DRUG DEVELOPMENT

Making modern medicines

The business side of drug development comes to the fore in a tale of two blockbuster blood cancer therapeutics

For Blood and Money; Billionaires, Biotech, and the Quest for a Blockbuster Drug
Nathan Vardi
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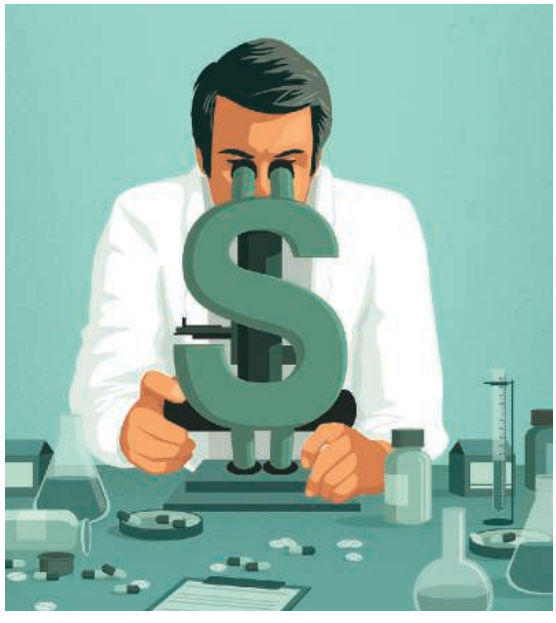
By **Adrian Woolfson**

Big pharma companies have in the past decade begun to focus their efforts on what they do best: late-stage clinical development, medical and regulatory affairs, sales, and marketing. As a result, they have become increasingly dependent on licensing early-stage drug candidates developed by smaller companies to bolster their pipelines. Two drugs developed to treat blood cancers by fledgling companies and brought to market by big pharma—the small-molecule Bruton's tyrosine kinase (BTK) inhibitors Imbruvica and Calquence—are canonical examples of licensed therapeutic agents that have emerged via this mechanism. In his new book, *For Blood and Money*, Nathan Vardi narrates the intriguing and improbable tale of how these two small-molecule compounds were rescued from obscurity and transformed lead investors into billionaires overnight.

In 2006, Pharmacyclics CEO Richard Miller fortuitously picked up Imbruvica (ibrutinib)—or CRA-032765, as it was then known—along with two other early-stage drug candidates from Craig Venter's failed genome sequencing company Celera, for just $6.6 million. Preliminary data from 16 patients presented by Pharmacyclics at the 2009 American Society of Hematology meeting provided the first evidence that the drug was efficacious.

This flicker of a signal, missed by many, caught the attention of one of Pharmacyclics' lead investors, Wayne Rothbaum, as well as the American investment firm OrbiMed, who avidly bought up Pharmacyclics stock. Their optimism was vindicated by a 2013 study published in the *New England Journal of Medicine*, which detailed a 71% overall response rate in patients with chronic lymphocytic leukemia that translated into extended survival (*1*). Two years later, in 2015, Pharmacyclics was acquired by AbbVie in a transaction valuing the company at an astronomical $21 billion, netting its largest shareholder and executive chairman, Bob Duggan—an eccentric investor and fervent scientologist with no prior experience in biopharma—an unprecedented $3.5 billion.

Meanwhile, a more selective and potentially safer BTK inhibitor (*2*), Calquence (acalabrutinib, then known as SCH 2046835), was licensed in 2012 for a paltry $1000, with 5% royalties by Acerta—headed by Rothbaum—from Organon, a small Dutch outpost of Merck that the company had obtained in 2009 as part of its acquisition of Schering-Plough. Rothbaum, Vardi reveals, had—in a moment of weakness—divested more than half his position in Pharmacyclics before Imbruvica's full potential had been realized. While still making a handsome profit, Rothbaum's panic selling ensured that the return on his investment was a fraction of what it would have been had he maintained his original position.



According to Vardi, Rothbaum was desperate to correct what was, undoubtedly, "the worst trading error of his career." He received his opportunity when he founded Acerta in 2012 with a group of former Pharmacyclics employees, including the company's former chief medical officer Ahmed Hamdy, whom Duggan had unceremoniously fired in 2011 when the pair disagreed on how best to approach regulatory strategy. By this time, however, the promise of BTK inhibitors had become more obvious, making a breakthrough more challenging for newcomers.

By the winter of 2014, Imbruvica had received two regulatory approvals, whereas Acerta had not yet even commenced its first-in-human study. To Acerta's great relief, however, the first patients treated with acalabrutinib had a pronounced clinical response. It later also became evident that the new drug's improved selectivity prevented some of the side effects that had led select patients to stop taking Imbruvica. Rothbaum's decision to form a new BTK inhibitor company turned out to be life-changing, both for blood cancer patients and for himself. In February 2016, Acerta was acquired by AstraZeneca in a deal worth up to $7 billion, securing Rothbaum a $2.8 billion windfall.

Vardi reminds readers that historical accounts are by necessity subjective, noting that key individuals are often omitted from such narratives for a variety of reasons. He attempts to address this by calling out some of the unsung heroes of this story, including the Chinese chemist Zhengying Pan, who designed and synthesized CRA-032765, as well as key clinical investigators such as Daniel Pollyea and Susan O'Brien, who helped design and secure patients for the clinical studies and interpret the data. Most importantly, Vardi acknowledges the critical role played by the patients who risked their lives by participating in the early BTK inhibitor clinical studies.

In the hands of big pharma, Imbruvica and Calquence have joined the hallowed pantheon of the most successful drugs of all time. In detailing the fascinating story of how this happened, Vardi has delivered a master class in the machinations of modern drug development. ■

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