Emerging paradigm of integrated platform-drug discovery and development companies

Technology was lauded as the saviour of the drug discovery and development (DDD) process during the late 1990s. A myriad of independent companies developed and offered 'innovative' tools, technologies and platforms (TTPs) to pharmaceutical companies in order to mitigate the time, cost and risk of developing new therapeutic drugs. However, comparative analysis of FDA-approved New Molecular Entity (NME) and New Therapeutic Biologic (NTB) annual historical numbers announced does not reflect any significant productivity enhancement impact of such efforts. More recently there has been some attempt to amalgamate platform technologies within start-up and early-stage DDD companies to increase drug candidate pipeline numbers. This strategy does not come without risks, but has quietly been implemented by a number of platform-DDD (PD3) companies. We explore this issue and use Moderna Therapeutics as our case study to highlight the limitations and potential impact on company valuation of such an integrated approach.

By Dr Urban A. Kiernan and Dr Stephen Naylor

In 2001 the consulting group Accenture published a landmark report entitled 'High Performance Drug Discovery: An Operating Model for a New Era'[1]. The authors proposed that pharmaceutical companies could enhance their productivity by focusing on six key strategic areas. The majority of the recommendations invoked the implementation and development of new and/or integrated platforms that included: i) analytical 'omic' technologies; ii) information gathering and knowledge determination capabilities; iii) decision making tools; and iv) access to early stage technology innovation through alliance and partnership arrangements. This report, plus others, stimulated the pharmaceutical sector to invest into a plethora of new technologies. However, with hindsight there appeared to be a somewhat arbitrary attempt to utilise such tools, technologies and platforms (TTPs) in their in-house Drug Discovery and Development (DDD) initiatives. We analysed these efforts and subsequently published our findings in a 2007 paper entitled 'Technology: Bane or Bonanza for the Pharmaceutical Industry?'[2]. We concluded that

indiscriminant use of tools, technologies and platforms in the DDD process was not the panacea for lackluster or stagnant productivity. We suggested that a more focused and integrated implementation of such TTPs should result in a significantly improved output of therapeutic drug products[2].

Alas, we were wrong in our optimistic pronouncements! In 1938 the USA Food, Drug and Cosmetic Act was enacted and heralded the advent of the 'New Drug Application' (NDA) and the 'New Molecular Entity' (NME) descriptors. These pivotal designations along with 'NDAs filed' and 'NMEs approved' have subsequently served as productivity indicators of the pharmaceutical industry. We have noted previously, that since the 1950s there have been perceptible downward trends of NDA filings as well as NME approvals by the FDA[2]. This downward spiral continued during the period 1997-2007 (**Figure 1**), even when there was a concerted effort by pharmaceutical companies to utilise more TTPs in the DDD process. The single year exception for productivity was in 2004, when both novel drugs approved and therapeutic drug filings increased. This was, coincidentally the year that the FDA introduced the new designation of Biologic License Applications (BLAs) and New Therapeutic Biologics (NTBs). After we wrote our article predicting the positive impact of technologies on the DDD process[2], NDA/BLA filings and NME/NTB approvals did not change significantly from 2008-17 (**Figure 1**), with the exception of 2017. Thus our pronouncement that the strategic utilisation of TTPs alone should improve therapeutic drug product output really did not materialise.

In the past, third-party service providers to pharmaceutical companies have developed such TTPs. Pharmaceutical companies then attempted to incorporate these TTPs in-house, but with limited success as discussed above. More recently there has been some re-evaluation of TTP incorporation and concomitant use in the DDD process. A small number of companies such as CombinatoRx (see below) attempted to create their own in-house, proprietary, integrated platform-DDD (PD3) approach. However, there was significant criticism of such efforts. It was suggested that most small pharma/biopharma companies did not have the bandwidth to carry out such an approach, since it would lead to dilution of effort, poor tactical and strategic decision-making and a lack of focus. More recently, a number of companies have not only ignored such criticism, but also forged ahead with an innovative, new model. In this article we discuss the issues facing such companies, and how to implement in-house PD3 efforts to populate individual company drug pipeline. We discuss the trials, tribulations and successes of the PD3 company Moderna Therapeutics, to highlight issues associated with this approach.

Platform technologies and Drug Discovery and Development

The words tool, technology and platform are often used interchangeably. However, in the biotech and DDD sectors a single tool is a component item (think hammer on a carpenter's tool-belt), which when combined together constitute a technology (think carpenter's tool-belt). A combination of technologies, when applied in a cohesive manner, can be labelled as a platform (think the carpenter him/herself complete with tool-belt, safety glasses, mode of transportation etc). In this article we use such relationships to provide a general perspective on what constitutes a platform, whether it is technological, biological, molecular or digital in nature.

Problems of individual technology and platform implementation

The original efforts by pharmaceutical companies to integrate TTPs into the DDD process were compromised by flawed implementation strategies. Pharmaceutical companies would attempt to bring such TTPs in-house from third-party development companies. However, most pharmaceutical management teams responsible for such decisions were often isolated and unaware of the complexities associated with technology development and implementation cycles. The global pipeline of TTPs was a complicated mishmash of 'products' at various stages of developmental maturity, and the rush to acquire them was often fraught with internal pressures and misunderstandings. This often resulted in the consideration and adoption of TTPs that were traversing various parts of the Technology Development Cycle[2].

The Technology Hype Cycle (THC) compounded the flawed decision-making process of which TTP to adopt[2,3]. The THC describes the enthusiasm that often greets new technologies and the subsequent disenchantment that follows. It consists of five stages: i) Technology trigger: product launch produces excitement; ii) Peak of inflated expectations: a 'frenzy of publicity' generates overenthusiastic assessment and unrealistic expectations; iii) Trough of disillusionment: expectations have not been met and advocates plus most general, interested parties abandon the technology/platform; iv) Slope of enlightenment: some businesses continue to evaluate and develop the technology/

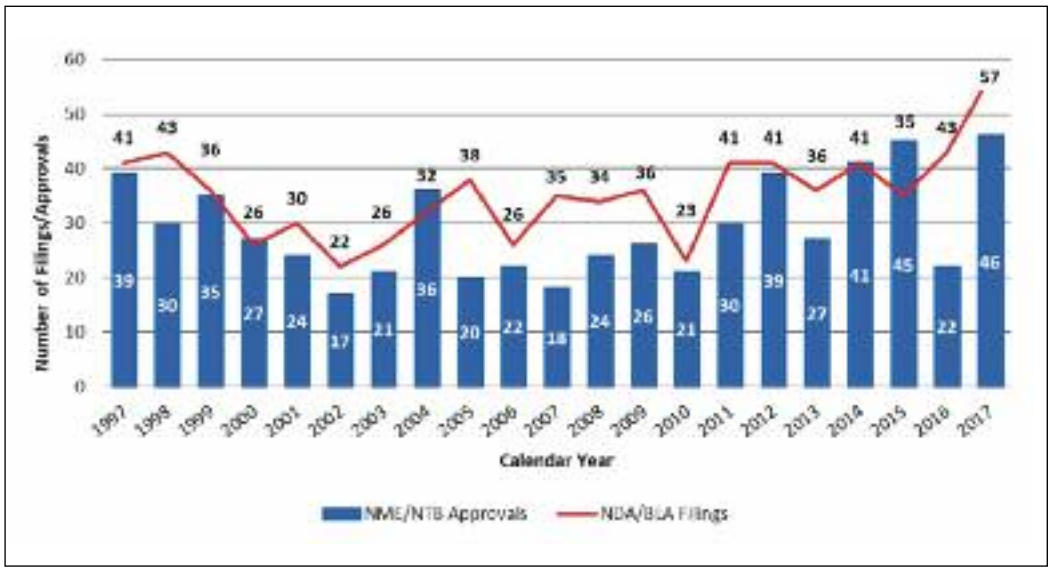

Figure 1
Annual NME/NTB drugs approved, and the number of NDA/BLA filings by the US FDA, on a calendar year basis

platform and determine its limitations as well as realistic and practical applications; v) Plateau of productivity: benefits of the technology/platform are demonstrated and it becomes stable evolving through further improved generations.

Pharmaceutical scientists and management were often caught up in the throes of the THC. There were significant pressures to adopt such hyped technologies in order to remain competitive with other pharmaceutical companies. The problems were compounded by the psychological factor of not missing the one technology that may affect that paradigm shift that everyone was seeking. Paradoxically, there was also the possibility that a promising new technology/platform could be prematurely abandoned if it was in the 'Trough of disillusionment' stage. In either scenario it was critically important that the decision process of adoption and/or abandonment of the technology was predicated on objective assessment of whether it met the tactical and strategic needs of the scientific, clinical and management teams. Hence, it was vitally important for any pharmaceutical management team to be acutely aware of the THC and its potential impact on acquiring any TTP.

Other factors that were poorly understood and usually ignored were the Technology Assimilation[4] and Technology Innovation Adoption (TIA) S-Curves[5]. The assimilation of technologies is determined by a simple set of criteria. Initially, teams experiment with the technology/platform, in a classic 'kicking the tyres' type scenario. Subsequently, the technology/platform is assessed for its efficiency and convenience factors followed by its effectiveness in carrying out a task or producing quality data output. Ultimately, the technology/platform is assimilated into constant use if it provides an unprecedented opportunity to carry out 'previously unthinkable' experiments or insight into solving a complex set of problems. In the case of the TIA S-Curve, it has been described previously in detail elsewhere[5]. It is initially characterised by a very small number of innovators (1-3% of adopters), who over a period of time (typically years) invent and champion the technology/platform. Depending on a variety of factors, additional cohorts of individuals will ultimately adopt the technology/platform and they include early adopters (~13-15%), opinion leaders, early (30-35%) and late majority (30-35%) adopters and the laggards (12-16%)[5]. Assessing the status of a technology/platform and where it is on the adoption curve is not a trivial matter. For example, the television was invented in 1926, but it was not until the 1960s, 40 years later, that the laggards finally adopted this now ubiquitous technology. Often the cycle of technology/platform adoption can take decades for successful technologies/platforms to reach levels of widespread acceptance, and in the majority of cases a technology/platform is ultimately abandoned.

It is clear that the evaluation and valuation of technologies/platforms was not a simple process. Many factors had to be considered including the status of the technology/platform in the Technology Development, THC as well as the Technology Assimilation and TIC S-Curves. Scientists and managers had to make pressure-ladened decisions about the implementation and adoption of technologies/platforms at various levels of maturity in an often

time-constrained manner. Under such circumstances it is not surprising that errors of judgment were made resulting in the acquisition and/or adoption of technologies/platforms that were neither mature, nor suitable for implementation into the DDD process. Given such scenarios it is not surprising that there was a lack of any significant increase in DDD productivity by pharmaceutical companies in the 1990s-2000s (see **Figure 1**).

Types of platform-DDD companies

What is a PD3 company? Borrowing from Robert Thong's thoughtful and well-articulated analyses such companies contain[6,7]:

i) Scientific and technological core competencies.

ii) These competencies are utilised to generate new therapeutic drug candidates.

iii) Enhanced application of such competencies across a range of disease indications.

These platform companies can consist of proprietary hardware, biological, molecular and digital technologies, or some hybrid mix of some, or all of them combined. They typically evolve through several stages of growth and development. Thong[6] has highlighted that the genesis of such platform companies can be through an academic-driven start-up or a spin-out from an existing pharmaceutical company. The company must be able to generate a revenue stream and so establish a 'credible technology and/or service provider' capability. They must be able to enter into service provision contracts with a number of pharmaceutical clients as well as complete the usual milestones associated with such deals. As the company evolves and develops a credible reputation associated with aggressive fund-raising, then it can start to fund its own platform-driven proprietary projects and create its own drug candidates in specific disease indications. In this stage of growth, the platform company will partner with large pharmaceutical companies who fund the expensive late-stage clinical trials and navigate the complex NDA/BLA discussions with the FDA. Finally, the company may ultimately transform itself into a fully-fledged pharma/biopharma company, suffering all the travails of risk but potentially enjoying all the rich rewards of its own drug candidates reaching market.

PD3 companies must create a credible reputation, which is intimately tied to successful fund-raising and revenue generation. As noted above, most such companies undergo a methodical evolution primarily determined by financial needs, and these options are described below[7]:

i) Platform technology partnering: Licensing of the platform and providing related services to pharmaceutical companies are a low risk, fast revenue-generating option. In addition it also serves as an expeditious route to platform validation. The client absorbs all the financial risk that includes upfront technology licensing fees, fee-for-service revenue stream and near-term preclinical milestone payments are earned irrespective of whether the project eventually results in an approved pharmaceutical product. The downside is that the client owns any pharmaceutical assets that emerge from the project, but the platform company may earn limited, single-digit royalties on marketed products.

ii. Asset creation and out-licensing: In this scenario the platform company develops its own drug candidates predicated on the platform and out-licenses such molecules to large pharma. The latter assumes responsibility for completing late-stage clinical trials and commercialisation of the drug. The financial returns can be considerable with significant upfront payments, milestones and double-digit royalties on future sales. In addition the PD3 company has mitigated cost and risk by transference to the pharmaceutical partner. The downside is that compared to a simple technology partnering play, the PD3 company has increased its own time and cost commitment as well as the necessity of acquiring appropriate disease domain expertise.

iii. Product development and commercialisation: A PD3 company that has its own candidate drug with in-house regulatory and commercialisation expertise can make the transition to a pharma/biopharma company. This option is attractive given the potential high financial return on a successful marketed drug. In this case the financial burden and risk exposure is greatly increased, and the company may lack the necessary expertise for late-stage clinical development, manufacturing scale-up, regulatory approval, payer reimbursement negotiations, commercial brand management and sales promotion.

iv. Hybrid approach: Most early-stage platform companies start with either the technology partnering or the asset creation and out-licensing approach. The former generates revenue faster with lower financial risk. With higher investor funding and a greater risk appetite, the latter generates a much better return if successful, and it might be essential in a very competitive situation where you initially have to demonstrate technological superiority with your own pharmaceutical assets. An increasing number of research-stage companies operate a hybrid business model that combines both these two approaches.

Examples of platform-DDD companies

Historically, there have been numerous attempts at creating PD3 companies resulting in mixed outcomes. One of the first such innovative companies was a Noubar Afeyan (Flagship Ventures, now renamed Flagship Pioneering) creation, namely Beyond Genomics. This was the world's first Systems Biology company that attempted a foray into PD3. The history, background and haphazard evolution of Beyond Genomics' effort is provided in more detail in the side panel titled 'The confused utilisation of the Beyond Genomics platform'. The problems encountered by Beyond Genomics were myriad in nature. While its systems biology platform was highly innovative, the company ultimately failed in its PD3 efforts because it was not purpose-built for DDD. In stark contrast, CombinatoRx was a purpose-built PD3 company, and many consider it the archetypical example. This is explained in more detail in the side panel entitled 'The rise and demise of the CombinatoRx platform-DDD efforts'. The failure of CombinatoRx was not due to its initial PD3 efforts and spectacular productivity of combination candidate drugs for a variety of disease indications. The company floundered on the jagged rocks of drug development. In the case of both Beyond Genomics and CombinatoRx, analysis of their failures is instructive. It highlighted the fact that to build a successful PD3 company requires a myriad of skill sets and expertise, and was certainly part of the reason why many analysts in the mid-2000s were skeptical about such endeavours as discussed in the opening section of this article.

Currently, it is estimated that there are more than 100 different PD3 companies. At least five of these companies are classified as 'Unicorns', which refers to a privately-held start-up/early-stage entity valued at more than $1 billion. As we noted above, the platforms of such companies can be technology, biological, molecular or digital-based or some hybrid combination. The size and valuation of these companies spans a considerable range that includes behemoths such as publicly-traded entities like Ionis Pharmaceuticals (http://www.ionispharma.com/), Akcea Therapeutics (https://akceatx.com/) and Ablynx (http://www.ablynx.com/). However the list also contains much smaller, privately-held companies such as Sirenas (http://sirenasmd.com/) and Melior Pharmaceuticals (http://www.meliorpharmaceuticals.com/).

More recently, the authors founded iMetabolic Biopharma Corporation (https://imbiopharma.com). We are a precision medicine PD3 company intent on developing biological therapeutics for the treatment of obesity-related diseases. Currently we are focused on the treatment of the hyperlipidemic disorder Familial Chylomicronemia Syndrome. We are assembling a platform that contains functional modules that span across a sophisticated Artificial Intelligence (AI) discovery capability coupled with a protein

The confused utilisation of the Beyond Genomics platform

Noubar Afeyan, (CEO of Flagship Ventures) founded Beyond Genomics Inc in February 2000. One of us (Dr Stephen Naylor) was part of the scientific founding team and served as the CTO for the early growth phase of the company. Beyond Genomics was the world's first systems biology company with a purpose-built platform, consisting of gene, protein and metabolite analysis capabilities, and bioinformatic, biostatistics, knowledge management and data visualisation tools. The proof-of-principle for this integrated platform was the systems analysis of the Apolipoprotein E3-Leiden transgenic mouse. Initially the company utilised the platform on independent, disease-specific research that included Alzheimer's Disease, atherosclerosis and oncology. The company also collaborated with numerous pharmaceutical companies, leveraging its platform across a portfolio of applications in DDD, biomarker discovery and diagnostics.

In June 2002, Beyond Genomics recruited Dr James Hauske as CSO. Hauske had a rich pedigree in DDD, with companies such as Sepracor and Pfizer on his resume. This hire reflected intent by the company to utilise its in-house systems biology platform for DDD purposes. These activities were reinforced in February 2005 when the company changed its name to BG Medicine and hired a new President, Dr Pieter Muntendam. He was charged with leading the company's business operations and strategy and to focus on high-value drug development applications using its proprietary 'Systems Pharmacology' platform. However, by 2008 another change in direction occurred and the company raised $40 million in new capital to help commercialise its first product, Galactin-3, a predictive biomarker of congestive heart failure. The company platform had morphed into a biomarker discovery engine. BG Medicine aggressively pursued development of Galactin-3 and it was granted FDA 501(k) approval in November 2010, followed shortly thereafter by a successful IPO, raising $40.25 million in February 2011.

Initial efforts to implement a platform-driven DDD initiative proved to be elusive for Beyond Genomics/BG Medicine. The systems biology platform developed by the company was innovative but was not purpose-built for DDD. A more pragmatic biomarker and diagnostics platform driven focus led to considerable business success and a successful IPO. However, it is noteworthy that its one product, Galectin-3, was actually in-licensed from ACS Biomarker BV (The Netherlands). At the end of 2015, BG Medicine was delisted from the NASDAQ and the stock is now listed on the OTC market and currently trades at ~3-5 cents per share. Mixed fortunes for a highly-innovative company, that lacked an integrated and sustainable plan for its first-in-class platform utilisation, particularly in DDD.

The rise and demise of the CombinatoRx platform-DDD efforts

CombinatoRx was a blazing star in the firmament of platform-DDD companies. The company was founded in 2000 by a group of Harvard/MIT scientists and entrepreneurs. They developed a proprietary platform technology to evaluate the synergistic activity of combination-pair approved drugs. A high throughput, cell-based screening assay platform was used in combination with a novel dose-matrix regime against a broad swath of major diseases including assorted cancers, rheumatoid arthritis, asthma, psoriasis and diabetes. Alexis Borisy (founding CEO) stated: "We wanted to explore how we could create platforms that would rapidly yield a portfolio of clinical product candidates. We took a very pragmatic approach of starting from known components: if you take a world of 2,000 known drugs, it gives you two million possible combinations. We created and patented the platform that allows us to systematically search for these novel combinations in multiple therapeutic areas." (Interview with Alexis Borisy. Wall Street Transcript (2003). http://www.twst.com/interview/15717).

This innovative platform-DDD initiative garnered significant investment and grant funding, IP and a vibrant early-stage drug development pipeline, which led to a successful IPO (~$42 million) in November 2005. However, by 2010 the company was in trouble. It had burned through $230 million in funding and had encountered the brutal world of conventional drug development. It sought to reinvent itself with a name change to Zalicus and the hiring of a new CEO, Mark Corrigan. The slump in high-flying performance had been caused in 2008 by the faltering of one of its lead candidates. Synavive failed to demonstrate any statistically significant benefits in a mid-stage clinical trial for the treatment of arthritis of the knee. In order to shore up its pipeline, CombinatoRx acquired the Canadian company NeuroMed Pharmaceuticals along with its opioid pain reliever, Exalgo. This single compound drug was subsequently approved by the FDA in April 2010. In addition it developed a new version of Synavive, but that failed to demonstrate improved efficacy in clinical trials when compared to marketed competitors, and the company abandoned all development efforts in September 2012. UK-based Horizon Discovery acquired the CombinatoRx/Zalicus service business and high throughput screening platform for $8 million in June 2014. Simultaneously, Zalicus announced a merger with Epirus, a Boston, US-based pharmaceutical company focused on rheumatoid arthritis, in a 10-for-1 reverse stock split. The demise of CombinatoRx/Zalicus was complete, and a simple, creative platform-DDD idea had floundered on the jagged rocks of drug development.

molecular dynamic simulation hybridised with an array of other innovative biopharma DDD modules. The implementation of this platform, even at such an early stage, has shown our ability to systematically translate data content into functional biology in the form of innovative protein drug candidates. We are just at the beginning of our journey, which is in stark contrast to the 'monster' PD3 company Moderna Therapeutics.

Integrated platform-DDD company Moderna Therapeutics

Moderna Therapeutics (originally called ModeRNA https://www.modernatx.com/) was founded in 2010 by Derrick Rossi (Harvard University), Kenneth Chien (Harvard University), Robert Langer (MIT) and Noubar Afeyan (Flagship Ventures/Flagship Pioneering). In 2011 the company recruited Stephane Bancel away from bioMerieux to become CEO. Moderna operated in stealth mode for the first two years of operation and most analysts mistakenly believed it was a stem cell therapeutic company. As the company removed its 'invisibility cloak' it became clear that the Cambridge (Massachusetts, USA)-based entity was actually developing messenger RNA (mRNA) therapeutics. In addition it had already raised $40 million, led by Flagship Ventures/Pioneering and a host of private investors!

History and evolution of Moderna

Noubar Afeyan has always thought expansively, and chased challenges most conservative investors avoid. The idea of being able to instruct a patient's own cells to create therapeutic proteins and antibodies to fight off all types of disease indications could change the DDD paradigm. So, the stated original, visionary goal of Moderna Therapeutics was to use mRNA therapeutics to treat diseases such as diabetes, cancer, heart disease and certain viral infections.

Secrecy, money and valuation: The early years of Moderna were shrouded in secrecy and some degree of uncertainty. An articulated, bold vision now had to be reduced to practice and in order to execute on the 'plan' monies had to be raised. The initial phase of such efforts followed a two-prong approach of federal grant funding and the more classical offering of services to large pharma in return for upfront as well as back-end loaded payments. In terms of grant efforts, the company raised $24.6 million in the form of a grant provided by the Defense Advanced Research Projects Agency (DARPA) in October 2013 (see **Table 1**). The funds were provided in order to develop an mRNA drug technology to fight infectious disease. Subsequently Moderna received a grant from the USA Department of Health and Human Services (Biomedical Advanced Research and Development Authority-BARDA) for $125 million (milestone driven) to develop mRNA-based vaccine against the Zika virus in September 2016 (see **Table 1**).

The company also embarked, in parallel, on an aggressive service play to large pharma. In March

2013, Moderna signed an agreement with AstraZeneca to develop mRNA therapeutics in a variety of major disease conditions. The agreement included an eye-watering up-front payment of $240 million, one of the largest licensing deals made that did not include a drug already in clinical trials. This mega-deal was followed by an agreement with Alexion Pharmaceuticals in January 2014. It agreed to pay Moderna $125 million for 10 orphan disease drug products. In addition, Alexion made a $25 million preferred equity investment into Moderna. The company then announced a deal with Merck for the development of vaccines against viral diseases in January 2015. Merck made an upfront payment of $50 million as well as a $50 million equity investment into the company. During 2016, Moderna expanded its deals with AstraZeneca (January) and Merck (January), as well as a new deal with Vertex (July). In the same year (June) the company entered into a new deal with Merck ($200 million up-front payment) to develop mRNA precision medicine vaccines to treat a number of different cancers. These relationships have continued to develop as candidate drugs have started to emerge, and a good example is the Moderna-AstraZeneca drug co-development deal signed in November 2017 for the mRNA treatment of heart disease (drug candidate AZD7970).

Moderna also pursued an aggressive, but stealth-like mode in seeking equity investments. As noted above, Noubar Afeyan at Flagship had provided the initial seed funding of $40 million in December 2012 (see **Table 1**). Flagship followed this up with another investment of $110 million in November 2013. Over the next three years, Moderna raised an astonishing $949 million in equity investment alone from a variety of sources, including pharmaceutical companies, institutional and private investors. All this occurred in the context that Moderna had no actual drug therapies on the market, and that the business model was still evolving. In spite of such uncertainty, lack of demonstrable progress and no translation of discovery into products, the estimated valuation post-money, after the $474 million investment in August 2016 was $2.974 billion (see **Table 1**). It appeared that secrecy could pay off if you have a talented management and advisory board team, and you have framed your potential product(s) (mRNA therapeutics) in an exciting and paradigm-shifting new light!

Problems and uncertainty: Any company that had a record of secrecy along with an 'evolving' business model, as well as an ability to expeditiously raise significant equity investments, write successful federal grants and generate substantial service-based revenues could be expected to have 'growing pains'. In an attempt to peek behind the Moderna curtain of secrecy, Damian Gade noted in a scathing commentary written in 2016 that "the company's caustic work environment has for years driven away top talent and that behind its obsession with secrecy, there are signs Moderna has run into roadblocks with its most ambitious projects"[8]. The most pointed criticism was leveled at Stephane Bancel, the CEO of the company. Apart from the usual character-flaw issues such as ego, assertive control and impatience, the most egregious complaint was that company valuation was the dominant force driving company function and not the science. This led to a toxic work environment that resulted in high management and staff turnover, which is rather unusual in well-funded, early-stage companies. Additional complaints levelled at the company included the fact that a focus on vaccines was shortsighted and even more damning was the fact that the company had published no data supporting its claims to produce mRNA therapeutics. Gade quoted an anonymous former employee of the company that appeared to capture the essence felt by many at the time, namely that "it's a case of the emperor's new clothes. They are running an investment firm and then hopefully it also develops a drug that's successful"[8].

In addition to personnel issues there was also the problem of a still uncertain and 'evolving' business model. Early in the life of the company, a venture unit was conceived that was responsible for the creation of new subsidiary companies associated with mRNA therapies in distinct disease indication areas. These companies were initially wholly-owned subsidiaries complete with their own management teams. This organisational structure was designed to facilitate a Moderna push forward on a multitude of therapy fronts simultaneously, while attempting to mitigate risk but maximise reward. The companies were:

i) Onkaido LLC: formed January 14, 2014, responsible for mRNA therapies in oncology.
ii) Valera LLC: formed January 2015, responsible for the development of mRNA products for the prevention of infectious diseases.
iii) Epidera LLC: formed May 2015, responsible for mRNA treatments in rare diseases.
iv) Caperna LLC: formed October 2015, responsible for precision cancer vaccines.

Unfortunately, this model never fully materialised, and the company announced in September

Table 1: Current fund-raising efforts and pre-money valuations of Moderna Therapeutics

DATE	ROUND[a]	INVESTORS[b]	AMOUNT	VALUATION[c]
12/06/2012	Seed	Flagship (+)	$40 million	
10/02/2013	Grant	DARPA	$24.6 million	
11/20/2013	Series A	Flagship (3)	$110 million	
01/14/2014	Series B	Alexion	$25 million	
01/05/2015	Series C	Assorted (6)	$450 million	$2.6 billion
01/12/2016	Grant	B&M Gates	$20 million	
08/24/2016	Series D	Assorted	$474 million	$2.5 billion
09/07/2016	Grant	BARDA	$125 million	
02/01/2018	Series E	Assorted (10)	$500 million	$6.5 billion
05/03/2018	Series G	Merck	$125 million	$7.5 billion

a These are arbitrary designations of each investment round
b Lead investor where designated, and ( ) number of investors for the round
c Valuation is based on pre-money estimates

2017 that it was shutting down all four subsidiaries and subsuming drug candidates back into the parent company[9]. Bancel explained that potential new investors struggled to understand what they owned versus existing investors. He went on to explain that internally, because of this organisational structure, R&D efforts were being duplicated and the addition complexity had led to higher, and unnecessary expenditures. This reorganisation proved costly and left a continued concern that bringing everything back into parent Moderna, may "stretch the [company] too thin"[9]. Finally both, Bancel (CEO) and Hoge (President) provided an optimistic perspective by stating "the benefits of having everything under their control outweigh the risks of managing several separate subsidiaries".

Unveiling the platform

Moderna had, in four short years (2011-15), raised considerable investment funds (see **Table 1**) and some notoriety. The secrecy surrounding details of the platform and suggestions by former employees that the company had not published any data supporting its ability to produce mRNA therapeutics gave cause for concern. In particular, a comparison to the scandal-plagued, blood diagnostics company Theranos[10] was inevitable, since unnerving parallels were becoming obvious. Moderna had shared almost no details in the peer-reviewed literature concerning its platform, and even the targets of drug candidates in Phase I clinical trials had not been revealed. Investors appeared to be operating on a blind faith basis as to the underlying value of the platform. In spite of high management and staff turnover, which had plagued the company, by 2015 Moderna had achieved 'Unicorn Status'. Such status brought additional scrutiny and potential skepticism as to whether promises made would be ultimately realised. Something clearly had to be done!

Moderna mRNA platform: In early 2017 Moderna disclosed its first drug candidates, which included vaccines for both flu and the Zika virus as well as treatment for heart failure, at the J.P. Morgan Healthcare Conference. It also agreed to provide unprecedented access to reporters from the journal *Science* to Moderna research facilities and details of the mRNA platform[11]. The Moderna scientific premise was elegantly simple, but profound. Introduce a specific, modified mRNA into a patient such that this single stranded molecule (drug) starts to produce proteins, utilising human cells (in the patient) to produce a corresponding protein. It has been compellingly argued that, "assembling these chemical instructions could be a faster and more adaptable way to make drugs than manufacturing the individual

proteins themselves in large bioreactors. And it would allow scientists to deliver proteins that act inside cells or span their membranes, which are a challenge to introduce from the outside. An mRNA drug would also be easier to control than traditional gene therapy"[11].

The elegance of the idea was undeniable, but the practicalities of implementation were immense. One major issue faced by Moderna was that mRNA is subject to degradation when introduced into the human body, along with a myriad of other significant hurdles. In order for the process to work, the mRNA has to avoid degradation, enter the patient's cells and be translated into a specific protein as determined by the 'computer' code of the mRNA base sequence. In order to overcome these difficulties Moderna had 'built' an mRNA molecular platform that consisted of the following:
i) Delivery: mRNA is formulated in a lipid nanoparticle which acts as the delivery vehicle.
ii) Avoid immune system: One of the mRNA bases (typically uridine) is chemically modified. This prevents activation of immune receptors that detect 'foreign' RNA and destroy it.
iii) Enhance protein production: The order and frequency of modified RNA bases affect how mRNA folds and controls the efficiency of the ribosome to produce larger quantities of the specific protein.
iv) Targeting correct cell: Other regions of the mRNA are modified to target specific cell types.

The Moderna platform consists of a variety of sophisticated chemistries; including nanoparticle chemistry and mRNA design algorithms, and of course the output of molecular mRNA therapies. Servick has written much more expansively about the platform[11], and additional descriptive detail can be found in the abundant patent filings of the company. Finally, in April 2017 Moderna announced positive interim data from a Phase I clinical trial. A double-blind, placebo-controlled, dose-escalation study in 31 patients demonstrated induced high levels of immunogenicity for its mRNA vaccine (mRNA-1440) against avian H10N8 influenza These results were the first data that, in effect, validated the Moderna mRNA platform[12].

Platform and reality: We have discussed above that pharmaceutical companies struggled with TTP implementation and integration into their DDD process. The lack of understanding of Technology Development, the THC, Technology Assimilation and TIC S-Curves was a pronounced contributory factor to "…a lack of any significant increase in DDD productivity by pharmaceutical companies" over the past two decades. Thus it was both startling and refreshing to read that in 2017, Dr Melissa Moore (CSO of mRNA Platform Development at Moderna) mused about the Gartner THC. "Where on this curve, she wondered was their [Moderna] technology?"[11]. The concern was that if the "trough of disillusionment" was ahead, then it "threatened to be deep".

The conclusions that Moore and senior management came to about the THC in regard to a PD3 company like Moderna were both surprising and enlightening. The company had become increasingly aware of the secrecy label and the potential damage being done to Moderna. Management pushed back and argued that detailed disclosure did indeed exist in the form of patents filed and issued, and that controlled release of information had clearly not hindered their ability to raise monies and amass a considerable war chest of financial resources (see **Table 1**). Moore suggested that "wealth and secrecy may … be protective"[11]. In addition she said "you don't have to ride up and down Gartner's hype curve [THC] if you can work through the biggest setbacks before the public ever sees them". She concluded that, "we've had failures. We've gone down blind alleys. But because we've been quiet about it, nobody's seen that". She continued, "that's why I think we're going to end up on the slope of enlightenment without passing the trough of disillusionment"[11]. Do these thought-provoking comments suggest that this may become the model of how to implement a PD3 approach when employing a concerted, nuanced but clear understanding of Technology Development, THC, Technology Assimilation and TIC S-Curves?

Valuation and platform-DDD

Noubar Afeyan was recently interviewed (June 7, 2018) on WBUR (a public radio station in Boston) about his views on DDD as well as Moderna Therapeutics[13]. Dr Afeyan was as usual, thoughtful, insightful and provocative. In particular, he clearly articulated the changing paradigm of DDD associated with a PD3 approach. He stated: "I'd say the one big shift that [we've seen] is that people are making this less of a bet on a single drug and more of a bet on a platform which can produce many drugs. All of our companies [Flagship Pioneering] have decided that the way to innovate and create new products in this field is not by betting on a drug, but to bet on a platform that can generate many. And in that regard, those companies require a lot more capital, but also provide a lot more opportunity for reward than the single bet

References

1 Accenture Report. High Performance Drug Discovery: An Operating Model For A New Era. https://newsroom.accenture.com/subjects/research-surveys/new-drug-discovery-model-can-drive-pharmaceutical-biotech-pipeline-and-growth-says-new-accenture-research.htm (2001).

2 Naylor, S, Culbertson, AW and Valentine, SJ. Technology: Bane or Bonanza for the Pharmaceutical Industry. Drug Discov. World. Fall Edition: 51-57 (2007).

3 Gartner Consulting. Technology Hype Cycle. https://www.gartner.com/en/research/methodologies/gartner-hype-cycle.

4 Haeckel, SH. About the Nature and Future of Interactive Marketing. J. Interactive Marketing 12: 63-71 (1998).

5 Rogers, EM. Diffusion of Innovation. 4th Edition, Free Press, New York (1995).

6 Thong, R. Bioscience Platform Companies and Their Lifecycle. SciTechStrategy. http://scitechstrategy.com/2015/01/bioscience-platform-companies-and-their-lifecycle/ (2015).

7 Thong, R. Everything You Need to Know About Biotech Business Models. LabTech.eu. https://labiotech.eu/features/young-biotech-business-models/ (2018).

8 Gade, D. Ego, ambition, and turmoil: Inside one of biotech's most secretive startups. StatNews. https://www.statnews.com/2016/09/13/moderna-therapeutics-biotech-mrna/. September 13th, (2016).

9 Fidler, B. Moderna Ends Venture Experiment, Dissolves Four Startups. Xconomy. https://www.xconomy.com/boston/2017/09/14/moderna-ends-venture-experiment-dissolves-four-startups/ September 14th, 2017.

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that used to be the biotech companies of the past."[13]

Afeyan suggested also that due to the complex structure of the Moderna PD3 approach, it is more appropriate to "…think of Moderna not as one company, but as an assemblage of five or 10 different companies. If you look at how many drugs they have in the clinic, it's about 10 times more than most other biotech companies at this stage"[13]. Such assertions strongly suggest that PD3 strategies can help facilitate increased valuation of such companies. Although, it should not be overlooked that Moderna does now possess a robust mRNA DDD pipeline in prophylactic and cancer vaccines, immuno-oncology, regenerative and systematic therapeutics. This consists of 21 mRNA drug candidates in preclinical (10), Phase I trials (10) and Phase II trials (1)[14]. However the company still does not have any successful products currently on the market in patients. We believe that the valuation of Moderna dramatically increased from $2.5 billion up to $7.5 billion (pre-money) mostly in part due to the platform capabilities. As can be seen in **Table 1,** the pre-money valuation of Moderna was estimated at $2.5 billion in August 2016. This was followed in early 2017 by the company highlighting the component parts of the platform[11] followed shortly thereafter by validation of the platform[12]. The subsequent valuation of the company skyrocketed to $7.5 billion (**Table 1**). Coincidence, or a reality-based phenomenon of PD3 companies?

Moderna Therapeutics has experienced a roller-coaster ride since its formation eight years ago. It has enjoyed meteoric financial success, in association with a plague of criticism. The company has clearly articulated the potential of its mRNA platform and has developed the beginnings of an early-stage, but burgeoning, pipeline of drug candidates. In return, investors have rewarded the company with a staggering valuation. Some have argued that such a valuation is unsustainable. We are not so skeptical. Moderna has clearly demonstrated the power of its PD3 capabilities and has set new standards for valuation considerations. However, we would also note that the current Board and Management team members have demonstrated an ability to define new paradigms as well as learn from past mistakes. In the latter case this is epitomised by the changed behaviour of CEO Stephane Bancel. Back in 2016 he was the focus of a highly-critical article predicated on a series of issues associated with Moderna. Last year he was voted an EY Entrepreneur of the year, and Moderna was voted in the top 25 'best places' to work in the Cambridge area. All of this combines to suggest an IPO is on the near horizon for Moderna Therapeutics.

Conclusions

The pharmaceutical sector failed to adequately implement TTPs into the DDD process. This has led to a stagnation of productivity as defined by 'flat' annual FDA NME/NTB approvals (**Figure 1**). In part this was due to a lack of understanding on how to optimise the choice of which technology/platform should be selected. More recently, a number of companies, including Moderna Therapeutics, have defined a new paradigm associated with the co-development of the PD3 model. It could be that indeed we were right in our 2007 assertion that a more focused and integrated implementation of TTPs should result in a significantly-improved output of therapeutic drug products[2]. We simply picked the wrong implementers!

Moderna and others have demonstrated that the implementation of a PD3 approach can significantly drive company valuation. The initial case studies appear to suggest that, in good part, this is fuelled by an innovative and validated platform. Although the complexities of such efforts should not be underestimated and an experienced and flexible management team is of vital necessity in order to produce drug candidates that fill the company pipeline. It is clear that the new paradigm driven by PD3 efforts is here to stay. The unresolved question is can such an approach finally drive the DDD process out of the mire it has been stuck in for several decades? For example is the uptick in productivity for 2017 (highlighted in **Figure 1**) just a part of the annual yo-yo effects of NDA/BLA filings and NME/NTB approvals or are PD3 efforts starting to have an impact? Only time will tell! DDW

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10 Carreyou, J. Bad Blood: Secrets and Lies in a Silicon Valley Startup. Alfred A. Knopf Publishing. (2018).
11 Servick, K. This Mysterious $2 Billion Biotech is Revealing the Secrets Behind its New Drugs and Vaccines. Science. http://www.sciencemag.org/news/2017/02/mysterious-2-billion-biotech-revealing-secrets-behind-its-new-drugs-and-vaccines . February 1st (2017).
12 Moderna Press Release. Moderna Announces Positive Interim Phase 1 Clinical Data Demonstrating First mRNA Vaccine Candidate, mRNA-1440, Induces High Levels of Immunogenicity. https://www.modernatx.com/newsroom/press-releases/moderna-announces-positive-interim-phase-1-clinical-data April 27th (2017).
13 Oakes, B and Amer, Y. One of Biotech's Biggest Investors Says the Industry Must be Unreasonable. WBUR Website-Bioboom. http://www.wbur.org/commonhealth/2018/06/07/noubar-afeyan-interview June 7 (2018).
14 Moderna Website. https://www.modernatx.com/pipeline Visited September 23rd, (2018).