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Fragment-based lead discovery: challenges and opportunities

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Abstract Fragment-based lead discovery has undergone remarkable changes over the last 15 years. During this time, the pharmaceutical industry has changed dramatically as well, and continued evolution of the industry is assured. These changes present many challenges but also several opportunities for executing fragment-based drug design. This article will explore some of the more significant changes in the industry and how they may affect future discovery efforts related to fragment-based initiatives.

Keywords Fragment-based drug design · Biologics · Off-shoring · Outsourcing

Introduction

Since the publication of the initial proof-of-concept back in 1996 [1], fragment-based screening and fragment-based drug design (FBDD) have become accepted and widespread practices in large pharmaceutical companies, smaller biotechs, and numerous academic labs [2]. During this expansion, there has been an evolution in the size and type of screening libraries, in the biophysical techniques employed to find fragment leads, and even in principles of fragment-based drug design [3–9]. While the ultimate measure of success of this paradigm will be new drugs available to patients, there are now numerous reports of drug candidates derived from fragment-based leads that are making their way through the clinic, such that the final validation of fragment-based drug design can be confidently expected [10, 11].

Of course, as fragment-based screening has grown and evolved, the pharmaceutical industry has also experienced many new challenges and changes. Much has been discussed about the decreasing productivity of pharmaceutical research despite the significant increase in overall funding [12]. Added to this are increased regulatory requirements and oversight, increased competition from generics, and changing patient populations and therapeutic opportunities. Over the last decade, most pharmaceutical companies have responded to these challenges in at least three significant ways to try and reduce costs and increase the probability of success: narrowing of disease area focus, outsourcing, and a shift to biologics. All of these changes present specific challenges and opportunities for fragment-based drug design, each of which will be dealt with below. We will also describe the evolution of fragment-screening at Abbott [3, 6, 7], focusing on changes in techniques and strategies for executing fragment-based drug design.

Disease area focus and strategy

Over the last several decades, many companies have narrowed and focused their early discovery efforts to only address key therapeutic areas of high unmet medical need that have the potential for significant return on investment [13]. This has resulted in the decrease or outright cessation of early discovery activities in several therapeutic areas, including antibacterial, anti-viral, neuroscience, and metabolic research. In addition, research in the remaining areas has changed significantly as the lack of translatability from pre-clinical to clinical settings has been a major source of compound attrition and lost opportunities. This has resulted

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in a re-invigorated use of complex phenotypic cellular assays as the primary engines for lead discovery and optimization, in the hopes that these systems more closely mimic the disease state [14–18].

These moves also have significant implications for FBDD. Fragment-based drug design works best on small soluble targets that are amenable to structural characterization through either NMR or X-ray crystallography. Given this dependence, FBDD has enjoyed the most success in disease areas such as Oncology or Anti-infective research, where a large fraction of the targets fall into this category. In addition, fragment-based initiatives have enjoyed significant success addressing target "platforms"—such as kinases—that span multiple therapeutic areas. It is important to note that many of the early fragment-based biotechs (e.g., Astex, Vernalis, others) focused almost exclusively (and successfully) on kinases and/or oncology platforms. As a result, companies with a strong Oncology/Anti-infective focus or a heavy emphasis on kinases (and other structurally amenable target classes) still have ample opportunity for driving fragment-based programs. On the other hand, companies whose target portfolios are increasingly filled with GPCRs and ion channels will find this approach less tractable. While there has been tremendous recent success in the isolation and X-ray structural analysis of membrane proteins [19, 20], routine application of FBDD to these targets is still some time away [21].

Outsourcing and off-shoring

In addition to the changing disease area focus, many discovery activities are being outsourced or off-shored in efforts to reduce costs while maintaining capacity and capabilities. This can take the relatively conservative form of simply "purchasing" services from vendors at reduced costs (relative to internal efforts), to the Integrated Discovery Sourcing (IDS) models, where entire programs or initiatives take place almost exclusively within the domain of the collaborator. In some cases, entire technology functions have been outsourced, while in other cases such collaborations augment internal capacity or provide access to specialized expertise. Fragment screening and drug design has in many ways benefitted from this increased openness on the part of large pharma to partner with smaller biotechs, as numerous companies with collaborative business models and a focus on FBDD have come into existence. As shown in Table 1, there are now numerous companies that offer fragment-based screening and/or design capabilities.

Such companies have dramatically increased the availability of FBDD to larger pharma. In addition, the ability of the biotechs to focus on leveraging one particular technology platform allows them to drive new innovation to advance the field. While NMR spectroscopy was the initial platform for fragment-based screening, a variety of techniques have now become available for identifying fragment

Table 1 A non-exhaustive listing of companies that offer fragment-based screening and design capabilities

Company	Primary screening method	Secondary technology	Library size
Astex	X-ray, NMR, ITC		1,600+
Beactica	SPR	SPR—titration	2,000
BioFocus	SPR	SPR—titration	1,500
Biosensor Tools	SPR	SPR—titration	1,500
Carmot Therapeutics	Chemotype evolution (tethering)		
Crelux	Microscale thermophoresis	X-ray	1,000
Crown Biosciences	X-ray, SPR	X-ray	3,400
Emerald BioStructures	X-ray, NMR	X-ray	2,000
Evotec	Fluorescence correlation spectroscopy	SPR, NMR, X-ray	24,000
IOTA Pharmaceuticals	SPR, biochemical, and NMR	X-ray	5,500
Kinetic Discovery	SPR	SPR—titration	700
Novalix	SPR array	MS, NMR	24,000
Pharma Diagnostics	Bead-based SPR		
Polyphor	SPR	SPR—titration	1,200
Proteros	TR-FRET	X-ray	18,000
Selcia	Capillary electrophoresis		1,300
Vernalis	NMR, biochemical, SPR, ITC	X-ray	1,400+
Zenobia	X-ray, SPR	X-ray	1,000
ZoBio	TINS[a]	NMR, SPR	1,500

All data were taken from websites, publications, or other publicly available sources

leads. As shown in Table 1, companies now offer a variety of different NMR techniques in addition to X-ray crystallography, surface plasmon resonance, and high concentration biochemical screens. Library sizes and design strategies also differ between these companies, allowing clients to tailor a fragment-based collaboration to the specific needs of the target of interest.

The shift to biologics

Finally, a relatively recent paradigm shift in the industry is an increased emphasis on biologic (e.g., antibody) as opposed to small molecule drugs [22, 23]. This has been accomplished either through internal re-structuring or through strategic acquisitions and mergers. The pull towards biologics mitigates against generic incursion (as the path towards generic "biosimilars" is unclear and likely difficult) and can potentially increase clinical success rates as biologics historically have exhibited lower attrition rates in clinical trials. As fragment-based drug design is by its very nature a tool for the design of small-molecule drugs, the "applicability domain" of FBDD is shrinking in many companies.

For biotechs with an exclusive focus on small molecule drug discovery, this change will have little impact. However, for larger pharma with a changing mix of small molecules and biologics, this move necessitates a critical evaluation of technologies and strategies for small molecule drug discovery. As discussed above, outsourcing some components of small-molecule drug discovery is one approach to redirect internal resources towards biologics. Furthermore, exiting certain disease areas that rely almost exclusively on small molecule approaches (e.g., anti-bacterial and anti-viral agents) can also free up internal resource that can fuel biologics research.

Evolution at Abbott

The implementation of fragment-based drug design at Abbott has evolved over the years to respond to these challenges. Some of these changes are summarized in Fig. 1, where the changes in screening, structural, and

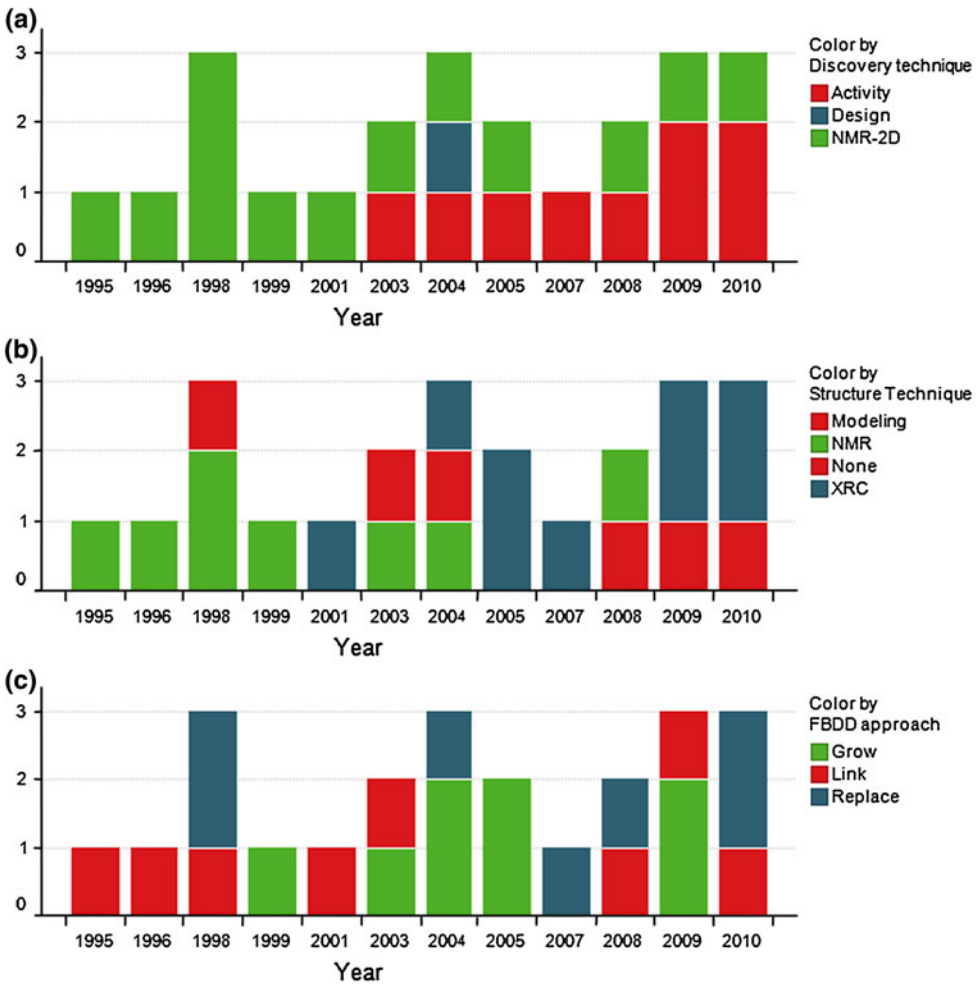

Fig. 1 Evolution of fragment-based **a** screening techniques, **b** structural techniques, and **c** design techniques employed by Abbott over the last 15 years. Shown are occurrences by year where an internal lead series derived from fragment-based screening and design exhibited potency less than 200 nM

design strategies over the last 15 years are illustrated. Before the year 2000, internal successes (defined here as driving a fragment-derived series to a potency better than 200 nM) were dominated by the application of NMR for both screening and structure. However, over the last 5 years, while NMR has continued to play a critical role, activity-based assays has been increased to be used for primary fragment screening. This has been, in large part, due to an evolving target portfolio—especially the increase in kinases that are typically amenable to structure-based design but difficult to routinely obtain for NMR studies. This shift in the target portfolio is also reflected in the observation that X-ray crystallography and modeling have become the dominant structural techniques to aid fragment-based drug design.

It can also be observed from this figure that fragment-linking, the original design concept of SAR by NMR, continues to be applied across this entire timeframe. However, alternative design strategies (such as "growing" or "replacing") have become the more common approached employed in recent years. As high concentration biochemical screens become more popular, it is quite difficult to detect simultaneous binding of multiple fragments, and thus linking as a strategy becomes less viable. This also appears to be true for screening by X-ray crystallography. While there have been several reports of ternary complexes observed via crystallographic screening, these appear to be rare and optimization via linking difficult [24, 25].

Concluding remarks

The pharmaceutical industry is undergoing significant change as it responds to the new and challenging environment for drug discovery and development. As one of the tools in the drug discovery arsenal, fragment-based drug design must also evolve and adapt to meet the changing needs of the Discovery environment. The strategies (both screening and design) for fragment-based lead discovery have blossomed over the last decade—allowing for a highly flexible approach that can be tailored to meet the needs of specific targets. In addition, the explosion in small biotechs offering collaborative FBLD services creates alternative options for larger pharma who can choose to supplement their internal Discovery activities through strategic outsourcing. Such collaborations will be especially important as many pharmaceutical companies are shifting internal resources towards Biologic research, and will need to augment their small molecule discovery efforts with fragment-based screening to maximize the probability of success.

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