Standard practices among nonprofit disease research funders places the most important decisions — how to allocate donor-raised dollars — in the hands of part-time, external, standing boards, who divvy up available funds across many basic research projects. Little to no funds are available for the translation of those discoveries into potential new medicines to be further developed and manufactured within the Pharmaceutical Industry. Beyond Batten Disease Foundation (BBDF) challenges this model, employing instead a full-time, in-house, formally trained PhD scientist supported by a targeted, high-impact network of consultants and advisors, with access to specialized translational expertise and resources alongside large-sum investments to attract the best scientific minds. This approach brings focus and direction to the juvenile Batten disease research pipeline which, to date, has been plagued by scattered, often conflicting data without access to a framework guiding the path to a cure.

The importance and limitations of basic research

In the United States, the majority of funding for biomedical research comes from the National Institutes of Health (NIH). Approximately 80% of NIH's annual $30 billion funding budget is spent on basic research—work intended to extend knowledge or understanding of a disease without specific applications in mind.[1] Basic research is the essential starting point of the disease research and drug discovery pipeline, providing a steady stream of new ideas and breakthroughs to fuel follow-on work. The non-profit medical research sector, for the most part, has followed NIH's lead and invests the majority of its funds in basic research projects as well. These projects end with results published in one of more than 28,000 scientific journals; adding to the growing body of scientific knowledge in disease research, but ill-positioned to inform future drug discovery and design applications.[2,3] For knowledge to be applied to enhance health; for mistakes in our genetic code to be exploited as drug targets to stop disease, for example; there must be real-world assessments and action plans capable of designing effective medicines.

Embracing applied science

Applied science is work that is intended to bridge the gap between basic research and clinical applications. For example, how might a new understanding of a disease reveal novel drug targets or inform the design of therapeutics to slow disease progression? Though clearly a linchpin in the disease research pipeline, applied science is rarely taught, funded, or rewarded within either traditional federal or non-profit research funding structures. As a result, there is a growing gap between the discovery of new information and its clinical application. Only recently has the issue of applied science (also called translational science) been addressed by the federal funding sector. The Office of Translational Research, within the NIH's National Institute of Neurological Diseases and Stroke, was formed in 2008.[4] The SMARTT program (Science Moving towArds Research Translation and Therapy), within the National Heart Lung and Blood Institute, and the National Center for Translational Science were both formed less than three years ago.[5,6] It is too soon to tell whether these specialized services and programs will succeed in linking basic research discoveries to work that can move disease research towards a cure. To find the existing

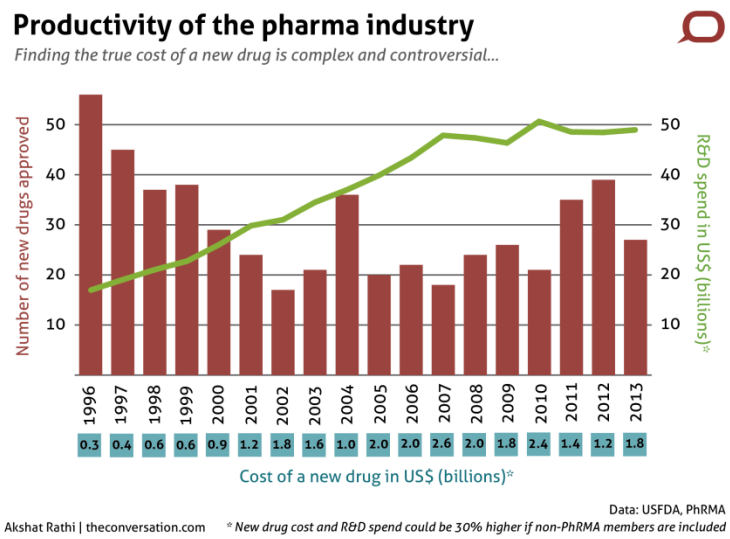
Applied scientists within the pharmaceutical Industry—those, with specialized expertise, access to technology, and large drug libraries are physically, technologically, and culturally separate from basic discovery research.

structure through which such progress has been made in the past we must look towards the pharmaceutical industry.

Translational research through the pharmaceutical industry

The pharmaceutical industry specializes in the identification of druggable molecular targets known to be significant in disease, industrializing the screening process for potential drug candidates, testing promising compounds, and optimizing those that produce the best results. In other words, pharmaceutical, biotechnology, and other members of the research industry sector have honed the practice of translational research. The industry thrived in the 1980s and early 90s, with investments exceeding federal research and nonprofit research budgets combined, with profit margins in the billions worldwide(Table 1).[7] However, a combination of factors, including patent expirations, rising costs, and lengthening development timelines have slowed the production of new drugs and therapeutics. This combined with significant, though short-lived, increases to the NIH (basic research) funding budget (1999-2003) has resulted in translational science losing ground against the tide of published scientific data—a so-called "Valley of Death" further separating academic scientists performing basic research and those with the specialized skills and resources necessary to develop new drugs based on that research.[9] This divide has even resulted in a lack of usable results.[8,9,10,11] For example, Scientists at Bayer and Amgen discovered that results from two-thirds of academic drug targets could not be validated.[12,13,14] The lack of a well-connected, iteratively informed, multisector research pipeline is wasting time – and lives.

The average length of time from target discovery to approval of a new drug currently averages ~15 years, the failure rate exceeds 95%, and the cost per successful drug is $1 billion ($2 billion after adjusting for failures, inflation and other costs).[15, 16, 17]



A shift in strategy

BBDF is leading a paradigm shift in how juvenile Batten (CLN3) disease research is funded. The traditional nonprofit strategy -- diversifying low levels of funding in basic discovery - will not result in reproducible, validated juvenile Batten disease drug target identification followed by drug development. Hoping the pharmaceutical industry will notice and act on juvenile Batten disease research information lost in a sea of published discoveries (1 every 23 seconds) will not obtain the results our children, young adults, and families need.[2,3]

Unlike BBDF, 90% of the 225,000 medical research foundations in the US, never reach the annual $1 million mark considered necessary to make a difference in their disease.[19]

BBDF is responding with a new strategy; one that supports the production of strong, promising, reproducible data while simultaneously providing connections to resources in applied and translational science. BBDF now funds the largest grants available for juvenile Batten research, larger even than those awarded by the NIH, effectively attracting the best minds to the goal of finding a cure for this devastating disease. In addition, our strategy involves taking a comprehensive and systematic approach to human target validation that goes beyond peer-reviewed publication. Thus, we apply an extensive, multi-disciplinary review and development process through which all funded research must demonstrate inherent druggability of relevant drug targets in human disease pathogenesis. Efforts toward this end continue throughout the life cycle of the project with quarterly calls, guided progress reports, access to raw data, and fail-fast system analyses alongside pharmaceutical scientists.

Getting to Clinical Trials

Once a drug target is identified and validated, the drug discovery process begins. Pharmaceutical scientists rapidly screen thousands of chemical structures against isolated biological targets. This is followed by studies to determine the effect of the drug on the body and the body on the drug. Therapeutic windows must be determined. Once these steps are taken, we will apply for Investigational New Drug (IND) designation from the Federal Drug Administration, giving us permission to enter clinical trials.[18] Clinical trials are essential to proving safety and efficacy and for determining critical usage parameters such as formulation and dosage. This last step can be a quagmire of study design parameters, poorly adapted preclinical data, and bureaucratic red tape.

BBDF maintains a comprehensive view of juvenile Batten disease basic research, translation, drug discovery and clinical trial development—partnering academic and pharmaceutical scientists (BBDF-funded or not) with each other while providing consistent financial and intellectual support to produce high-quality results as quickly as possible. Knowing that not all theories will ultimately lead to actionable results, our focus is on identifying those ideas most likely to have a significant impact on the lives of juvenile Batten disease patients and shepherding the most promising drugs and therapeutics through the clinical trials process in the shortest timeframe possible.

While we take pride in all of our accomplishments to date, ultimately we have only one definition of success: finding effective treatments and cures for children and young adults with juvenile Batten disease. We will not stop until there is a cure.

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