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Culture of innovation-ASAP (iASAP): Ask powerful questions; Seek the outliers; Accept defeat; Populate astutely.

Drug discovery in the next decade: innovation needed ASAP

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Pharmaceutical companies must find a better way to increase their output of truly new drugs for the benefit of patients and for their business survival. Here, I highlight a general perspective from within pharmaceutical research as it pertains to research advances in chemistry, biology, pharmacology, pharmacokinetics and toxicology that, if well integrated, stands to put the industry on a productive path. In addition, I provide a complementary perspective on the corporate culture aspect of innovation. I also introduce a new concept, termed 'innovation ASAP' (iASAP; asking powerful questions, seeking the outliers, accepting defeat and populating astutely) and provide support for it using examples of several successful drugs.

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Introduction

The pharmaceutical sector, a cornerstone of the healthcare industry, is undergoing dramatic change, primarily caused by reduced output of new medicines from research and development (R&D) laboratories, drug pricing pressures, stricter regulatory environments and the overall current economic downturn. This makes demands of all pharmaceutical companies to find better ways to increase their output of new drugs, through innovation, to both treat patients and meet their shareholders' expectations.

This article highlights a general perspective from within pharmaceutical research as it pertains to research advances in drug discovery [including chemistry, biology, pharmacology, pharmacokinetics (PK) and toxicology] and offers a complementary perspective on the corporate culture aspects of innovation. A new concept, termed 'innovation ASAP' (iASAP: asking powerful questions, seeking the outliers, accepting defeat and populating astutely) is introduced and supported by several successful examples in drug discovery and business in general. The goal of this article is to add value to all ongoing efforts aimed at innovation in medicine, as a potential driver to revive both the healthcare sector and contribute to the economy in general.

The current state of the pharmaceutical industry is undeniably dour. A combination of falling success rates in the development of innovative therapeutics, pending patent expirations for major drug classes, in addition to the conditions stated above, have created a perfect storm for the industry [1–5]. This has resulted in: (i) increasing rates of mergers and acquisitions; (ii) strategic shifts toward generics and emerging markets; (iii) dramatic numbers of job losses over the past

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three years; and (iv) rapid shifts toward the use of lower-cost contract research organizations (CROs) in all aspects of the industry (research, development, manufacturing, among others), coupled with a trend toward decreasing internal R&D budgets. This latter point is of timely importance, because the use of external R&D support tends to perpetuate the same approaches or strategies that got the industry into this state of affairs in the first place, and does not involve a real new strategy toward innovative products. The claimed lower costs, through CROs, might not be truly value adding, because outsourced full-time employees come at a higher cost of management and the potential loss of an opportunity to innovate. As Tom Peters states: 'You can't shrink your way to greatness' [6]. Finally, the image of the pharmaceutical industry, as a well-respected business that improves health, has been tarnished by price increases as well as news reports of medical, marketing and political lobbying, and direct-to-consumer marketing, all resulting in record fines [7].

More pointedly, by chasing 'low-hanging fruit', target-based pharmaceutical research has forced most companies to compete on similar targets and approaches, resulting in duplicative and nonproductive investments. Finally, it appears as though previous investments in high throughput screening (HTS), combinatorial chemistry, genomics and proteomics over the past two decades (the very technologies that were supposed to keep the industry from the abyss) have yielded a low return on investment. Arguably, these perfect storm conditions also provide numerous opportunities and remind the industry that necessity is the mother of invention.

On the brighter side, over the past two decades, the pharmaceutical industry has produced some remarkable medicines to treat several conditions, ranging from human immune deficiency virus infections (HIV) to cardiovascular diseases (CVD), resulting in reduced mortality rates, and rheumatoid arthritis through anti-tumor necrosis factor (anti-TNF) biologics, to name just a few. Additionally, from the research scientific and operations standpoint, much progress has been achieved in key areas of drug discovery, despite the perceived notion of the opposite. Such advances, if well integrated, will counter this downturn and set drug discovery on a more productive and successful course. Here, I provide a look forward and offer possible solutions toward a more integrative, innovative and, probably more productive R&D environment. So, how can the industry claw its way back from the edge?

In chaos lies opportunity

A recent survey of the top 25 most innovative companies, encompassing all types of business, did not include a single pharmaceutical or biotechnology company (http://images.businessweek.com/ss/10/04/0415_most_innovative_companies/index.htm). However, a survey of the top 20 most innovative pharmaceutical or medical device companies, and endorsed by Wall Street, showed a strong correlation between the value creation of a product, as measured by market capitalization, and its novelty, as measured by clear clinical and market superiority (http://www.innovaro.com/pressReleaseFiles/Innovation%20Index%202010%20Q2%205-11-10.pdf). These reported rankings are argued to be a clear demonstration of the demise of the blockbuster business model, as currently practiced by large pharmaceutical companies, given how sparsely these large companies are listed amongst the top 20 innovators. From these reports, it is evident that the most innovative companies, and thus the most value-creating ones, are those that master the art (and science) of understanding necessity rather than creating it. Perhaps that it is the multitude of 'follow-on's' or 'me-too's' to the blockbuster drugs that are the culprit (vide infra).

To set the stage for a discussion on innovation, a definition is necessary. There are many ways to define innovation but, in essence, it is 'ideas that ship out', as such linking fresh thinking to final products. Others define it as 'a new match between a need and a solution', where the novelty can be either in the solution or the need (all depending on how one defines need); or in a new marriage of the two [8]. From the innovation–valuation standpoint, one could define the result of innovation as product or service that both enables a positive return on investment and creates sustainable valuation for its owners.

Arguably, 'the devil is in the details' and much high-quality work occurs from the inception of an idea all the way through to product packaging. The point is that identifying the right necessity or medical need (every company professes to focus on unmet medical needs, but it all depends on how that is defined) and empowering people to work toward that goal, is the way forward. So how does one navigate through the maze of tribulations, ups and downs all the way to value creation?

Me-too drugs are failed innovations

The (mega) blockbuster business model has had a profound effect on the pharmaceutical industry, both positive (earnings) and negative (culture). Nobody could argue, in this capitalistic world, against marketing a drug to achieve great revenues. Revenue enables further investment, with the goal of repeating an even greater achievement. Most major pharmaceutical companies have adopted this paradigm and invested heavily in R&D over the past two decades, more so than any other industry as a percentage of sales [9]. This approach has forced R&D-intensive companies to focus mainly on opportunities with >US$ 1 billion annual market potential, which, in return, has created blind spots toward many diseases and perceived medical needs that did not meet these return levels. In addition, it tended to attract several players into similar markets, which led to many years of heavy investments to demonstrate clinical non-inferiority or marginal superiority to gain Food and Drug Administration (FDA) approval. The current trend to catch the current biologics or bio-similar(s) wave, could well backfire in a similar way to small-molecule follow-on approaches, over the next few decades. Furthermore, commercial functions have been in the driver's seat in clinical trial design, which has led to a business- rather than science-led clinical trial approach, often leading to failure. Although large revenues were sometimes achieved through this model, it seems to have led the industry to the edge of a cliff, given how difficult it has been to reproduce it routinely [10]. The argument is that the business operates in the 'outlier space' and repeats are rare. So, what is an operationally viable new business model for the next cycle?

Revenue versus value creation

Drug classes that work through similar general mechanisms, such as statins (e.g. Lipitor®, Zocor®, Crestor®, Vytorin®, Lescol® and Caduet®), antiulcerants (e.g. Nexium®/Losec®, Takepron®, Rabeprazole® and Protonix®) and antipsychotics (e.g. Seroquel®,

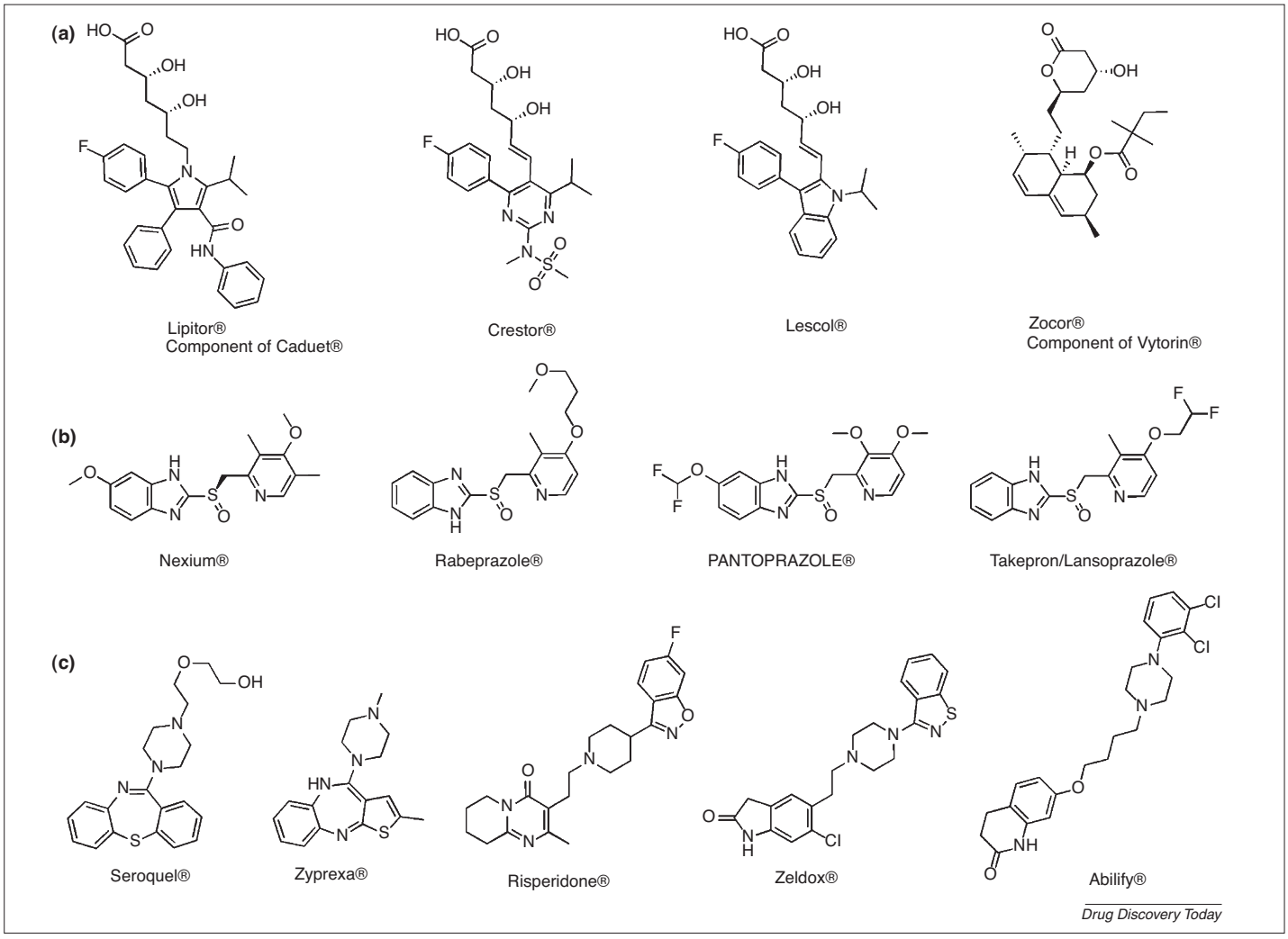

FIGURE 1

Representative drugs from the statin **(a)**, antiulcerant **(b)** and antipsychotic **(c)** classes.

Zyprexa®, Risperidone®, Abilify® and Zeldox®; Fig. 1), garnered almost US$ 25 billion, US$ 20 billion and US$ 20 billion in sales during 2008, respectively. However, during the period from 2008 to the present, the very companies that sell these drugs have seen their valuations drop by 20–40% (relatively similar trends for most big pharmaceutical companies apply from 2001 to 2010). I do not wish or need to highlight any particular company in regards to revenue versus valuation. However, simple research through http://www.wikinvest.com leads to the observation that increased revenue or gross margins (over up to 5–10 years) correlate inversely with corporate value creation as measured by lower stock prices and, thus, lower market capitalization for most large pharmaceutical enterprises.

In other words, price/earnings ratios for some of the pharmaceutical companies dropped from mid-twenties to high single-digit levels. For these companies, catching up one another by competing in similar markets, rather than investing in innovative ways to treat disease, has clearly back fired. This demonstrates the flaws associated with this business model, which has led to the loss of several tens of thousand jobs. Many associations exist, where a few products (e.g. Epogen®, Avastin®, Tamiflu®, Revlimid®, Provigil®, Depakote® and Velcade®; Fig. 2), have driven strong value creation for their respective companies, by virtue of their uniqueness and, thus, differentiation.

It is now undeniable that increased investments in R&D have not resulted in increased numbers of new molecular entities (NMEs). Additionally, recent large-scale phase 3 failures (e.g. Axitinib/Pfizer; Elesclomol/Syntha-GSK; AS404/Antisoma-Novartis; Figitumumab/Pfizer; Iniparib/BiPar-Sanofi; Vandetanib/AstraZeneca; and Torcetrapib/Pfizer) and scarcity of late-stage assets [11], coupled with imminent patent expirations for most blockbuster drugs, bode ill for the future of research-based pharmaceutical companies, and for the industry as a whole.

Innovation in drug discovery as a survival necessity

The conundrum associated with innovation is as follows: you know that you are innovating, when your supervisor says 'Are you crazy'? Or, is it: you know you are 'crazy' when your supervisor says 'Are you innovating'?

Innovation is a necessity for improving human prosperity and well-being. It is imperative that the pharmaceutical industry invests, engages and manages (with a long-term view and commitment from executive management) its resources to ensure that new (not 'me-too') and value-creating products emerge from its

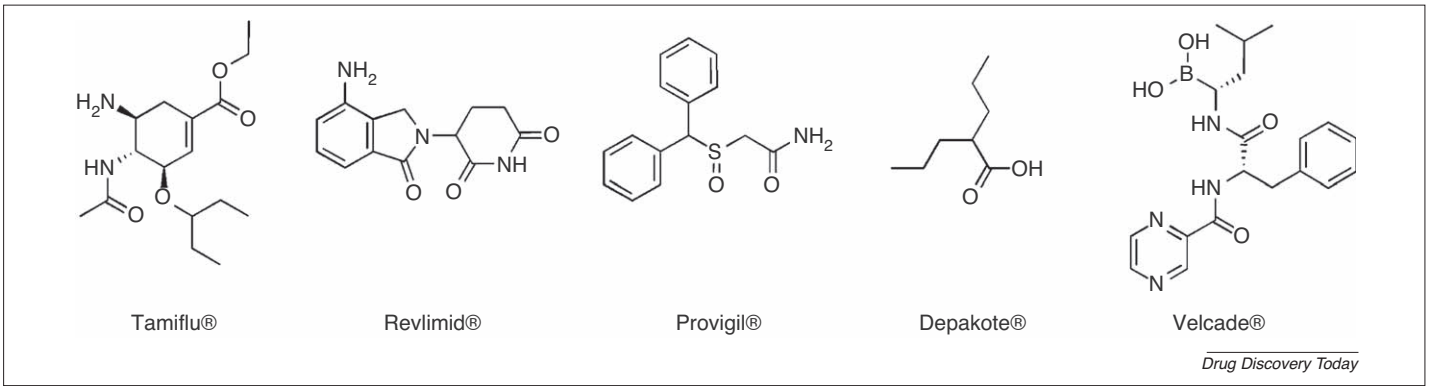

FIGURE 2

Examples of high-value creation drugs without major follow-ons.

R&D operations. Innovation in the health sector is more important than in many other sectors of the economy, as it stands to provide well-being enhancers (medicines, devices, surgical procedures, nutrition, among others) for people; powering them to create innovative products in all other sectors. The industry has become a culture of copycats, with a hurry to satisfy pressure from the very investors who would benefit from a good medicine and not 'quick and dirty' one-offs. In this regard, the following important questions come to mind: why do companies all work on the same targets? Why did they all do combinatorial chemistry? Why do they all use outsourcing? Why do they all use the same consulting firms for strategic advice? Answers could vary as widely as their scope allows: 'The Gold Rush', too many people chasing too few good ideas; good target validation is scarce, thus highly attractive; 'short-term' commitment to any target or approach; everyone reads the same journals, attends the same conferences and, thus, works on similar projects, and so on. Perhaps a larger perspective might be what is commonly called the 'herd effect' or the fear of being left behind: the genomics era promised a wide array of new targets, opening up new biology and novel approaches to disease management, which attracted everyone in the field to invest further in sequencing, computational biology or systems biology, combinatorial chemistry, and so on, which has clearly not paid off. Finally, business-consulting firms need to advise on a corporate-individualized manner and better manage comparative analyses, given the success level that has been achieved over the past two decades of advice. An extreme perspective might be that those involved in drug discovery need to learn how to focus on, and believe in, their own internal research as a guiding light, rather than jumping on any new information that moves elsewhere. The basic premise of this article is that those working in the pharmaceutical R&D community need to take the bull by the horns and, through 'directed innovation', create new possibilities.

Innovation has been the buzzword of the decade; although there are books, conferences and even retreats on the subject, there appears to be no formula for it. One common thread to these has to do with the culture that organizations create to foster 'valuable newness'. Companies that can harness the ability to build on scientific advances, the 'right' organizational changes, as well as cultural and business drivers, will propel the industry into more prosperous times and create high value for their shareholders. So how does one marry these advances with the appropriate creative-spirit cultures of the future?

Drug discovery and the way forward

'A good scientist is someone who succeeds in getting the different scientific disciplines to work in harmony with one another' Paul A. Janssen [12].

Chemistry-based advances

Chemistry (synthetic, analytical, computational and physical) is at the heart of problem solving in the pharmaceutical industry, so long as the right questions are asked, debated and answered. Synthetic chemistry, in particular, has reached an unprecedented level of sophistication and execution [13–17]. The current plethora of methods available to chemists provides them with the confidence and tools necessary to tackle difficult chemical and/or synthetic targets. These range from the synthesis of complex natural products to conducting numerous chemical reactions in water (e.g. DNA-templated organic chemistry). The current wave of human mass action on synthesis, through chemistry outsourcing to lower-cost organizations, is certainly enabling, but not yet capable of solving the real problems plaguing drug discovery and development or strategic directions of the industry [18]. The pharmaceutical industry demands more from chemists than just synthetic skills; for success, it needs more complex problem solving and innovative chemistry technologies to lead to effective and safe human therapeutics. Medicinal chemistry, a discipline requiring working knowledge of (among others) biology, biochemistry, biophysics, PK, pharmacology, toxicology and pharmaceutical sciences, might today be compared with organic chemistry during the 1960s. Medicinal chemistry suffers from largely homogeneous screening decks (mostly based on simple chemistry, or built from same the vendors), a current inability to target key organs or tissues specifically and a failure to accept the current lack of predictive tools in drug design, solubility, target residence, absorption kinetics or intracellular penetration, as well as rapid PK or toxicology problem solving, to name a few. Although prowess in synthetic chemistry can be highly enabling, medicinal chemistry is not a commodity just yet. It is the

aggregate mastery of all the knowledge from the above-mentioned disciplines, and practical, integrative use of such acumen that will lead the way to truly new medicines. As such, it has a long way to go to address routinely the many pitfalls in moving from a HTS hit to a new chemical entity (NCE), and eventually to marketed NME, in a faster and more reliable manner. Conversely, for future major advances, practitioners in all the disciplines mentioned above, will need to become more knowledgeable in areas currently less familiar to them.

Numerous examples can be found within R&D organizations where a synthetic chemistry, medicinal chemistry observation or a formulation breakthrough has added value while creating a new drug (my intent here is to highlight the topic of observation and questioning, rather than conduct an exhaustive listing of value-adding observations). This is particularly applicable when solving affinity, selectivity, *in vitro* or *in vivo* activity and/or properties, including PK or toxicity issues. Examples of these are retrospective analyses of approved drug properties leading to several rule sets and perspectives, ranging from physicochemical attributes of drugs, to formulation sciences and application of continuous improvement–efficiency models applied from manufacturing and indeed, even to evolving concepts on 'druggable' targets [19–30]. So, how does one move forward in medicinal chemistry?

Biology-based advances

The conundrum in biology is the interplay between deductive and inductive biology. Parts of it are well understood and integrated within medicinal chemistry and drug discovery, whereas others remain at bay:

- Deductive biology: where the whole is broken down into smaller bits is well managed in current pharmaceutical research practice [e.g. gene mapping, protein production, screening assays, biochemical readouts, soluble protein structure and structure-based drug design (SBDD)] [31,32].
- Inductive biology: or putting the puzzle back together, after a phenotype readout, remains a mixture of art and science and, as such, is a fertile area for innovation (e.g. membrane and cytosolic protein structural dynamics, signaling nuances, disease biology relevance, compensatory mechanisms and cross-species translation) [33–39].

Better tool molecules (e.g. small molecules, peptides, RNA- or protein-based forms) from chemistry or biology will aid in faster and better elucidation of newer disease-relevant findings, but only in the context of improved biological modeling of human disease physiology. As examples, recent advances in G protein-coupled receptors (GPCR) signaling have begun to offer a glimpse of what is possible through better appreciation of allosteric modulation [40–42], whereas open–closed states of ion channels [43–47] and protein-folding dynamics are shaping new understanding of structural biology [48]. The emerging field of stem cell biology, through therapeutics and small-molecule modulation [49], primary human tissue models [50] (normal and pathological) or three-dimensional (3D)-cultures of the relevant cell contexts, is likely to boost the quest for better medicines. So how is greater precision reached in the biological sciences?

PK-based advances

It is undeniable that better understanding of the chemical and pharmaceutical properties of newly synthesized molecules leading to better PK parameters has had a major effect in minimizing the attrition of preclinical and early clinical molecules. Better integration of solubility, cross-species liver microsomal stability, permeability and absorption, as well as cross-species metabolism, have been well integrated within the medicinal chemistry community. As examples, the observation that Ritonavir® could be used as an exposure booster for Lopinavir® (and other drugs) through cytochrome P-450 isoform 3A (CYP3A) inhibition; the observation of a metabolite of a histamine 1 (H1) blocker with biological activity leading to Allegra® and Zyrtec® (Fig. 3), are just a few examples of asking the right questions and the power of pharmacological observation. However, prediction of human PK–pharmacodynamic (PKPD) properties has been less than reliable, which points to the next area of endeavor for this area of drug discovery [51]. So, how does one raise the PKPD sciences to greater predictability levels in the human setting?

Animal pharmacology-based advances

Practitioners in pharmaceutical R&D, and medicinal chemists in particular, are all familiar with how drugs were invented during the 1950s through to the 1990s. The type of question asked then

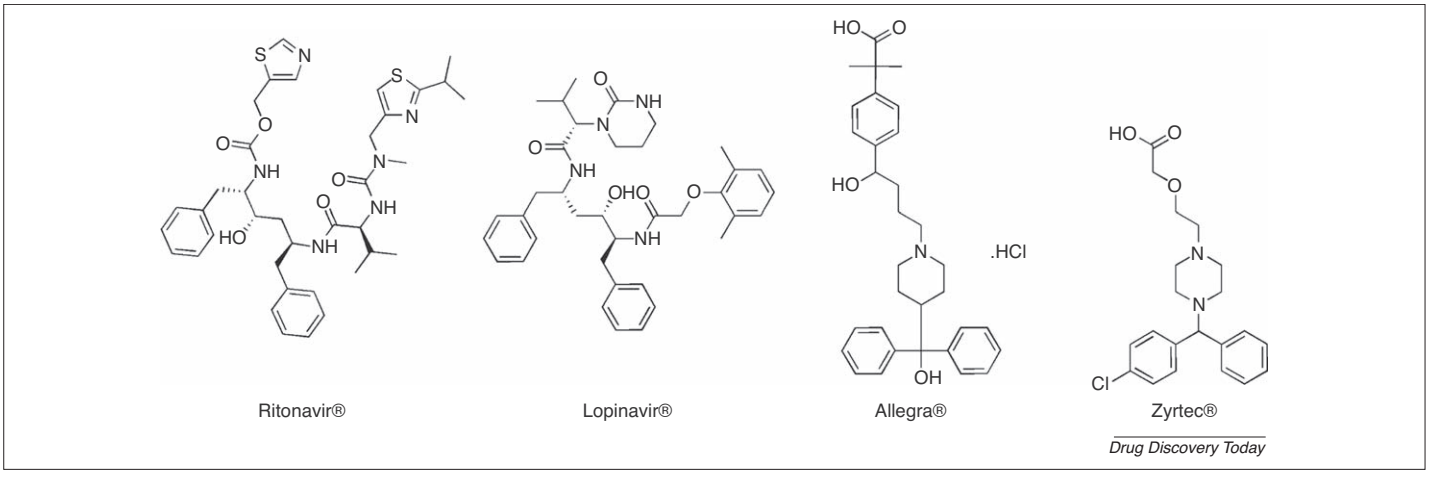

FIGURE 3

Representative drugs emerging from pharmacological observations.

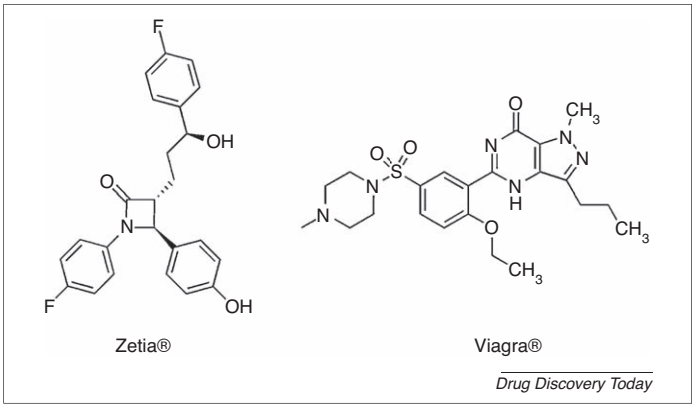

FIGURE 4

Representative drugs emerging from newer pharmacological or mechanistic observations.

might have included (as examples): how can we reverse an epileptic shock? (leading to Depakote®; Fig. 2) [52]; how can we reduce cholesterol uptake? (leading to Zetia®) [53]; and the fortuitous finding that led to a weak antihypertensive becoming Viagra® (Fig. 4), to name but a few [54].

In this area, gene knockout technology has provided supporting evidence for expected phenotypes and increases confidence in particular target investments [55]. The burgeoning area of biomarkers (previously named phamacogenomics/individual gene mapping or personalized medicine; originally expected more than ten years ago) promises to further refine disease biology focus, as well as enabling precise and early clinical readouts and patient stratification in clinical trials [56].

However, one key component of animal model-based thinking is the admission that we do not know a lot of what we should know (or think we know): currently, several animal disease models are not predictive of clinical outcome [oncology, immunology, central nervous system (CNS) and other neurological conditions or pain], whereas other models tend to be more reliable: for example, some viral diseases [e.g. influenza, but neither HIV nor hepatitis-C viral (HCV) infections]; bacterial and fungal infections; CVD through measuring high- and low-density lipoprotein (HDL and LDL, respectively) and simple blood chemistry-based readouts (e.g. glucose or cholesterol). One could argue that, in a typical research project, 20–30% of the time is spent fine-tuning molecules to fit the animal model of disease 'perfectly'. The cost of which, if invested in a 'fast' proof-of-concept in the human clinical setting, could easily answer the key question. Pharmaceutical research aimed at cancer treatment, neurological or psychiatric diseases, in particular, are areas in utmost need of new therapeutics, yet the most underserved from the discovery-to-clinical-success standpoint. As mentioned above, animal models in these disease areas are not predictive, yet regulatory agencies require preclinical investigational new drug (IND) packages to contain *in vivo* animal efficacy and data based on nonpredictive or nonrelevant disease models. It is sad to see that many companies are giving up on these diseases rather than tackling the fundamental biological, pharmacological and developmental causes of the failures. Perhaps the industry needs to tackle this very problem to demonstrably affect change in the success rate of oncolytics, neurological agents or neuroleptics, to name but a few.

Given that the goal of animal pharmacology drug discovery is to demonstrate target engagement in living species, with functional consequence and minimal adverse effects, further research in more variants of humanized mice will probably help in this area [57–64]. So how, and when, should animal pharmacology be best integrated, if at all, going forward?

Toxicology-based advances

Currently, the greatest contributors to preclinical and clinical NME failures remain toxicology and translational biology for efficacy. Striking the right therapeutic window, with a safe profile is often a challenge in discovery settings. Much research is being applied to bring value from the toxicological standpoint: for example, screening for mutagens, clastogens and general cellular toxicities [cytotoxicity panels, hepatocytes, phospholipidosis, transporters and human-ether-a-go-go related gene channel (hERG) blockade], *in silico* predictions of toxicophores, rapid early animal-based toxicological readouts and multi-species cardiovascular readouts [65–67]. The field is still plagued by clinical idiosyncratic toxicities, particularly in combination settings where drug levels suffer from output from metabolizing enzymes and their putative effects on many organs. Much effort is needed to predict accurately patient safety outcomes through preclinical screening. Therefore, how can the industry, in a similar manner to that achieved in PK (less of a contributor to clinical drug attrition), maximize translational safety or minimize idiosyncratic toxicity from NMEs?

So far, I have highlighted the necessity for innovation, the perspective of how investor pressure has led the industry to where it currently is, and the advances and challenges of all the necessary scientific disciplines that harbor and feed into medicinal chemistry. Several questions were raised but not answered. The whole concept of the culture of innovation in the drug discovery setting remains nebulous, given the multitude of 'pressure points: investment, competition, science knowledge, time, management', the diversity of sources of innovation and the still-unpredictable nature of medicinal chemistry, drug discovery and clinical outcomes [68–70].

Integration

Despite the advances, and the challenges ahead in the various drug discovery disciplines, their integration into a functional, timely and productive output is an open question. The above-mentioned statement by Jenssen captures the essence of a major pitfall of current drug discovery issues: integration of the above-discussed disciplines. Some differences occur between academia and industry: for example, in graduate studies, there is an emphasis on the individual and not the team, and cross-department collaborations are very new in the academic setting, whereas cross-department teamwork is important for success in industry; innovation is generally fostered in academia, yet some pharmaceutical organizations tend to redefine the word 'new' as 'me-too' or 'me-better'. Additionally, higher education systems are organized around scientific disciplines and departments, whereas researchers naturally tend to congregate around similar models in the industrial setting. Alternatively, the industry tends to be organized around diseases or therapeutic areas, with emphasis on centers of excellence. There are few organizational models based around 'drug

discovery excellence' or 'integrated disease discovery and development centers' or, better still, 'chemical biology–pharmacology', 'pharmaceutics development', and so on. The point here is that much innovation, speed, productivity are probably lost through lack of better integrative organizational, cultural and scientific communication models. Innovative organizational and management models, along the entire spectrum of R&D, will be key in helping address current shortcomings [71].

The following paragraphs are an attempt to capture some of the cultural attributes that are necessary to maximize the chances for new products, with particular examples in the small-molecule R&D setting. I propose iASAP as a set of organizational behaviors that could help ignite innovation.

Ask powerful questions

The art of asking powerful questions (why, how and what are more powerful than when, where or yes/no questions) in any research setting leads to inquiry, insight, open ideas and depth of thought.[a] Asking questions, such as how can one find the best treatment for diabetes? Why do some people develop schizophrenia or Alzheimer's disease? Is more profound than asking, for example, when are we going to have something that works for diabetes?

Asking powerful questions will tend to: (i) stimulate reflective thinking; (ii) challenge assumptions; (iii) shake dogma; and (iv) generate energy. This simple rule of engagement on what is important to work on, why is it important and how to solve it, should help researchers better channel their ideas. As Peter Medawar said: 'any scientist of any age who wants to make important discoveries must study important problems. Dull or piffling problems yield dull or piffling answers' [72].

Organizations should work hard at, and foster, asking the right questions rather than be pulled by marketing demands for me-too products. Although me-too medicines provide a short-term relief from the financial pressure of losing market share, they foster a culture of innovation complacency. Organizationally, having teams of 'scary-smart' scientists is necessary, but not sufficient for innovation: talented scientists need to be channeled into asking inspiring questions, for the right results to happen. This is a fundamental difference between drug hunting (or making medicines that work in humans) as opposed to 'academic work', where great science might be done, often without immediate applicability to human pathology.

Rules are barriers to innovation

Currently, much effort is being devoted to retrospective database mining (literature and patents) to encode knowledge and find the cure to pharmaceutical product drought. These exercises range from understanding what constitutes a 'perfect' drug space, what physicochemical attributes drive good pharmacokinetic outcomes (which does not necessarily translate well across species) through PKPD predictive modeling and allometric scaling, to minimizing idiosyncratic toxicity and defining the physicochemical properties of blood–brain barrier-penetrating compounds [73]. Rules are inherently deductive; that is, they break down data, behaviors or thought processes into discrete measurable bundles of activity that can then be ordered, thus leading to answers. Although this can be value adding, blindly following rules and guidelines can also lead to 'blindness' (whereas scientifically based, these guidelines have to be taken with a grain of salt). Given that rules come from retrospective analyses, they can stifle creativity and serve as barriers to future breakthrough innovations. Rules, in general, tend to suppress the 'individual' and many medicines are 'individuals' operating in exception or outlier space. Rules- or guidelines-based drug discovery does fit within current understanding of process and, as such, is a manager's dream. It does not require much creativity to follow a set of guides, or standard operating principles previously worked out to generate data. Is part of the problem that we, as a society, have learned to live with the crutches of technology, where everything is in 'kit' form and the underlying principles and processes are no longer understood (or worse) cared about?

Another aspect in drug discovery is that of contradictions, if one only paid attention to them. As examples:

- Many anilines are mutagenic yet many successful drugs contain anilines, including the best-selling drug worldwide, Lipitor.
- Excellent team work is at the heart of successful drug discovery, yet success requires the extraordinary contributions of individuals.
- Productivity is crucial to success, yet quantitative goals are typically meaningless.
- Performance is measured on an annual basis and is metric based, even down to the number of assays run, yet true progress of research is completely independent of either the calendar or such metrics.

Science should move ahead through both integration of the past and observation of the unusual, valuing contradictions [74], as well as directed powerful questioning. So why does the industry, follow sets-of-rules so diligently, rather than explore the more innovative outlier space?

Seek the outliers

Outliers, as defined here, are a composite of key individuals, teams, observations, research approaches, work environment, corporate tolerance for, and reinforcement of, different perspectives, adequate reward systems and the ability to seize those 'aha' moments: innovation is all about culture. Outliers are not necessarily individual contributors; they are observations, unique data relationships that do not fit the hypothesis or dogma, or that cause a rethink of assumptions [72].

Individual outliers and outlier teams

Good innovators are good problem solvers (who might or might not be outliers), skilled in the art of visual observation, data integration and listening. Their ability to identify the right need, through powerful questioning, will naturally lead to value-creating ideas, concepts, solutions and, eventually, products. 'Rational' problem-solving theories leading to practical techniques [75] are successfully used in various industrial settings [76]. However, the concept of 'gut feeling' is also present to some extent in the drug discovery environment [77]. It is generally associated with key individuals who, for some reason, end up either making the best

[a] The word 'powerful' can be substituted by: *relevant, probing, inquisitive, provocative, incisive, bold, thought-provoking*. See Vogt, E.E. *et al*. The Art of Powerful Questions: Catalysing Insight, Innovation, and Action; for pdf article: http://www.theworldcafe.com/articles/aopq.pdf.

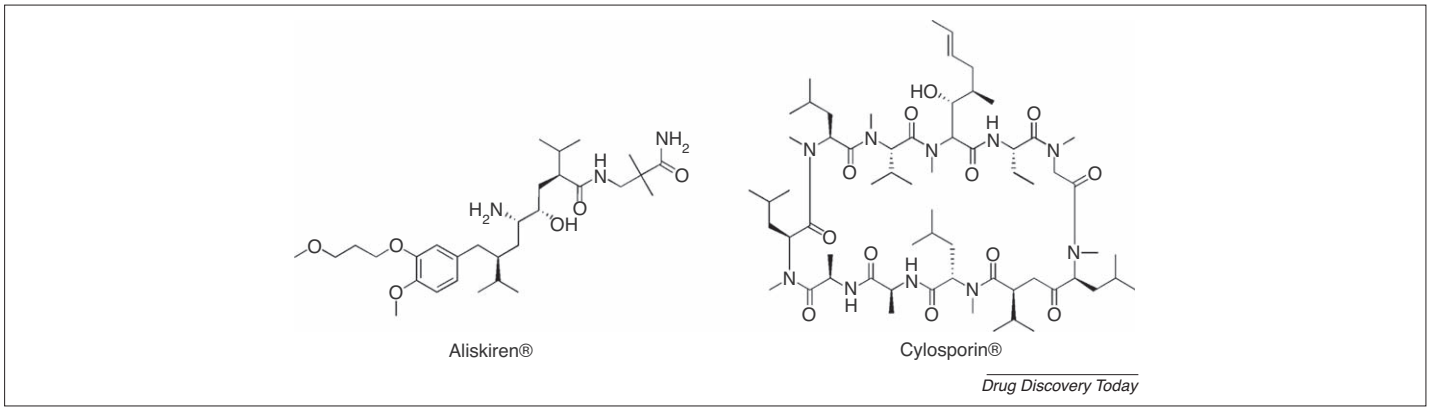

FIGURE 5

Drugs with unusual physicochemical characteristics and high medical value.

molecules or leading others in the right direction of key problem solving. Although much effort has been directed toward fitting binary codes to many pieces of the discovery puzzle through database mining or knowledge encoding to identify why some individuals 'just get it', the answer remains elusive [78,79].

Benchmarking

One of the key issues currently facing scientists and drug hunters (not all outliers) is the simple fact that they do not know what they do not know. Too often, the problem is over-intellectualized, and only the very powerful questions are asked, rather than the 'wonder questions', such as 'why not?', 'have we considered?' and 'I wonder' about how something works, or ought to or could work? It is important to remember that most, if not all, scientists thrive on solving great problems and live to tackle big challenges. Although it is important to observe the present and study the past, benchmarking can be dangerous in leading to only incrementally inventive products. The drug discovery business, just like every other one, requires intense teamwork. Teams need not comprise only outliers, but should have some onboard and pay attention to their perspectives. Benchmarking one's strategies, projects, teams and efforts is a futile exercise, as it generally leads to duplicative and noninventive work.

Drugs falling under 'outlier space'

Given the current success rate from conception to market, which could easily be qualified to be $\leq$1%, for most drug projects, one can assume that the drug discovery industry operates in the outlier space, in general, of what is typically acceptable in many other industries.

In small-molecule drug discovery, 'high probability chemical and/or drug space' can be defined by the properties that correlate with successful drugs; whereas 'outlier space' can be defined as space falling outside the 90% cluster between any three or four of the following parameters: partition coefficient (Log *P*), molecular weight (MW), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), polar surface area (PSA), solubility, potency, permeability, absorption, and so on, in a 3D relationship. In other words, 'outlier space' defines molecules having one or two key properties lying in 'non-conforming' space. This space can be 'populated' by unusually effective drugs, despite their 'non-fitting' properties, or their pharmacokinetic-disposition profiles or mechanism of action, that fall outside the 'norm'. Several valuable medicines tend to fall under the outlier space rather than meet all the 'rules'. Here are just a few examples:

- Aliskiren® [Fig. 5; MW, 551; PSA, 146, HBA, 23; human %F (percentage oral bioavailability), 3; $T_{1/2}$, 40 hours; bioavailability is limited by low permeability, PGP efflux and first-pass hepatic extraction; potent drug on renin, high dose effective, exposure variability tolerated] [80].
- Cyclosporin® (Fig. 5; MW, 1202; PSA, 287; Log *P*, 14.3; HBD, 6; orally absorbed by passive diffusion, requires microemulsion formulation, approved and valuable for patients) [81].
- All natural product-based drugs [Lovenox®, Oxycontin®, Taxotere®, Tacrolimus®, Pulmicort® and Nasonex® (quinone steroids) (Fig. 6); erythromycin-based antibiotics, β-lactam-based antibiotics etc.] fall within this outlier space, given that molecules of such beauty or complexity are not usually designed [82–84]. Nature seems to strike the right balance between potency, selectivity and physicochemical properties, taking full advantage of metabolizing enzymes and transporters when needed. She also takes time to make such exquisitely beautiful and effective molecules and tests and refines them extensively [85].
- Some outlier molecules, which would tend to be avoided in current design projects; for example, Singulair®, Plavix® (Fig. 7) and Nexium®, which all label proteins *in vivo* [86]; Zetia® (contains a β-lactam, not involved in the mechanism of action) [87] and Velcade®, which contains a boronic acid [88], also form another outlier group.
- Several molecules, currently undergoing clinical trials, such Telaprevir® (HCV protease inhibitor with MW of 680, peptidomimetic, orally bioavailable and safe and efficacious in patients with HCV) [89,90]; or the effective cancer therapeutic Lupron® (a peptide, depot formulation, has high efficacy and results in excellent financial returns) [91]. Many other examples can be found, including peptide antibiotics (e.g. Cubicin® [92]) and antifungals (e.g. Cancidas® [93]) (Fig. 8).

One could also argue that molecules in the 'outlier space' will tend to be harder for follow-on programs and lead the way to market with minimal competition (one exception being the ATPase proton pump inhibitors). More precisely, researchers tend

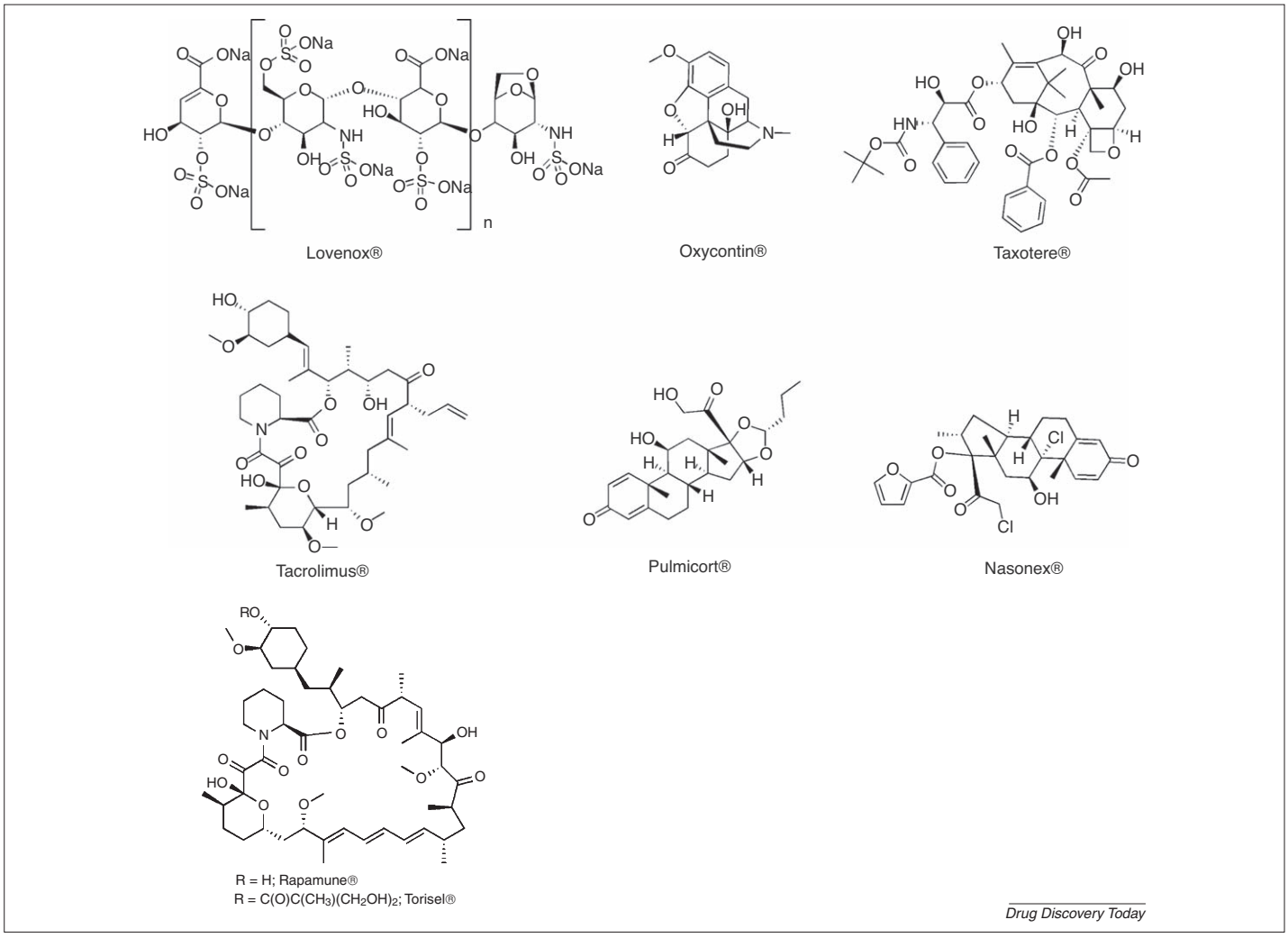

FIGURE 6

Representative examples of drugs from natural sources.

to seek the perfect prototype as early as the hit-to-lead stage, which boxes them early on into a set of operational constraints that might not help in answering the 'big' question originally asked. Some of the reasons for this might be both the classic ones, such as selectivity, toxicity, target validation, biology–clinical translation or, alternatively, that researchers are not good observers of outlier space. Drug discovery researchers usually average toward the middle or safe ground, and like deductive rules because they are easy to understand, safe, and anyone can follow them.

Sources of innovation

Where does one find problems? Not where answers already exist. As such, fast-follower- or 'me-too'-type programs do not really constitute a new scientific or medical problem to be solved. This

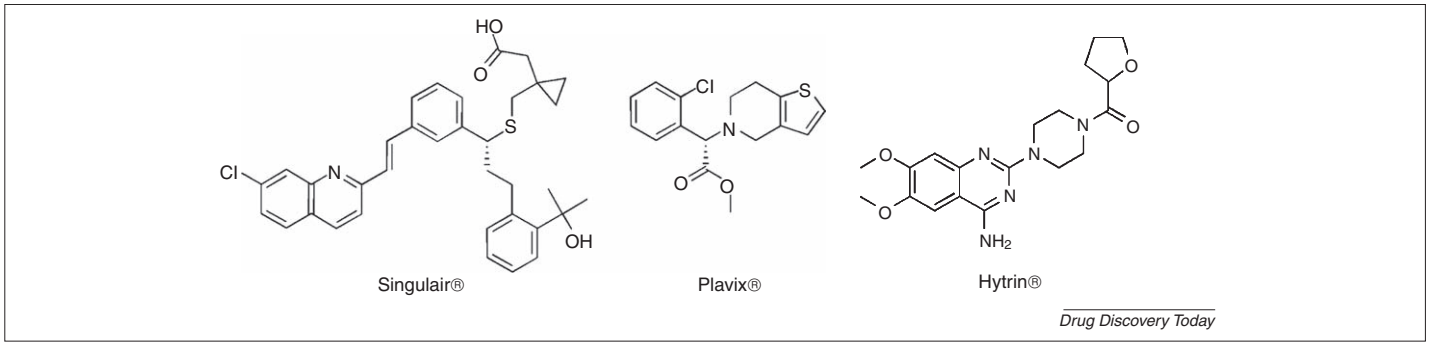

FIGURE 7

Examples of highly effective, commercially successful drugs that label proteins *in vivo*.

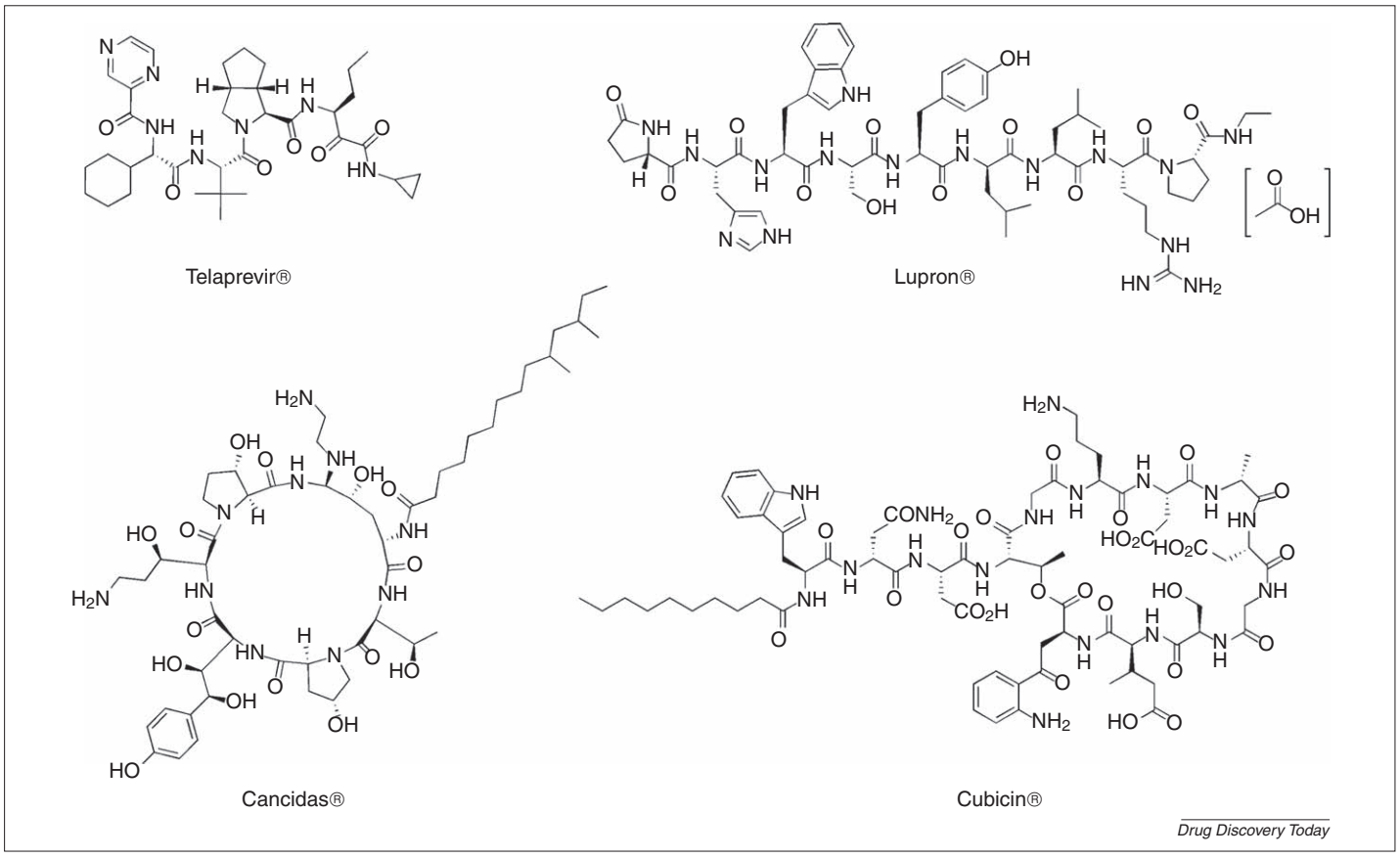

FIGURE 8

Representative examples of peptide-based or peptido-mimetic clinical agents or successful drugs.

careful selection of endeavor promotes research in areas where there is less competition, which means more time to search a wider area.

Szent-Gyorgyi [72] advises one to renew old knowledge, and several classic stories come to mind here. For example, rapamycin was toxic to animals, which put a halt to the project during the mid-1970s. Almost 20 years later, the immunosuppressant properties of this natural product were biologically better understood, paving the way to two approved drugs in immunology (Rapamune®) [94] and oncology (Torisel®) [95]; Thalidomide®, originally approved as an antiemetic agent, was removed from the clinical setting, but later found approved use in oncology [96]; Hytrin® (Fig. 7), originally developed as antihypertensive agent, later found use as a treatment for benign prostate hyperplasia [97]. Each R&D organization has a wealth of historical, corporate research knowledge to tap into, and too much of this is likely to be going untouched and/or unexamined.

By contrast, Pasteur's method [72] is to find contradiction between theory, or dogma, and data. A particularly interesting and potentially valuable measure of discoveries is a contradiction between what was expected and the newly generated data, where one or other must be wrong; in such situations, something useful can usually be learned. A classic example is the discovery of Zetia®, where the team was targeting acetyl-coenzyme A acetyltransferase (ACAT) inhibitors; however, no correlation was observed between compound inhibitory concentration on ACAT and *in vivo* efficacy in lowering cholesterol absorption [54]. Following the *in vivo* efficacy structure–activity relationship (SAR), led to this important discovery and, subsequently, to the identification of its trans-membrane cholesterol transporter protein. The contradiction is obvious in this case: shallow *in vitro* SAR, with inverse correlation to *in vivo* efficacy.

Langmuir's principle [72] was to simply turn the problem on its head: 'Sometimes neither serendipity nor planning cooperates with the desires of the scientists'. When a desired effect is hindered by various interfering factors, one should deliberately focus on the undesirable factors so as to exaggerate or understand their bad effects. Perhaps something new will be uncovered as a result. As an example, erythromycin, one of the first successful macrolide antibiotics, had a side effect that resulted in gastrointestinal motility. It turned out that the culprit was not erythromycin itself, but a rearrangement derivative (hemiketal furan) produced, under the low pH of the stomach, which activated motilin receptors, thus leading to gastrointestinal movement [98]. Capitalizing on this 'side effect' led to research into motilin agonists for the treatment of both gastroesophageal reflux disease and diabetic gastroparesis, and the discovery of the motilin receptor [99–101].

Outliers can be successful

In his book *Outliers: The Story of Success*, Malcolm Gladwell argues that success is attributed to exceptional people and those who operate at the extreme outer edge of what is statistically possible [102]. Identifying coworkers with such skills and providing just the right environment for them to operate will undoubtedly lead to valuable innovation.

Another analogy can be drawn from the business strategy mantra: Blue Ocean Strategy. In the latter, the metaphor of red and blue oceans describes the market universe [103].

'Red Oceans are all the industries in existence today—the known market space. In the red oceans, industry boundaries are defined and accepted, and the competitive rules of the game are known. Here companies try to outperform their rivals to grab a greater share of product or service demand. As the market space gets crowded, prospects for profits and growth are reduced. Products become commodities, and cutthroat competition turns the ocean bloody. Blue oceans, in contrast, denote all the industries not in existence today—the unknown market space, untainted by competition. In blue oceans, demand is created rather than fought over. There is ample opportunity for growth that is both profitable and rapid. In blue oceans, competition is irrelevant because the rules of the game are waiting to be set. Blue Ocean is an analogy to describe the wider, deeper potential of market space that is not yet explored.' (http://en.wikipedia.org/wiki/Blue_Ocean_Strategy).

Applying the above metaphor to drug discovery becomes self-explanatory, and invites innovators to chart new 'Blue ocean-like drug discovery' maps, where competition is lower, but risk and reward are higher, yet more value-creating (Fig. 9). Although the above perspective might have a 'pie-in-the-sky' sentiment to it, practitioners in drug discovery and development, as well as executive management teams, need to think hard about the future of where their investment activities need to be. Duplication, in strategy and scientific endeavor, of what has happened over the past two decades will be futile, if not incremental. There remain many seriously underserved diseases [e.g. cancer (all forms), schizophrenia, depression, multiple sclerosis, Parkinson's, Alzheimer's, Huntington's and amyotrophic lateral sclerosis (ALS) diseases; infectious diseases (influenza, gram-negative bacterial infections), cystic fibrosis, and many more]; that will require new approaches. Attacking these diseases, with novelty, patience and vigor, will undeniably create opportunities for corporations to reap financial benefits. The red ocean has been tried and it is time to discover new 'territories'. A complementary perspective covering discovery management, corporate size and why failure to understand scientists' psyche and motivational drivers has contributed to drug R&D failure has recently been published [104].

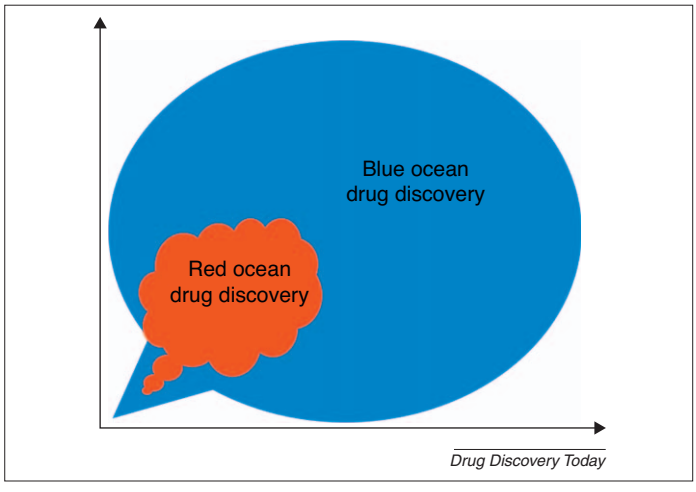

FIGURE 9

Representation of iASAP 'property space' by analogy to the classic Log *P*–PSA graph for 'drug space'. The *X*-axis indicates risk/reward, whereas the *Y*-axis indicates innovation.

So how do we set ourselves up for success?

Scientists must become better observers and listeners. As examples: (i) much creative thinking happens at the more junior levels in organizations (fresh thinking). Promoting such behavior and finding mechanisms to exploit it rapidly, without middle-management stifling, is likely to pay dividends; (ii) many mistakes, mishaps, or difficulties occur in the execution of any project and, if properly observed and astutely questioned (why, how, what), could create a new momentum; (iii) a disgruntled coworker might be suggest ways to change standard operating procedures; (iv) a repeat-failure might be suggesting repositioning for a new system; and (v) an untreated or ill-treated disease signals the need for an entirely new paradigm, as is the case for Rapamycin (Rapamune and Torisel) (Fig. 6) and Hytrin (Fig. 7).

Accept defeat, then go back

'If you can meet with Triumph and Disaster And treat those two imposters just the same': Rudyard Kipling, from his poem "If".

It might appear that inventiveness is a personality trait, rooted in the brain, and that is part of an inquisitive personality. The desire to seek the better, more efficient, 'never-discovered' approach is generally revered and could be attributed to only a few individuals. However, all inventors will easily admit they 'almost' quit many times on any given project, and thus potentially missing important inventions. In the process of coming up with a 'new thing or idea', one will need to accept failure as par for the course and not get discouraged. In the business of innovation, one could argue that character, the ability to deal with failure, is more important than intellect. The challenge here is that most scientists are trained to persevere (and not accept defeat) in the face of negative research outcome, which makes this a harder case to deal with.

The ability to both accept defeat and manage plans moving forward is essential to keeping goals in check. In *The Neuroscience of Screwing Up*, Jonah Lehrer eloquently describes how the ability to recognize when to give up, helps one see challenges in a very different way than before [105]. He cites several examples, including the story behind the physics leading the Big Bang theory and awarding Penzias and Wilson the 1978 Nobel Prize in physics.

In the drug discovery business, researchers are 'wrong' approximately 90% of the time on preclinical candidates and on ≥90% of the projects (as measured by NCEs into the clinic). Compound-related attrition owing to PK or toxicology; disconnects between biological target and disease; lack of proper clinical efficacy, target-based toxicity or clinical trial design problems, generally contribute to these failure rates. Additional contributions to this minimal

success can be strategic, organizational, tactical or cultural in nature. I do not argue for giving up early, but rather for appreciating the net positive effect of 'accepting being wrong', early. Despite all the planning and assurance, one can be wrong at any stage. Such an acceptance will lead to mind-openness and the ability to see clearer and hopefully minimize error-repeat. As thoroughly described in the drug discovery business, the cost of failure is high.

The key here is 'directional problem solving'; are the right question(s) being asked (here it is important to have hypotheses and not just open-ended questions) and are the results moving the team in the direction that they need to go? When that stops happening, it is imperative to question whether the team has truly failed or has reached the limits of its current ability to move forward: for those scientists who have a hard time letting go, either use the concept of 'back-burnering', where the project can simmer but not distract, or park it altogether.

Populate astutely

Literature on sources of innovation reveals that most influential high-value inventions and/or business ideas were produced by at least two people (not one, as is commonly believed). Examples abound in the business, scientific and artistic areas, including HP (Hewlett and Packard), Microsoft (Gates and Allen); Google (Paige and Brin); Apple (Wozniak, Jobs and Wayne); the Beatles (Lennon and McCartney); DNA (Watson, Crick and Franklin) and DNA sequencing (Maxim, Gilbert and Mirzabeckov); asymmetric epoxidation (Sharpless and Katsuki) and LDL metabolism (Brown and Goldstein) [105]. A study of the personal characteristics of these pairings (and groupings in research environments) points to the complementary nature of those involved and to them having asked powerful questions that led to their success.

Of course, many important inventions were attributed to single individuals, but this seems to no longer be the norm, given the complexities now involved to bring a differentiated product to market and the coordinated teamwork necessary for success. On the human resources side, a key component of hiring or forming a new team is striking a fair balance between people who disagree with you and those that execute orders. Organizations should learn from these studies and populate their various innovation incubators with the appropriate complementary personalities to fuel future innovations. Many of the examples cited above, and probably many internally kept stories, add credence to this point of view. Additionally, many pharmaceutical organizations are experimenting with lower-cost drug discovery models (http://www.slate.com/id/2267688/; http://www.slate.com/id/2267342/, [106]), and scientific crowd-sourcing approaches, however, the future remains uncertain about how truly innovative or value-adding these will be.

Innovation in the pharmaceutical sector is very different from that in many others (particularly non-science based businesses), simply because when researchers embark on a truly new project, they generally have no idea what the final product will 'look like'. Additionally, equating innovations among the various disciplines of drug discovery is useless, the sum of all is much greater than the total. Finally, research-intensive organizations seeking truly innovative products, need to reward publicly and handsomely true innovation and innovators (teams and individuals), rather than rewarding 'me-too' or 'fast-follower' products.

Summary

The future of the pharmaceutical industry remains bright, despite this momentary lapse of appreciation from the business and political communities. Dramatic advances in chemistry, biology, pharmacology, PK, toxicology and medicine have occurred during the past 15 years (which is approximately the cycle time from discovery to market). This, in concert with some nurturing of more innovative cultures within the individual companies, will result in new, improved medicines to fight disease. Innovation is not an averaging down toward a middle ground of best practice, as is the traditional 'consultation' mentality, but rather an expression of the individuality and creative strengths of each company. Apple is not Microsoft, yet both are creative and successful in different ways; innovation is not something to be processed, instead it is to be nurtured, watered and measured in years and not in quarters or months.

In summary, I have shared here my perspective on what behavioral attributes could help move non-innovative cultures toward innovative ones, and to capitalize on their existing talent to help reshape the pharmaceutical R&D business toward effective prosperity. By linking the four components of ASAP (ask powerful questions; seek the outliers; accept defeat and populate astutely), one has a practical, and potentially useful, working formula to stimulate innovation in the research environment and beyond. As the saying goes: 'culture eats strategy for lunch, every time'.

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[b] Author's note: it is expected that the reader will see attributes of her/himself in this brief dialog on Innovation: be neither complacent nor kind on yourself or your organization; this is about challenging yourself to be better, for your organization, and the benefit of all.

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