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Case study: technology initiative led to advanced lead optimization screening processes at Bristol-Myers Squibb, 2004–2009

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In this paper, we review the key solutions that enabled evolution of the lead optimization screening support process at Bristol-Myers Squibb (BMS) between 2004 and 2009. During this time, technology infrastructure investment and scientific expertise integration laid the foundations to build and tailor lead optimization screening support models across all therapeutic groups at BMS. Together, harnessing advanced screening technology platforms and expanding panel screening strategy led to a paradigm shift at BMS in supporting lead optimization screening capability. Parallel SAR and structure liability relationship (SLR) screening approaches were first and broadly introduced to empower more-rapid and -informed decisions about chemical synthesis strategy and to broaden options for identifying high-quality drug candidates during lead optimization.

Introduction

Lead optimization is one of the most crucial steps within the early drug discovery process, aiming to turn the most promising compounds into early candidate nominations (ECNs) for clinical development [1]. Multiple rounds of SAR testing are needed to optimize and mold initial chemical hits into druggable profiles where every compound has been characterized by numerous *in vitro* and *in vivo* biological tests. During the past two decades, however, the process supporting lead optimization has been significantly challenged by two major industry trends. The first is a significant increase in the number of hits being identified, using multiple high-throughput technology platforms, that then have to be assessed and potentially optimized [2–4]. The second is the growing pressure around increasing the quality and success rate of drug candidates advancing from preclinical research to clinical development [5,6].

The first trend is probably a consequence of the fact that automation has been broadly applied to increase the compound screening capacity significantly at all major pharmaceutical companies, as well as at several academic research institutions [7,8]. This has increased the volume and speed of discovery for initial chemical hits against a wide range of target types. As a result, most HTS groups at major pharmaceutical companies can complete a screening campaign against millions of compounds in their collections in a month or less. This subsequently increases the number of hits that need to be prioritized, optimized and comprehensively annotated in the lead optimization phase.

The second trend has emerged from a drive to increase the number of drug candidates getting through proof-of-concept in the clinic and ultimately progressing to full development. Thus, identifying the key causes for the decline in drug candidate output has become one of the more crucial missions for pharmaceutical companies in recent years. During the past decade, poor clinical safety and lack of efficacy have been the main causes of drug attrition [9,10]. These circumstances have led pharmaceutical companies to work more aggressively to develop effective strategies for improving drug candidate safety and efficacy. One of the potential approaches used to tackle this problem is to gather as much knowledge about target validation and lead molecule qualities during the lead optimization process. The faster and better the lead optimization process is performed, the greater the number of compounds that can be tested per unit of time, and the more-diversified compounds can be developed to gain competitive advantages and provide better 'tool molecules' for target validation and *in vivo* efficacy studies.

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Both of these trends demand a much higher capacity for generating diverse sets of data and the ability to analyze them rapidly before and during lead optimization. However, in 2004 the common screening support models for lead optimization across industry were within project teams at individual therapeutics area. To manage these increased demands, project teams were forced to adopt different methods to triage hits before they initiated full lead optimization activities owing to a lack of robust screening technology infrastructure. Significant informatics filters, data-mining tools as well as templates for druggable and non-druggable characteristics [11] were used to triage screening hits and select potential leads before any actual 'wet biology' testing could be carried out. However, triaging hits based on limited biological data can potentially impede researchers from identifying and optimizing a broad range of leads at the early stages of the drug discovery process. This issue is further exemplified when novel targets with limited literature information are pursued for drug discovery. In this case study, we describe the efforts taken at Bristol-Myers Squibb (BMS) between 2004 and 2009 to build an expertise-centric, technology-integrated and highly efficient lead optimization process to support all drug discovery programs. Harnessing, implementing and expanding diverse technology platforms were key processes required to meet the diverse needs of each therapeutic group and accelerate the delivery of more-detailed biological annotation on every compound undergoing lead optimization at BMS. This, in turn, significantly enhanced our ability to create a comprehensive compound activity data package containing potency, selectivity and liability. Such enriched information enabled a more efficient and faster drug candidate selection process.

Establishing a highly efficient lead optimization process at BMS

Genesis

The strategy for building the technology infrastructure in drug discovery at BMS has always been centered on achieving integrated processes, maximizing efficiency, enhancing capacity and improving timelines [12]. The 'leveraging technology' strategy applied to hit identification since 1999 [13] has generated a fully integrated compound management process and cutting-edge HTS platform for hit identification. In early 2000, high-throughput lead profiling functional capability established at BMS enabled the project teams to conduct *in vitro* profiling including solubility, permeability, stability, ADME, protein binding and cytochrome P450 (CYP) inhibition. Implementation of this high-throughput lead profiling capability during lead optimization successfully demonstrated its use regarding the identification of drug candidate issues related to poor pharmacokinetics (PK) and bioavailability early on [14,15]. However, in 2004 we observed that the *in vitro* screening capacity for assessing SAR was limited in all therapeutic areas at BMS. An urgent need to address this functional gap was identified by the following three drivers.

First, the compound collection at BMS had increased over tenfold from 1998 to 2004. Although this quantum leap was well handled by robust compound management infrastructure [16,17] and expanded HTS capabilities at BMS [15], this trend indeed put significant capacity pressure on the beginning of the lead optimization process owing to significant amplification of verified hit molecules. Therefore, the challenges that confronted the project teams from all therapeutic groups in 2004 were: how to mine HTS data effectively, how to triage verified hits into a manageable size, and how to expand chemical series options – and, more importantly, how to do all of these rapidly before and after lead optimization initiation.

Second, in the period around 2004, high-throughput chemical library synthesis and traditional medicinal chemistry approaches started to converge across the industry [18–20]. Chemists at BMS began searching for ways to simplify synthetic protocols and implement technology platforms to speed synthesis cycle times [19,21,22]. As a result, the lean thinking approach was applied to establish a highly efficient process for focused chemical library generation at BMS. These focused libraries created in real time were used broadly to explore chemical space for ongoing discovery projects during lead optimization. It was anticipated that this approach would lead another wave of compound generation at BMS. Enhancement of lead optimization screening support capability had a crucial role in enabling the deliverables of the BMS chemical technology initiative.

Finally, in early 2000 the BMS research organization became committed to enhancing capability to deliver high-quality drug candidates and enabling a pipeline sustainability strategy. In doing so, rigorous criteria for drug candidate selection were applied broadly at every step of the drug discovery processes at BMS. Identification of functional capability gaps such as lead optimization process became the crucial step for reshaping the drug discovery lead optimization strategy at BMS.

Leveraging technology strategy

An in-house survey conducted in 2004 illustrated that during the lead optimization process >90% of drug discovery programs were using low- and/or medium-throughput manual *in vitro* bioassays. Based on this analysis, BMS developed a strategy with the goals of accelerating the *in vitro* assay data timeline and streamlining the lead optimization process through improved access to technology. The main pillars of the 'leveraging technology' initiative were the following:

i. Commit HTS technology investment for hit assessment and lead optimization.
ii. Establish fully integrated 'lean' lead optimization process supported by a fully accountable organization: a centralized lead evaluation group that co-localizes with each therapeutic group.
iii. Deliver more complete and rapid *in vitro* data packages to enable earlier influence on chemical synthesis and also better decisions about compound selection for *in vivo* disease model testing.
iv. Release therapeutic area scientists from the 'burden' of compound testing enabling them to work on research activities including target identification, target validation and mechanistic studies.

Handing over accountability of *in vitro* assay support for all BMS therapeutic areas to a centralized lead evaluation group was a highly contentious proposal at the time because each project group at BMS had 'ownership' of a project and carried out lead optimization assays using their own methods. Of course, this led to a diversity of approaches and a less efficient use of resources when viewed through an enterprise lens. The challenge would be showing that a centralized lead evaluation group could execute all the diverse

programs needs with the necessary speed, quality and rigor, and do it in a much more efficient way. We decided to analyze the lead optimization process thoroughly and see which parts could be enhanced and centralized in an integrated fashion. We believed that the success of this strategy would rely on establishing a robust lead optimization process, strategic integration of diverse skill sets across research, selective technology investment to meet needs from each therapeutic area, high-quality deliverables of the centralized lead evaluation group and strong partnership with chemistry and biology teams at BMS. More importantly, we committed to achieve these goals under a constrained resource environment.

Designing an enhanced lead optimization process

Assessing SAR for a given chemical series during lead optimization is often conducted iteratively in a focused and linear fashion. Therefore, bioassay accuracy and reproducibility is essential for establishing strong data connectivity from one cycle to another. However, in some cases, modified *in vitro* assay processes must be introduced to accommodate the need to dissect mechanisms of action of a lead chemical series and/or to understand the efficacy required for *in vivo* models. Therefore, an effective lead optimization process must not only support highly repetitive operations in a reproducible manner but also tolerate continual process adaptations simultaneously.

Crucial process components for lead optimization

There were four crucial process components within the lead optimization process after compound synthesis including: compound preparation for assays, bioreagent preparation, bioassay execution and data handling. It was important to establish the capability of each component to maximize the throughput and, at the same time, enable customization of processes according to the evolving needs of the programs. In addition, it would be essential to identify the best technology solution that would minimize the rate-limiting steps for each component without shifting the bottlenecks from one step to another.

Selecting the right technology solutions to accelerate the compound preparation process

Prior to 2004, compound preparation for lead optimization at BMS was all handled manually. Each project group had their own processes to submit, prepare and track compounds for lead optimization. To gain process efficacy, we had to establish technology hardware solutions to standardize lead optimization compound preparations as well as develop informatics tools to link compound flow from submission to assay report in real time. Therefore, three guiding principles have been applied to enable this functional capability.

i. Implementing the 'Six Sigma' concept [23,24] to build a lean and rapid compound preparation process that integrates and synchronizes with downstream assay execution for lead optimization.
ii. Reducing compound consumption for each assay data point to maximize compound usage across multiple assays.
iii. Creating just-in-time compound assay-ready plates to minimize compound precipitation and aggregation, etc. for high-quality SAR support.

In summary, we evolved our existing compound preparation platforms from work stations to fully integrated automation systems, resulting in a 100-fold reduction in compound consumption

TABLE 1

Key implementation milestones of novel and proprietary informatics tools enhanced speed of compound tracking, data analysis, data report generation and record capture

	Novel IT tools	Description	Enabling impact
2004	PlateMaker	Compound submission/sorting/preparation	Just-in-time local compound preparation & distribution
	ToolSet	Assay raw data visualization & quality control (QC)	Rapid data aanlysis & rigorous QC
	CurveMaster	IC50/EC50 data analysis & reporting	Data cycle time reduction
2006	Data extraction	Automated data transfer from detection system to data anaylsis tool	Real-time data viewing & automated data analysis
	Point master	Single or dual point data analysis & outlier Identification	Cost-saving & removal of non-valued added data execution
	Report forms	Assay result extraction & data report generation	Speeding data communication between lead evaluation group & project teams
2009	Panel request	Automated compound ordering & global routing to assay panels	Parallel SAR & SLR assay execution
	Reagent tracker	Cellular & biochemical reagent ordering & inventory management	Just-in-time cellular & biochemical reagent generation
	Notebook generator	Automated data transfer from CurveMaster to electronic Lab notebook	Increases Efficiency of data record capture & compliance

for each assay data point, a tenfold increase in compound capacity and a sixfold speed enhancement in preparing compound serial dilution plates. Novel in-house informatics tools including PlateMaker and Panel Request (see Table 1) were also delivered to enable automated compound submission, sorting, preparation and routing to assay execution and data reporting.

Enhancing just-in-time cellular reagent preparation to support assay execution

In 2004 >90% of discovery programs at BMS required at least six weeks to complete their *in vitro* assay data packages. In addition to suffering from insufficient assay capacity and low assay throughput, limited cellular reagent availability was a key factor that forced the lead optimization project teams to choose a 'vertical' or linear screening approach. The overall screening tier was therefore designed around the throughput of the rate-limiting *in vitro* assays. This kind of screening approach restricted the ability to help chemists make rapid decisions about which compounds to synthesize next at lead optimization. Thus, in 2004 the goal at BMS was to transition this traditional 'vertical' screening testing tree into a more 'horizontal' or parallel screening approach. To achieve this goal, we had to identify a solution to help accelerate the cellular reagents delivery process in addition to the compound preparation step all within a centralized group.

To establish a 'horizontal' screening testing tree for lead optimization it was essential to create high capacity to advance cell-based assays from second- to first-tier screening trees. Two important activities were initiated to assess our technology options. First, we analyzed the industry-wide experience of working with various cellular reagent technology platforms that supported cell-based assays. Second, we detailed the specific cellular reagent needs of the lead optimization programs at BMS in terms of quantity, cycle time and ability to work with multiple cell lines in parallel. Based on this analysis, we implemented two crucial solutions. The first was to introduce a robust technology platform, SelecT™, to enhance the capacity for producing just-in-time cellular reagent supplies. More importantly, we developed multiple quality control checkpoints to ensure the reproducibility and quality of cellular reagents that were produced by SelecT™. The second solution was to use cryo-preserved cells in our process [25,26] to improve assay flexibility and to reduce the overall manpower resource demands for supporting daily cell culture routines. Together, these two solutions resulted in a quantum leap in the cell culture capability for lead optimization at BMS and enabled the lead evaluation group to meet a 12-fold increase in cell-based assay demands from 2004 to 2009.

Today, we can respond more quickly, flexibly and efficiently to project teams requiring heavy cellular reagent needs during lead optimization. These technology platforms implemented at BMS have permitted us to drive the paradigm shift: moving cell-based assays from the second tier to the first tier for SAR screening testing trees. The data in Fig. 1a indicate that: (i) the number of individual lead optimization programs supported by the lead evaluation group increased from ten in 2004 to 70 in 2009; and (ii) the percentage of programs using biochemical and cell-based assays as the first tier increased from 20% in 2004 to 80% in 2009.

Developing an in vitro *lead evaluation assay panel screening strategy*

It is clear that robust and reproducible *in vitro* assay execution capability is the key enabler for the iterative compound design and synthesis for every high-quality SAR process. Realizing this, the primary goal in 2004 was to establish a centralized lead evaluation group that could support all of the lead optimization programs at BMS efficiently. The first mission of this group was to automate individual target assays to differentiate selectivity between subtypes of a specific target family as quickly as possible. To gain assay execution efficiency, the panel screening strategy emerged as the most optimal way to support lead optimization at BMS.

The origin of the lead evaluation panel screening strategy was target-based assay panels. Identification of common assay formats was the key for reducing assay cycle time for similar target classes, such as G-protein-coupled receptors (GPCRs), kinases, nuclear hormone receptors, proteases and ion channels. This panel screening strategy enabled us to achieve high levels of synergy among different discovery programs. For example, synergy could be achieved by cross-fertilizing lead chemical series from one program to another, expanding proprietary chemical space from target-related families, delivering tool molecules for target validation and addressing program-specific issues.

This target-based panel screening strategy served as a firm foundation to grow the lead evaluation function at BMS and had a tangible, positive impact on the BMS discovery portfolio. In 2008, we expanded the target-based panel screening strategy to support structure liability relationship (SLR) in parallel with SAR [27,28]. As an example, we introduced drug safety screening panels that addressed central nervous system (CNS) liability and cardiotoxicity across various programs. Since then, we have continually added newly identified targets to lead evaluation assay suites to apply them broadly across multiple lead optimization programs at BMS. The target-based panel screening strategy significantly enhanced our ability to address SAR/SLR issues across multiple and different lead optimization programs.

The parallel biochemical and cell-based assay screening approach implemented at BMS in 2009 (Fig. 1a) demanded further evolution of the panel screening strategy from target panels to disease panels (Fig. 1b). Enhancement of the cellular reagent support capability enabled a transition to a disease target panel approach such as the immunology panel containing multiple immune markers [tumor necrosis factor (TNF)α, nuclear factor (NF)κB and interleukin (IL)2, etc.] and immune cell lines (T cell, B cell and macrophages, etc.). This approach permitted screening of multi-mode functional assays within a disease-relevant cellular context and also the use of multi-parameter endpoint *in vitro* assays. In summary, the panel screening strategy catalyzed lead evaluation functional growth and guided the technology options for rapid and efficient lead optimization processes at BMS.

Harnessing state-of-the-art technology platforms to drive the panel screening strategy

It is well known that automation platforms have a vital role in supporting screening campaigns for hit identification [4,15,29]. The hardware used to configure an automation platform for hit identification varies from one system to another. Nevertheless, all such automation systems do have some common features. These

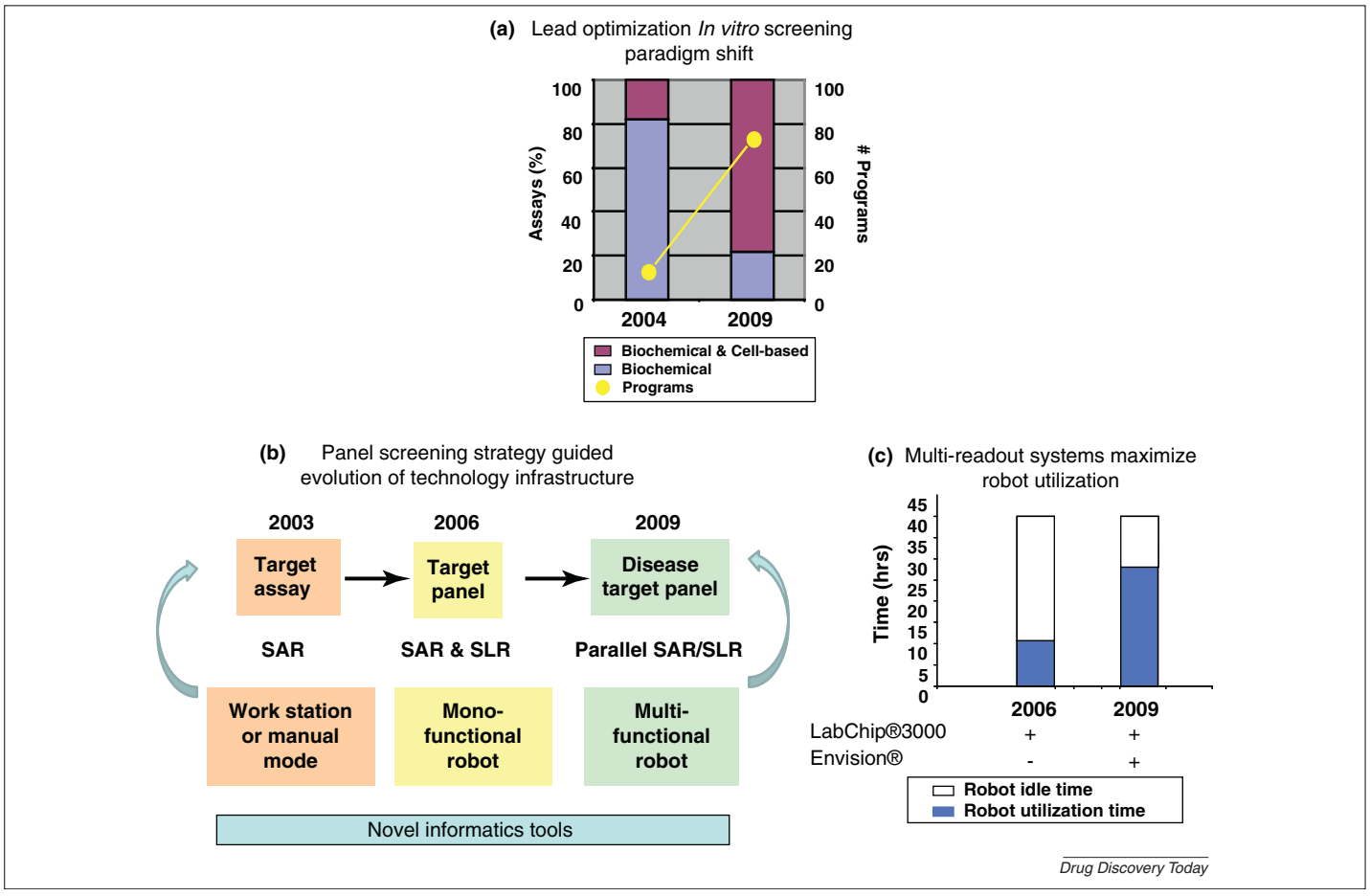

FIGURE 1

The lead evaluation panel screening strategy guided lead optimization technology infrastructure. **(a)** The number of lead optimization programs (yellow dot) supported by the lead evaluation group increased sevenfold from 2004 to 2009. In 2004, 80% of SAR assays were biochemical assays (blue bar). By 2009, cell-based assays were elevated to the first tiers of screening trees and conducted in parallel with biochemical *in vitro* assays (red bar). **(b)** Tailored automation systems and implemented novel informatics tools met the needs of the panel screening strategy, which evolved through three phases including target assay, target panel and disease panel strategy. Evolution of automation systems from a work station in 2003 (orange box) to a mono-functional robot in 2006 (yellow box) and a multi-functional robot in 2009 (green box) enabled BMS transition from an SAR to a parallel SAR and SLR screening strategy. **(c)** Addition of an Envision® multi-readout detection system in the kinase assay robot containing a LabChip®3000 enabled the support of kinase and cell-based cytotoxicity assays in parallel, which increased the system usage from 10 h per week in 2006 to 30 h per week in 2009.

include four basic components: a robotic arm, plate and tip carousels, liquid handlers and a detection system. One important question was: can we use similar automation systems at BMS to support the lead optimization process? The answer was that we could take advantage of the fundamental components of the screening automation platforms but we had to modify their configuration to meet the needs of the panel screening strategy for lead optimization. This is owing the fact that HTS platforms for hit identification are configured to test millions of compounds through one assay format, whereas a lead optimization screening platform would have to be configured to test hundreds or thousands of compounds through multiple assays in parallel (Fig. 2b).

As a result, two crucial solutions were introduced to the automation systems used to support lead optimization at BMS. First, identification of rapid dispensing tools in 2006 became crucial for enabling simultaneous and rapid handling of multiple bioreagents needed to support lead optimization assay panels. Non-tip dispensing apparatuses, including Multidrop®, Flexdrops™ and Multidrop®Combi, were the best types of liquid handlers used to dispense multiple bioreagents per assay panel run. This transition to non-tip-based liquid handling systems significantly enhanced the assay execution speed and reduced the dead volume of bioreagents. Second, to implement the disease-based panel screening strategy, in 2009 the automation systems were upgraded further to support multi-mode readouts for biochemical and cell-based assays. As a result, multi-mode readers such as Envision® were integrated with the automation systems containing a mono-detection system such as LabChip®3000. These two solutions enabled us to transition from a mono-functional robot to a multi-functional robot with the ability to run different assay suites in parallel (Fig. 1c). More importantly, this newly developed automation configuration significantly reduced robot idle time by 20 h and enhanced assay capacity by 30% without additional capital investment. Currently, this multi-functional robot enables the screening of >40 kinase biochemical assays in parallel, weekly, with 14 cytotoxicity cell-based assay panels. These two technology solutions led to several advanced lead optimization automation systems, which laid the foundations to support the evolution of our panel screening strategy at BMS.

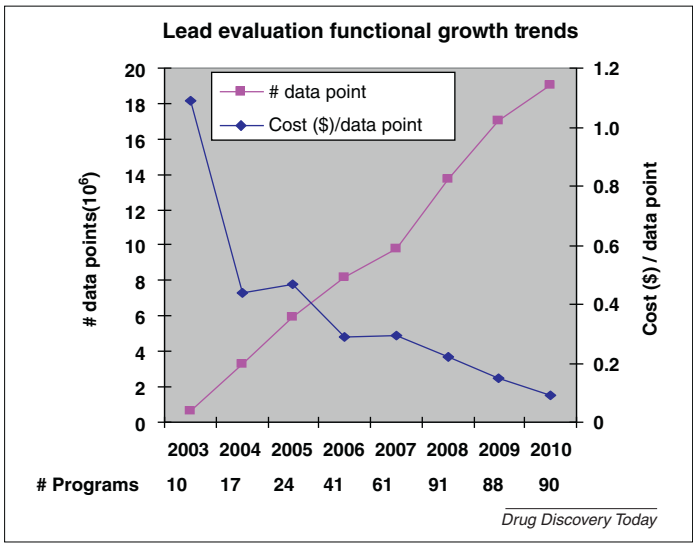

FIGURE 2

The Leveraging Technology Initiative led to lead evaluation functional growth. Owing to technology innovation, the lead evaluation function grew 30-fold in the number of data points screened. By contrast, the assay cost per data point was decreased tenfold by 2010, which enabled the lead evaluation group to increase ninefold program support capacity from 2003 to 2010.

Integrating novel informatics tools to enhance overall lead optimization efficiency

Since we began the initiative to 'leverage' technology infrastructure for the lead optimization process at BMS, developing and implementing novel informatics tools became one of the key tasks required to advance each phase of the panel screening strategy (Table 1). The goals for implementing these informatics tools were to:

i. accelerate decisions on data QC processes (e.g. created 'ToolSet' in 2004 for rapidly monitoring assay data quality in real-time);
ii. reduce non-value-added workload (e.g. developed 'Point-Master' software in 2006 for rapidly assessing compound activity using one or two compound concentrations);
iii. streamline assay workflow from one process to another process (e.g. created a data extraction informatics tool for automatically loading data in 2006);
iv. capture standardized assay reports electronically (e.g. applied Report Forms in 2006 and established Notebook Generator in 2009); and
v. remove process bottlenecks (e.g. launched a 'Panel Request' tool for compound submission, preparation and compound routing to assay panels in 2009).

These novel informatics tools enabled the overall capability and operational efficiency of the lead evaluation group.

Conclusions

A modernizing lead optimization process has been built at BMS over the past six years. Subsequently, the company's *in vitro* biochemical and cellular lead optimization screening capability has been significantly enhanced. Expansion of the lead evaluation panel screening strategy between 2004 and 2009 has delivered impact beyond our initial anticipation. It has fundamentally changed how BMS performs lead optimization. The impact of this 'leveraging technology' strategy has been clearly demonstrated in the following four ways.

First, the Leveraging Technology Initiative at BMS enabled the establishment of a centralized lead evaluation function with greatly enhanced productivity and capacity over the former operating model (i.e. individual laboratories within different therapeutic areas) for the lead optimization process. By 2010, our panel

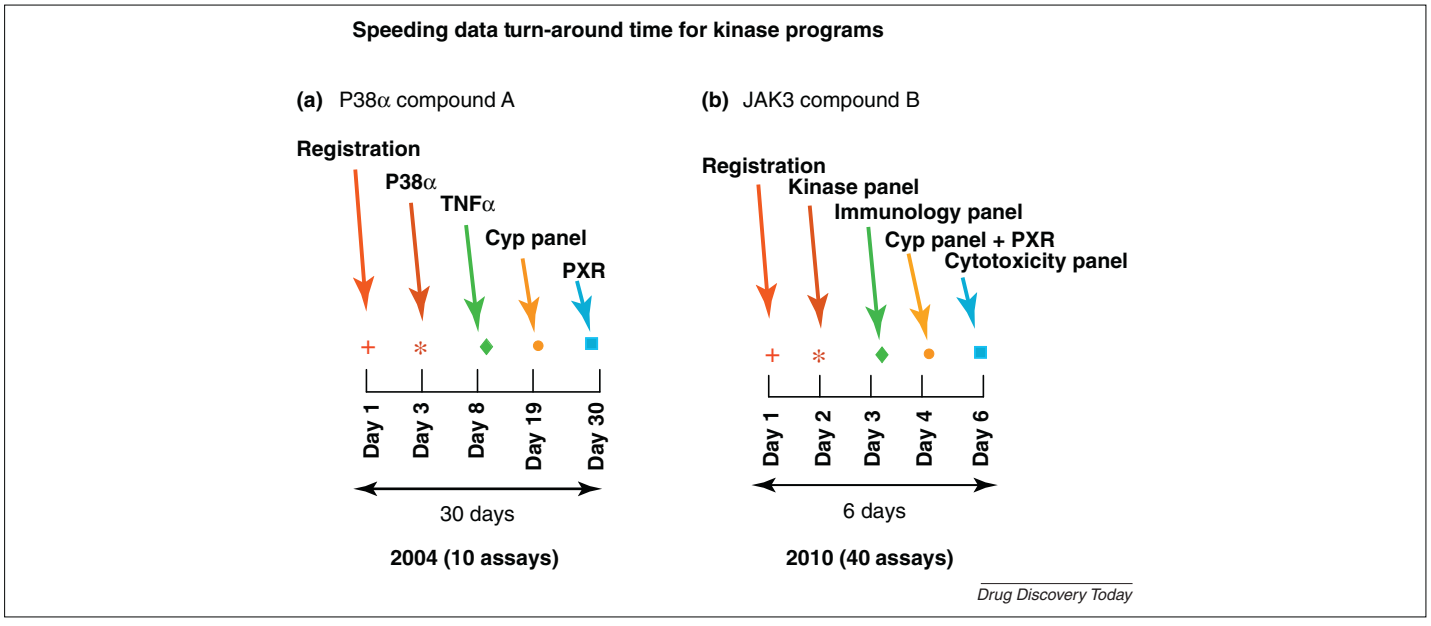

FIGURE 3

Delivering rapid and comprehensive *in vitro* data packages for kinase program lead optimization. **(a)** The *in vitro* assay testing timeline for compound A of the P38α program was 30 days in 2004 from compound registration to completion of a ten assay data package. **(b)** In 2010, the *in vitro* assay testing timeline for compound B was six days for the JAK3 kinase program to receive a 40 assay data package after compound B was registered.

screening strategy succeeded in delivering *in vitro* assay data packages to >90 discovery projects (Fig. 2). Continuous process optimization resulted in tenfold cost reduction per data point by 2010. The centralized lead evaluation group at BMS produced 30-fold more data points by 2010 (Fig. 2). The primary assays used to monitor SAR for a typical program compound during lead optimization increased from one assay in 2004 to five assays in 2009. These were achieved with only a twofold increase in manpower. The Leveraging Technology Initiative definitely delivered what it promised to deliver and more.

Second, the Leveraging Technology Initiative at BMS not only increased the capacity but also enhanced the speed of delivering comprehensive data packages to the majority of discovery programs. For example, the major challenge in kinase drug discovery is to overcome selectivity issues. However, in 2004 our ability to support kinase programs was limited. Approximately 30 days were required to obtain a complete *in vitro* data package for a typical kinase program compound such as 'compound A' from the P38α program (Fig. 3a). Within these 30 days, ~200 additional program compounds were made by the chemistry team before completing the *in vitro* biological tests for compound A. Consequently, many of the *in vitro* results obtained for compound A influenced neither the *in vivo* compound selection nor the next-generation compound synthesis strategy. To address kinase selectivity issues, only crucial compounds were screened against a broad kinase selectivity assay suite using a contract research organization. By contrast, by 2010 all kinase program compounds at BMS such as compound B from the JAK3 program (Fig. 3b) were evaluated using kinase selectivity assays. In addition, 20 cell-based assays including cytotoxicity and immunology assay panels plus ADMET profiling suites were also screened in parallel. This comprehensive data package only took six days to be completed. The speed of data package generation was increased fivefold and the number of kinase assays screened increased fourfold. This greatly enhanced speed of data delivery for the kinase panel enabled earlier influence on the next generation of compound synthesis. The high-through-

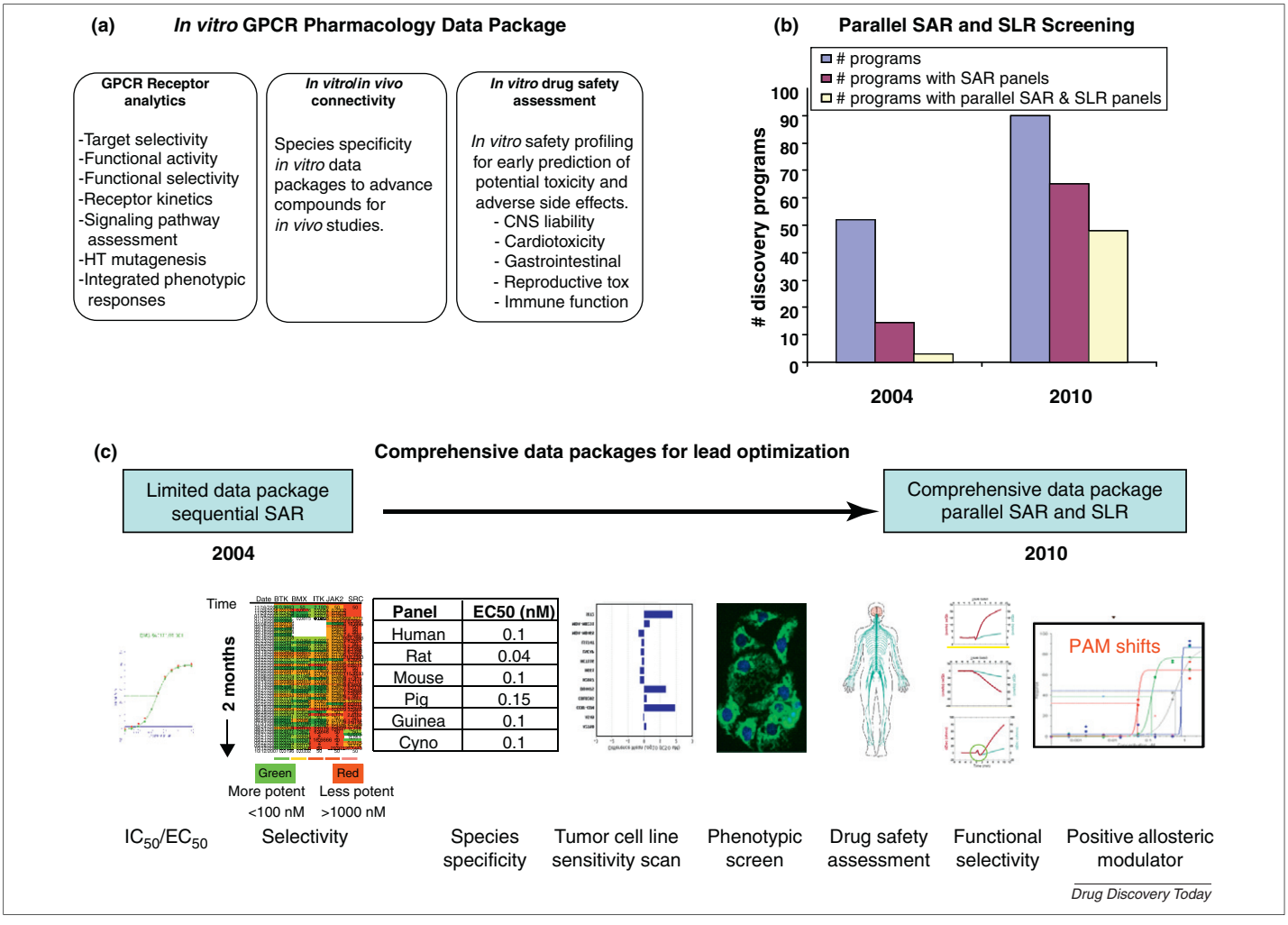

FIGURE 4

Modernizing processes at BMS led to paradigm shift in lead optimization. **(a)** Comprehensive *in vitro* GPCR data packages enable informative decisions on hit assessment, lead optimization, *in vivo* compound selection and drug candidate nomination. **(b)** The parallel SAR and SLR screening strategy enhanced capability to address selectivity and liability at the early stage of drug discovery programs. In 2010, lead evaluation enabled parallel SAR and SLR support for ~70% of drug discovery programs (yellow bar) with a 25-fold increase compared with 2004. **(c)** The SAR lead optimization data packages evolved from limited IC_{50}/EC_{50} datasets obtained through sequential SAR in 2004 to comprehensive parallel SAR and SLR datasets in 2010 to provide as much valuable information early on to impact the drug discovery programs positively.

put technology infrastructure supporting the kinase portfolio at BMS enabled rapid growth of the kinase panel to navigate the kinome and to facilitate the cross-fertilization among kinase discovery programs.

Third, the Leveraging Technology Initiative significantly enriched the *in vitro* data content for each lead optimization program. Fig. 4a provides one example of how the lead evaluation group handled a paradigm shift in supporting GPCR drug discovery programs at BMS. We progressed from measuring one ligand and single activity in 2004 to assessing multiple ligands, dissecting differential pharmacology and understanding multiple mechanistic events for GPCR targets by 2010 (Fig. 4a). In addition, species selectivity assay panels (Fig. 4a) were elevated to the first screening tiers for >90% of GPCR discovery programs across the discovery portfolio. Significantly, this has led to enriched information enabling early decisions on compound scale-up and *in vivo* study planning. High-throughput assay suites containing GPCRs, enzymes, transporters, ion channels and nuclear hormone receptors related to CNS liability, cardiotoxicity and other off-target liabilities were also developed and implemented in 2008. These assay panels closed screening gaps in early drug safety assessment.

Fourth, the Leveraging Technology Initiative led to significant resource savings across discovery at BMS. Scientists previously conducting *in vitro* assays manually during lead optimization were available for new discovery programs. This impact can be attributed to the fact that the number of discovery programs at BMS increased about twofold from 2004 to 2010 (Fig. 4b). A parallel SAR and SLR screening approach was first and broadly introduced at BMS as a result of streamlining the lead optimization processes, expansion of the panel screening strategy and implementation of novel informatics tools. By 2010, the parallel SAR and SLR panel screening approach was applied to ~70% of the discovery programs. By contrast, only two programs in 2004 piloted the parallel SAR and SLR panel screening approach.

In summary, the Leveraging Technology Initiative not only laid a solid technology foundation that enhanced the capacity and speed for lead optimization but it also seeded many advanced technology platforms that positively impacted discovery programs. After several years of efforts in this arena, the lead evaluation group modernized lead optimization processes at BMS. The lead optimization screening testing tree at BMS evolved from a sequential screen strategy in 2004 to a parallel SAR and SLR screening strategy in 2010 (Fig. 4c). This approach enabled an iterative cycle guided by a rapid and complete SAR and SLR data package for lead optimization. Today, this comprehensive data package includes target selectivity, species specificity, cellular functional activity, drug safety assessment and phenotypic readouts in physiologically relevant cell lines. Going forward, this robust lead optimization process at BMS will continue to take an essential role in empowering earlier decisions, maintaining pipeline sustainability and driving high-quality drug candidates for clinical development.

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