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Hypothesis driven drug design: improving quality and effectiveness of the design-make-test-analyse cycle

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In drug discovery, the central process of constructing and testing hypotheses, carefully conducting experiments and analysing the associated data for new findings and information is known as the design-make-test-analyse cycle. Each step relies heavily on the inputs and outputs of the other three components. In this article we report our efforts to improve and integrate all parts to enable smooth and rapid flow of high quality ideas. Key improvements include enhancing multi-disciplinary input into 'Design', increasing the use of knowledge and reducing cycle times in 'Make', providing parallel sets of relevant data within ten working days in 'Test' and maximising the learning in 'Analyse'.

Introduction

Progress in all scientific endeavour is based on the ability of the researcher to construct and test hypotheses, carefully conduct the experiment and analyse its associated data for new findings and information. In drug discovery, this central process is known as the design-make-test-analyse (DMTA) cycle. Our previous attempts to improve the synthesis and purification (or 'Make') contributions have been described [1,2]. However, the acceleration of a drug project requires a smooth and rapid flow of good quality ideas, aligned to the project strategy and required candidate profile, through the DMTA cycle [3–5]. Each individual step relies heavily on the inputs and outputs of the other three components. Therefore we hoped to improve the speed and quality of hypothesis-testing by tightly integrating the DMTA workflow across traditional functional boundaries represented by chemistry, biology, DMPK, safety and other disciplines. Herein, we report our findings and results.

Design

During the course of a project different issues are inevitably identified. Hypotheses are generated to address these issues and compounds are designed to test the hypotheses in an attempt to solve the problems or build understanding. Because the quality of a compound is fixed at the point of design, we considered it important to apply more rigour and quality control at the design stage where the cost of ideation is low, but the probability of success is variable and the potential impact on outcomes is high.

In the past, 'Design' has often been led by the medicinal chemist or chemistry team, and has sometimes focussed on producing a large number of synthetically tractable molecules designed against a small number of readily accessible test parameters such as *in vitro* potency. To improve the quality and effectiveness of our work and to achieve multi-parameter designs, then multi-parameter and multi-disciplinary perspectives would be required at the point of conception. To meet this challenge dedicated 'Design Teams' consisting of competence from medicinal chemistry, synthetic chemistry, computational chemistry and DMPK were introduced (Fig. 1). Other competencies are included on an issue-driven basis. This diverse membership ensures all parameters and issues are understood and all knowledge and data are exploited effectively. Molecular structures and compound properties, including physicochemical properties, are central to discussions and therefore need to be understood by all team members. With a shared responsibility for the quality of design, Design Teams ensure that all the required understanding, perspectives and insights are taken into consideration before the larger investment of resources to synthesise and test the molecules.

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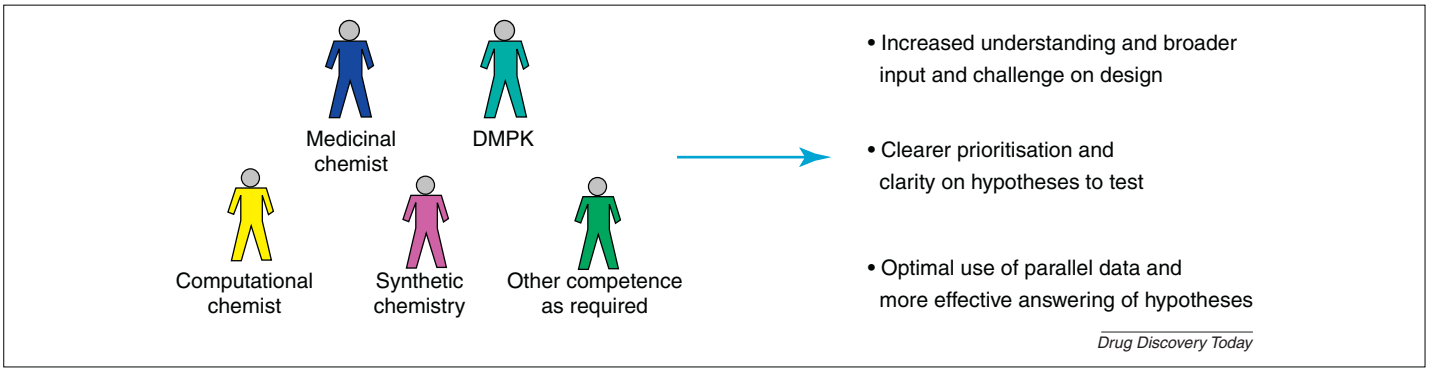

FIGURE 1

Competencies involved in the Design Team and key observed benefits.

The introduction of Design Teams required more open and collaborative behaviours and demanded close communication between team members. It is also vital that the members prepare thoroughly for discussions to ensure sharing of their data and knowledge in a clear and transparent way to avoid barriers to effective collaboration. Furthermore, it is important that there is an open climate where members can challenge one another constructively and prioritise ideas so effective, good quality decisions are made and the best ideas progress. Good ideas around new hypotheses and specific compounds can also originate from outside the Design Team, in particular from chemists, and this should be encouraged. However, all ideas, regardless of source, needed to be reviewed in the Design Team to maintain consistent quality.

To facilitate idea capture from all sources, formulate good testable hypotheses, provide consistent quality review, and track progress of ideas through synthesis and testing to a recorded outcome, a tool was needed. Previous experience with simple solutions, such as spreadsheets and shared documents on a network, has shown that they do not always facilitate shared learning because they can easily become out of date, duplicate copies get produced, and information retrieval can be difficult. A main drawback of these solutions is that they require additional work, which is omitted when time pressures are felt. Thus, we created a tool that was not additional but fully integrated into the DMTA workflow.

The new tool inspiration was obtained from emerging Web 2.0 technologies, such as wikis, blogs and social networks [6], which facilitate communication and collaboration by enabling multiple users to constantly update and edit content, whilst bringing in additional data from multiple sources, and presenting this in a way that can be easily understood by the users. Hence, it was ensured that people always viewed the most up to date information and that it was easily accessible from any networked PC. Although others have created similar tools [7], ours seeks to improve the usability and integration into all stages of DMTA. The tool was prototyped using wiki-based technology (named 'Compound Design Database') [8] and it was subsequently delivered as a full production tool ('Design Tracker'), keeping the same philosophy but without the limitations of the wiki environment (Fig. 2).

Each design hypothesis is recorded and supporting information can be added to assist subsequent analysis. All ideas are captured, hence avoiding repetition or loss of ideas and enabling others to build on ideas to further increase quality and novelty. The system tracks the design hypothesis as it progresses from attachment of compounds for synthesis through selection of tests for each compound to recording the analysis outcome and the conclusion drawn. By fully integrating the Design Tracker tool into the DMTA workflow minimises the extra effort to track the progress and collect data whilst maximising learning from each design set, facilitating decision-making and helping to generate the next hypotheses.

To judge the quality of design sets and prioritise between ideas, all available methods to predict properties, such as primary pharmacology, ADME and *in vitro* safety outcomes are used before synthesis is initiated [9]. The importance of physicochemical properties, such as $c\log P$, $\log D$, molecular weight and polar surface area to balance all properties required in a successful drug candidate has been reported extensively [10–15]. As a result, compound design has been driven harder into this 'optimal' area of physicochemical space whilst still enabling room outside when there is a good reason or hypothesis [16]. This has, for example, resulted in a significant improvement in the lipophilicity profile of compounds synthesised over the past 4 years (percentage of compounds with measured $\log D < 4$ increased from 53% to 82%). Whereas previous improvements in synthesising compounds with a low predicted potency at the *hERG* encoded potassium channel have been sustained (>90% of compounds have predicted *hERG* $IC_{50} > 3$ μM over the past 4 years) [17]. Compounds with predictable problems can be deprioritised by the Design Team, but it is essential that appropriate feedback is provided to the originator. This enhances learning, encourages generation of new ideas and enables open challenge in case of disagreement.

Despite improvements in predictive models these are still far from perfect. Ideas outside the desired project design space must also be encouraged to provide opportunities to discover the unexpected and learn something new [16]. However, if Design Teams progress such ideas after appropriate consideration they will do so with greater understanding of potential liabilities, which can be rapidly tested and assessed.

Make

Synthesis (and testing) is labour intensive in contrast to design, emphasising the importance of high quality design of compounds for synthesis. However, the value of an elegant design will only be realised if the compounds can be made and purified, thus high quality synthetic chemistry is essential. Hence, it is imperative that chemistry teams are highly skilled in synthetic chemistry, and that all knowledge is fully used before deciding and embarking on a

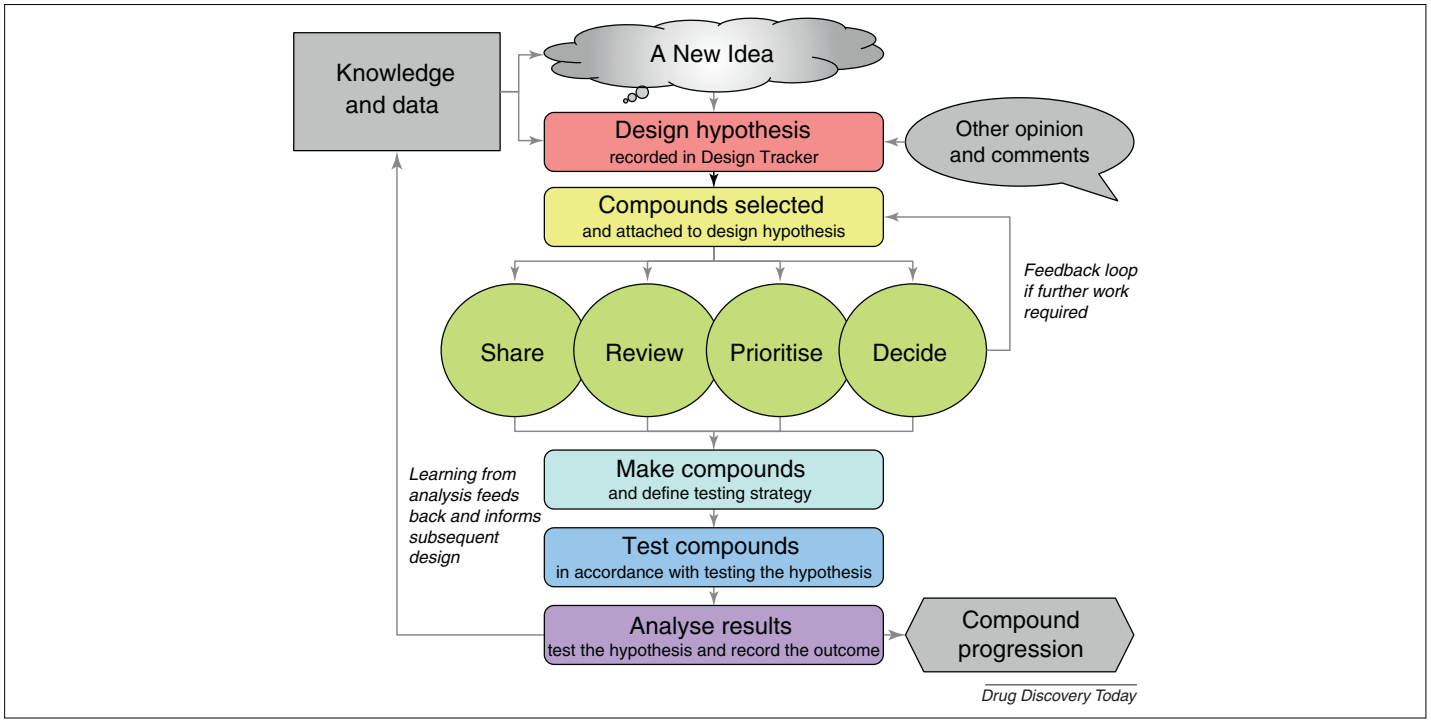

FIGURE 2

Workflow of Design supported by the 'Design Tracker' tool.

synthetic route [18]. This will maximise the chances of succeeding in the first synthetic attempt, and finding a robust route to deliver the product in a high yield and within a short time.

Our previous efforts to improve both the speed and quality of 'Make' have been reported [1,2]. Key improvements were identified including: first, maximising all knowledge before synthesis by introducing forward looking chemistry meetings; second, reducing lead times and their variation through visualising and reducing work in progress and more cooperative team work; and third, increasing the quantity of compound made to avoid unnecessary delays due to resynthesis. This work was complemented with significant improvements in the purification services to increase flexibility, reduce cycle times and increase quality of the delivered samples. These improvements led to significant reductions in lead times and variation, for both synthesis and purification (Table 1).

Since implementation, to ensure continuous improvements are made, we focused on enhancing the supporting infrastructure for chemists to reduce time spent on non-value adding activities. This includes, making routines for standard laboratory procedures easily available, enhanced ordering and stocktaking of chemicals, improvements in maintenance and upkeep of instrumentation for analysis and purification and chemists assembling and making

TABLE 1

Objectives to make the contribution of 'Make' (synthesis) to the DMTA cycle more effective and data demonstrating the progress of the objectives

Objective	Before implementation (2007–2008)	After implementation of first set of improvements (2008)	After implementation of further improvements (2010)
Reduce lead time for synthesis (working days)	Median: 17[a]	Median: 9[b]	Median: 8[c]
	Mean: 23[a]	Mean: 13[b]	Mean: 12[c]
Reduce lead time for plate purification[d] (working days)		Median: 5	Median: 5
	Range: 10–22	Range: 4–7	Range: 3–7
Reduce lead time for single compound purification[e] (hours)	21	4	4
Increase quantity of compound made in first batch[f] (% >33 μmol)	~60%	~65%	~70%

[a] Data from 6 lead optimisation (LO) projects [1].
[b] Data from 15 LO projects [1].
[c] Data from 7 LO projects.
[d] Data from plate purification process used to purify sets of compounds and libraries from lead generation and lead optimisation projects [1].
[e] Data from single compound purification service [2].
[f] Data from 5–6 lead generation and 10–12 LO projects run in parallel.

robust preferred procedures for synthetic transformations that can be applied to a wide range of substrates widely available in the electronic laboratory notebook. All this was further underpinned by enhancing transparency and team work within and across chemistry teams, including sharing practical solutions in short 'Tips & Tricks' sessions. The combined impact has resulted in improved lead times and increased batch one quantities (Table 1). In parallel, both productivity as measured by reaction starts and compounds synthesised, and quality (synthesis of information rich compounds with more drug-like physicochemical properties) has been increased.

Test

Ullman and Boutellier [3], defined the DMTA cycle as being composed of an input-dependent process ('Analyse' and 'Design') and an input-independent ('Make' and 'Test') process. It was proposed that the input-independent process could be measured on process quality, on-time delivery, variance of delivery and turnaround times, and the greatest efficiency gain could be made by focussing on decreasing long lead times and high variances in 'Make' and 'Test'.

The key objective for 'Test' was defined as timely delivery of relevant data for all specific project hypotheses. The objective for 'Test' was therefore set to deliver 80% of all *in vitro* data within ten working days after ordering. This included delivery from compound management facilities, testing, raw data capture and refinement, quality control (QC) checks, and uploading to the corporate data repository. To meet this demand assays needed to be run weekly and have a capacity to meet the 'normal' demand from the Design Teams. When this new screening process was rolled out the lead times for DMPK and physical chemistry assays, and their variation, gradually decreased over a 2-month-period (Fig. 3). Over the past 10–15 years the capacity to screen compounds within bioscience and ADMET [19–21] has dramatically increased. Using these technical advances, screening paradigms have historically been implemented based on serial test cascades where information is collected in a series of steps [22–25]. As screening capability increased further there was a shift to a parallel testing process for *in vitro* data [23,24], with the primary motivation usually being time saved in the optimisation phase. However, loss of information is likely to be the most crucial liability of the serial test cascade, because each step is used as a filter to remove compounds. The purpose of compound filtering is cost saving for testing, but the disadvantage is a decrease in the breadth of project relevant information available for each design cycle [25–27]. The use of parallel data for design opens up chemical space that would have been filtered out in serial testing. Although Fig. 3 shows the time gain after introduction of weekly scheduling of assays, it also shows that shortening the assay cycle times improved the synchronized delivery of complete sets of parallel data. We considered this consistent delivery of data as the first of two key requirements in enabling multi-parameter design.

It was not obvious that parallel data delivery in itself would automatically meet the basic objective for screening (i.e. timely delivery of relevant data for specific project hypotheses). Advances in screening have mainly been technology driven and thus screening cascades have tended to be populated by a small number of automation friendly and cheap assays. Although this was a major improvement, it does not in itself guarantee delivery of what is truly required to optimally drive design in a given project. For example, take a project lacking *in vivo* exposure due to metabolic instability in the compound series. In general, metabolic stability in microsomes, which is a commonly automated test assay, will provide relevant data to assess this. However, if the instability is caused by phase II metabolism then this assay will not provide the insight and information required by the project. Thus screening in hepatocytes would be the relevant assay. Furthermore with metabolic instability, driving design requires a structural understanding of the metabolic

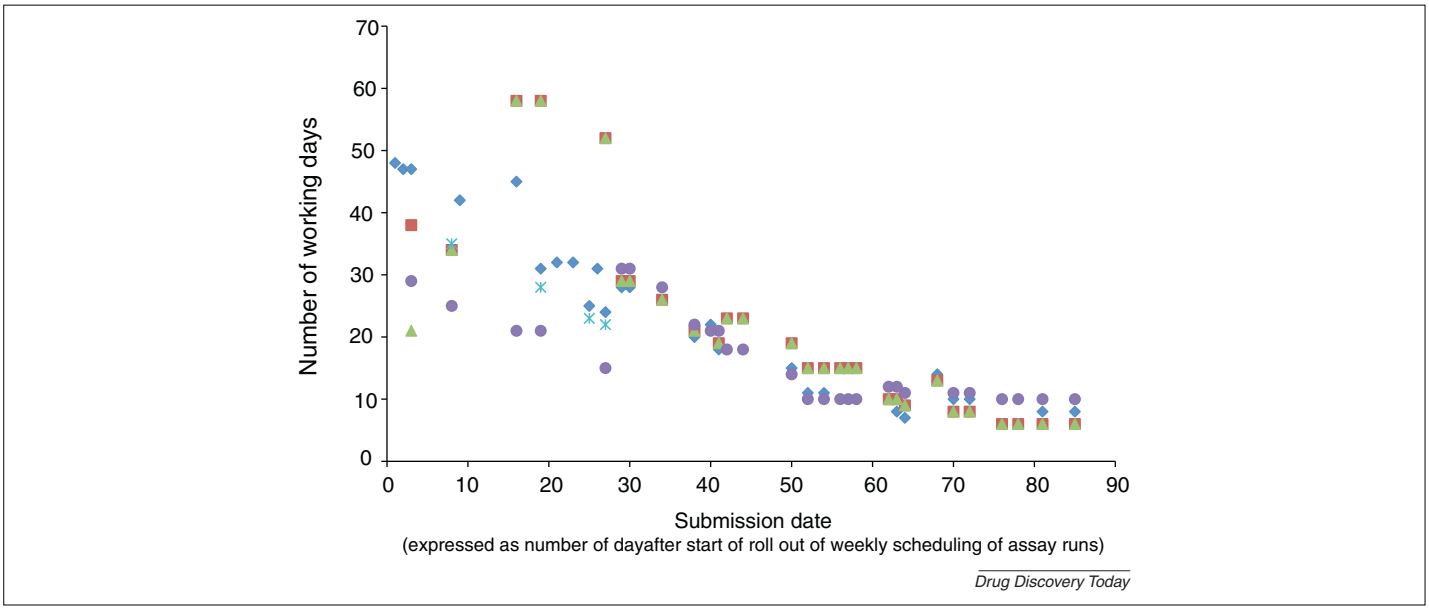

FIGURE 3

Effect on lead times for the key DMPK/physical chemistry assays in a lead optimisation project in the DMTA cycle during the roll out of the weekly scheduling of the assays. DMTA: design-make-test-analyse. ◆ Solubility; ■ metabolic stability in rat microsomes; ▲ metabolic stability in human microsomes; ● Caco2 permeability; ✳ pK_a.

soft spot, thus requiring metabolite identification as part of the screening cascade.

The combined criteria for 'Test' were thus defined as delivery of data sets with 10-day cycle times, where each dataset would be individualised by projects based on their specific design hypotheses. The change process was started by defining a set of *in vitro* assays for running weekly based primarily on what was available that could meet the expected capacity. Subsequently, 'Voice of the Customer' activities revealed several other assays considered crucial that lay outside the required 10-day cycle time. An example was cytochrome P450 (CYP) inhibition, where reversible inhibition had been part of the first wave as a manual assay and then automated in a second step. Feedback, however, highlighted that several projects had issues with time dependent inhibition. In response, higher throughput and technically facile assays were developed resulting in an expansion of the assay package. Today an array of 15–20 DMPK/physical chemistry assays are running weekly to meet the most common needs of the projects. Bioscience screens are of course more project specific, but also the crucial needs of the project determines if assays, including primary, secondary and selectivity assays, are run in parallel.

The shift to a new screening paradigm affected how the test organisation functioned. To deliver all the required parallel screening assays, dedicated teams applying robust processes were required. This change started within DMPK but was followed in bioscience by the creation of primary screening teams. The teams were an important part in minimising handovers, which had been identified as one of the major non-value adding components contributing to long lead times. The shift also spawned continuous improvement activities across the test organisation, the primary focus to (i) secure agreed turnaround times through introduction of visual planning, individual ownership of assay quality and team ownership of weekly project deliveries, (ii) expand the number of available assays, and (iii) improve assay quality through expanded validation work.

Analysis

For DMTA to work at its most efficient data must be rapidly turned into knowledge. Thus, performing the right analysis, aligned to the stated hypotheses, is essential for learning and the ability to make rational decisions that lead back to 'Design' and the statement of a new hypothesis. 'Analysis' is therefore essential and is a key part of the DMTA process. It should be planned for already at the point of design where each hypothesis should have clear criteria for success, such as improvement in a stated property that is not detrimental to others. It is then important to select compounds for synthesis that enable clear decision making around the success of the hypothesis. Whether this is done by designing focussed libraries or by making bespoke compounds, all the ideas that contribute to design are stored. Compounds are frequently designed to test the effect of a newly proposed substructure. To facilitate analysis, these can be defined as matched-molecular pairs to current benchmark compounds (ideally pairs of more than one compound are made to give statistical weight to the outcome). The effect of the substructure change can then be clearly observed using matched molecular-pairs analysis [28].

It is also essential to perform a more general analysis of the data obtained for new compounds within the series. When looking at new data in the context of previous data it is crucial to check the results against pre-conceived ideas and prediction models. Where there is disagreement, outliers can often be identified. Outliers might be caused by errors in measurement or data handling and spotting these early is important to prevent incorrect conclusions from being drawn. Outliers might; however, be genuine and, where associated with beneficial properties, they might represent a breakthrough in the project. Thus rapid identification of such positive outliers is important for rapid project progression [29].

As a consequence of parallel testing, 'information rich' data are now collected for every compound. It is imperative that the maximum information and value is quickly extracted from these data to be fed back into new design. However, analysis of multivariate data is a complex task and there is a wealth of methods available [30,31]. Doing this in an ill-disciplined fashion risks 'Analysis' becoming the new bottleneck of the DMTA cycle. To prevent this the storage of the data has been secured in a uniform fashion to make it easy for users to extract all relevant data (measured or predicted) on a set of compounds (typically designed against a single hypothesis). Each project can have a standard visualisation template to enable rapid and consistent data visualisation in a meaningful way. As such a project can have a view of its key design criteria, for example ligand efficiency, selectivity and *in vitro* clearance, against preidentified reference compounds.

In this way rapid, quality analysis is enabled, whilst freeing up more time for intricate analyses as required. Key to this has been the linking of our compound databases and prediction tools into the Design Tracker environment. The conclusions are then shared transparently in the Design Tracker tool facilitating follow-up discussions and peer input in the project team. Performing the right analysis, aligned to the stated hypotheses, is essential for learning and the ability to make rational decisions that lead back to 'Design' and the statement of a new hypothesis.

Implementation and overall improvement

As with all change processes in large organisations, implementation can be difficult [32]. To succeed it is essential to involve staff that will be affected in all stages, communicate frequently on the changes, enable time for team discussions and ensure leadership buy-in. Following the work presented in this article anonymous surveys of employee opinions were conducted to obtain a broad spectrum of views on the change process and its impact. Overall, the responses ranged from positive to very positive, including agreement that there was a need to continually improve and that everyone has the opportunity to contribute to improving both their own and their teams work. More specifically, the reported fast turnaround of parallel relevant data and the multidisciplinary composition of the Design Teams were both perceived to improve the quality of hypothesis testing and lead to higher quality compounds. The key feedback collected from the surveys included that it has been important to ensure that the time freed up is used effectively (e.g. for more thorough data analysis, improving synthetic routes and developing improved assays). The surveys also highlighted areas for further improvement, including the supporting IT infrastructure, appropriate training, ensuring that the potential of all team members is maximised and that the increase in teamwork is rewarded effectively.

At the outset, improving both the quality and the rate of hypothesis testing was believed to lead to improvements in overall effectiveness. Faster and more information-rich DMTA cycles would enable maximum value and learning to be extracted and clear outcomes to be reached. To date, considerable overall improvements in compound progression and project execution have been observed; the improvements in the DMTA cycle making important contributions to these overall benefits [33]. For example, the lapse time from the date of registration of a new molecule into the corporate database to the date of a downstream *in vivo* test, such as rodent pharmacokinetics, should be facilitated by faster DMTA cycles and improved decision-making. Gratifyingly, substantial reductions in the time it takes for promising compounds to progress to these points in the downstream test cascade have been seen, and interestingly, an apparent convergence of the mean and median results over time suggesting an overall reduction in variation (Fig. 4a). Furthermore, data are available on some projects that enable the length of the DMTA cycles to be examined in greater detail. Figure 4b shows the mean DMTA cycle times for three representative projects that were running before and after the implementation of improvements described herein. It is clear that the time taken for design, make and test has been reduced (the average for these three projects is a 46% reduction in cycle time). The large reduction for the time taken in design is particularly notable, further details of which will be included in a subsequent paper. The longer analysis times for the second period were attributed to delay whilst waiting for secondary data (not part of the parallel testing cascade).

Finally, the operating unit cost of the research area over the years has been closely monitored. A substantial drop (~50%) in the unit cost of a candidate drug produced has been seen (Fig. 4c), this is owing to an increase in several drug candidates reaching regulatory safety testing (first Good Laboratory Practice Dose), this was supported by generally flat or decreasing budgets in recent years. This is further evidence of improvement in the efficiency of drug discovery overall.

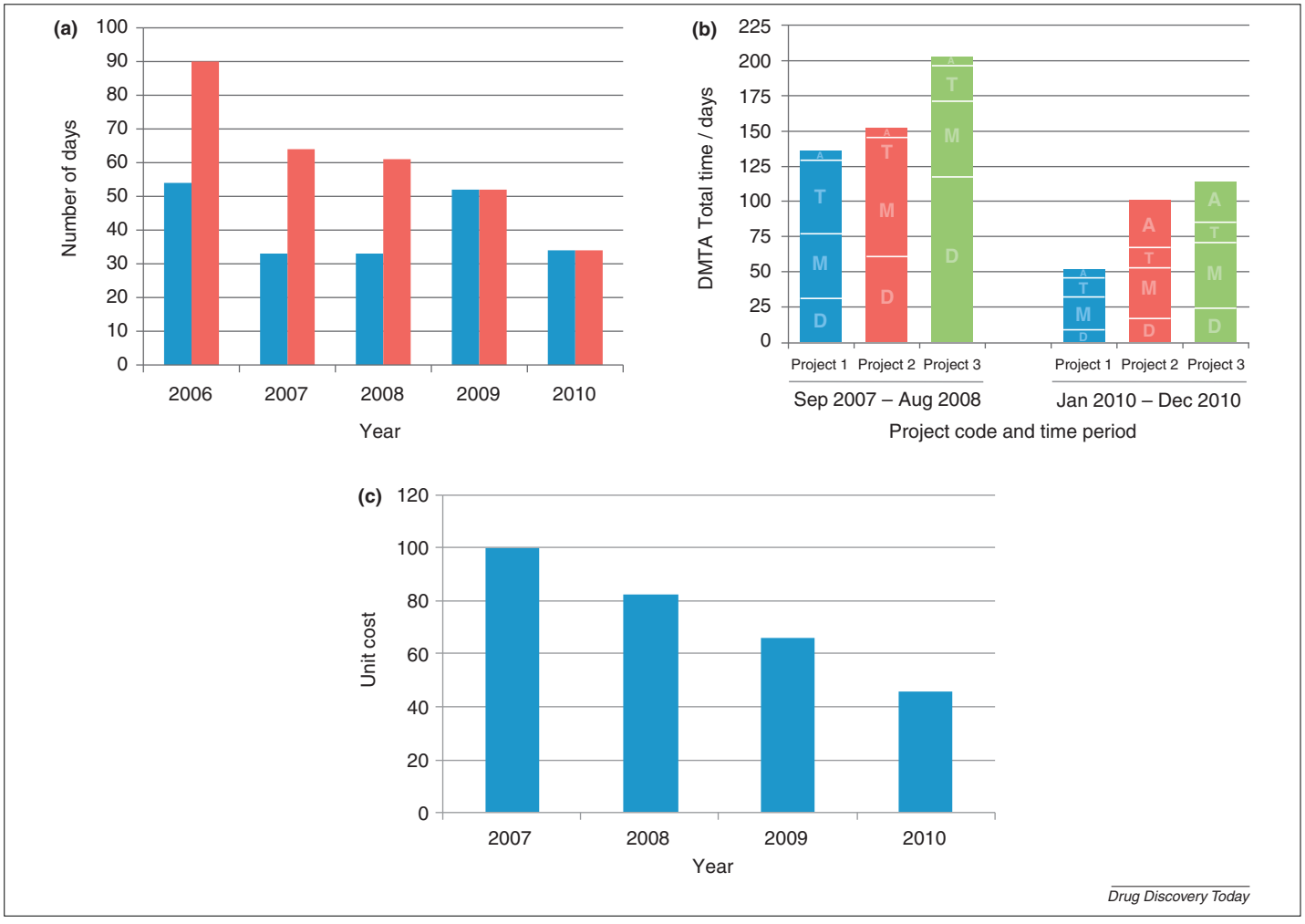

FIGURE 4

(a) The number of calendar days lapsed between the registration of a new compound into the AstraZeneca corporate database to the first rodent pharmacokinetic study. The year shown is the year of registration of the compound. Blue columns are medians, red are means. **(b)** The mean number of calendar days for the entire DMTA cycle per design hypothesis for three representative projects. Two 12-month periods are shown with the former being before implementation of improvement projects and the latter being after improvement projects have embedded (note that time for analysis was not formally recorded in the initial time period and has been set to 7 days as a conservative estimate). **(c)** Unit cost is calculated from the research area budget divided by the number of candidate drugs achieving First Good Laboratory Practice Dose in safety assessment. DMTA: design-make-test-analyse.

Concluding remarks

Herein efforts to accelerate drug discovery projects through hypothesis driven drug design by the smooth and rapid flow of high quality ideas through a fully integrated and effective DMTA cycle are reported. Formulation of a hypothesis that drives compound design is a key value adding step in drug discovery. To strengthen this, cross-functional Design Teams have been introduced to ensure all knowledge and data is used effectively and to capture and prioritise ideas and hypotheses in projects. However, to reap full value from 'Design', this step needs to be linked to integrated and effective ways of working in 'Make', 'Test' and 'Analyse'. Through a multitude of improvements major reductions in lead times for 'Make' were achieved and sustained, whilst the quantity of the material made in the first batch was gradually increased. In 'Test', relevant assays to answer project hypotheses were set up and run in parallel to deliver 80% of all *in vitro* data within ten working days of ordering. Finally, structured and careful procedures for analysis were put into place to handle the increased volume of data generated at a higher pace, and to secure the capture of knowledge as a platform for design. Implementation of an efficient DMTA cycle is of little value unless it yields overall improvements in project operation and delivery. Substantial reductions in the time required for promising compounds to reach downstream *in vivo* tests, such as rodent pharmacokinetics and faster DMTA cycles have been observed. In parallel a substantial reduction (~50%) in the cost of delivery of candidate drugs into regulatory safety testing was obtained. In addition, increased innovation in the way that teams work both in and across disciplines and the ability to solve problems based on diverse input and relevant delivery of data has been witnessed [34]. Within the lifetime of a project, DMTA represents just one contributory sub-process toward delivering a successful Proof of Concept (PoC) and ultimately a drug. So far there has been insufficient time to assess if the overall increase in quality has led to increased project success in development but we feel this is an important step on the journey to achieving this ultimate goal.

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