

Integrated platform-drug discovery and development companies

Part II: comparative analysis

Large pharmaceutical companies have struggled to efficiently implement tools, technologies and platforms into their drug discovery and development (DDD) programmes. More recently there have been attempts by small-to-medium-sized pharmaceutical companies to create in-house, integrated platform-DDD (PD3) capabilities. This strategy does not come without risks, but has quietly been implemented to increase drug candidate efficacy/safety and pipeline numbers. In some cases this has resulted in much-vaunted success, as epitomised by the Moderna IPO in late 2018. Although the complexities of such efforts should not be underestimated, it is clear that the new PD3 business model is being adopted and utilised. We evaluate this new paradigm and discuss the common traits and themes of successful PD3 companies.

By Dr Stephen Naylor and Dr Kirkwood A. Pritchard Jr

Last year small-to-mid sized pharmaceutical companies were much more successful than their larger counterparts by 68% to 32% respectively, in producing FDA-approved New Molecular Entities (NMEs) and New Therapeutic Biological Products (NTBs)¹. The flexibility of small-to-mid sized companies facilitates dexterity of thinking and rapid adaption and adoption of new approaches. One such example is the development and utilisation of an integrated platform-DDD (PD3) model. Recently, we described this phenomenon and discussed the vagaries of implementing a PD3 approach¹. We suggested that Moderna Inc and others have demonstrated that implementation of such efforts can significantly

drive company valuation. Furthermore, initial case studies appear to suggest that the valuation is fuelled by an innovative and validated platform. Although the complexities of such efforts should not be underestimated, we concluded that “...it is clear that the new paradigm driven by PD3 efforts is here to stay”¹.

In stark contrast, Ben-Joseph and Manning have questioned the relevance and necessity of a PD3 approach for smaller companies². They argued that “...the platform concept, with a few notable exceptions, [is] seldom capital efficient” and has “...failed to offer a commercial return”. The focus of such companies should be on the “...lead product and allocation of time and money in a capital-

efficient manner toward that very product". In addition they opined that small-company management teams fail to differentiate the value of a technology-derived product, ie a therapeutic drug, versus the value of a specific platform technology. This is an oft-cited criticism, and it has been argued that most small pharmaceutical companies do not have the bandwidth to carry out such an approach. The consequences are dilution of effort, poor tactical and strategic decision-making, lack of focus and considerable risk enhancement. Ben-Joseph and Manning concluded that such an approach is "...best left to big pharma"²! We discuss these contrarian viewpoints of companies utilising PD3 approaches and assess such contributions to valuation.

Moderna and PD3 revisited

We recently described a PD3 company as a corporate entity that contains¹:

- i. Scientific and technological core competencies.
- ii. Competencies are utilised to generate new therapeutic drug candidates.
- iii. Enhanced application of competencies across a range of disease indications.

The platform of such companies can consist of proprietary hardware, biological, molecular and digital technologies, or some hybrid mix of some or all of them combined. Thong has suggested that these companies must initially be able to generate a revenue stream and establish a "credible technology and/or service provider" capability (Platform Technology Partnering Company)^{3,4}. As the company evolves and develops a sustainable 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. During this stage of growth, the platform company should partner with large pharmaceutical companies which fund the expensive late-stage clinical trials (Asset Creation and Out-Licensing Company). 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 (Product Development and Commercialisation Company).

Moderna valuation

We have described in detail the history, platform, drug pipeline and business model of Moderna¹. The company was founded in 2010 and went public in December 2018⁵. However, Moderna does not have any commercially-available drugs on the market. The valuation of the company was primar-

ily driven by the mRNA platform. Noubar Afeyan in an interview last year on WBUR (a public radio station in Boston) articulated his views on 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. And in that regard those companies require a lot more capital, but also provide a lot more opportunity for reward than the single bet that used to be the biotech companies of the past"⁶. Afeyan asserts that PD3 strategies can help facilitate increased valuation of DDD companies. Indeed, we have opined that the valuation of Moderna dramatically increased from \$2.5 billion up to \$7.5 billion prior to the IPO, mostly due to its perceived platform capabilities¹. But, it should not be overlooked that Moderna now possesses a robust mRNA DDD pipeline of 21 mRNA drug candidates, which clearly contributes to its stratospheric valuation.

Moderna IPO

Moderna executed a successful IPO on December 7, 2018. In this much-anticipated event, Moderna raised \$604.3 million by selling 26.3 million shares at \$23 per share, valuing the company at \$7.5 billion⁷. This was the largest IPO in the biotech sector to date for a pre-revenue company. The company started trading on the Nasdaq stock exchange under the ticker symbol 'MRNA'. However, the irrational exuberance of the Moderna IPO quickly soured as the new shares lost a fifth of their value on the first day of trading. Investors took stock of a company with no market drug products, and a class of potential drugs that had never been assessed nor approved by any US, European or Asian regulatory authority. In addition, cash burn had been very high, with the company spending \$548.3 million in total operating expenses in 2018, and it had incurred net losses each year since inception in 2010. At the end of 2018 the company had an accumulated debt of \$865.2 million. The stock ultimately hit a low of \$13.52 on December 26, 2018, but more recently (January-March 2019) has been trading in the range of ~\$19-22. Investors have priced in the value of the innovative platform of Moderna, but are now waiting to see whether it can deliver in terms of marketable drug products.

Comparative analysis – PD3 companies

Currently, there are more than 100 different PD3 companies. At least five of these companies are classified as 'Unicorns' (privately-held companies valued >\$1 billion). The size and valuation of these

companies spans a considerable range that includes behemoths such as publicly-traded entities like Ionis Pharmaceuticals, Akcea Therapeutics and Ablynx. However the list also contains much smaller, privately-held companies such as Sirenas. We now discuss and compare a number of these smaller companies along with their business models and valuations.

RNA PD3 companies

RNA-based therapeutic approaches have generated significant attention in recent years. They include antisense, RNAi, aptamers, microRNA, mimics/anti-miRs and synthetic mRNA technologies. Moderna is the epitome of such companies, and has enjoyed marked financial success in its PD3 mRNA drug therapy endeavours. It is interesting to compare and contrast Moderna's success (current market capitalisation of \$7.12 billion-March 18) with that of some of its PD3 competitors. For example consider:

CureVac (www.curevac.com) is a biopharmaceutical company that develops mRNA therapeutics in direct competition to Moderna. The company was founded in 2000 and is located in Tubingen, Germany. It has ~390 employees and an annual revenue stream of ~\$300,000. The company has raised \$431.5 million, and it remains privately held. The drug therapy pipeline consists of 17 potential drug candidates in cancer, prophylactic vaccines and molecular-based therapies. Four candidates are in Phase I, eight in preclinical stages, and the other five are still in discovery. It is currently valued at ~\$1.65 billion.

Regulus Therapeutics (www.regulusrx.com) develops microRNA drugs for fibrosis, cardiovascular and immune-related disorders. The company was founded in 2007 and is based in San Diego, California (USA). The company sprinted to an IPO in October 2012, and has raised ~\$175 million that includes the IPO of \$45 million. It currently employs ~60 individuals. The pipeline consists of eight potential drug candidates, one Phase II, one Phase I and the remaining six in preclinical evaluation. Revenues for 2018 were < \$1 million and the current market capitalisation (March 2019) is only \$9.53 million, down from the IPO valuation of \$136.5 million.

Alnylam Pharmaceuticals (www.alnylam.com) was the very first commercial entity to attempt the development of RNAi therapeutics in a variety of disease states. The company is based in

Cambridge, Massachusetts, USA and was founded in 2002. The company filed for an IPO in February 2004 raising \$26.4 million, and has accrued \$417.5 million to date in equity investments. The company has more than 1,000 employees. The platform built by the company was not as focused and directed as a typical PD3 company. It was assembled out of necessity since Alnylam pioneered the therapeutic use of RNAi therapeutics. This has resulted in a robust pipeline of drug candidates that includes five Phase III and four Phase II drug candidates. One candidate, Givosiran, is being registered as a commercial drug in an NDA filing. In addition Patisiran (brand name Onpattro) was the first ever FDA-approved RNAi therapy for the treatment of hereditary transthyretin-mediated amyloidosis. The current market capitalisation of Alnylam is \$9.1 billion.

Moderna is a purpose-built PD3 company. The articulation by Noubar Afeyan on the value of such an approach has been leveraged by a lucrative fund raising and valuation/market capitalisation effect in the past ~eight years. This is in spite of the company being several years away from demonstrating the efficacy and validation of the platform by producing a regulatory-approved drug. It is edifying to compare the fortunes of CureVac, a direct competitor of Moderna. The former has not been aggressive in promoting its PD3 capability and has a much longer history, but with a comparable drug candidate pipeline to Moderna. However, privately-held CureVac only comprises ~25% of the market cap of Moderna! Even more noteworthy is the comparative performance metrics of Regulus Therapeutics. This PD3 company, in its 12-year existence, has experienced dramatic highs (IPO 2012) and lows (current market capitalisation \$9.53 million). Ben-Joseph and Manning might argue (see above) that Regulus Therapeutics is a company which allowed platform development to be distracting from the true mission of producing new RNA therapeutic drugs².

The contrast in the history and performance metrics of Moderna versus Alnylam is instructive. The latter has been active for 17 years and pioneered the use of RNAi therapeutics. Alnylam developed a PD3 approach out of necessity and has for the most part in its history emphasised its DDD capabilities and the development of a robust pipeline. The current Alnylam pipeline is impressive and includes a marketed product Onpattro. The regulatory approval of this RNAi drug is a validation of the Alnylam platform. This is in stark contrast to the more modest pipeline of Moderna

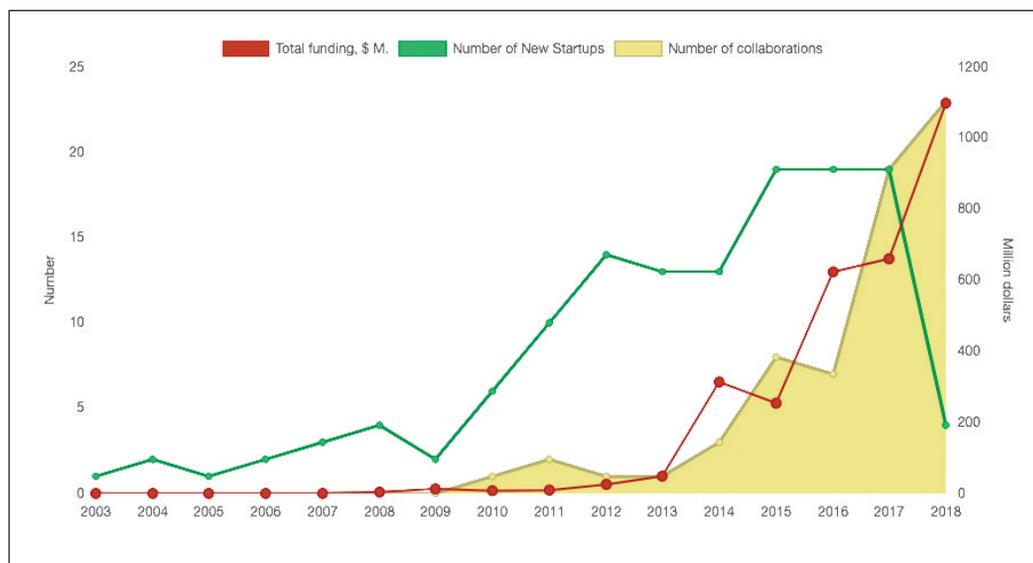


Figure 1
The number of AI-DDD companies that have been created each year. In addition the amount of equity investments made in AI-DDD companies. Finally the number of AI-DDD company collaborations with large pharmaceutical companies. These data are adapted from the work of Arnii Buvailo at BiopharmaTrend.com (<https://www.biopharmatrend.com/m/charts/>)⁹

and as yet, non-validated platform. In spite of these significant metric differentials, the current Moderna market capitalisation is still a comparable ~80% of Alnylam's valuation.

Artificial Intelligence PD3 companies

Data analytics, knowledge management and Artificial Intelligence (AI) have experienced explosive growth trends over the past decade. In particular the advent of AI-DDD efforts is noteworthy (see Figure 1). It is estimated that ~130 small companies now have business expertise and focus in AI-DDD, and most large pharma companies have also attempted to develop or bring-in-house such capabilities, as exemplified by the dramatic increase in large pharma collaborations in AI-DDD (see Figure 1)^{8,9}. The breakdown of small company AI-DDD capabilities is as follows; software/AI services ~66%, operational services ~14%, drug candidates as a service ~14%, and in-house drug development candidates (ie AI-PD3 companies) 6%⁹. This has attracted frenzied activity on the part of the investment community and venture capital/private equity monies are now readily available for AI-DDD companies as highlighted below (as shown in Figure 1).

BenevolentAI (www.benevolent.ai) is an AI-DDD company specialising in machine learning. The company was founded in 2013 and is located in London, UK. It employs ~300 people and last year had annual revenues of ~\$2 million. The company has raised \$207.7 million and is a privately-held entity. BenevolentAI currently offers both operational and drug candidate services to third parties and has no

drug candidate pipeline. However, based on this focused AI-DDD approach, the company is valued at \$2 billion! It is also now transitioning into an AI-PD3 company with an emphasis on ALS.

CureHunter Inc (www.curehunter.com) is a pioneer in the application of AI to DDD through its proprietary Machine Learning/Graph-Network Theory Platform. The company was founded in 2007 and is located in Portland, Oregon, USA. During the initial years the company provided AI-based, evidence-based medicine services to patients on a subscription basis. It transitioned into also providing potential drug candidates to pharmaceutical companies and then into generating its own drug candidates as an AI-PD3 company. Currently the management team is reassessing the business model. (Disclosure: Dr Stephen Naylor, one of the authors of this paper, serves as a Board Advisor to the company.)

Verge Genomics (www.vergegenomics.com) is a purpose-built AI-PD3 company founded in 2015 and located in San Francisco, California, USA. It employs ~20 people, with annual revenues of \$3 million (2018). The company has raised \$36 million and has developed strong academic partnerships with a focus in ALS and Parkinson's disease. The company does not yet have a drug candidate pipeline given its recent formation, and has a modest valuation.

BenevolentAI is a Unicorn company with a valuation of ~\$2 billion. The company is transitioning towards becoming an AI-PD3 company with a focus on developing in-house drug candidates in ALS.

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However, the current valuation of BenevolentAI is predicated on its AI-DDD efforts providing services and drug candidates to third party clients. Ben-Johnson and Manning would vociferously support such focused efforts². In contrast it could be argued that CureHunter is testimony to a company lacking focus. The company struggled to attract equity investments in both its AI-DDD and AI-PD3 endeavours. However, in this case it would be an oversimplification. CureHunter was almost a decade ahead of all competitors in terms of AI-DDD. It enjoyed some real success in terms of its Evidence-Based Medicine subscription model, but struggled to convince investors as to the value of AI-DDD before it became the 'shiny new bouncing ball' that everybody now chases today. Thus part of the lesson from consideration of the CureHunter situation is the matter of timing and the punishing effects of the Technology Hype Cycle¹.

Verge Genomics is a dedicated AI-PD3 company. This young company is still building out its corporate infrastructure and developing alliances with major academic institutions to pursue the development of drug candidates in ALS and Parkinson's disease. It is too early to determine the trajectory of this company, at present, but the investment community enthusiasm for AI-PD3 has facilitated the company's fund raising efforts with a war chest of \$36 million. A number of other AI-PD3 companies find themselves in a similar predicament and includes a number of other dedicated AI-PD3 companies such as AI Therapeutics, Auransa Inc, Berg Health, Insilico Medicine and ReviveMed. Future evaluation of this sector will determine whether PD3 companies are a fad or a real trend.

Drug Repurposing PD3 companies

Drug Repurposing (DRPx) is used as a catch-all term that is defined as 'the concept of an active pharmaceutical ingredient, at any stage of the life cycle and regardless of the success or misfortune it has encountered, serving a therapeutic purpose that is significantly different from the originally intended one'. We have written extensively on this subject in past editions of *Drug Discovery World*¹⁰. A number of DRPx companies qualify as PD3 corporate entities and several are discussed below.

Biovista (www.biovista.com) is a pioneering company in both DRPx and PD3, long before both approaches were included in the popular lexicon. The company was founded in 1993 by the Persidis brothers and is based in Charlottesville, Virginia, USA, as well as Athens, Greece. It currently has three employees, with annual revenues of an esti-

mated \$2.2 million in 2018 and is still a privately-held company. The company was originally an AI-PD3 company with a vibrant drug candidate pipeline. However, more recently it has transitioned to an AI-DDD company providing operational and drug candidate services to the pharma sector using its proprietary AI systematic drug-repositioning platform.

Recursion Pharmaceutical (www.recursionpharma.com) is a dedicated DRPx-PD3 company founded in 2013 and based in Salt Lake City, Utah, USA. The company has approximately 120 employees with ~\$5 million in revenue for 2018. The company has raised \$141.3 million in a combination of equity investments as well as debt financing. The current pipeline consists of 10 drug candidates with two in Phase I trials and the remaining eight in pre-clinical stage with a current valuation of an estimated \$275 million.

Melior (www.meliordiscovery.com; www.meliorpharmaceuticals.com) is a DRPx-PD3 company predicated on its theroTRACE mouse phenotype model screening platform. The company was founded in 2005 and is based in Exton, Pennsylvania, USA. The company has ~25 employees (Melior Discovery) with an annual revenue of ~\$10 million in 2018. The company raised ~\$10 million in a Seed Round for Melior Discovery. However, since then Melior Discovery has provided service-generated revenues to support the PD3 efforts. The current business model is different from other DRPx-PD3 companies. Each time a drug candidate is identified, a new corporate entity (Melior Pharmaceuticals I, II, etc) is formed that holds the IP and drug candidate development responsibilities. Currently, two Melior Pharmaceutical companies exist focused on Type II diabetes (completed Phase II) as well as NASH (preclinical evaluation) in Melior Pharmaceutical I, and Parkinson's disease (entering phase II) in Melior Pharmaceuticals II. The valuation of these companies combined is predicated on the innovative PD3 self-sustaining model of Melior Discovery and the drug candidates in the pipeline of Melior Pharmaceuticals I and II.

Biovista started as a DRPx-PD3 company before the concept was even articulated. This was done in concert with service provisions as a source of revenue. Biovista demonstrated innovation, creativity and initial success with a pipeline of drug candidates. However, problems ensued in attracting investment funds to develop drug candidates. The parallels with CureHunter are striking and another

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example of a company being too far ahead of the acceptance curve. In contrast, Recursion Pharmaceuticals started its DRPx-PD3 programme in a much more conducive timeframe (founded 2013) where investors at least understood the potential advantages (as well as disadvantages) to such an approach. This acceptance has manifested in the form of significant investments into Recursion Pharmaceuticals, which has facilitated a burgeoning pipeline and steady growth of the company.

Dr Andrew Reaume, Founder and CEO of Melior Discovery/Pharmaceuticals, has stated that the company(s) “is(are) comprised of a self-sustaining discovery core and risk-laden, value-generating pharmaceutical companies”. He also suggests “valuation is very much a perceptual quantity. The Melior business approach has kept us away from the investment community and like Moderna in stealth mode, but for an entirely different reason. I have no basis to say that, as a PD3 company, we are receiving increased valuation because we are not testing this in any way”. While the statement by Reaume is understandable, it can also be argued that the way that Melior has constructed its PD3 approach is highly innovative and led to a company with high quality drug candidate assets and a process that is self-sustaining as well as significantly derisked. The epitome of how to increase value in your company!

Conclusions

The argument concerning the valuation of PD3 companies articulated above is still being contested. The examples discussed here provide ammunition to support either supposition. However, Saxe has argued that the PD3 model has given the rise to the “third wave” biotech IPOs, wherein “public companies’ technology has evolved to the point of providing personalised medicine backed by wide-ranging biological platforms, that is, underlying tech that can be used to produce an eclectic mix of drugs across the disease spectrum, has given both drug makers and investors more cover”¹¹. In the case of Moderna, the PD3 approach has provided 21 different drug candidate assets. In the minds of investors this means that a single failure of a drug candidate does not necessarily mean catastrophe for the company, since other pipeline candidates can supplant the failed entity. This argument by Saxe is dependent on the fact that the underlying platform technology is valid and continues to provide *bona fide* drug candidates. Whether or not that happens is still somewhat of an unknown. But Saxe predicts that public offerings by PD3 companies will continue to thrive in 2019¹¹. In business,

arguments are often settled by the refrain ‘follow the money’ in determining success.

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