TAXPAYER FUNDED DRUGS & A PRICING CRISIS

P4 AD

SICKLE CELL TREATMENT

Sickle Cell Disease (SCD) results from a mutation in the gene that tells the body how to produce hemoglobin. The devastating disease affects about 100,000 Americans and disproportionately affects African American communities.[1] People with SCD have abnormally shaped hemoglobin — the protein responsible for transporting oxygen in the body — which results in severe pain, infections, and fatigue.[2] Currently, the only cure for SCD is a bone marrow transplant; this option is only available to a small number of young patients due to the difficulty of finding bone marrow matches. Until the gene can be repaired, most SCD patients are left with no options other than symptom management.

TAXPAYER INVESTMENT IN A SICKLE CELL CURE

The National Institutes of Health (NIH), a taxpayer-funded federal agency, has prioritized curing SCD and currently spends more than $100 million a year on research into the disease.[5] In addition to supporting recent advances in potentially curative gene therapy, the NIH has spent decades investing billions of taxpayer dollars into basic science on Sickle Cell Disease and the human genome.[7,8]

There is increasing optimism that the taxpayer investment is about to pay off for patients living with SCD. In March 2019, NIH Director Francis Collins remarked, "I am daring to say a cure for sickle cell disease may even be now at hand." [9]

Dr Collins is referring to new gene therapies that are being studied within the walls of NIH. Two of the therapies, LentiGlobin BB305 and BCL11a shRNA (miR), enable patients to make normal shaped hemoglobin —[10] essentially curing the disease.

BY THE NUMBERS:

1 in 365

BLACK OR AFRICAN AMERICANS ARE BORN WITH SICKLE CELL DISEASE.[1]

210

TOTAL NUMBER OF NEW DRUGS APPROVED BY THE FDA BETWEEN 2010 AND 2016 – ALL DEVELOPED WITH TAXPAYER INVESTMENT THROUGH THE NIH.[3]

$1-$2 million

THE PRICE TAG ON RECENTLY APPROVED GENE THERAPIES.[4]

$100 million

AMOUNT THAT TAXPAYERS INVEST ANNUALLY ON RESEARCH INTO SICKLE CELL AND POSSIBLE CURES.[5]

$300 million

AMOUNT THAT TAXPAYERS INVESTED INTO TWO POTENTIAL CURES FOR SICKLE CELL DISEASE.[6]

According to an analysis by Patients for Affordable Drugs, taxpayers invested more than $300 million into BCL11a shRNA (miR) and LentiGlobin BB305 (see Table 1).

THE PROBLEM

After taxpayer-funded research helps lead to the discovery of a new drug, the NIH licenses intellectual property to a pharmaceutical company to bring the drug to market. After patents are transferred, the company sets the drug price without regard to taxpayer investment, and at the highest price possible.[11] Unless appropriate regulatory guardrails are established, this system enables pharmaceutical companies to turn taxpayer investment into unrestrained profit without regard to affordability or accessibility.

When pharmaceutical companies are allowed to price gouge for publicly funded discoveries, the American people pay three times. First as taxpayers investing in research at the NIH, second as patients at the pharmacy counter, and a third time through tax dollars that support America's largest health insurance programs — Medicare and Medicaid.

Given the $1 to $2 million price range of recent gene therapies, we are concerned that a sickle cell cure will be brought to market at a price that is unaffordable for patients and for the taxpayers who supported its development. The NIH should use all levers in its power to ensure the final price accounts for public investment.

REQUEST TO NIH

As the NIH continues to lead scientific advances, it must also develop new policies on licensing taxpayer-funded research to private corporations. Instead of funding breakthrough treatments and transferring the intellectual property to a company for a small royalty and without regard to the final price, the NIH could:[12-13]

- Receive a commitment from a drug manufacturer – upon acquiring the NIH-supported patent – to limit the U.S. price of a drug to no more than the average of comparable OECD nations.
- Receive a commitment from a drug manufacturer that licensing agreements are contingent on the drug company agreeing to price the drug based on specific metrics. Metrics could include:
    - Manufacturing costs, royalty payments, clinical trials and R&D as reported to the IRS, and the value of tax credits received in exchange for the drug's development (i.e. orphan drug credits).
    - Amount of money taxpayers invested in the drug.
    - A profit margin based on the company's historic reported profit and loss over a recent five-year period.
- Create an outside advisory committee to assist NIH in developing a methodology to determine reasonable prices.

"A cure for this disease would change the lives of so many people across the country. However, the cure will not help those who cannot afford it."

Amy Mason-Cooley is a sickle cell patient and advocate. She was diagnosed with SCD at the age of 5 years old and has been managing the disease ever since. She uses her experience to help educate and provide support for those in the sickle cell community. Join her Facebook group @CruisingwithSickleCell

CONCLUSION

Public research dollars must prioritize public health — not private profit. Allowing the pharmaceutical industry to make unlimited profits off taxpayer-funded research is harmful to patients and unsustainable for our health care system. Taxpayers are fueling innovation through the NIH and then paying high prices at the pharmacy counter — far more than patients in any other country.

It may have been acceptable for the NIH to be indifferent to final price when transferring the patent of a drug priced at $200, but with new gene therapies priced at $2 million dollars, price must be an element of technology transfer agreements to the private sector.[4]

The NIH should use its authority to require that inventions developed as a result of taxpayer investment be available at a reasonable price that balances incentives for innovation with patient access.

CITATIONS

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3. https://www.pnas.org/content/115/10/2329
4. https://www.bloomberg.com/news/articles/2019-04-07/gene-therapy-was-hailed-as-a-revolution-then-came-the-bill
5. https://www.nih.gov/news-events/news-releases/nih-launches-initiative-accelerate-genetic-therapies-cure-sickle-cell-disease
6. See Table 1 in Appendix.
7. https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=116&key=S
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APPENDIX

Table 1: Public Investment In LentiGlobin BB305 and BCL11a shRNA (miR)

Funding Source	Grant Recipient	Core Project	Title of Grant	Total # FYs	Funding Amount
NIH Institute	*Academic Institution*	*ID Number*	*Most Recent Title Published*		*Nominal USD*
NHLBI	Boston Children's Hospital	P01HL032262	Developmental Biology of Human Erythropoiesis	33	$50,924,599
NHLBI	St. Jude Children's Research Hospital	P01HL053749	Lentiviral Gene Therapy for Sickle Cell Disease And Immunodeficiency Disorders	21	$39,266,890
NCATS	University of Pennsylvania	UL1TR000003	Institutional Clincal and Translational Science Award	5	$38,869,598
NCATS	University of Pennsylvania	UL1TR001878	Institutional Clincal and Translational Science Award	4	$30,360,638
NIA	Salk Institute for Biological Studies, University of California San Diego	P01AG010435	Gene Therapy for Alzheimer's Disease	21	$27,925,988
NINDS	Washington University	U01NS042804	Silent Cerebral Infarct Multi-Center Clinical Trial	7	$20,652,240
NIDDK	Boston Children's Hospital	P30DK049216	A Center of Molecular Developmental Hematopoiesis	21	$19,240,501
NHLBI	St. Jude Children's Research Hospital	U54HL070590	Comprehensive Sickle Cell Center Composite:Basic & Translational Research Program	8	$13,785,347
NHGRI	Altius Institute for Biomedical Sciences, University of Washington	U54HG007010	A Comprehensive Catalog of DNASEL Hypersensitive Sites	5	$11,215,970
NHLBI	Boston Children's Hospital	R01HL032259	Molecular Analysis of Normal and Thalassemic DNA	31	$10,515,725
NHLBI	Boston University Medical Campus	R01HL068970	Genetic Modulation of Sickle Cell Disease	9	$6,994,877
NHLBI	Boston University Medical Campus	R01HL087681	Genome-Wide Association Studies in Sickle Cell Anemia and in Centenarians	3	$5,997,280
NIA	Salk Institute for Biological Studies, University of California San Diego	R01AG008514	Cell Genesis in the Intact and Injured Substantia Nigra	18	$5,589,699
NIAID	Salk Institute for Biological Studies, University of Pennsylvania	R01AI052845	Favored sites for HIV cDNA integration in the human genome	10	$3,913,422
NHLBI	Johns Hopkins University	U54HL090515	Comprehensive Sickle Cell Center at JHU and UAB	3	$3,830,239
NIAID	University of Pennsylvania	R01AI082020	Massively Parallel Analysis of Integration in Therapeutic Gene Transfer	9	$3,483,285
NIDDK	Boston University Medical Campus	R01DK069646	Genetic Modulation of HbF in Beta Thalassemia	5	$2,867,888
NIAID	University of Pennsylvania, Wistar Institute	T32AI007324	Training in Virology	5	$1,845,894
NHGRI	Dana-Farber Cancer Institute	R01HG005085	Toward a systematic understanding of targeting mechanisms for epigenetic factors	4	$1,713,741
NHLBI	Brigham and Women's Hospital	R01HL090921	Cell selection strategies for the gene therapy of the beta-hemoglobinopathies	4	$1,667,868
NHLBI	Johns Hopkins University	R01HL091759	Longitudinal SIT Trial Plasma Proteomic Biomarker Discovery and Validation in SCI	4	$1,596,279
NHGRI	National Human Genome Research Institute	ZIAHG200340	Gene Therapy for Hemoglobin Disorders	2	$1,125,110
NIAID	Salk Institute for Biological Studies	R01AI037510	HIV-1 Infection of Non- Proliferating Targets	3	$879,140
NIA	National Institute on Aging	ZIAAG000675	Aging-related Traits and Disease Risk Factors in a Sardinian Population Cohort	2	$750,540
NIDDK	Boston Children's Hospital, UT Southwestern Medical Center	K01DK093543	Mechanistic roles of BCL11A in globin switching and fetal hemoglobin silencing	6	$732,079
NIDDK	Boston Children's Hospital	K08DK093705	Epigenetic regulation of BCL11A in the hemoglobin switch	5	$679,395
				Grand Total	$306,424,232

Methodology

Patients For Affordable Drugs conducted an analysis from May 14, 2019 to June 2, 2019 to identify funding for the development of LentiGlobin BB305 and BCL11a shRNA (miR) gene therapies. The analysis identified three seminal events that led to the development of these therapies, including: (1) gene target (BCL11A) identification, (2) use of lentivirus vectors for gene editing, and (3) the development of LentiGlobin BB305. We identified critical publications that contributed to these seminal events by running a key term search on the EMBASE database and a NIH Director's Blog post on breakthroughs in sickle cell gene therapy. In addition, more publications were further identified by following citations within the background sections of key publications related to LentiGlobin BB305, lentivirus applications, and discovery of the BCL11A target.

Publications related to clinical aspects of gene therapy that were not unique to sickle cell gene therapy were not identified for analysis. Consequently, publications related to Plerixafor, a bone marrow stimulant used in tandem with many gene therapies, were not included.

PubMed Identifiers (PMID) for each publication were matched to corresponding core projects using the NIH RePORTER. Core projects and all associated funding were cataloged into an excel sheet with grants divided into funding by fiscal year (FY).

Finally, the analysis compiled a list of all publications related to each core project ID. P4AD used RStudio to systematically perform a keyword search to filter publications. Publications were only included if their titles included one of the following keywords: "sickle", "thalassemia", "gene therapy", "BCL11A", "beta globin", "lentivirus", "lentiviral", "gene transfer". After removing publications that did not contain the keywords, we performed project description analyses of the remaining publications to determine relevancy and inclusion of FY funding. If a project description indicated that the main purpose of the research was to study lentivirus vectors, sickle cell disease, beta-thalassemia disease, BCL11A, or gene therapy, all FY funding was included. If an abstract was closely related to keywords but did not strongly relate to the above subjects, FY funding was excluded if it: (1) occurred after the date of the key publication, or (2) occurred three years before the oldest publication.

All remaining fiscal year amounts were added to create a final estimate of NIH investment in LentiGlobin BB305 and BCL11a shRNA (miR) therapy development (see **Table 1**).

Limitations

The final estimate of $306 million in public funding invested into LentiGlobin BB305 and BCL11a shRNA (miR) gene therapies is an underestimate. The analysis Patients for Affordable Drugs implemented only examined the components of the therapy related to lentivirus vectors and target identification of BCL11A. There are many more broadly applicable components of sickle cell gene therapy (i.e stem cell mobilization technologies) that also maintain a long history grounded in public funding, but were not explored within the scope of this current analysis.

There are also inherent limitations to the utilization of the NIHRePORTER Database. NIHRePORTER only reports public funding from 1985 onwards, but public investment into sickle cell disease research dates back farther than 1985. Other limitations include incomplete reporting of PMIDs, inconsistencies on project duration, and limited reporting on ClinicalTrials.gov identifiers. Due to limited information about the breakdown of funding within a single fiscal year (FY), it was not possible to discern within a project how much total funding was specifically allocated towards a key publication. However, the full monetary support of core research project/laboratory gives investigators the freedom to select their priorities. Such freedom is what allowed investigators to produce the key publications that contributed to the ultimate development of LentiGlobin BB305 and BCL11a shRNA (miR). Thus, the total funding amount within a FY was included in the final estimate. Additionally, since a study found that there is usually a three-year lag time between funding and publication, the final estimate included every FY up to three years before the oldest publication on the list produced by RStudio.[1]

The final estimate of $306 million is not adjusted for inflation, making the total amount an underestimate. If adjusted for inflation using the US Bureau of Labor Statistics consumer price index for all urban consumers and 2016 as reference, the total amount of public funding into LentiGlobin BB305 and BCL11a shRNA (miR) would be $361 million.

[1] Boyack KW, Jordan P (2011) Metrics associated with NIH funding: A high-level view. J Am Med Inform Assoc 18:423–431.