

Disruptive approaches to accelerate drug discovery and development

part I: tools, technologies and the core model

Tesla intends to implement and practise an ‘open source’ philosophy to its large patent portfolio and claims it would not pursue any legal action against anyone using them in good faith. This is a hard pill to swallow for the industry at-large. But, the pharmaceutical industry ought to seriously consider such an inclusive strategy to enhance the pace of drug discovery and development for the benefit of humanity’s welfare.

The staggering failure rate of experimental drugs in clinical trials indicates that despite huge investments in novel technologies, productivity gains in the pharmaceutical industry remain elusive. The pharmaceutical industry is facing a serious innovation deficit. The current biopharma model is therefore unsustainable and disruptive approaches are needed to remedy the status quo. It is incumbent upon the biomedical research community to harness the collective intelligence of pharma, biotech, academia, governmental agencies, non-profit research foundations and patient advocacy groups to accelerate innovation. Disruption – the force that both fuels and rises out of innovation – continues to affect every industry on the planet, from financial services to healthcare to telecommunications. For example, consider the recent breakthrough innovation models: Uber, the world’s largest taxi company owns no vehicles; Facebook, the world’s most popular media owner creates no

content; Alibaba, the world’s most valuable retailer owns no inventory; and Airbnb, the world’s largest hotelier, owns no real estate. Most recently, three large US corporations, Amazon, Berkshire Hathaway and JPMorgan Chase, have announced the formation of an independent healthcare company for their employees in the United States to deal with the soaring cost of health insurance premiums and pharmaceuticals. In ‘The Evolution of

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“Tesla Motors was created to accelerate the advent of sustainable transport. If we clear a path to the creation of compelling electric vehicles, but then lay intellectual property landmines behind us to inhibit others, we are acting in a manner contrary to that goal.”

Elon Musk, CEO and Chief Architect of Tesla Motors

Everything: How New Ideas Emerge' (Harper, 2016), Matt Ridley provides stunning perspective on innovation, it is as compelling as controversial, as authoritative as ambitious.

So, the question we have to ask is who actually drives innovation: the public or private sector? For more than a half century, it has been an article of faith that basic science would not get funded if the government did not do it, and economic growth would not happen if science did not get funded by the taxpayer. It may be a bitter pill to swallow, but the hard truth is that government funding of basic science was necessary because it is cheaper to copy than to do original research. Then, there are those who think there is less need for government to fund science because industry will eventually do this itself, having made innovations, it will then pay for further innovation.

In reality, intellectual property rights through issued patents dampen innovation. The original rationale for granting patents was to encourage inventors to share their inventions, not just to reward inventors with monopoly profits. A certain amount of intellectual property law is plainly necessary to achieve this. But it has gone too far. Most patents are now as much about defending monopoly and deterring rivals as about sharing ideas. And that discourages innovation! However hard and bitter it may be, the pharmaceutical industry needs to consider following the example set by Elon Musk... for society's sake.

Science drives technology, often resulting in patentable inventions. Invention leads to innovation. Both scenarios are inherently and fundamentally intertwined. For the betterment of humanity, it is imperative upon us, the guardians, to see that science-driven inventions ultimately lead to technology-based innovations¹.

While biotechnological advances, genomics and high-throughput screenings or combinatorial and asymmetric syntheses have long promised new vistas in drug discovery, the pharmaceutical industry is facing a serious innovation deficit. The costs of drug development have escalated, the number of drug withdrawals has increased to historic highs and the transition from bench to bedside has been long and arduous².

There are many reasons for this unsustainable business model. Most importantly, none of the pharmaceutical companies openly share the reasons for the failure of their clinical candidates in real time to effectively navigate the 'industry' from committing the same mistakes. It is time for the pharmaceutical industry to embrace, metaphorically-speaking, a community-driven 'Wikipedia' or

'Waze'-type shared-knowledge, openly-accessible innovation model to harvest data and create a crowd-sourced path towards a safer and faster road to the discovery and development of life-saving medicines. Pharma ought to give serious consideration to such a game-changing concept¹.

Breakthrough innovations at the drug discovery front

It may seem at times that we are losing the battle against many of the diseases that inflict humanity; in reality, we have made great strides. We now live longer, with a life expectancy that has almost doubled over the last 150 years. Improvements in nutrition, sanitation and housing, combined with advancements in public health, including the use of prophylactic vaccines and antibiotics, have eradicated deadly diseases that claimed millions of lives across the globe. However, with changing lifestyles, new diseases are emerging, age-associated co-morbidities are increasing and many old diseases still remain incurable. There are ~36 million deaths worldwide attributable to non-communicable diseases³.

Our knowledge of disease modalities is expanding. Over the last decade researchers, primarily academia and supported by public funds, have identified more than one thousand new biological changes that could translate to new targets or biomarkers of disease and its progression. Genome-wide association studies have uncovered a multitude of gene variants that may be contributing to complex diseases, such as schizophrenia, coronary artery disease and diabetes. Unfortunately, the translation of many of these discoveries into therapeutics has not been realised. Limitations in capacity, funding and even culture in an industrial setting make the selection of the best new therapeutic targets from the overwhelmingly-large list unlikely³.

Altruistic role for pharma

The pharma industry can help stimulate breakthrough on the discovery front. What if pharma's in-house facilities could become available for academic entrepreneurs, small biotechs or other spin-off's looking for 'ready set-up' labs and just wanting access to equipment and bench space, at cost? Tax breaks to the company could allow for this. Perhaps the more significant benefit is if the institution's programmes being shut-down, abandoned or placed on the shelf could be viewed by small biotech and academic labs for the potential of gaining access in order to complement programmes/research already on-going in their not so cutting-

edge labs. When business decisions often force pharma to shut down a mature programme, it potentially allows interested academic researchers and small biotechs to utilise the knowledge to accelerate other related programmes and could provide future benefit to pharma. One can consider this much like having an independent research group working on increasing the value of an asset that was deemed to be of little value, with no cost. Surely the possibilities exist that if 20 such project accesses were granted, perhaps one would provide returns and possibly a later stage programme of significant value. A simple framework for this could be as simple as non-confidential summaries that could be put in a web-based storefront. Deals would have to be relatively simple so as to not impede development of the technology or possible future business deals – perhaps with the pharma having a time-limited first rights for negotiation down the way.

While the business case for the development of certain drug leads which have undergone a signifi-

cant amount of pre-clinical and often clinical assessment may no longer be appealing to pharma; academia, foundations and non-profits may still find value and reposition or repurpose these fallen angels through their in-house programmes starved of promising candidates. This, of course, requires that pharma does not attach strings that are arduous for the development path. We propose and seek an obligatory mandate by the FDA and other drug approval organisations for the promoting company to provide the unformulated drug for non-profit and academic uses.

Open science and data sharing

The open science mantra has initiated some excitement of the possibilities of gaining a better grasp on science/data often hidden away behind locked doors, or just merely left on the lab bench to decay and rot. The concept behind open science is not new – openly share results of pre-clinical discovery in hopes that the information will enable new ideas and concepts to emerge and push drug development

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forward. As it operates mostly in the pre-clinical space, it does not hamper drug development, but as proponents say, it will enhance it. The Montreal Neuroscience Institute (a working hospital and research institute) and partners have spearheaded such an endeavour in neuroscience, an area which has seen few new drug approvals and a drastic failure rate, but all areas of science could benefit from such an approach (Montreal institute going 'open' to accelerate science doi:10.1126/science.aae0265). Talking the talk is easy in this case, as everyone can say "we publish our results so we are open science". However, walking the walk is a bit more challenging and will require new thoughts on how one really creates an open environment. Publication of results in a timely manner is one facet, but in reality, it happens only with 'failed' research projects, or when the impact has fallen off the cliff. One of the biggest and perhaps most valuable aspects is also the inclusion and/or publication of negative results. Think about it. Each year, billions of dollars are provided to academic labs to pursue ideas, and each year a large number of research papers are published. It is, however, rare to see the research that did not work. Yet, the same experiments are often carried out by other researchers, who would have not travelled the path and wasted significant resources had they known. Negative data is good data to have, particularly as we move towards an era of employing artificial intelligence to enhance discovery and development. But how does one employ this in a world which only rewards positive results through publications and grants? One potential way would be to utilise a self-curated Wikipedia-like contribution which has some data entry standards employed to make the data easily searchable with respect to field, technology used and results portrayed.

Outsourcing

To harness the best avenues possible in the most cost-effective way, pharmaceutical industry now actively pursues and outsources many of its activities, and academic partnerships have become a key element of early pipeline strategies³. When we outsource research, we risk losing serendipity and chance observations/findings that quite often fuel innovation and pave the path towards uncharted territories. For this not to happen, outsourced research projects must be managed actively, with an eye towards 'negative' results and unexpected findings.

Phenotypic and cell-based screening

Along with phenotypic screening comes the challenge of identifying genes/proteins/compounds that

can alleviate a syndrome. Previously we have relied on si/shRNA knockdown to investigate which genes are necessary from an expression point of view with the hopes of uncovering potential targets for our compounds. Miniaturisation of the technology, utilising reverse transfection technology has been able to provide the interrogation of thousands of genes, via siRNA or CRISPR (clustered regularly interspaced short palindromic repeats) technologies on a glass slide that can easily be viewed by high content instruments. Persomics, Inc (<http://www.persomics.com/>) has pursued this technology and, once it becomes validated in the community, one could envision larger arrays covering the entire genome. If the phenotypic assay is run on one slide, one could quickly determine the effects of RNA expression on assay readouts and this would perhaps lead one to be able to identify pathways which would be appropriate to drug. With the advance of CRISPR technologies, this has become simpler and perhaps more practical in that genes are knocked out providing a clearer picture of protein involvement in a disease.

CRISPR

CRISPR has revolutionised the way we do discovery biology. This exquisite technology comes from a bacterial defence mechanism used to destroy invading DNA. The small DNA repeats in the bacterial genome producing short RNAs which recognise and bind to the invading DNA while bringing the DNA cleavage enzyme Cas9 to its location to cut the DNA so it becomes ineffective, while ensuring a copy of the short piece of invading DNA is reproduced and inserted into the bacterial genome to ensure 'memory' of this invading species. Since 2013 CRISPR technology has generally replaced other gene-editing/modifying systems due to its precise and efficient abilities. Examples include knocking out specific genes in cells and in animals, gene editing of human embryos to correct mutations, as well as extraction of HIV from a living organism thus preventing the progression of a latent infection.

As we delve more and more into the disruption of protein-protein complexes to create a newer generation of drugs, we need to be aware that a knock out (KO) of that protein may not provide compelling proof of target validation. Quite often, a KO is lethal, causing drug developers to drop the target – unless your field is oncology. But in other fields, it is not a KO that is required but more of an inhibition of an interaction with a neighbouring protein that is critical to prevent the disease or outcome. By modulating that interaction, one could

have created a therapy. But once again the challenge is very often protein-protein interactions and often these surfaces do not have big pockets or clefts for a small molecule to bind into. The question is still out as to how to do this. CRISPR may provide a potential answer. Recently Salk scientists have adapted the CRISPR mechanism to modulate expression of genes – rather than knock them out (DOI: <https://doi.org/10.1016/j.cell.2018.02.033>). They have done this by utilising a defective Cas9 which cannot cleave but can still target the gene specificity by the appropriate guide RNA. Thus, there is the ability to turn genes off and on at the transcriptional level, which enables a number of key experiments that drug developers have been wishing for – the ability to modulate components of a protein complex without having to clone all the genes involved. This next round of CRISPR reagents will have a profound effect on how we look at altering gene expression with the abilities for turning genes on or off or to potentially disrupt a translation of a portion of a protein (DOI: <https://doi.org/10.1016/j.cell.2017.10.025>). By removing specific domains of proteins, we can better learn the full potential of drugging them and hopefully zero in on the regions or interactions that are critical.

Genetic modalities

Genetics is often the route chosen for target identification and validation, a result of Genome-Wide Association Studies (GWAS) linking certain genetic variants or mutations to a disease condition or having a direct biomarker in the gene causing the disease. While we utilise the results of genome-wide sequencing data and incorporate gene expression data within the rationale for pursuing drug discovery efforts of specific pathways and proteins, the use of genetics to aid in finding a cure is often left behind. Compensatory mutations that can rescue the original mutation is an area of genetics that has been the focus in model organisms for quite some time. Its possible application to drug development adds another avenue to consider when searching for a disease modifying drug. Can a drug against a protein in another pathway solve/prevent the condition caused by the original mutation? A similar approach has been harnessed in drug development for cancers – synthetic lethality, or in the drug development world, chemical lethality – as a means of selectively destroying cancer cells. In this case the cancer cells have a mutation which in part is responsible for their phenotype. When this mutation is combined with another mutation (which also by itself has no effect on the cell) the cell is

doomed – hence being synthetic lethal. Finding compounds that cause this effect are a potential source of new drugs and a new mechanism of action for treating cancers. If two mutations can work together to provide lethality, could the reverse not also be true – synthetic health. This approach would seek non-related mutations which cure the phenotypic disease or at least slow it down. This strategy could also be used in drug combination types of approaches and creation of chimeric compounds.

Death of a dogma: CDS and ORFs

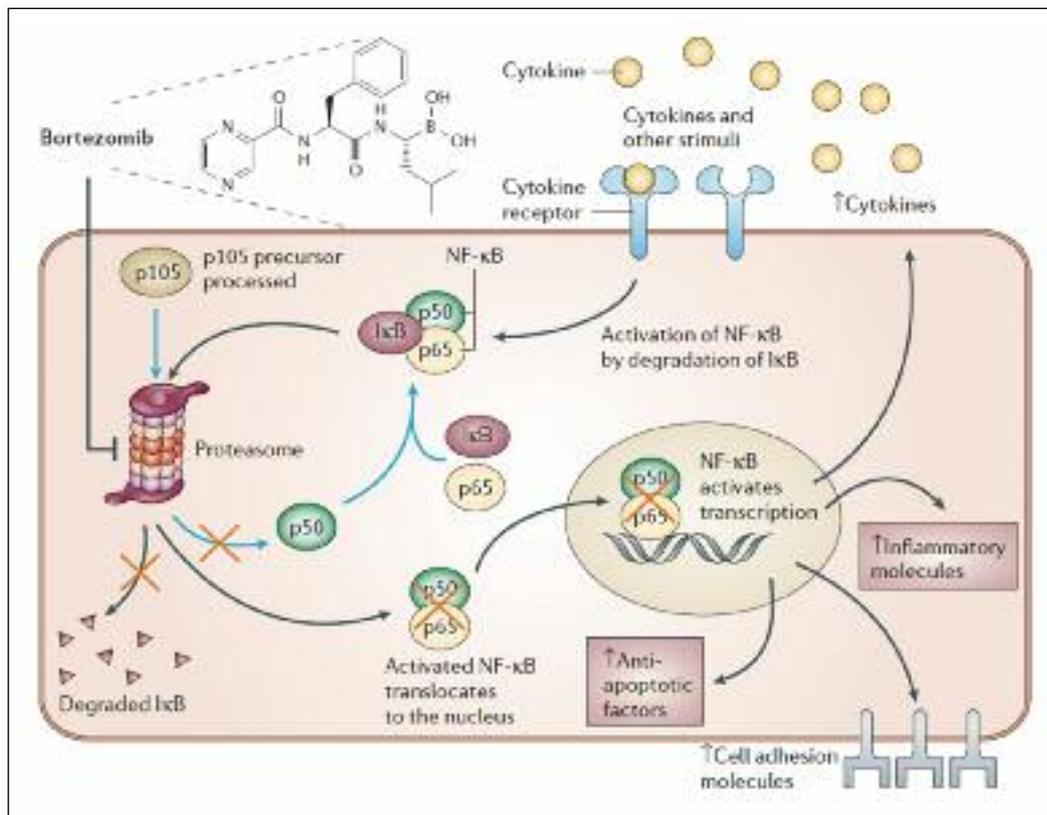
In the world of big data, it is often useful to remind ourselves as to how data is being analysed and ask ourselves to go back and visit the bioinformatics' algorithms applied and the curated data generated. What was relevant and cutting edge then, may not be so now with our ever-expanding knowledge base. Years ago, this fault was demonstrated in the RNA world as we became aware of siRNA's being important in both gene regulation and mRNA stability/translation and more recently with exosomal RNA, RNA transported via exosomes to other cells and snoRNAs.

Now we see the same with proteins. In the early days of genomics and bioinformatics, one mRNA coding sequence (CDS) was considered to be associated with only one protein-coding gene. But now we know that eukaryotic mRNAs contain not a single refCDS but usually several ORFs. The single CDS dogma has artificially limited our view of the coding capacity of mRNAs and has prevented the discovery of alternative proteins despite some clues in the literature over the years. Functional relationships between reference and alternative proteins expressed from the same gene may help identify a new layer of regulation of protein activity. Previously, the definition of a protein was classically defined as a stretch of 100+ amino acids with a start and stop codon, with some minor variations. The algorithm has broadly been used to 'identify' the number of proteins in the genome of just about every organism sequenced. Of course, variations of these parameters have been made but back in the 80s, with the limited knowledge available, it made sense. However, today it is becoming increasingly apparent that one has to closely look at our definition of a protein. Spearheaded out of the University of Sherbrooke by the Roucou lab (www.roucoulab.com), the Alt-Prot analysis of the genome has lowered the requirement of a protein to 30 amino acids. The protein coding potential of eukaryotic mRNAs has surely been underestimated (see

Figure 1

The proteasome, nuclear factor- κ B and bortezomib. The proteasome is a barrel-shaped multiprotein particle that destroys proteins that have been marked for degradation by conjugation to ubiquitin. Binding of the transcription factor nuclear factor- κ B (NF- κ B) to the inhibitor protein I κ B in the cytoplasm renders NF- κ B inactive. Cellular stimuli, such as cytokines, antigens, oxidants, viruses and other agents, trigger a cascade of signal transduction events that phosphorylate and ubiquitinate I κ B, leading to its degradation by the proteasome, which in turn liberates NF- κ B for translocation into the nucleus. Once in the nucleus, NF- κ B binds to the promoter regions of genes coding for proteins that are involved in the activation of transcription, growth, angiogenesis, anti-apoptotic factors and cell-adhesion molecules. By inhibiting the proteasome, bortezomib inhibits the activation of NF- κ B (orange crosses) and subsequent events that can promote tumour cell survival and proliferation.

Source: Sánchez-Serrano, I. Success in Translational Research: Lessons from the Development of Bortezomib. *Nature Reviews Drug Discovery*, 5 (2):107-114 (2006)



www.Openprot.org). It has already demonstrated that another body of knowledge around possible targets for drug discovery is becoming relevant and will provide a treasure trove of knowledge for future drug discovery scientists to think about and perhaps revisit fallen programmes where ‘knock-out’ data confirmed an interaction but drugging the ‘protein’ never provided the anticipated results. Lots of rationale of why the drug may not have worked, but perhaps the wrong protein was drugged. What if it was an alt-protein responsible for the effect?

Biologicals

Monoclonal antibodies are the hot topic of pharma industry as these drug approvals are picking up and the ability to utilise them in CAR-T and other technologies is gaining momentum. The roots of creating and selecting these monoclonals has diverse streams, however; the common one from academia is the creation of a mouse mAb utilising hybridoma methodology as a starting point. While this has produced great tools for biology and sometimes is the starting point for development of a humanised version for drug development, we now realise that this is a tricky and complicated development path involving time-consuming

screening for the right potency, selectivity and ‘humanised’ lead. In the past few years, the idea has emerged to begin with fully human, not mouse, antibodies as the starting point to alleviate some of the challenges of developing drug candidates. Much like the chemists have defined useful backbones for compound drug development, biologists have now defined a number of scaffolds based on those that have been in Phase I and combined that with V-regions and alleles that are shared by all human populations. Along with selecting specific CDR regions and creating a diversity of 76 billion Abs allows for quick selection of mAbs with high specificity and good clinical perspective. This ‘Bio Superhuman library 2.0’ – a synthetic monoclonal Ab library – claims to reduce monoclonal lead discovery and development to about two months (<https://www.distributedbio.com>).

The phoenix: core model approach to drug discovery and development

Given the crucial importance of the pharmaceutical industry in the world’s healthcare systems⁴⁻⁶, it is very surprising that little attention has been paid to the understanding of the ways in which the pharmaceutical industry has succeeded in bringing remarkable novel drugs to the market in its

approximately 150 years of history and to whether there is a paradigm that could explain how the public-private sector interaction has both driven the growth of this industry and brought economic, social and healthcare benefits for society.

Back in 2004, one of the authors (Ibis Sanchez-Serrano) was investigating the multiple factors that could account for the success and failure of biotechnology firms in the United States and Europe. Some of the variables involved in this analysis – eventually published in 2006 in *Nature Reviews Drug Discovery*⁷ – were the relationship between early-stage biotechnology firms and their parental academic organisations and other academic institutions; the collaborations that these firms established with pharmaceutical companies and private investors; the role of federal-funding agencies in the translational process between academia-industry/private-public sector; the support that early stage firms received from philanthropic organisations and advocacy groups; and considerations of the impact of secrecy and intellectual property (IP), as described by the ‘Tragedy of the Anticommons’, a type of paradoxical setting, in which too many separate rights-holders of a single resource can block each other’s use of that resource⁸.

In studying the story-case of many successful and failed biotechnology companies throughout the world, the story-case of the development of bortezomib for the treatment of multiple myeloma by the Cambridge (US)-based biotechnology company Myogenics/ProScript (later acquired by Millennium Pharmaceuticals), seemed both highly unusual and a quintessential example of what it takes to develop a drug in the biotechnological field.

On May 13, 2003, the FDA-approved Velcade (bortezomib), a proteasome inhibitor (Figure 1), under ‘Fast-Track’ Application for the treatment of multiple myeloma, an incurable cancer of the blood that affects approximately 14,000 patients in the US annually. The story behind the development of this drug is quite unique and remarkable for many reasons, including:

(i) The initial fragile funding base of the original company that discovered and developed it (Myogenics/ProScript).
 (ii) The risks involved in pursuing a new molecular target (the proteasome) with a new and ill-reputed class of inhibitor (boronates).
 (iii) Internal struggles and disagreements in the firm between the academic founders and the management regarding the indication for which the drug was to be developed.

(iv) Change of the original company’s business model (from cachexia to inflammation to cancer) and subsequent change of the firm’s name – from Myogenics to ProScript.

(v) Enormously-disruptive drop by Hoechst Marion Roussel of proteasome inhibitors for inflammation and cancer and its return of its license rights on the drug to ProScript.

(vi) Change in leadership.

(vii) Depletion of initial funding and inability to secure further funding for clinical trials.

(viii) The general lack of interest and total disbelief of the biopharmaceutical industry on bortezomib.

(ix) The resulting merging of ProScript into Cambridge-based LeukoSite and, six months later, purchase of LeukoSite by Millennium Pharmaceuticals.

In spite of all these major obstacles, that would have quickly destroyed any company or drug development programme, bortezomib managed not only to make it to the market, but to do so in record time and at a significantly lower cost than the biopharmaceutical industry’s average.

Why did bortezomib – which was doomed to failure from the beginning – became a success story unlike other countless well-funded examples in the industry? How did it manage to reach the market in record time?

The Core Model

Without knowing or planning it, Myogenics/ProScript used an organisational model, coined ‘The Core Model’ (Figure 2), grounded on the ‘trade of assets’ (exchange of personal connections, knowledge, materials, animal models, etc) between academia and industry, between the public and private sectors, in a very systematic and effective way to advance scientific research. According to this model, the company’s ‘Core’, formed by the founders, internal people and resources and the drug ‘champions’, were very focused on demonstrating the revolutionary therapeutic application of using proteasome inhibitors – and in this specific case, of boronates – based exclusively on the scientific data available and following the biology at every turn. From the beginning, the ‘Core’ realised that, given its extremely low economic and technological resources, they needed to acquire more knowledge about the effects of inhibiting the proteasome *in vivo*, and this could only be accomplished via collaboration and bi-directional interaction with academia and with external, non-competing scientists interested in similar mechanisms or problems. These external collaborators were crucial in securing, in many

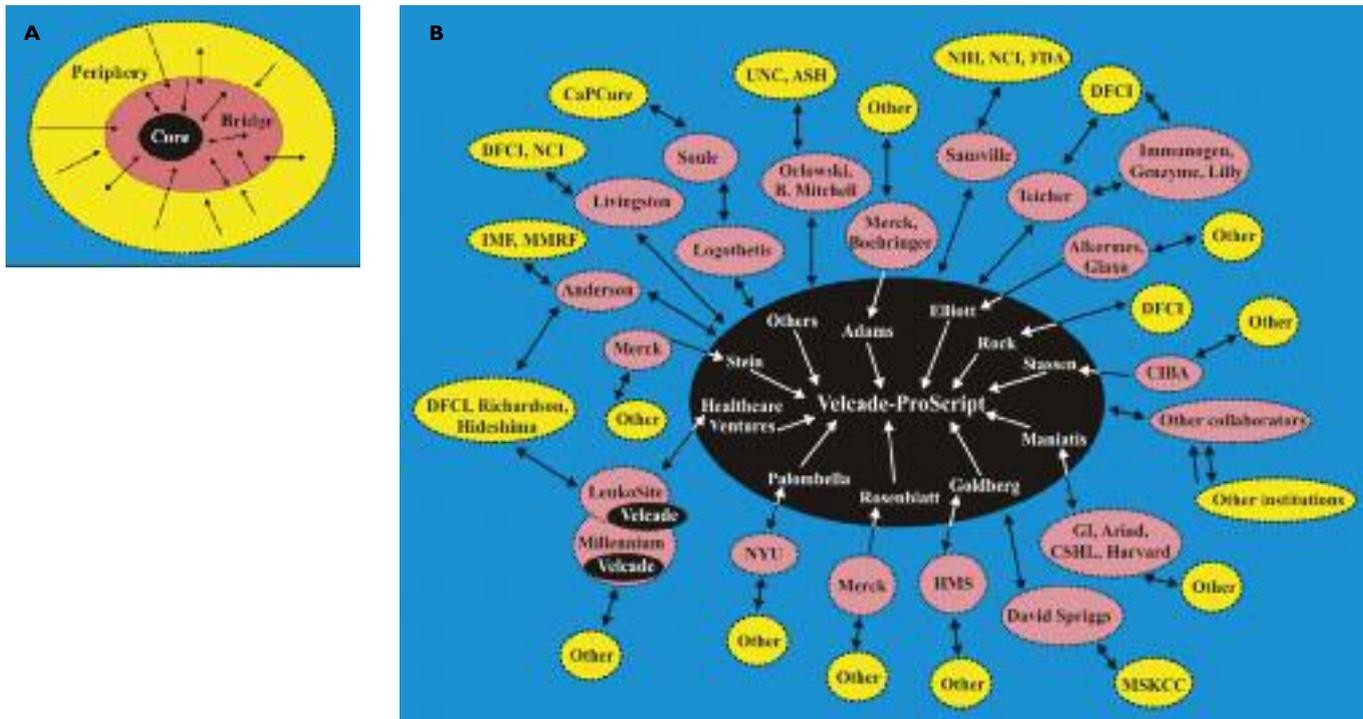


Figure 2: The Core Model

A This model has three major elements: the ‘core’, the ‘bridge’ and the ‘periphery’. In a biotechnology start-up company, the core represents the company’s internal resources and people who are hired because they have assets that are directly related to the core’s objective – making drugs. The core needs a strong leader who is capable of keeping the enterprise focused and is able to secure collaboration with external people. The ideas of the core are protected by patenting and secrecy. The bridge represents the immediate collaborators of the core and the private institutions to which the core has indirect access through the external collaborators. The bridge contains external scientists interested in similar problems or whose research would be enriched as a result of the collaboration. It also includes consultants and Scientific Advisory Board (SAB) members (non-founders) working in exclusive and non-exclusive ways. The periphery contains the institutions/agencies interested in what the core has to offer for the benefit of society, as well as the funding and regulatory structures that support the core and the bridge. The periphery is an open, public and co-operative system. The goal of the core is to absorb efficiently and legally as much relevant knowledge and information as possible from its surroundings in three ways: via the leverage of the assets, professional backgrounds and connections of the people within the core; via the assets, connections and expertise of the external collaborators within the bridge; and via the support, relevant public knowledge and know-how within the periphery.

B Illustration of the roles of selected people involved in the development of bortezomib using the core model.

Source: Sánchez-Serrano, I. *Success in Translational Research: Lessons from the Development of Bortezomib*. *Nature Reviews Drug Discovery*, 5 (2):107-14 (2006)

different ways, further knowledge relevant to a better understanding of the biological mechanisms associated to the proteasome and its inhibitors while providing animal models and validation. They actually allowed the company to save an enormous amount of time, human capital, infrastructure and money, and fundamentally acted as a ‘Bridge’ or ‘catalyst’ between the ‘Core’ and the ‘Periphery’ – that is, all those public resources available in society to sponsor and foster innovation with the objective of creating economic and healthcare benefits for its members. The ‘Periphery’ includes federally-funded agencies, advocacy groups, philanthropic organisations, consortia, regulators and all those organisations interested in the well-being of society. In summary, ProScript developed bortezomib through a ‘Core’ *modus operandi* using knowledge transfer (collab-

oration established with external people to exchange assets), knowledge integration (incorporation and assimilation of external assets) and knowledge translation (the conversion of all, internal and external, assets into a commercial therapeutic product).

Myogenics/ProScript carried out collaboration with outside groups exceptionally well, as explained by the Core Model, and so particularly benefited from these collaborations at crucial points, both when the company needed scientific knowledge to move forward and when it lacked the necessary economic resources. Even though today some companies form collaborations in their programmes, these collaborations are more opportunistic than planned. More importantly, there is little understanding, in all the collaborative sides, of the dynamics and benefits of such collaborations

within a major, logical framework or paradigm rooted in basic economic principles. As a result, collaborations are underexploited and the entire process of drug discovery and development, the business of science, and the public policies that regulate and fund basic, applied and translational science remain sub-optimal or deficient, bringing severe penalties on the economy and the global systems of healthcare.

Furthermore, in spite of the realisation that collaboration is essential for the progress of science, there is still a great deal of secrecy, misunderstanding, and misuse of intellectual property, hindering collaborative efforts. Of course, secrecy and protection of intellectual property are necessary in the business of science (or are they?), but the attitude toward it has become obsessive and paranoiac resulting in many useless patents that do nothing but block scientific progress in related areas. All of this adds to the economic burden of developing new drugs.

‘Old-school pharma’ and the Core Model

In examining the Core Model further and the history of the biopharmaceutical industry, it becomes clear that this model is not only a paradigm for the development of present-day biotechnology drugs (it also solves the ‘Paradox of the Anticommons’), but actually a universal model that has been in use to great effect in the development of drugs since the beginning of the pharmaceutical industry. Though it is impossible to discuss here in detail the abundant specific cases of drugs that were successfully-developed in this fashion (see references 1-3 for the history of drug discovery and development), several examples of drugs and companies that benefited from this approach need to be noted. For instance, the success of the German chemical and pharmaceutical company Hoechst lay in its ability to secure strong ties with academia and academic scientists, such as Robert Koch (and later with Clemens von Pirquet and Koch’s student Arnold von Libbertz) for the development of tuberculin as a testing agent for tuberculosis; with Emil von Behring, who discovered the diphtheria antitoxin and developed a serum therapy against diphtheria (together with Emile Roux) and tetanus; and, among many others, with Paul Ehrlich, who postulated the theory of receptors, coined the term chemotherapy, found a cure for syphilis (Salvarsan), and carried out impressive studies on autoimmunity. The development of these agents in a commercial manner was the direct result of close collaboration between the

‘Core’” (in this case academic inventors and Hoechst), the ‘Bridge’ (other academic scientists working in related problems), and the ‘Periphery’ (public hospitals, the German government and other not-for profit organisations). Other German firms (such as Merck & Co, Afga and Bayer), the major Swiss firms (Ciba, Hoffmann-La Roche, Sandoz) and European and American firms followed a similar pattern in the second half of the 19th century, cementing the great success of the pharmaceutical industry ever since. In the 20th century, medicines such as penicillin (first produced in a mass-scale by Merck & Co in the United States), insulin (commercially released by Eli Lilly), the first sulphonamide, Prontosil (Bayer) and antibiotics, in general, were also developed in the same fashion. Late in the 20th century, the birth of the biotechnology industry and the development of the first biotechnology drugs can be explained by the Core Model, with a close and systematic collaboration between academia, industry, investors, government agencies and philanthropic organisations/advocacy groups, via knowledge transfer, integration and translation.

The bio-pharmaceutical industry challenges today

One of the greatest challenges that the bio-pharmaceutical industry has to face today is the high cost of research and development (R&D)¹. According to recent estimates by the Tufts Center for the Study of Drug Discovery and Development (TCSDD), it takes, on average, more than \$2.558 billion (pre-tax, 2013 dollars) and 10-15 years to develop a new drug⁹. Although these exact figures are controversial – and we should bear in mind that the actual expenditure depends on the drug and whether it is developed by a pharmaceutical or a biotech company – it is a fact that drug discovery and development is a very complex, difficult, unpredictable, risky and capital/labour-intensive endeavour. Furthermore, over the last years the amount of money invested in this field has dramatically increased while the number of new chemical entities (NCEs) brought to the market has lagged behind. This situation calls for a careful examination of the reasons accounting for the increase of overall R&D cost as well as for novel ways to optimise the process.

Pharmaceutical drugs form an essential component of the global healthcare system. They are needed even for preventive-prophylactic programmes. But the high price of innovative drugs and the lack of drugs in some important and specific disease areas is perhaps the greatest challenge

Table 1: The most expensive specialty drugs (2017)
 Source: Drugs.com; <https://www.drugs.com/slideshow/top-10-most-expensive-drugs-1274>; October, 2017

DRUG NAME	COMPANY	INDICATION	PRICE/Year
Glybera (alipogene tiparvovec)	uniQure	Lipoprotein lipase deficiency	\$1.2 million
Ravicti (glycerol phenylbutyrate)	Horizon Pharma	Cycle Disorder	\$793,000
Brineura (cerliponase alfa)	BioMarin Pharmaceutical	Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a form of Batten disease	\$700,000
Carbaglu (carglumic acid)	Orphan Europe	N-acetylglutamate synthase deficiency	\$419,000 - \$790,000
Lumizyme (alglucosidase alfa)	Genzyme	Pompe disease.	\$524,000 - \$626,000
Actimmune (interferon gamma-1b)	Horizon	Life-threatening osteopetrosis	\$244,000 - \$572,000
Soliris (eculizumab)	Alexion	Hemolytic uremic syndrome (aHUS)/ paroxysmal nocturnal hemoglobinuria (PNH)	\$432,000 - \$542,000
Folotyn (pralatrexate)	Allos Therapeutics	Relapsed or refractory peripheral T-cell lymphoma (PTCL)	\$96,000 - \$472,000
Demser, (metyrosine)	Valeant Pharmaceuticals	Pheochromocytoma	\$96,000 - \$472,000
Ilaris (canakinumab)	Novartis	Periodic Fever Syndromes; Active Systemic Juvenile Idiopathic Arthritis	\$379,000 - \$462,000

for these systems⁴. As our understanding of diseases has become more sophisticated and as diseases have, in some cases, become more complex and difficult to treat due to the combined influences of unhealthy lifestyles, changing global environmental conditions and demographics, and constant exposure to harmful chemicals and infectious agents; and as important variables among the human population which affect both the nature and the experience of disease, such as gender-specificity, ethnicity, age, among others, are taken into consideration for drug discovery and development, there is an ever greater need to find more effective

ways to develop drugs. Unfortunately, achieving this goal is becoming more challenging every day given the increasing complexity of the process, the higher regulatory hurdles for drug approval, and the larger amount of information that needs to be taken into consideration and evaluated during the entire undertaking.

In our consumerist and pharmaco-dependent society, it is expected and demanded to have access to the best possible drugs with the lowest number of side-effects. However, like consumer goods, people get what they pay for. So, it is not surprising that access to the best drugs (for which more

investment, capital and otherwise, have been needed) will require the payment of a premium. This, in fact, is becoming a novel trend in the industry (see **Table 1** for a list of recently-developed drugs with staggering prices). Since the actual cost of specific drugs is not disclosed by biopharmaceutical companies, nowadays it is difficult for the consumer to know which drugs required more investment than others, as drugs are being priced according to whatever the market can bear. Unfortunately, this strategy and all the marketing expenses involved in selling new drugs are unsustainable both for the pharmaceutical industry as well as for the healthcare systems. Therefore, it is no wonder that we are facing a world's healthcare crisis⁴.

To compound the problem over the last few years the bio-pharmaceutical industry has needed to deal with several important issues such as the massive patent expiration of some of its best-selling drugs, lower productivity output, deficient pipelines, pressure from investors, litigation issues regarding the safety of drugs or related to intellectual property, more stringent regulatory requirements, etc. Given this situation, the pharmaceutical industry has implemented a wide range of strategies to contain costs and maximise profits, such as massive layoffs, R&D cuts, divestitures, mergers and acquisitions (M&A), patent ever-greening, increment in the number of clinical trials, expansion of indications, pursue of niche markets, price increase, reorganisation, etc. Even biotech companies have followed a similar pattern in order to survive, as recently demonstrated by Celgene and its acquisition of Impact Biomedicines¹². In fact, the sale of early stage biotech firms to big pharma right after proof-of-concept in humans or at the end of Phase II clinical trials has become both fashionable and profitable. In most of these cases biotech companies have become the R&D arm of big pharma, while big pharma have become powerhouses for clinical trials and marketing. The large size of most pharma companies, which has come as a result of the heavy M&A activity that we have experienced in the last decade, has created additional layers of management and dramatic changes in the dynamic of these organisations, which have made it more difficult for them to be managed, to be efficient and to be focused on productive R&D.

From a scientific perspective, the information provided by the sequencing of the human genome, higher sophistication of experimental models in animals and in humans, new genetic engineering techniques (such as CRISPR, among others), the advent of proteomics, systems biology,

metabolomics, Big data, etc, have all represented a mine of information that will facilitate a better understanding of how the cell and living organisms work. This will eventually have a great positive impact in finding better treatments and cures for disease. However, handling all this information all at once today has made the biopharmaceutical industry situation even more complicated. So, there is not really clarity about which models, both at the R&D and business levels, the biopharmaceutical industry will pursue in the years to come.

Thus, we are at a very crucial point in which, more than ever, it is necessary to align pharmaceutical innovation with global healthcare policies for the benefit of patients and the survival of the world's healthcare systems. But how do we deal with these challenges?

Benefits of the Core Model and its approaches today

Understanding the Core Model – which brings to a convergence point all the elements necessary for successful drug discovery and development – and understanding the nature and contribution of each one of its constituents (see **Table 2**) could be of great assistance to the biopharmaceutical industry in the creation of better strategies to improve drug discovery development and serve as a guide to governments to formulate and implement better pharmaceutical, innovation and healthcare policies. It could help governments, investors and philanthropic organisations/advocacy groups on how to allocate and deploy funding and economic resources in an optimal way.

At present, the Periphery of the Core Model is becoming more dynamic than ever. For instance, patient groups as well as health systems, which are partners of the pharmaceutical industry in clinical trials, are now playing an active role beyond advocacy, including actual financing of drug development, especially in rare diseases. This was the case, for instance, with the Cystic Fibrosis Foundation financing Kalydeco with Vertex, and thus bypassing big pharma. Patient opinion leaders and online communities are now collaborating in clinical trials and conducting their own observational studies, as in the case of PatientsLikeMe and its 600,000 members. The importance of patient-reported outcomes in collecting real-world evidence is covered in several policy journals, such as *Health Affairs* and *Value in Health*. These initiatives are becoming a novel and important model for improving drug development.

Frustration with the biopharmaceutical companies' high pricing of drugs, sudden increase in

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Table 2: Selected summary of assets of the constituents of the Core Model

ATTRIBUTE	ASSET
Core	Highly sophisticated ideas, narrow and focused objectives, revolutionary technologies, enthusiastic and highly qualified staff, connections with colleagues and outside institutions, effective leadership, economic incentives, concentration on productivity, dynamism, flexibility, etc.
Bridge	Personal connections (academia, biotech, pharma, hospitals, regulators, investors, philanthropic organizations, etc.), tests and animal models, clinical trials and funding for clinical trials, tissue banks, new/complementary technologies, reagents, new approaches and paths to drug discovery and development, new perspectives to improvement, “free” or low cost labor force (via collaboration), scientific knowledge, problem solving, technological facilities (e.g. mice facilities), special software, cell lines, advice, translational studies. All of this leads to savings time, money, and effort. It increases knowledge and data that most of the time lead to important publications.
Periphery	Funding, infrastructure, promotion, lobbying, recruitment of patients for clinical trials, “free” labor, equipment, positive public image, knowledge, data, know-how, technology, tips by regulators to correct wrong paths, guidance on how to be efficient, translational science, saving time and money while guiding the Core on how to succeed.

pricing of old, off-patent drugs such as the heart medicine Nitropress, and shortages of essential medicines, such as morphine, as well as by the manipulation of the market by investors, has led a group of large hospital systems in the US¹⁰, spearheaded by Intermountain Healthcare, and involving Ascension – a Catholic system that is the nation’s largest non-profit hospital group – and very possibly the Department of Veteran Affairs, to the bold decision of creating a not-for-profit organisation to create generic drugs to battle shortages and high-prices in hospitals. In another bold movement, three large US corporations, Amazon, Berkshire Hathaway and JPMorgan Chase, have announced the formation of an independent health care company for their employees in the United States to deal with the soaring cost of health insurance premiums and pharmaceuticals¹¹.

Two other important initiatives adopting the Core Model are, firstly, the NIH-National Center for Advancing Translational Sciences’ Industry

Partnerships Initiative (launched in 2012) to foster collaboration between pharmaceutical companies and the biomedical research community to advance therapeutics development as part of the NIH New Therapeutics Use Program. The objective of this initiative is to match researchers with a selection of ‘pharmaceutical assets’ to help the scientists test ideas for new therapeutic uses¹². The second is Partnership for Accelerating Cancer Therapies (PACT), a \$215 million public-private partnership with 11 pharmaceutical companies over a five-year agreement to advance research in new immunotherapy treatments that equip the immune system to attack cancer via the identification, development and validation of biomarkers. This initiative not only involves the partners just mentioned, but also the NIH Foundation, important academic research centres in the US, the Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers Association (PhRMA) and the Department of Health and Human Services, among others¹³.

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All these examples attest to the flexibility of the Core Model and its universality. Today, when the bio-pharmaceutical industry does not know where it is going, and with the extraordinary necessity of coming up with more efficient ways to produce new drugs – given the extraordinarily big impact that the high price of novel drugs has in the global healthcare systems and in some countries' economy – it is extremely important to review the Core Model paradigm and adapt it according to specific circumstances.

Concluding remarks

Despite considerable technological advances, the pharmaceutical industry is experiencing a severe innovation deficit, especially in the discovery of new drugs. We have tried here to initiate discussion about the complexities that face drug discovery and development beyond their current horizons. Indeed, older methodologies that have for years been the basis of scientific discovery need to be reviewed to determine if all the hypotheses they were built on are still valid. We propose innovative network science that addresses the general need for improved applications in the discovery and development of drugs.

The 'Core Model', an economic and organisational paradigm for drug discovery and development, is elucidated through the story-case of the development of the anticancer drug bortezomib. Some of the remarkable progress that has taken place is illustrated in the 'Periphery' (a constituent of the model) and its ever-increasing active role in the financing of drug discovery and development efforts to treat important diseases and in the collecting of crucial real-world data for clinical development. In the current pharmaceutical and healthcare scenarios, drug leads that may otherwise languish in the laboratory could fully capitalise on the use of 'Core Model' approaches to make it to the patient, saving time, labour and capital.

In summary, the survival of the pharmaceutical industry and of the world's healthcare systems will ultimately depend on innovation, on a better understanding of disease, on the efficient development of novel drugs and on preventive measures coupled to an efficient use of our limited societal resources.

Imagine a world free of diseases. What a wonderful thought and sight. A pinnacle of unimaginable human achievement, a defining hallmark of excellence in human endeavour and a lofty goal from times immemorial, but NOT yet achieved. The utopian thought is nowhere near our distant sight. Or, is it ever achievable? That's the question.

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