US$65 040
Immune Complexes: Origin and Effects in HCV Infection	NIAID	1R01AI060561-01	Lynn Dustin	Rockefeller University	2003	US$138 133	US$188 511
		5R01AI060561-02			2004	US$421 250	US$559 972
		5R01AI060561-03			2005	US$421 979	US$542 559
		5R01AI060561-04			2006	US$412 571	US$513 886
		5R01AI060561-05			2007	US$400 606	US$485 262
Cellular Genes that Control HCV Replication	NCI	1R01CA108304-01	Francis Vincent Chisari	Scripps Research Institute	2003	US$362 469	US$494 666
		5R01CA108304-02			2004	US$362 353	US$481 680
		5R01CA108304-03			2005	US$403 153	US$518 354
		5R01CA108304-04			2006	US$373 281	US$464 948
		5R01CA108304-05			2007	US$371 351	US$449 826
Functional Analysis of Hepatitis C Virus Glycoproteins	NIAID	1R01AI050798-01A1	Jane A. McKeating	Rockefeller University	2004	US$337 000	US$447 978
		5R01AI050798-02			2005	US$337 667	US$434 155
Analysis of Hepatitis C Virus Tropism in the Liver	NIDDK	1F32DK070497-01	Andrew J. Syder	Rockefeller University	2005	US$48 296	US$62 097
		5F32DK070497-02			2006	US$50 428	US$62 812
		5F32DK070497-03			2007	US$52 898	US$64 077
Characterization of the HCV NS5A Protein	NIAID	1K22AI067645-01	Timothy L. Tellinghuisen	Scripps Research Institute	2006	US$157 840	US$196 601
		5K22AI067645-02			2007	US$108 000	US$130 823
Novel Role of NS2 in HCV Infection	NIAID	1F32AI069693-01A1	Cynthia de la Fuente	Rockefeller University	2007	US$46 826	US$56 721
Characterization of the HCV p7 Protein	NIDDK	1F32DK081193-01A1	Christopher T. Jones	Rockefeller University	2007	US$51 278	US$62 114
Identification and Characterization of Cellular Factors Involved in HCV Entry	NIAID	1R01AI072613-01	Charles Rice	Rockefeller University	2007	US$422 500	US$511 783
						US$37 967 400	US$53 213 251

(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 incorproated 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 and2007 (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$11.2 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 recieved 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.

Acknowledgments

We would like to acknowledge the help of Elvira D'Andrea with the statistical calculations. Research funded by The Engelberg Foundation. A.S.K.'s research is also supported by Arnold Ventures and the Harvard-MIT Center for Regulatory Science.

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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