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Expanding roles for academic entrepreneurship in drug discovery

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An assessment of inventors of US Food and Drug Administration (FDA)-approved medicines reveals a growing role for academic entrepreneurship in general and National Institutes of Health (NIH)-supported investigators in particular. For all small-molecule therapeutics approved between 2001 and 2019 (383 in total), 8.3% listed an academic inventor in the Orange Book. Remarkably, an additional 23.8% listed an inventor from a company founded by an NIH-funded academic inventor. Over time, the relative inventive contributions from academia has progressively increased, including nearly one-third of medicines approved since 2017. These findings suggest a surging role for academic inventors and founders, perhaps in combination with a faltering of traditional private sector dominance of drug discovery.

Introduction

The means by which new medicines are discovered has fundamentally changed since the beginning of the new millennium. During the early decades of the contemporary pharmaceutical 'Golden Era', which roughly coincided with the quarter century after the end of the Second World War, most research and development of new medicines was strictly controlled by private sector companies [1]. In particular, the earliest stages of discovering new medicines were conducted by and within large and established companies with storied names such as Eli Lilly, AstraZeneca, Roche, Burroughs Wellcome. and Bristol-Myers.

Studies have demonstrated that the research dominance of traditional 'big pharma' began to wane during the 1970s and accelerating thereafter [2,3]. In large part, these were conscious decisions predicated upon a recognition of the declining efficiency of drug discovery. Termed 'Eroom's Law' (a playful inversion of Moore's Law, a measure of increasing computing efficiency), the costs needed to develop a new medicine have been increasing at an exponential rate since at least the 1950s [4]. Since its recognition, all efforts to break (or at least brake) Eroom's Law have consistently failed. These attempts have included industry consolidation, outsourcing. and in-licensing, each of which paradoxically not merely failed but ensured continued adherence to Eroom's Law and, thus, a further decline in overall industry efficiency.

All the while private sector attempts to circumvent Eroom's Law were being tested, the public sector (which is defined herein as encompassing both governmental and academic organizations) was emerging as a key player in drug discovery. A catalyst for these efforts was passage of the 1980 Bayh–Dole Act, which granted licenses for government-sponsored research (e.g., underwritten by Federal grants) back to academic inventors [5–7]. This was a crucial outcome because grant dollars distributed by the National Institutes of Health (NIH) are the primary driver of public sector biomedical research activities [8].

The pivotal Bayh–Dole legislation coincided with not only recognition of the damages inflicted by Eroom's Law, but also revolutionary changes in our understanding and ability to manipulate DNA and proteins. Together, these two separate events synergized to inspire and enable the biotechnology era, a period characterized by a burst in academic-focused entrepreneurship. Previous work demonstrated evidence that NIH-funded investigations underpinned most (>90%) of the most highly prescribed medicines [9]. For example, NIH-funded research contributed to the discovery of

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novel mechanisms of health and disease that would later be exploited by innovative medicines.

For the current study, we sought to examine more deeply the impact of NIH-funded academic investigation. We placed particular emphasis upon intellectual property because patents provide an objective means to assess the inventors of pharmaceutical products. To accomplish this goal, we deployed the Clinical Drug Experience Knowledgebase (CDEK), a novel knowledgebase developed at Washington University in St Louis, to aggregate information about FDA-approved and experimental medicines [10]. This unique resource allowed us to compile a list of all new molecular entities (NMEs) approved by the FDA from 2001 to 2019, 712 NMEs in total.

Patent inventors

An objective assessment of intellectual property was enabled by the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* or, as it is more widely known, *The Orange Book*. Among the information conveyed in *The Orange Book* is a listing of the patents for each product that would-be generic manufacturers are obliged to honor (www.accessdata.fda.gov/scripts/cder/ob/index.cfm). With this in mind, we assessed the inventors on all patents listed for NMEs approved between 2001 and 2019. Although we were disappointed to find that adequate records are not catalogued in *The Orange Book* for biologics, cell-, or gene-based therapies, the key patents are listed for nearly all small-molecule therapeutics; 383 evaluable NMEs in total.

Our initial analyses evaluated the role of academic inventors who directly contributed to the discovery of an FDA-approved NME. For the purposes of this paper, we define an invention as a patent listed in *The Orange Book*. We presumed that academic inventors listed in *The Orange Book* would be rare, if found at all, because the individuals who develop small-molecule therapeutics have tended to be dominated by pharmaceutical industry chemists. These professionals craft molecules by blending key fea-

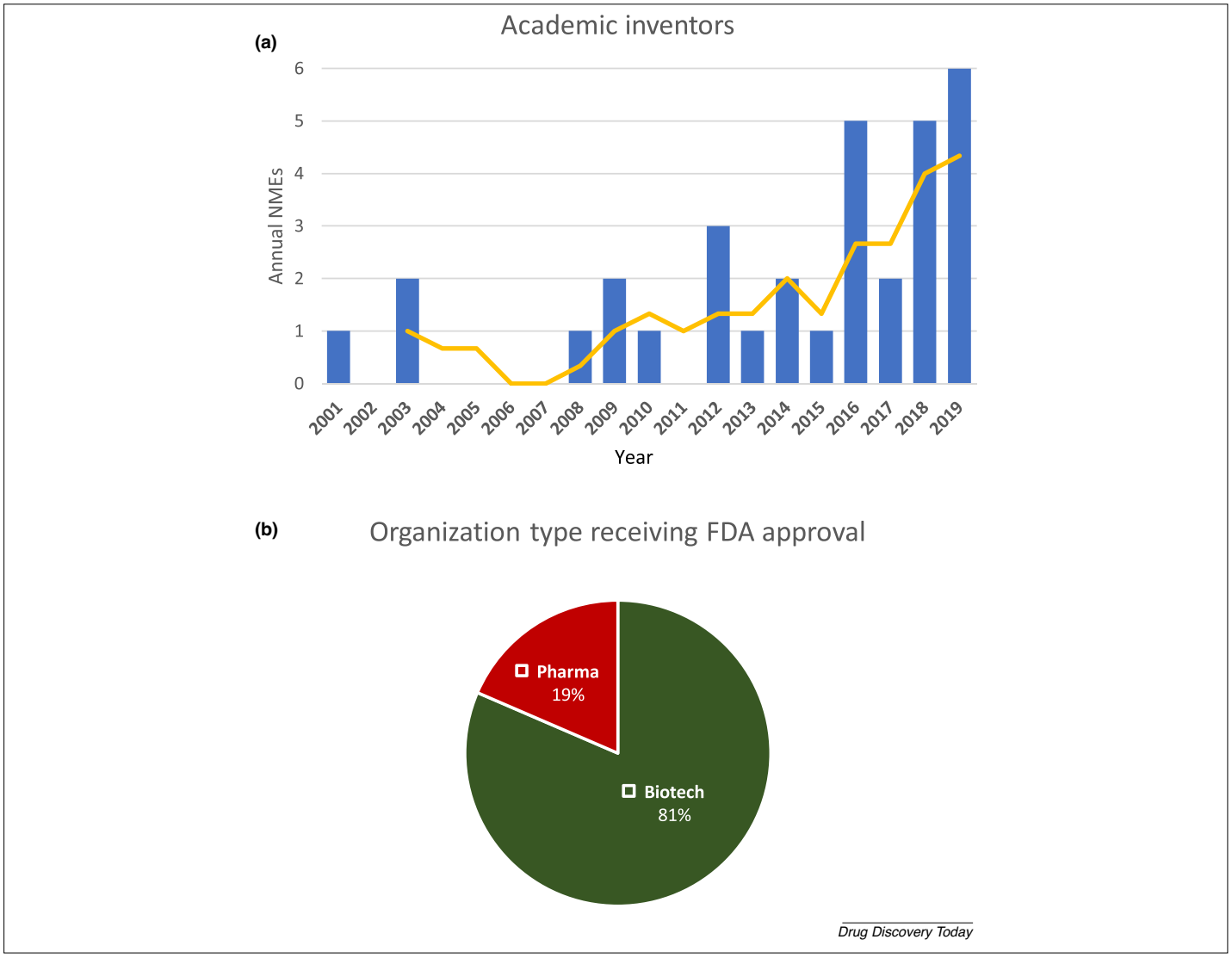

FIGURE 1

Academic inventors in drug discovery and development. **(a)** Academic inventors were assessed for all new molecular entities (NMEs) approved by the US Food and Drug Administration (FDA) from 2001 to 2019 as listed in *The Orange Book*. The yellow line denotes the 3-year running average of NMEs with at least one academic inventor. **(b)** The licensees of patents with academic inventors is indicated, revealing that most academic partnerships occurred with biotechnology companies founded after 2001.

tures such as safety, efficacy, and developability (a catch-all term reflecting everything from pharmacology to manufacturing and stability). In parallel, these chemists must simultaneously optimize the development of an intellectual property estate meant to avoid infringing extramural patents while maximizing the ability to hold off competition. In assessing the key patents in *The Orange Book*, our conjecture that academics would be excluded proved inaccurate because public sector inventors were identified for 32 of 383 (8.3%) evaluable NMEs approved between 2001 and 2019 (Fig. 1a).

More surprising still, the contributions of academic inventors have trended ever higher in recent years. Whereas only three drugs listed public sector inventors throughout the first 5 years of our analysis (2001–2007), the rate of academic inventive contributions has increased to an average of more than four per year (six NMEs in 2019). When evaluating the 3-year running average of academic inventorship, the rate did not exceed one drug per annum between 2001 and 2009. Nonetheless, this rate steadily increased thereafter, clocking in at an annual average of 4.3 NMEs with academic inventors in 2019.

Organizations and academic inventions

We then assessed the type of organization that ultimately in-licensed the academic invention, broadly dividing these into pharmaceutical (established before 1971) and biotechnology (founded after 1971) companies. This distinction revealed that most (81%) academic patents for FDA-approved drugs had been licensed to a biotechnology company, with a minority of products ending up with more conventional pharmaceutical companies (Fig. 1b).

Since passage of the Bayh–Dole Act, academic inventors have been incentivized to act as

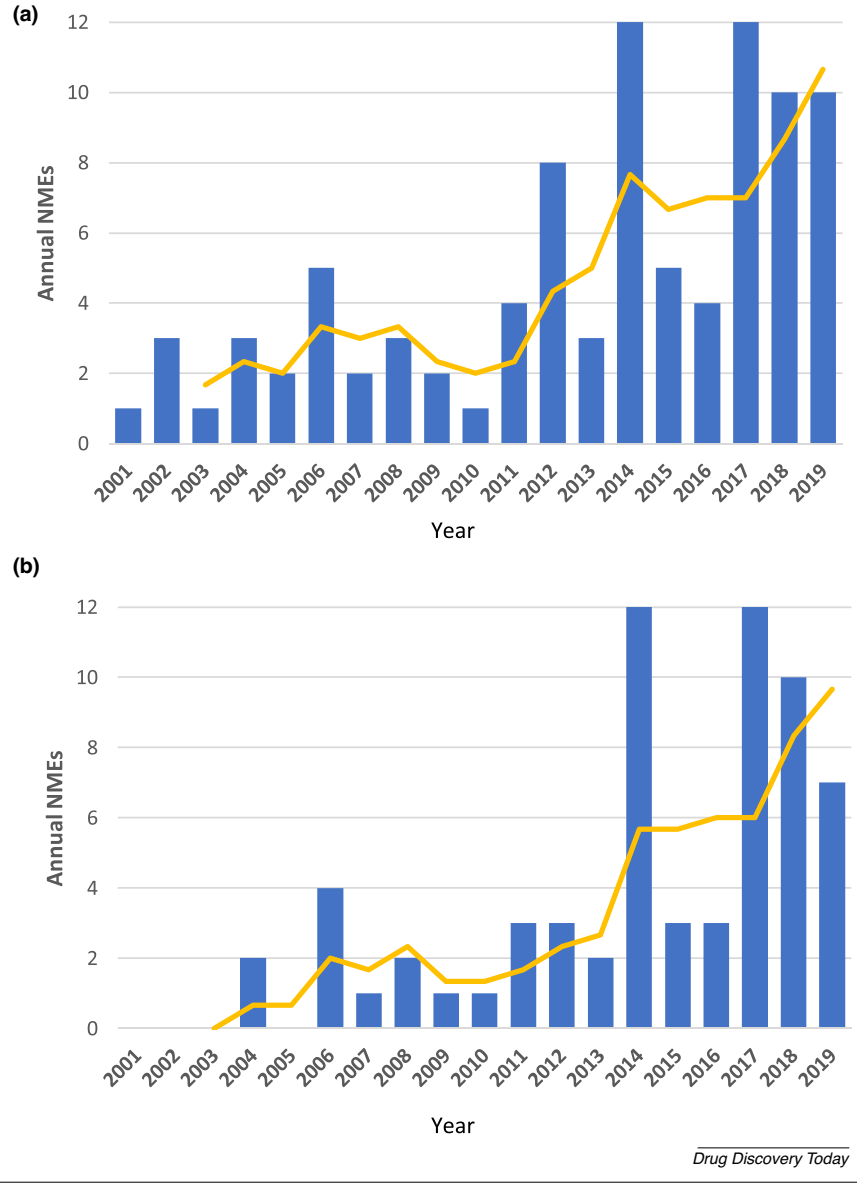

FIGURE 2

Academic founders in drug discovery and development. **(a)** New molecular entities (NMEs) awarded to a biotechnology company with evidence of at least one academic founder are shown (yellow line indicates the 3-year running average. These results did not include the NMEs identified in Fig. 1 to avoid double-counting academic contributions. **(b)** The results from (a) were focused upon NMEs awarded to a biotechnology company within the first 20 years after their foundation.

entrepreneurs by founding upstart companies. Appreciating that this option provides an alternative outlet for the inventive contributions of academics (beyond licensing patents to established companies), we expanded our analyses to evaluate patents arising from inventors within biotechnology organizations founded by an NIH-funded academic. We defined the act of founding a company herein as 'entrepreneurship'. We avoided double-counting the impact of academia by excluding the 32 drugs that had direct academic inventors. In total, 91 of the 383 (23.8%) NMEs approved between 2001 and 2019 were awarded to biotechnology companies with an academic founder. Looking over time, the rate of approvals for companies with academic founders has increased, both in absolute and relative terms (Fig. 2a). For example, 32 NME approvals were awarded to companies with academic founders in the years spanning 2017–2019 alone, which reflects nearly one-third (31.9%) of all evaluable approvals from that period.

We then considered that our approach might overestimate the contributions of academia. Specifically, we reasoned that companies founded by an academic evolve over time and eventually will not reflect the direct impact of their founders. To address this, we invoked a fundamental feature of patents, which have a finite term of 20 years. Consistent with this approach, studies have demonstrated that more than 10 years are required, on average, for clinical investigation of new medicines alone. Given that additional time is required for foundation events and preclinical development, the 20-year period appeared appropriate. Therefore, we reassessed the role of academic founders by counting only those approvals received within the first 20 years after founding. By adopting this approach, the total number of NMEs awarded to companies with academic origins shrank from 90 to 66. Yet, this reduced number still represented 17.2% of all evaluable approvals. Looking further, the increase in academic founders over time remained pronounced and these 'recent' academic-founded companies still continued to capture nearly one-third of all evaluable NMEs approved between 2017 and 2019.

NIH funding and academic inventors and founders

Returning to our original motivation to assess the role of public sector funding upon drug development, the final set of studies asked whether academic inventors or founders had received NIH funding before their entrepreneurial contributions (Fig. 3). This question was addressed by determining whether the academic inventors and founders had received an NIH grant based upon information provided by the NIH Reporter website. Importantly, the topic of the grant directly related to the final drug product. This approach revealed that 28 of the 32 academic inventors of an FDA-approved drug had received at least one NIH grant (the others worked outside of the USA and did not qualify for NIH support). Likewise, companies founded by NIH-funded academics contributed an additional 46 NMEs. This fact is consistent both with the concepts advanced by Marianna Mazzucato of the NIH as 'public venture capital' and with Holden Thorp's thesis that academics increasingly serve as the 'Engines of Innovation' for the American economy [11,12]. Consequently, the overall number of NIH-funded medicines encompasses 74 of 383 NMEs; or nearly one in five evaluable new drugs approved from 2001 through 2019. This rate has steadily increased over time and now stands at ten NMEs per year (nearly one-third of all new medicines).

Concluding remarks

In summary, the major finding of this study is a demonstration that academic organizations have an increasingly important role in drug discovery, primarily through preclinical studies that define new targets and molecular entities for disease. These contributions include both direct inventorship of the final drug product (which was unexpected) as well as the more widely understood roles as founders of upstart biotechnology companies. Our results are novel not only because of the surprising finding that NIH-funded academics in particularly now routinely contribute to one-third of the newest medicines, but also because these data are consistent with concerns that have been widely whispered for years: that the current model for discovering and developing biopharmaceutical might be faltering, perhaps irreversibly.

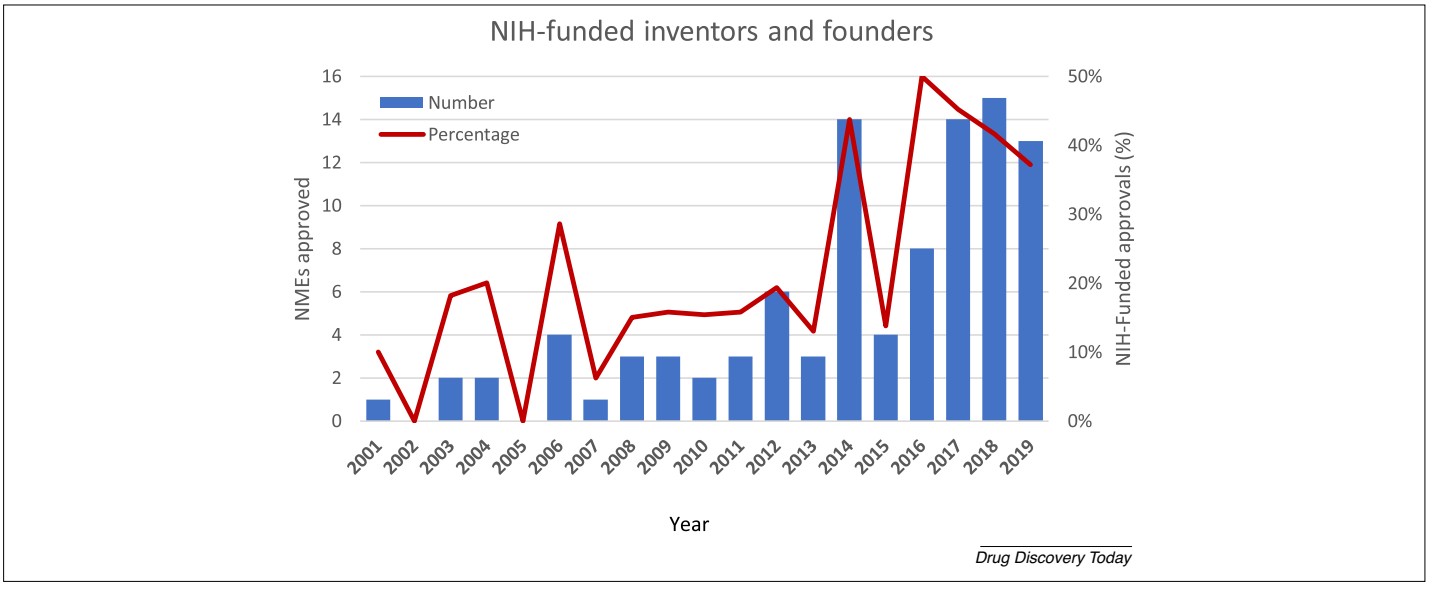

FIGURE 3

National Institutes of Health (NIH)-funded academic inventors and founders. Shown are NIH-funded inventors and founders who contributed to the approval of an US Food and Drug Administration (FDA)-approved new molecular entity (NME). Note that the results are indicated both as the absolute number of approvals in the year indicated, as well as a percentage of all evaluable drugs approved that year.

We entered into this project under the assumption that academics would merely have supportive roles, identifying targets, validating mechanisms, and so on. The key (and surprising) finding is the prominent role uncovered for academics in the drug discovery process, in which NIH-funded university-based inventors and entrepreneurs increasingly are the inventors of composition of matter patents (and not merely method of use patents).

On the one hand, a greater reliance upon academic research to discover new medicines could be seen as a positive, reflecting an alternative to the private sector. Indeed, the Bayh–Dole Act was signed into law with this exact intention. Given that Eroom's Law began decades before Bayh–Dole and has persisted at a steady pace since, the inclusion of academic patents and entrepreneurship suggests that adherence to this law did not impact Bayh–Dole. With rare exception, academic investigators are generally neither trained nor practiced in the art of developing new medicines. The term 'art', rather than 'science', is applicable because the discovery and efforts needed to gain FDA approval for a new medicine involve a blend of chemistry, pharmacology, regulatory affairs, experimental medicine, business development, manufacturing, and patent law expertise, to name but a few specialties. Consequently, the increased role of academic organizations in drug development might be considered yet another warning sign of private sector instability. To ensure a continued delivery of future therapeutics, it will be necessary to reassess why the private sector might be faltering, with an emphasis upon innovative ways to circumvent Eroom's Law as well as new paradigms to discover, develop, and distribute new medicines.

Such an outcome could have drastic consequences, impeding or precluding our ability to develop novel medicines against diseases, old and new. The ongoing Coronavirus 2019 (COVID-19) pandemic is a reminder, if needed, of the need for new therapies. Yet, Eroom's Law, industry consolidation and outsourcing are all symptoms of a larger problem, suggesting that the long-standing model of private sector development of new medicines is facing obsolescence.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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