Failure and Success in Modern Drug Discovery: Guiding Principles in the Establishment of High Probability of Success Drug Discovery Organizations

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Abstract: The pharmaceutical industry currently suffers unsustainably high program failure rates despite our best efforts to implement drug design methods and to develop high throughput biochemical screening technologies over the past 20 years. While much of this failure is rationalized to be due to uncontrollable late stage drug development issues and clinical events, it has become increasingly clear that the choices we make in early drug discovery are vital to the ultimate failure or success outcomes of our drug discovery programs. The judicious selection of high probability of success therapeutic modalities, the rigorous determination of leadlikeness and druglikeness, and the all-important selection of high probability of success enzyme and receptor targets are the vital drivers of failure and success in small molecule drug discovery as it is performed in the age of biochemical screening. Consideration of these guiding principles will improve our chances of success in drug discovery, and increase our ability to address unmet medical need in the future.

Key Words: Failure in drug discovery, success in drug discovery, therapeutic modalities, biochemical assays, gene therapy, antisense therapy, stem cell therapy, protein therapy, antibody therapy, small molecule therapy, nonleadlikeness, leadlikeness, nondruglikeness, druglikeness, chemical conditioning, conditioned extracts, library purification.

1. INTRODUCTION

Scientists who have worked for years in the pharmaceutical industry have become accustomed to the comfortable rationales for our many program failures. Discovery groups in pharma routinely imply that uncontrollable factors including unreliable biological target validation, unpredictable toxicological outcome, precarious intellectual property issues, and fickle market drivers conspire to undermine our programs and result in our staggeringly high rates of program failure. Our teams in clinical development tell a similar story. Nine out of ten of our clinical programs fail. It seems that a 90% failure rate in discovery coupled with 90% failure in the clinic results in an unsustainably high program failure rate in pharma.

It is the intention of this commentary to propose that many of the reasons for our failure are, indeed, under our control and that the decisions made in the earliest stages of drug discovery dictate the failure and success outcomes of our programs. The following intends to identify the vital drivers of failure and success in drug discovery, and to propose a template for high probability of success drug discovery organizations.

2. THE LEADERSHIP ROLE OF DISCOVERY GROUPS

The simplified "cone of resources" cartoon Fig. (**1**) is intended to depict the downstream effect of our discovery-stage decisions on the resources committed by pharma organizations program-for-program. The screens we launch and the new lead compounds we select at the earliest stages in discovery spawn new drug development programs and lock our organizations into budget and staffing decisions intended to support these programs for years to come. It is very likely that failure and success is determined at the point of the decisions made in discovery. Imagine 10, 20, or even 100 of these cones superimposed on each other to represent all the programs ongoing in a drug discovery organization. The unfortunate reality is that >95% of our resources are supporting programs that are essentially already failed due to our early decision making. How can we make decisions in early discovery to assure that this high rate of program failure does not persist in the future?

The collective intellectual, scientific, and financial resources in pharma organizations represent an immense potential for success. We need to design high probability of success drug discovery organizations to engage these resources productively. Research leadership must choose high probability of success programs and also proactively cull low probability of success programs. There are multiple levels on which these decisions need to be made. The following discovery-stage decisions are the most important factors in determining failure and success in drug discovery:

- Therapeutic Modality Selection
- Biological Target Class Tractability
- Leadlikeness and Druglikeness

This commentary will identify the drivers of failure and success that we can control. It will draw attention to the exceptionally significant role of leadership in our discovery

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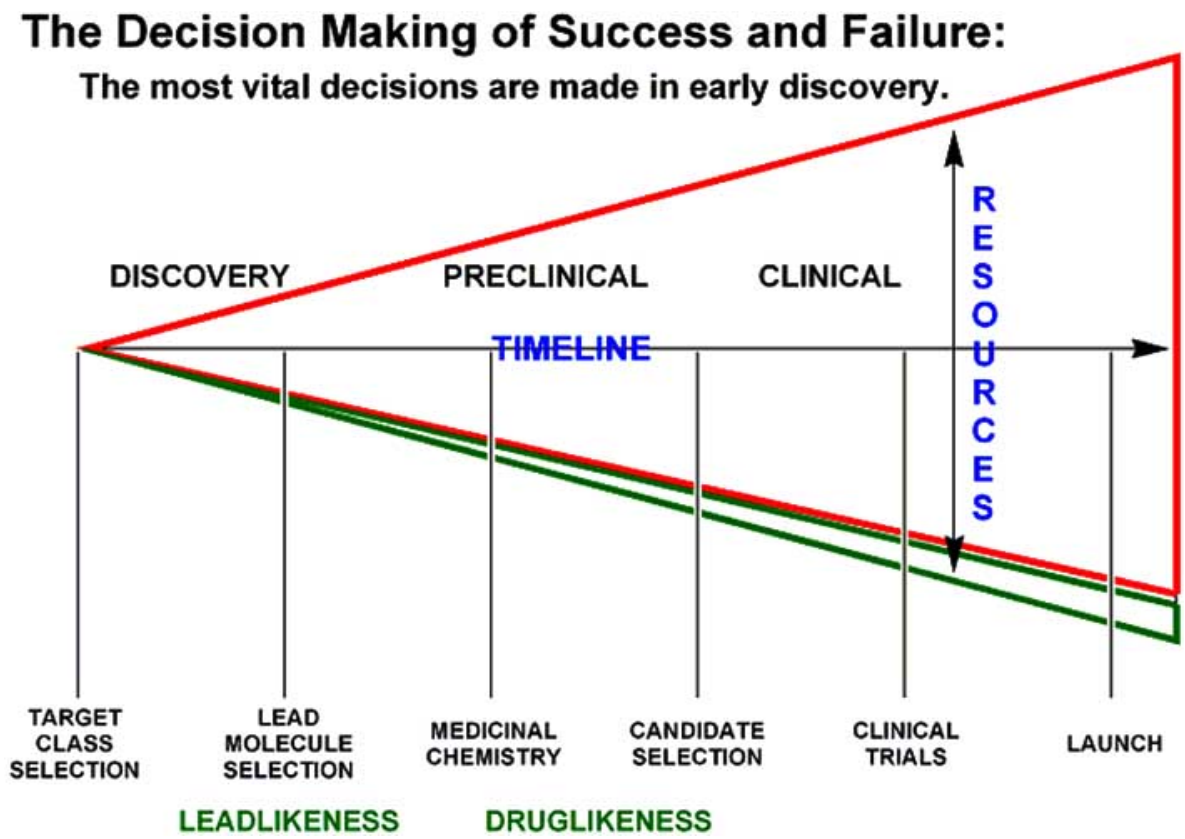

Fig. (1). Timelines and Resources. The earliest decisions, including target class selection and lead molecule selection, lock a drug discovery organization into significant resource and time commitments. It is likely that failure and success are determined by these early decisions, and that a majority of pharma resources are being committed to already failed projects (red cone).

and research organizations. It will offer guidance for effective decision-making in the early stages of drug discovery to insure that our programs are on track for high probability of success outcomes.

3. THERAPEUTIC MODALITIES

One of the most important decisions a drug discovery organization can make is in the selection of therapeutic modalities. There is much boardroom opinion and literature debate concerning the viability and financial opportunity afforded by the traditional and the emerging therapeutic modalities. The following discussion will, no doubt, be controversial. However, it seems time to evaluate therapeutic modalities, not on their blue sky future potential, but on their relative probability of success and their potential to impact pharma pipelines and unmet medical need.

Therapeutic Modalities

- Gene Therapy
- Antisense Therapy
- Stem Cell Therapy
- Protein Therapy
- Antibody Therapy
- Small Molecule Therapy

Consider the therapeutic modalities represented in the above figure. Given the immense financial and human resources to assign, pharma companies can claim to assemble the "balanced portfolio", ostensibly balancing "high risk – high reward" modalities with "low risk – low reward" modalities. Given the state of success and failure profiles in pharma, it seems time to identify high probability of success therapeutic modalities and to focus on "low risk – high reward" strategies.

3.1. Low Probability of Success Therapeutic Modalities

The design of high probability of success drug discovery organizations involves, most importantly, the exclusion of low probability of success therapeutic modalities. While remaining open-minded to the possibility of future progress and even isolated clinical successes in some of these emerging modality areas, pharma leadership must exclude some of these from consideration as therapies. As of 2005 it has become painfully obvious that gene therapy and antisense therapy (including sRNA and RNAi) are not high probability of success therapeutic modalities. Also, despite its recent political attention, stem cell therapy does not deserve serious consideration as a high probability of success therapeutic modality. This is not to say that these are not promising sciences. They are just not high probability of success therapeutic modalities. Among the many challenges facing these experimental therapies, tissue specific

modification of genetic material and targeted tissue implantation methods may well confound development of these technologies for decades to come.

In the high probability of success drug discovery organization, gene science, antisense science, and stem cell science will be resourced for their true value as enabling technologies in drug discovery. They will be used for new target identification, new target validation, knock-in experiments, and knock-down experiments. The high probability of success drug discovery organization should exclude these from consideration as therapies and avoid downstream preclinical and clinical resourcing for these.

Low Probability of Success Therapeutic Modalities

- Gene Science
- Antisense Science
- Stem Cell Science

High Probability of Success Therapeutic Modalities

- Protein Therapy
- Antibody Therapy
- Small Molecule Therapy

Exclusion of the low probability of success modalities will simplify this important decision for drug discovery organizations. We are now left with the high probability modalities: protein therapy, antibody therapy, and small molecule therapy.

3.2. High Probability of Success Therapeutic Modalities

3.2.1. Protein Therapy

Protein therapy has enjoyed an incredible season of success since the heyday of molecular biology. Some of the most important drug products of the last 20 years are not really drugs at all. They are the recombinant human proteins that have been harvested from mammalian and bacterial cell lines. This is a fabulous technology and these are fabulous therapies. On the downside, the hugely successful protein therapies currently on the market are not just the "low hanging fruit" of the biotech revolution; they might be the absolute "best in show". While the great biotech companies including Amgen, Genentech, and Biogen have already demonstrated the future promise of modified proteins, soluble receptors, and all manner of biologics, it is likely that these companies will essentially control the protein therapy modality in the future. The list of protein therapeutics is not long, and the delivery challenges of leptin, BDNF, and GDNF are now well known. Protein therapy remains a niche modality and the world's leading biotech companies have artfully monopolized that niche. The next world-class opportunity in protein therapeutics will be in their generic manufacture and sale.

Given a combination of scientific considerations, intellectual property issues, and market drivers, we are left with two high probability of success therapeutic modalities: *antibody therapy and small molecule therapy*. These modalities are, by far, the best choices for the high probability of success drug discovery organization. This is not only due to the successful track record of these modalities. It is due, in large part, to the significant issues of drug delivery and biological target class tractability that will be discussed later in this commentary. Antibody therapy and small molecule therapy, properly implemented along with consideration of target class tractability, are the best avenues for success in launching new therapeutic products and for addressing unmet medical need in the future.

3.2.2. Antibody Therapy

Antibody therapy has made great strides in a very short span of time in establishing itself as a viable high probability of success therapeutic modality [1]. As high affinity binders to growth factor receptors, the potential value of antibodies was never in doubt [2,3]. However, it has been the pharmacokinetic profile of the antibodies that has been so remarkable. Weekly (and even monthly!) injections of therapeutic antibodies seem a reality beyond which we had even hoped for. Further, given the possibility of antibody engineering [1] to modify receptor binding and to adjust pharmacokinetic profile, it would seem there is a rich vein of antibody products that will emerge from pharma pipelines in the future. The industry leaders, Abgenix and Medarex, along with their pharma partners, are currently at the head of the cue in launching new products. However, there seems to be no limit to the new intellectual property that could be generated through product improvements by antibody engineering. In an era where news of failure and weak pipelines seem to dominate the pharma industry headlines, therapeutic antibodies will provide a well-needed and stimulating elixir.

3.2.3. Small Molecule Therapy

Small molecule therapy has historically been, and continues to be, the most general and lucrative therapeutic modality. Small molecule drugs span all therapeutic areas and, ultimately, offer the best hope for the development of daily administered medicines to treat chronic disease. However, despite these advantages, based on the dismal performance of our drug discovery organizations over the past 20 years it is hardly accurate to characterize our recent efforts in small molecule drug discovery as being "high probability of success". It would seem that our adoption of biochemical tools and high throughput methods has had the undesired effect of increasing program failure in our discovery programs. The remainder of this commentary will focus on high probability of success strategies in small molecule drug discovery, particularly focusing on small molecule drug discovery in the age of the biochemical assay.

4. SMALL MOLECULE DRUG DISCOVERY IN THE AGE OF THE BIOCHEMICAL ASSAY

Our modern dependence on isolated protein assays, including enzyme assays and receptor preparations, has resulted in a generation of drug discovery scientists who maintain an "*in vitro* perspective". This perspective can be powerful and perfectly effective in the drug discovery arena given the proper biological and pharmacological context. However, an apparent neglect of biological and pharmacological context has resulted in of our misuse of biochemical screening data and a legacy of program failure.

Our analyses of failure and success in pharma include issues such as the physiochemical properties of leadlikeness [4-6] and druglikeness [7], chemical diversity [8-10], chemical space and biological target space [11], and biological target "druggability" factors [12,13]. All of these are important considerations for success in small molecule drug discovery. However, one important issue that has been largely overlooked has been the limitations of our modern biochemical assay methods.

4.1. Operating in the Biochemical Context

Since about 1990, in some respects, we have been immersed in the dark ages of biochemical screening. No doubt, there have been huge successes in the use of biochemical tools in, for example, HIV protease inhibition and ACE inhibition. On the other hand, our dependence on and misuse of biochemical tools has increased the probability of program failure overall. It seems we had abandoned the fundamental *in vitro* principles of pharmacology that were elegantly pioneered by great scientists such as Michaelis, Menten, Lineweaver, and Burk.

When chemists and biochemical pharmacologists are reviewing biochemical screening data, it should go without question that our biochemical assays are designed to enable us to identify non-covalent, reversibly binding, high affinity ligands that bind to their protein target in leadlike ways (lipophilic binding, hydrogen bonding, and in some cases, ionic bonding) [4]. Given this simple premise it is shocking to see over ten thousand citations in the primary medicinal chemistry literature that document medicinal chemistry programs based on covalent-acting electrophilic carbonyl compounds such as peptide aldehydes and trifluouromethyl ketones. This alkylating agent or "suicide inhibitor" approach has been extended to electrophilic heteroaryl ketones, aliphatic nitriles, Michael acceptors, and even epoxides. The situation was made even worse by the thousands of metal chelator "inhibitor" citations that are purported to address the MMP targets. Medicinal chemistry programs aiming to develop covalent-acting "inhibitors", warhead chelators, and covalent-acting metal bonders have been a horrific waste of time and of medicinal chemistry resources. The thousands of programs that feature covalent-acting or chelating inhibitors are based on artifact *in vitro* data, essentially *in vitro* false positives, and they have failed uniformly. Clearly, there has been a breakdown in the interpretation of binding data generated in biochemical assays.

It should be understood that, despite the fact that many anti-infective agents and anti-neoplastic agents are covalent-acting alkylating and acylating cytotoxins, that these sorts of reactive agents cannot be discovered and developed using biochemical screening methods. Covalent-acting cytotoxic agents must be developed using whole cell functional selective cytotoxicity assays. In the biochemical arena, when a reactive agent forms a covalent bond with, for example, an enzyme target, the assay readout is representative of chemical reaction kinetics, not enzyme inhibition kinetics. In biochemical assays, reactive agents including electrophiles, [4] chelators, frequent hitters, [14] and aggregators [15-17] give a false readout. The biochemical assay of mammalian enzymes and receptors can only be effectively used to study the non-covalent, non-chelator binding of high affinity ligands.

4.2. Nonleadlikeness and Leadlikeness

Medicinal chemists and biochemical pharmacologists must join together in their understanding that we use biochemical assays to find new pharmacophores, not new drug candidates. The search for a new pharmacophore by biochemical screening is not dependent on properties of "druglikeness". The search for a new pharmacophore in a biochemical assay must be governed by the issues and qualities of "leadlikeness". Binding studies in our artificial biochemical assays are meant to produce low molecular weight noncovalent-acting high affinity binders. These leadlike compounds provide high probability of success chemical lead structures for medicinal chemists to use for what they do best: the synthesis of structural analogues to optimize physiochemical properties within a series of inhibitors or binders.

The evaluation of leadlikeness is different from, and complementary to, the evaluation of druglikeness [4-7]. A nonleadlike compound is "non-hit-like". It is an artifact false positive in your biochemical assay and it is not amenable to triage. Every new analogue prepared based on a nonleadlike false positive is another nonleadlike false positive. Your program has failed even before it has begun. The decision to select a high quality lead compound from a biochemical screening program is second in importance only to the selection of a high probability of success target class as being the most impactful decision made in the drug discovery arena. The selection of a new lead compound is a decision usually made by committee but, there is no doubt, this decision is the domain and the responsibility of an organic chemist. Let your chemists choose their new lead compounds. Then, hold them accountable for their choice.

4.3. The Complementary Roles of Leadlikeness and Druglikeness

It is at the later stage of medicinal chemistry and during clinical candidate selection that the guidelines of "drug-likeness" come into play. The well-communicated "rule-of-five" is our best guide to select compounds that are membrane permeable and thus, are probably orally bioavailable [18]. Leadlikeness and druglikeness are each important considerations for the high probability of success drug discovery organization. Both have appropriate application. Leadlikeness need be applied in early biochemical screening, and druglikeness in later-stage medicinal chemistry and pre-clinical drug development. We will revisit the issues of leadlikeness later in this commentary.

4.4. Target Class Tractability in Small Molecule Drug Discovery

The single most important decision in terms of the success and failure of small molecule drug discovery (using biochemical screening) is the judicious selection of high probability of success enzyme classes and receptor classes. Importantly, this presumes the exclusion of low probability of success target classes. It is not enough in the high probability of success drug discovery organization to simply

"balance the portfolio" based on ill-defined metrics of risk and reward. We must be proactive in our selection of high probability of success targets for small molecule drug discovery.

SMALL MOLECULE TARGET CLASS TRACTABILITY [19]

High Probability of Success:

- GPCR's
- Ion Channels
- Proteases
- Non-Signal Transducing Enzymes

Low Probability of Success:

- Kinases
- Phosphatases
- nuclear receptors
- nuclear enzymes

No Probability of Success:

- Cytokine receptors
- Growth factor receptors (good target for antibodies)
- protein-protein interactions assayed biochemically

Traditionally, drug screening was done using functional cellular assays, selective cytotoxicity assays, and animal studies. Given about 50 years of this "non-directed" screening, and what was clearly a rigorous pharmacological approach, it was demonstrated that we could successfully discover and develop anti-infectives, selective cytotoxins, GPCR binders, ion channel binders, and certain classes of enzyme inhibitors. It should be straightforward then to learn from this data and to conclude that these are the high probability of success target classes.

However, the introduction of "directed" biochemical screening methods has resulted in the opposite response to this historical data. Given the availability of powerful biochemical tools for measuring inhibition, binding, and selectivity, it seems that the drug discovery community expects a complete reversal of fortune in the discovery of new drugs at the low probability of success targets. Discovery groups seem to have decided that, despite well-documented and repeated failures at some target classes, we should move forward with our biochemical tools and try to solve the unsolved problems. Since 1990, much of our valuable resource and effort has gone into the biochemical study of low probability of success target classes including kinases, phosphatases, nuclear receptors, nuclear enzymes, and even protein-protein interactions. The reversal of fortune has not materialized.

What needs to be stated here is this: The reason drug discovery groups were traditionally unsuccessful in discovering and developing drugs at low probability of success targets was not because they didn't have biochemical tools at their disposal, and it's not because they were not "smart and fast". The reasons that certain classes of small molecule drug targets have had such a low probability of success include fundamental drug discovery hurdles such as:

- Tissue distribution of the target.
- Delivery of the drug to the target tissue.
- Tissue distribution of the drug upon dosing.
- Toxicology outcome due to issues above.

As pharma gears up to assemble high probability of success drug discovery organizations we must embrace the truth of our industry's past efforts. The high probability of success targets for small molecule drug discovery are GPCRs, ion channels and non-signal-transducing enzymes such as esterases and proteases. Screening these targets and estab-lishing specialty groups in these target platform areas are the best ways to establish a high-probability of success small molecule drug discovery organization. Importantly, the proactive exclusion of low probability of success target classes will remove the burden of near certain program failure.

4.5. The Problem with Kinases

The development of small molecule kinase inhibitors provides the perfect topic for discussion of the above principles concerning failure and success in drug discovery. Due in large part to the intensive effort toward the development of an anti-inflammatory p38 inhibitor at SmithKline in the early 1990's, kinase inhibition was thrust onto center stage as the "new" target class. The kinome was foisted upon pharma as the approach of choice to designing "directed" or "magic bullet" inhibitors of signal transduction. The presumption was that, given the ready availability of expressed kinases and the ease of assay development, the discovery and development of highly selective kinase inhibitors should be possible. As with any "new" area in drug discovery there was much action taken and many kinase inhibitor programs initiated to keep up with the new wave of discovery and the potentially huge market opportunities in inflammation, cancer, and even central nervous system and metabolic disease targets. Unfortunately, the drug discovery community paid no attention to the historical failures in the kinase inhibition area.

The structure of ATP was determined 75 years ago and the first chemical analogues of ATP (designed to inhibit "neoplasm") began to appear shortly thereafter. Over the years thousands of ATP analogues, particularly pyrimidines, were screened as anti-cancer agents. By the mid-1980's, pharma groups had isolated the various protein kinase A's, B's, and C's and launched directed screening efforts at these targets. By 1990 several companies had invested significant resources in small molecule EGFR and VEGF (KDR) programs. The fact is, there have been thousands of failed kinase inhibition programs in drug discovery and, in the early 1990's, there was still some healthy opposition to launching countless kinase programs to attempt this magic bullet inhibition of signal transduction.

The truly transformational event occurred in the mid-1990s when the much anticipated approval of Gleevec came

to pass. There is no doubt that Gleevec is remarkable in its action and efficacy. However, as of the Gleevec approval, it might be said that the rate of success in kinase inhibitor drug discovery was less than 0.1%. Gleevec has been touted as a specific inhibitor of bcr-abl, a kinase expressed only in the target leukemia cells. That would make perfect sense, except that now it has come to our attention that Gleevec has at least four kinase targets and that c-kit and others might actually be more important than bcr-abl. Since the Gleevec approval, there have also been the approvals of Tarceva and Iressa. These agents each have there own advantages and drawbacks. It remains to be seen if they will be well-used in the clinic as novel "directed" therapies, or if these drugs will become essentially lost in the pharmacopoeia of the various cytotoxic therapies.

Certain conclusions can be drawn at this stage. In the future, kinase inhibitors will occupy a niche clinical space occasionally being administered as acute anti-neoplastic agents. It is likely that this space will not accommodate multiple blockbuster drug products. There is likely a limited market future for kinase inhibitors, and currently pharma is seriously over weighted in kinase inhibitor development programs. Importantly, application of small molecule kinase inhibitors to the lucrative chronic disease markets including arthritis, central nervous system disease, or metabolic disease would seem to be out of the question.

So, what is the problem with kinases? The collective answer coming from pharma scientists worldwide is commonly; "The lack of kinase selectivity is the problem". Unfortunately, this is untrue. Pharma scientists have spent too much time and resource optimizing biochemical kinase inhibitor selectivity profiles. The real problem with small molecule kinase inhibitors is that toxic outcome is the result of tissue distribution of the orally administered kinase inhibitor. Toxic outcome is not the result of a given biochemical selectivity profile.

Orally administered kinase inhibitors concentrate significantly in the vital organs; the GI, the liver, the kidneys, the heart, and the brain. This statement is more or less true for most lipophilic small molecule drugs; however, the difference is that most lipophilic small molecule drugs are not ATP-competitive inhibitors of signal transduction. Cell permeable ATP-competitive signal transduction inhibitors will accumulate in the vital organs and inhibit signal transduction in those tissues non-selectively. Tissue distribution dictates that this inhibition of signal transduction will occur regardless of the biochemical kinase "selectivity" profile that we work so hard to build into the inhibitor. Consider the typical relative concentrations of drugs in the various organs in a high-dose orally administered rodent toxicology study [19]:

GI tract: 0.5-1 mM

Liver: 100-500 uM

Blood: 100-500 nM

Heart: 100 nM

Kidneys: 100 nM

Target tissue: 0-100 nM

This tissue distribution profile dictates that toxic outcome in high dose rodent toxicology studies will be completely uncoupled from the biochemical kinase selectivity profiles that we spend so much time assaying and optimizing for (usually at concentration between 0.5 nM and 10 uM). The important question we need to address concerning the toxicology of kinase inhibitors is, in general, what is the consequence of the inhibition of signal transduction in the vital organs and in the brain? Our biochemical assays will not address this question. Only rigorous animal toxicology will inform us of particularly clean or particularly toxic kinase inhibitors.

On an optimistic note, given the guaranteed high concentrations of a kinase inhibitor in the liver, it seems that liver-associated cancers and metastasis might be the best possible clinical target for an orally administered kinase inhibitor. This could be the key dynamic to explain the efficacy of the approved kinase inhibitors. Another optimistic point is that we've begun to understand that therapeutic antibodies are superior inhibitors of signal transduction in that they act at the cell surface growth factor receptors and so don't concentrate in the vital organs the way that the cell permeable ATP-competitive small molecule kinase inhibitors do.

It is likely that the inhibition of signal transducing enzymes using cell permeable ATP-competitive kinase inhibitors will not be generally fruitful. While there have already been some isolated clinical successes, small molecule kinase inhibition has limited application and should not be regarded as a high probability of success approach.

5. HIGH PROBABILITY OF SUCCESS SMALL MOLECULE DRUG DISCOVERY

The judicious selection of high probability of success target classes (i.e.; GPCRs, ion channels, non-signal transducing enzymes) and the selection of a high quality leadlike compound (noncovalent-acting, high affinity ligand) will put your organization on the path to high probability of success drug discovery and drug development programs. There are some present day examples of such high probability of success programs. Perhaps the most dramatic examples would be certain of the small pharma "biotech" companies. Success at a small company might seem virtually impossible based on the high rate of failure at an extremely well-resourced big pharma company. However, while big pharma has maintained just baseline success over the past 15 years, the demonstrated ability of some of some of the small companies to be successful has perhaps been the most illuminating event in our industry.

5.1. Small Company Success in the Therapeutic Antibody Modality [19]

The therapeutic antibody companies have been extraordinarily successful in advancing product candidates. While Abgenix and Medarex are probably over-burdened with their big pharma partnerships, their focus and productivity has been incredible. Given all the publicity and investment lavished on ImClone's single antibody product, Erbitux, it would seem that there must be significantly more value at

Abgenix and Medarex considering that they've advanced many more product candidates into development. This high probability of success therapeutic modality promises to buoy pharma product pipelines over the next decade. And, given the remaining opportunities for generation of new intellectual property through antibody engineering, it also promises to inspire the formation of new startup companies that can claim relatively low risk in discovery and relatively short timelines in development.

5.2. Small Company Success in the Small Molecule Therapy Modality

In the small molecule arena there exists a cadre of highly successful discovery groups that have combined a focus on high probability of success target classes and high quality leadlike and druglike compound collections. These small companies, particularly at their beginnings, typically had discovery groups made up of 20 or less chemists and biologists. Success in drug development with a small organization might seem improbable, but by now it should be clear that size has little bearing on success and failure. The companies in this list have each promoted multiple compounds into clinical development and some have launched their first (and even second!) small molecule products.

SMALL PHARMA, BIG SUCCESS: Focus on High Probability of Success Therapeutic Modalities, High Probability of Success Biological Targets, Leadlikeness and Druglikeness Physiochemical Properties.

Therapeutic Antibodies

- Abgenix
- Medarex

Small Molecules

- Sepracor
- NPS Pharmaceuticals
- Neurogen
- Neurocrine
- Arena
- Athena
- Etc.

There is no secret to the success achieved in these small drug discovery organizations. These companies have implemented the guiding principles for high probability of success drug discovery introduced at the outset of this commentary:

- Therapeutic modality selection
- Biological target class tractability
- Leadlikeness and Druglikeness

Attention to these principles will dramatically increase the probability of success in your drug discovery organization.

6. MOVING INTO THE FUTURE WITH HIGH PROBABILITY OF SUCCESS PROGRAMS

A focus on the guiding principles for establishment of high probability of success drug discovery organizations will have beneficial ramifications over time. An emphasis on a high probability of success therapeutic modality, on a tractable target class, and on high quality small molecules will enable a discovery group to build expertise in high probability of success areas year over year. For example, in the small molecule therapy modality, building a collection of high quality small molecules designed to bind a particular family of GPCRs will be valuable in countless future programs involving this target class. Or, the development of one or more protease assay platforms would encourage the synthesis of a collection of high quality protease inhibitors. The development of this sort of modality focus, target class expertise, and ligand design specialty in your organization will create significant leverage for success.

An emphasis on high probability of success approaches as described above will also have significant positive impact on some of our previously established drug discovery paradigms, for example, extract screening and parallel chemistry. Our acknowledgement of the limitations of biochemical screening tools and rigorous attention to the issues of high quality biochemical data and small molecule leadlikeness promises to rejuvenate some of the drug discovery paradigms and technologies that have seemingly faltered in the recent past.

6.1. Chemical conditioning and pre-fractionated natural extracts: A Modern Revolution in the Screening of Extracts [20]

The pharmaceutical industry has largely abandoned the practice of screening natural extracts to find new drug leads. This is not because natural extracts have become any less valuable, or because they now contain less interesting and less structurally diverse compounds. The problem is that for the last 15 years we have depended on highly sensitive biochemical assays for our first tier drug screening efforts. These sensitive biochemical assays are ineffective for the screening of natural extracts because the extracts tend to contain non-druglike chemically reactive compounds along with various high molecular weight polymeric materials that cause artifact data in biochemical assays and undermine our search for new drug leads.

Classically, natural extracts were screened using functional biological assays. In this modern era of biochemical screening, "chemical conditioning" [20] of natural extracts will be required to destroy chemically reactive compounds that occur in the extracts and result in false positives in our biochemical assays. Chemical conditioning methods might include simple hydrolytic or reductive chemistries. Such chemical conditioning to destroy reactive compounds will also result in the creation of novel (un-natural) and chemically stable ligands suitable for testing in sensitive biochemical assays. Chemical conditioning methods, used in combination with certain enzymatic treatments, would cleave polymeric materials such as cellulose, protein, peptides, and nucleosides to create novel, chemically stable, low molecular weight leadlike frag-

ments of these biomolecules. “Conditioned extracts” [20] so obtained can now be pre-fractionated efficiently using parallel chromatography methods including supercritical fluid chromatography. The chemically conditioned and pre-fractionated leadlike materials can be rapidly formatted into plated libraries with the help of automation.

Furthermore, the current state-of-the-art in analytical methods is significantly superior to that of the methods used during the classical period of natural products extraction and screening. Spectroscopic methods have become so advanced that the daily structural characterization of novel chemical compounds of unknown structure is an altogether practical proposal. Even x-ray crystallography and the co-crystallization of small molecule ligands in the binding sites of their protein targets have become well-developed methods and even parallelized processes. It would seem that the screening of natural and un-natural compounds of unknown structure is now, more than ever, a practical and promising proposal for the discovery of new drug leads. Given an extensive and replenishable collection of leadlike compounds from conditioned extracts, one might expect to discover and characterize novel drug leads with relative facility.

6.2. Embracing Parallel Chemistry Methods, Again![20]

The new revolution in drug discovery referred to as combinatorial chemistry arrived with great fanfare in the mid-1990s. The perceived ability to prepare large numbers of compounds coupled with the availability of sensitive biochemical assays was hoped to accelerate the discovery of potent and selective agents for drug development. Over more than a decade now, combinatorial chemistry methods have fallen far short of the high expectations placed on them to accelerate drug discovery. The failings of combinatorial chemistry have been described as being due to everything from a lack of druglikeness in the design stages to a lack of purity of the final products.

An even more important factor than these was the fact that many of the impurities found in combinatorial libraries were the reactive agents used in the synthesis of the libraries [4]. These were usually electrophiles such as aldehydes, acid chlorides, sulfonyl chlorides, isonitriles, activated esters, coupling agents, etc. Such reactive impurities, even when they were present in relatively small amounts, resulted in countless false positives in our biochemical assays. False hits led to wasted time performing re-purification and re-synthesis of a library compound only to find that, once purified, the compound had no biological activity.

The good news about the combinatorial chemistry revolution is that it spawned what are now very powerful methods of parallel synthesis, parallel purification, and parallel chemical analysis [21-23]. Importantly, efficient solid phase-supported reagents [24] and scavenger agents have been developed to enable efficient multi-step synthesis and to remove reactive impurities from library products. The problem of reactive impurities causing false positives should now be minimized.

7. CONCLUSIONS

Our understanding of the physiochemical properties associated with leadlikeness promises to improve the quality of libraries. And, our emerging awareness of high probability of success biological target classes seems to be encouraging the design of high quality libraries that are GPCR-focused, ion channel-focused, protease focused, etc. Drug discovery groups have learned to make good use of parallel methods of synthesis and purification, and also to incorporate intelligent design to produce high probability of success parallel synthesis libraries.

There is no end to the new scientific frontiers that we explore, and to the new technologies that we develop, in our efforts to facilitate and accelerate the drug discovery process. New scientific understanding and new technology development will always be a vital component of the science of drug discovery. Importantly, however, there is so much to be learned from the decades of historical data in our field, and from our historical failures and successes in drug discovery projects. The principles of high probability of success therapeutic modality selection, small molecule target class tractability, leadlikeness, and druglikeness described in this commentary will enable drug discovery organizations to establish high probability of success programs, to avoid repeated failure, and to use our newly developed drug discovery technologies in the most productive ways possible.

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