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Translational Medicine Guide transforms drug development processes: the recent Merck experience

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Merck is implementing a question-based *Translational Medicine Guide* (*TxM Guide*) beginning as early as lead optimization into its stage-gate drug development process. Initial experiences with the *TxM Guide*, which is embedded into an integrated development plan tailored to each development program, demonstrated opportunities to improve target understanding, dose setting (i.e., therapeutic index), and patient subpopulation selection with more robust and relevant early human-based evidence, and increased use of biomarkers and simulations. The *TxM Guide* is also helping improve organizational learning, costs, and governance. It has also shown the need for stronger external resources for validating biomarkers, demonstrating clinical utility, tracking natural disease history, and biobanking.

Introduction

Q4 Merck believes that emphasizing translational medicine approaches from lead optimization through clinical proof of concept (cPoC), offers opportunities to disruptively improve Phase II and Phase III clinical success rates. Over the past three years, Merck has realigned its science, refined its decision processes, and begun changing program team mindsets to place translational medicine at the core of its drug development approach.

Despite the increase in the number of new molecular entities (NMEs) approved by the US Food and Drug Administration in 2014 [1], the most recent evidence from the Tufts Center for Drug Development indicates that the cost per approved NME continues to rise [2]. In 2010, a team from Eli Lilly & Co. demonstrated that Phase II and Phase III clinical trial failure rates were the most important contributors to the drug development productivity crisis [3]. Their findings are consistent with the experience of Merck.

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Translational principles

Merck is a leading science and technology company in healthcare, life science, and performance materials, and is headquartered in Darmstadt, Germany, with its biopharmaceutical business operating in the USA as EMD Serono. Its development pipeline focuses on oncology, immuno-oncology, and immunology. As a mid-size biopharmaceutical firm, the incremental translational medicine process becomes transformative by delivering more robust cPoC, such as with its anti-programmed death ligand 1 (PDL1) program (avelumab) partnered with Pfizer Inc. and recent orphan drug, fast track, and breakthrough designations granted by the FDA for metastatic Merkel cell carcinoma.

Public consensus is building on the approaches and rigor required for successfully translating basic science into clinically useful therapeutic candidates [4]. Translational medicine advances in areas such as disease model validation, human cell- or tissue-derived models, molecular characterization of retrospective human materials through biobanks, bioinformatics, and translational pharmacokinetics/pharmacodynamics (PK/PD) all suggest opportunities to learn more preclinically, which should derisk

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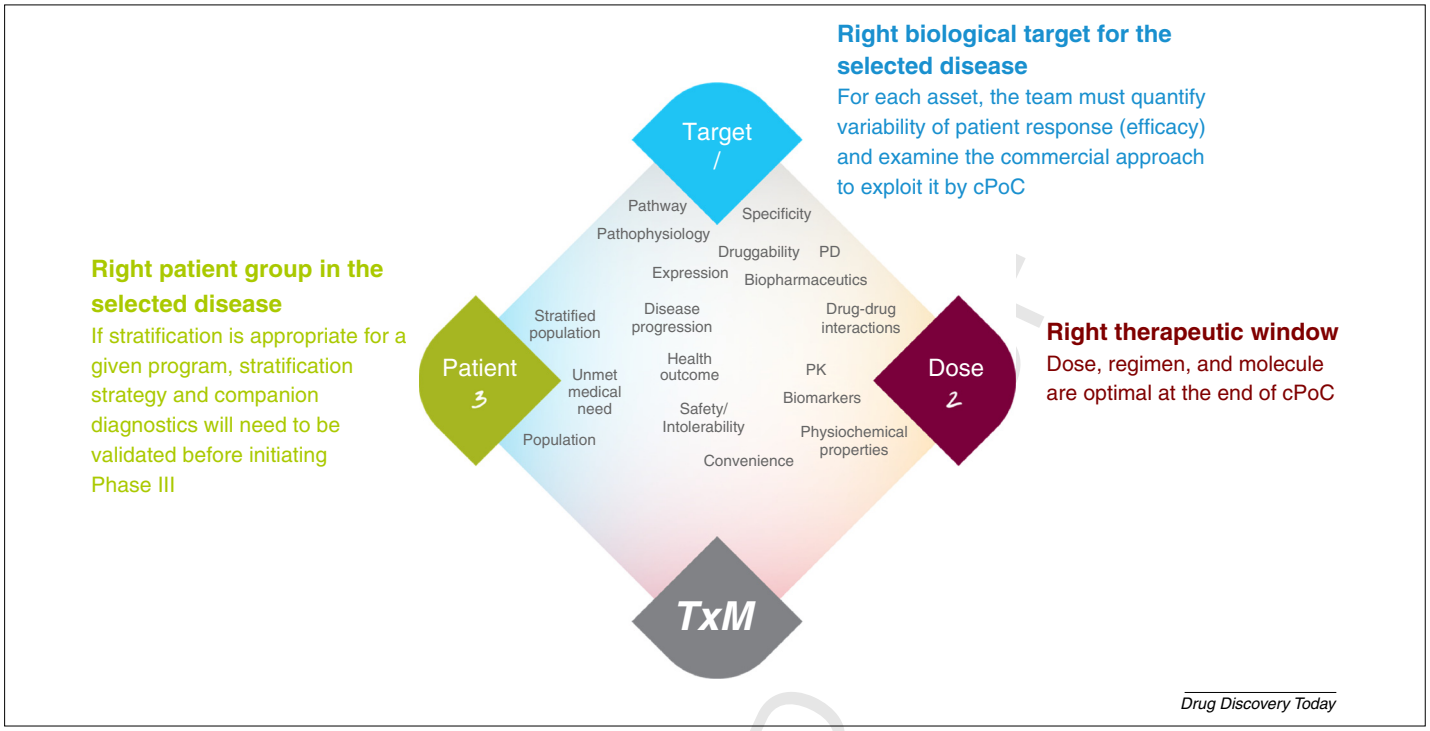

FIGURE 1

The three translational medicine aspirations with representative techniques for each. *Abbreviations*: cPoC: clinical proof of concept; PD, pharmacodynamics; PK, pharmacokinetics; TxM, translational medicine.

clinical development. In addition, harnessing translational medicine biomarkers into new clinical trial designs, such as adaptive trials, is providing hope and early evidence that stratified medicine[6] will also improve therapeutic success rates.

Moving from exceptional examples of translational medicine success to systematic improvements in drug development productivity requires consistent orchestration of translational medicine thinking and methodology into the routine rhythms of drug development. Implementing translational medicine requires changes in scientific management and mindset as well as scientific technique. Frameworks such as the AstraZeneca 5R framework [5] and the Pfizer Model Based Drug Development [6,7] similarly emphasize the integration of scientific and process innovation. These frameworks provide compelling principles but do not reduce them to practical tools for use by program teams that are adaptable to each therapeutic area and that encourage scientifically appropriate and financially feasible evidence generation at each development stage.

Actionable aspirations: target, dose, and patient

The Merck *TxM Guide* condenses the process to asking the right questions to develop the right evidence at the right decision point timing to achieve three actionable TxM aspirations (Fig. 1): (i) 'Trust in Target': identify the right biological target and understand its role in a particular disease. This aspiration requires evidence demonstrating that modulating the target generates clinically relevant physiological effects. In addition, we aspire to quantify the variability of patient response (efficacy) to that target modulation, and examine the commercial approach to exploit that variability by end of cPoC; (ii) 'Trust in Therapeutic Window': identify the right molecule that delivers the right exposure at the target site of action and elicits the desired target modulation over the stated time period (dose, regimen, and molecule), without compromising patient safety by the end of cPoC. To focus teams on the critical outcome(s) of this pillar, and for graphical simplicity, the title of this aspiration is sometimes shortened to 'dose' or 'dose & drug'; and (iii) 'Trust in Targeted Patient Population': define the right patient population with any needed stratification strategies and companion diagnostics validated before initiating Phase III trials.

These three aspirations grew from experiences both with successful and disappointing drug development programs. A catalyzing experience for Merck was the success of the epidermal growth factor receptor (EGFR) and then KRAS biomarkers to select patients with colorectal cancer who were most likely to respond to cetuximab (Erbitux®), which demonstrated the power of the Trust in Targeted Patient Population aspiration. This postauthorization KRAS stratification success pointed to the intense translational science required to make stratified medicine a systematically prospective development strategy rather than a serendipitous, life-cycle management exercise.

Trust in Target was prompted by a second set of positive oncology experiences involving the increased availability of human-derived preclinical research resources, such as nonimmortalized cell lines (i.e., explant models), mouse xenograft models,

[6] 'Precision medicine', 'targeted therapies', and 'personalized medicine' are all terms used to describe different nuances of employing molecular and other translational techniques to better match treatments with the patient populations that will most benefit from them. We use 'stratified medicine' consistently throughout this article as an approximate synonym for all these terms.

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biobank sample access, improved bioinformatics, translational informatics, and translational PK/PD capabilities. Evidence of drug target-associated human cell death and human tumor xenograft shrinkage combined to provide stronger (or weaker) human translation preclinical evidence for candidate drugs than that provided by traditional rodent models. The Nanovacc example (Box 1) illustrates therapeutic vaccine optimization using human *in vivo* T cell approaches.

The Trust in Therapeutic Window aspiration combines efficacy and safety, which the frameworks referenced above separate. Efficacy and safety are intimately interconnected through the candidate drug interactions with intended and unintended targets. Properties such as its structure, distribution, and disposition are best assessed simultaneously to understand whether a dosing regimen that provides significant clinical benefits with acceptable safety profile is likely to exist.

Negative program experiences resulting from poor translational medicine understanding of these connected factors motivated this combination. Dosing uncertainty from inadequately understood target engagement reduced early clinical trial informativeness, which in turn contributed to some programs requiring expensive multiple dose arms in Phase III trials (e.g., cilengitide). This can be mitigated by using semimechanistic population PK models to estimate appropriate dose regimens, as demonstrated by the abituzumab program (Box 2).

Deceptively simple, these TxM aspirations require profound changes to build the scientific evidence by the stated timing. For instance, understanding varying target modulation impact on patient response requires deep disease biology understanding as well as early clinical trials powered to understand variability, not simply to test average responses. In general, each aspiration requires deeper scientific understanding using better, more humanized models or banked human samples and larger, multiobjective early clinical trials. We believe that achieving these three results will result in robust cPoCs, improved success rates in Phase II and Phase III trials, and ultimately higher drug development productivity that benefits patients and the healthcare ecosystem from discovery to payers.

Creating the *TxM Guide*

The *TxM Guide* is the centerpiece of the translational medicine strategy at Merck to connect the three translational aspirations to practical, creative activity across the drug development stages. It uses a series of strategic drug development questions from lead optimization to cPoC to prompt project teams as they create candidate therapy development plans. The questions balance immediate actions with long-term thinking and ensure that translational medicine approaches are leveraged whenever possible. The *TxM Guide* also fosters knowledge sharing throughout the research and development (R&D) value chain. Finally, it enhances the go/no-go decision-making processes at both project and portfolio levels.

The *TxM Guide* began in 2011 with efforts to systematically encourage translational medicine. Emerging out of biomarker and stratified medicine visions, a broad effort gathered a summary listing of more than 200 translational medicine questions and criteria. In mid-2013, Merck R&D leadership commissioned a *TxM Guide* creation process to: (i) create a common understanding of the required available science from decision to start lead optimization (DPLO) to cPoC to meet its translational medicine aspirational goals; (ii) encourage development-stage appropriate strategies for generating patient-focused, quantitative translational evidence via a question-based approach; and (iii) guide project teams and functions to create well-designed quantitative experiments to answer the required phased questions

The process engaged a cross-functional team from the research and experimental medicine functions, therapeutic areas, and the strategy and program management office. The *TxM Guide* was delivered to senior management in December 2013, who authorized rollout of the process and training materials company wide to begin in Q1 2014. Project teams implement the *Guide* as they approach their next decision point, resulting in a natural, staged dissemination.

Although each project is unique, the *TxM Guide* is designed for use by all therapeutic areas and nearly all projects, whether small molecule, biologic, or cellular. It also supports joint development projects and the inlicensing evaluation of external opportunities.

TxM Guide highlights

An integrated process

The *TxM Guide* is embedded in the integrated development plan (IDP), which itself is the primary mechanism for driving program strategy, planning, and investment governance at Merck. Functional and clinical development plans are subsequently constructed in context of the IDP, to conduct the experiments to answer the identified strategic questions by the required dates and within the agreed budgets. We believe that it is important that translational medicine becomes integral to existing development processes, not separate from them. Although these processes focus on individual projects, a separate portfolio process draws from the program IDPs, but is beyond the scope of this paper.

One *TxM Guide* objective is to encourage long-term thinking within project teams and for the governance process. Therefore, in addition to answering the questions for the immediate decision point, teams presenting their product strategy to the decision bodies include proposed approaches for achieving success at each of the next two decision points. They articulate the needed experiments and recommend go/no-go decision criteria for each strategic question.

Connecting TxM aspirations to decisions

The *TxM Guide* links each TxM aspiration to the standard development phases by tailoring the strategic questions to each development phase and by clearly defining four TxM milestones to achieve during those phases, with cPoC as the last. Figure 2 illustrates where the four TxM milestones are expected to be achieved along the classic development stages, but they are not strictly tied to those positions. This duality allows straightforward integration of the new translational science milestone concepts into the existing stage-gate drug development process and governance. Figure 2 also shows the Merck names for the decision gates between each classic development stage and, through the arrows, shows that each stage and TxM milestone consider the target product profile (TPP), which describes the intended claims the candidate drug much achieve to provide value to patients and the healthcare system. Before a full TPP, the candidate drug target

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BOX 1

Nanovacc: target pillar

TxM strategic question(s)

DPLO; Dose & Drug: What are the optimization parameters to meet the candidate drug target profile and how much optimization is required?

Impact example

Developing a therapeutic cancer vaccine candidate through optimization of the physical and/or chemical characteristics of its drug substance and drug product.

Impact

A therapeutic cancer vaccine, Nanovacc, was developed that introduces a recombinant human survivin protein to the host immune system. Nanovacc was built upon lessons learned from earlier tecemotide (formerly Stimuvax) and Survivac vaccine programs. An integrated and crossfunctional approach was utilized in the development process.

Background and context

Nanovacc is a therapeutic cancer vaccine candidate that targets the tumor antigen, survivin. Survivin represents an ideal target for cancer immunotherapy because it is selectively overexpressed in most human malignancies and promotes the survival of cancer cells by inhibiting the intracellular apoptotic machinery. Nanovacc introduces a recombinant human survivin protein to the host immune system by encapsulating the protein in a liposomal nanoparticle containing the cationic lipid DOTAP as a potent vaccine adjuvant (Fig. I). Nanovacc is designed to efficiently engage the adaptive immune system, leading to the induction of survivin-specific $CD4^+$ and $CD8^+$ T cell responses and the development of survivin-specific antibody titers.

Project objectives

(i) Determine the balance of antigen-specific $CD4^+$ and $CD8^+$ T cell responses desirable for a therapeutic cancer vaccine; (ii) identify immunological readouts that qualify as relevant surrogates for anticancer efficacy; and (iii) determine which vaccine properties need to be assessed and how to generate the required bandwidth of candidate properties for identification of optimal pharmacological benefit.

Outcome

A cancer vaccine candidate was developed that has antitumor activity in a monotherapy setting, and can also be combined with standard-of-care chemotherapy and novel immune-based therapies from the Merck Serono portfolio. Nanovacc was extensively optimized for physical and/or chemical characteristics that induce a balance of survivin-specific $CD4^+$ and $CD8^+$ T cell responses *in vivo*. Importantly, the optimization process balanced *in vivo* performance with the requirements of a pharmaceutical drug product.

Key lessons

The optimization process for Nanovacc required a cyclical interaction among protein and cell sciences (PCS), chemical and pharmaceutical development (CPD), and immuno-oncology (iONC), in which one aspect of the vaccine was altered while attempting to keep all other physical and/or chemical characteristics constant. The results of *in vivo* pharmacology testing by iONC were provided as feedback to PCS and CPD to inform the next round of optimization. Through this iterative process, the final physical and/or chemical characteristics of the Nanovacc vaccine (Table I) were identified as being optimal for both a pharmaceutical product and a therapeutic cancer vaccine.

Nanovacc benefited from earlier vaccine programs. Where possible, discovery program teams should study the discovery and development phases of related molecules to glean lessons learned from earlier projects. Early input from manufacturing, clinical, and regulatory colleagues can improve the efficiency of discovery phase projects.

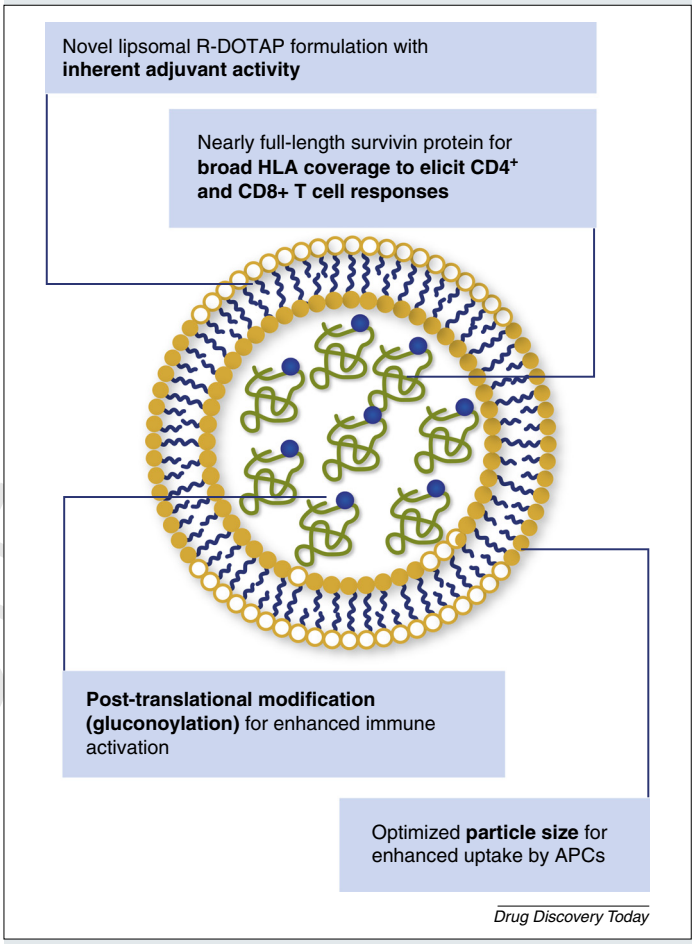

FIGURE I

Nanovacc: a next-generation vaccine. *Abbreviations*: APC, antigen-presenting cell; HLA, human leukocyte antigen.

TABLE I

Optimization parameters

Parameters	Values
R-DOTAP concentration	4 mM
Particle surface charge	+18 mV
Vaccine payload	0.5 mg/ml
Particle size	200 nm
Helper lipid composition	Phosphatidyl cholines, cholesterol
Excipients of cryopreservation	2.5% sucrose
Survivin protein sequence	2–120 amino acids
Survivin protein modification	40% gluconoylation

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BOX 2

Abituzumab: dose pillar

TxM Guide **strategic question(s)**

DP2; Dose & Drug: what is the refined, predicted exposure–response relation using Phase I and available nonclinical data?

Impact example

Establishing the concentration profile saturating the target for a monoclonal antibody (mAb) without a reliable biomarker or clinical endpoint.

Impact

A semimechanistic population PK model was developed to guide dose selection for a mAb for Phase II trials.

Background and context

Abituzumab (EMD 525797, DI17E6) is a deimmunized monoclonal immunoglobulin (Ig)G2 antibody directed against the alpha-V subunit of human integrin receptors and is being developed for the treatment of cancer. It has been demonstrated that members of the alpha-v-integrin family have a direct role in tumor progression, tumor angiogenesis, and metastasis. Abituzumab binds specifically to the alpha-V-chain, thereby inhibiting ligand binding to all alpha-v heterodimers. Therefore, abituzumab has the potential to inhibit tumor progression by blocking tumor-induced angiogenesis, preventing tumor growth by targeting tumor cells directly, and affecting metastatic tumor cell migration.
During the initial clinical development of abituzumab, no biomarkers or clinical endpoints were available to guide dose selection for Phase II. Therefore, dose selection was guided by PK, under the assumption that the nonlinear component of the clearance was a surrogate for the binding of the antibody to its target.

Project objectives

(i) Develop a semimechanistic population PK model for abituzumab incorporating receptor occupancy that forms the basis of a model-guided dose rationale; and (ii) predict the likelihood of different dosing regimens to achieve predefined target occupancy levels in the study population.

Outcome

The PK of abituzumab in humans is best described by means of a two-compartment model with a linear and a nonlinear saturable elimination pathway, the latter using a quasi-equilibrium (QE) approximation of target-mediated drug disposition (Fig. I, Table I). The saturable elimination pathway was assumed to constitute receptor-mediated uptake (QE assumption) and subsequent intracellular degradation through binding of abituzumab to its putative target alpha-V-integrin. Inhibitory concentrations (IC_{50}, IC_{80}, IC_{90}, IC_{95}, and IC_{99}) for integrin binding in humans were calculated based on the point estimate for Michaelis-Menten constant (K_m) determined in the population PK analysis. Monte Carlo-type stochastic simulations with 500 replicates were then performed with the population PK model for different doses and dosing regimens. Based on these simulations, the likelihood of achieving the predefined target occupancy levels during a dosing interval were determined (Table II).

Key lessons

PK modeling and simulation could provide a rational basis for supporting dose selection of mAb for Phase II studies in the absence of proximal or distal biomarker. However, it is strongly recommended that the exposure–response relation be established with measured biomarkers.

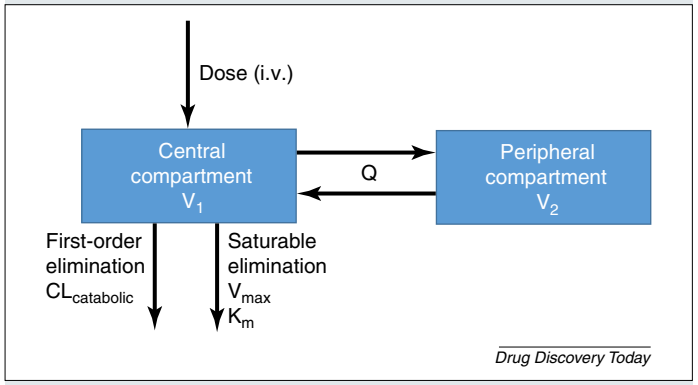

FIGURE I

Title. *Abbreviations*: $CL_{catabolic}$, catabolic clearance; i.v., intra-venous; K_m, Michaelis–Menten constant; *Q*, intercompartmental clearance; V_1, central compartment volume; V_2, peripheral compartment volume; V_{max}, maximum rate.

TABLE I

Population PK model parameter estimates and bootstrap confidence intervals[a]

PK parameters	NONMEM		Bootstrap	
	Point estimate	Between-subject variability (%)	Median	90% Confidence interval
V_{max}, μg/h	493	21.4	498	447–552
K_m, μg/ml	0.571	ND	0.561	0.272–0.795
Increase of V_{max} in patients with mCRPC (%)	35.3[b]	NA	29.0	–8.5–60.4
V_1, L	4.41	22.0	4.43	4.20–4.67
V_2, L	3.44	40.4	3.48	2.92–4.05
Q, L/h	0.0444	56.9	0.0436	0.0349–0.0556
$CL_{proteolytic}$, L/h	0.00857	25.8	0.00861	0.0069–0.0113

[a] *Abbreviations*: $CL_{proteolytic}$, proteolytic clearance; mCRPC, metastatic castrate-resistant prostate cancer; NA, not applicable; ND, not determined; *Q*, intercompartmental clearance; *V*, volume; V_{max}, maximum rate.
[b] To be re-evaluated in future analysis iterations.

TABLE II

Probability of achieving predefined target occupancy in serum for dosing regimens with a 2-week dosing interval

Dose every 2 weeks, mg	Probability for trough concentration to exceed, %				
	IC_{50}	IC_{80}	IC_{90}	IC_{95}	IC_{99}
250	41	31	23	12	0
375	91	89	84	77	10
500	99	98	98	97	49
750	100	100	100	100	95
1000	100	100	100	100	100
1500	100	100	100	100	100

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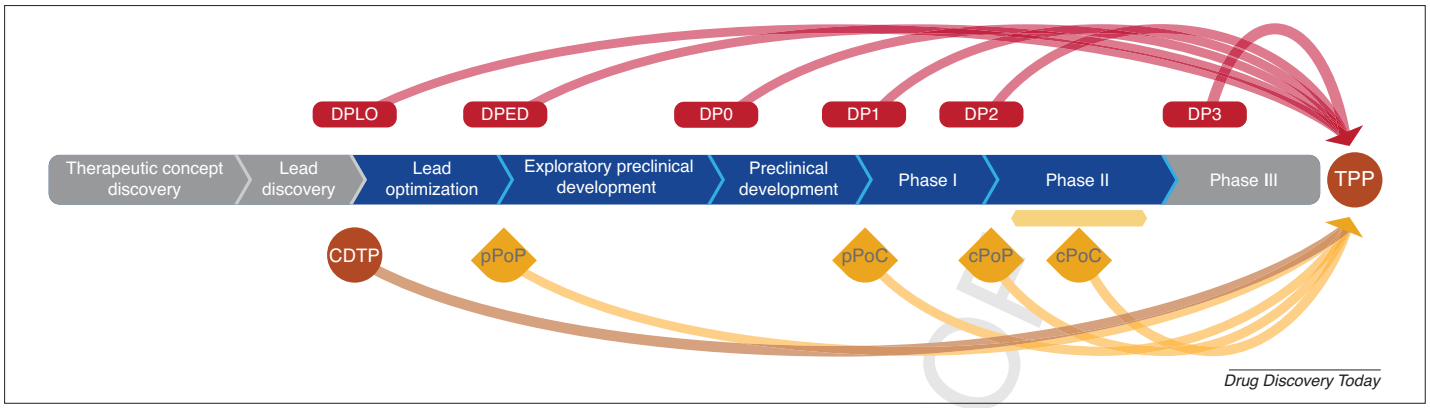

FIGURE 2

Overlaying translational medicine milestones onto the stage and/or gate of the drug development process. Proof of principle: demonstrate the beneficial therapeutic effect on the targeted disease process or pathophysiology (i.e., demonstrate that target modulation and/or activation modifies the desired disease biology). Proof of concept: demonstrate that modified disease biology translates into a beneficial therapeutic effect on clinical outcomes. *Abbreviations*: CDTP, clinical discovery target profile; cPOC, clinical proof of concept; cPOP, clinical proof of principle; DP, decision point; DPED, decision point exploratory development; DPLO, decision point lead optimization; pPOC, preclinical proof of concept; pPoP, preclinical proof of principle; TPP, target product profile.

profile (CDTP) defines the desired preliminary candidate drug attributes enabling the future TPP. Given that it is focused on the path for a single program, Fig. 2 does not illustrate the reverse translation that occurs from late-stage programs to earlier stage ones.

The TxM milestones progress from demonstrating target modulation relevance to fundamental disease biology to gross phenotype impact in disease models to then demonstrating in humans that target modulation produces disease-relevant biomarker changes, and ultimately, human phenotypes of clinical significance. These TxM milestones emphasize understanding the translational medicine of efficacy and augment rather than replace the stage-gate decision point criteria, which are replete with safety, manufacturing, competition, and other criteria. Although the emphasis may shift from target to therapeutic window to patient groups, all three translational aspirations are addressed at each milestone: (i) preclinical proof of principle (pPoP): the demonstration of a beneficial therapeutic effect by a precandidate drug on a targeted disease process or pathophysiology, showing modulation or activation of the target in the desired disease biology. pPoP is mainly assessed based upon distal PD biomarkers, such as markers of proliferation or apoptosis; (ii) preclinical proof of concept (pPoC): the demonstration that disease biology modified by the precandidate drug translates to a beneficial therapeutic effect on outcomes in disease-relevant, preclinical models, such as nonimmortalized human xenograft shrinkage. In some cases, pPoC can be shown with a well-characterized surrogate molecule; (iii) clinical proof of principle (cPoP): the demonstration of a beneficial therapeutic effect of the candidate drug in the identified patient population on a specific disease process or pathophysiology. At cPoP, therapeutic effect evaluation is typically based on distal PD biomarkers, such as downstream gene expression or elevations of blood-circulating markers of metabolic or apoptosis effects. In some cases, clinical scores that demonstrate gross phenotype changes in inflammation or mobility this may already be available; and (iv) cPoC: the modification of disease biology by the candidate drug translating to a beneficial therapeutic effect on clinical outcome in the identified patient population. cPoC should be based on clinically significant outcome or surrogate end points whenever possible.

The TxM Guide *questions*

Rather than providing a checklist of required evidence and only a list of criteria for each decision point, the *TxM Guide* uses a question-based approach aligned to key decision points. Others have demonstrated the advantages of a question-based approach [8], while the FDA has adopted a question-based review (QbR) approach for Office of Pharmaceutical Science evaluation of new drug applications (NDAs) in conjunction with the International Conference Harmonization (ICH) guidance [9]. Our design fosters scientific and critical thinking by the teams to ensure the delivery of the right science at the right time.

The *TxM Guide* provides teams with a set of strategic drug development questions (strategic questions) aligned to each decision point from lead optimization through Phase II clinical development, arranged by themes such as biomarkers and companion diagnostics (Fig. 3) or organized by TxM milestone (not shown). All the strategic questions for a decision point must be addressed by the team. Generally, there are fewer than ten, as shown in Fig. 3a for DPED. The questions were developed to apply to all programs: small molecule, biologic, or cellular therapy; in any of our therapeutic areas. Phrased as open-ended queries, they highlight the core science findings required to move a program forward. Strategic questions are not a long list of detailed yes/no questions regarding, for instance, whether every preclinical regulatory study has been performed. Those detailed requirements are tracked by other operational management systems. Rather, as shown in Fig. 3, the DPED 'Dose & Drug' column contains only two deceptively simple strategic questions: 'Has at least one precandidate drug been identified with the desired exposure–response relationship and translatable biomarkers?' and 'What is the expected therapeutic window based on preliminary nonclinical safety data?'. These questions prompt productive scientific discussions, but do remove the comfortably simplistic scoring metrics of yes/no checklists, or red/yellow/green scorecards.

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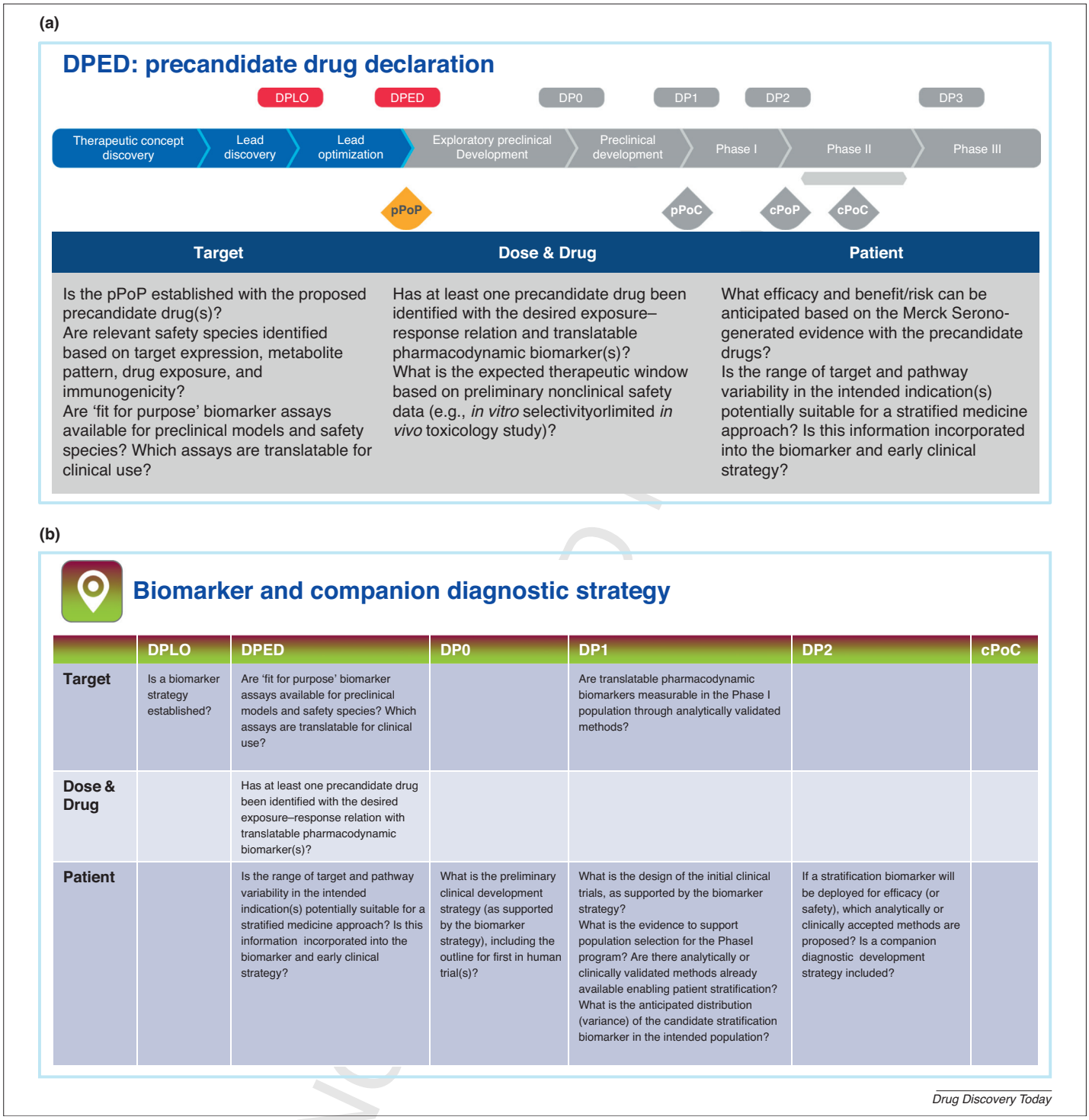

FIGURE 3

Translational Medicine (TxM) Guide strategic questions. The questions are always arrayed by the three pillars. **(a)** They are usually grouped by decision point to provide an overview of all the TxM issues that need to be addressed to move a program forward. To move forward, a project team must demonstrate evidence for each question for the decision point plus a plan to generate the required information for the next two decision points. **(b)** The strategic questions also can be arrayed by major theme, such as the biomarker and companion diagnostic theme, to facilitate planning for evidence strengthening over time. *Abbreviations*: CDTP, clinical discovery target profile; cPOC, clinical proof of concept; cPOP, clinical proof of principle; DP, decision point; DPED, decision point exploratory development; DPLO, decision point lead optimization; pPOC, preclinical proof of concept; pPoP, preclinical proof of principle; TPP, target product profile.

To further help teams answer the strategic questions, a set of tactical drug development questions (tactical questions) serves as a helpful tool to keep teams focused on detailed translational medicine best practices by asking whether specific approaches, designs, tools, animal models, simulation techniques, and other factors could prove effective for this particular candidate.

The question-based approach extends to senior management program go/no go decision making. Merck leadership desires

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evidence-based, scientific discussion of development options focused on the critical uncertainties rather than a single recommendation for a binary decision. This requires a cultural change as well as a mindset change among the meeting participants and a restructuring of meeting agendas to reserve appropriate time.

The three translational medicine aspirations drive the strategic questions and provide the urgent, transformative power that the decision process harnesses and directs. For example, the therapeutic window (dose) goal to understand the therapeutic index by the cPoC requires strong preclinical modeling to set the Phase I regimen and superb PD and target engagement biomarkers to assess whether optimal modulation has occurred. Without such advanced translational medicine, we cannot understand whether a dose could be lowered to improve patient safety while maintaining strong efficacy.

Achieving this aspiration requires attention, and investment, far earlier in the process to develop the biomarkers, establish the exposure–effect relation models, and understand the translatability of animal model evidence to human response projections. For example, the biomarker strategy (Fig. 3b) prompts identification and even selection of human translatable PD biomarkers as a question to be addressed before exploratory development (decision point DPED). This means human translatable biomarker science must begin during lead optimization, three development stages before first-in-human trials.

Successfully achieving the target aspiration proves critical in assessing whether a disappointing clinical outcome resulted from inadequate target engagement or because the target itself does not have the disease intervention power for which we hoped and planned. Historically, these uncertainties could cause us to pursue high-risk Phase III trials with multiple dosing arms; launch products with nonoptimal dosing regimens; or even cancel programs due to inadequate formulations and inadequate time to create them.

The patient aspiration to define the stratified patient population complete with a validated companion diagnostic (where relevant) before entering Phase III requires that Phase II trials no longer act as exploratory human functional genomics experiments searching to discover both treatment response variability and a biomarker to distinguish that variability. Rather, the *TxM Guide* prompts the search for clinically relevant pathway and target variability back at the decision point to enter lead optimization, even when the therapeutic concept itself does not target a genetic mutation. Without the clearly stated goal to define the target patient population and, in relevant cases, validate the companion diagnostic before Phase III trials, the impetus to explore and invest in human preclinical evidence would be significantly lower.

Early experiences

While it is too early to statistically evaluate the *TxM Guide* (embedded into the IDP) impact on the Merck pipeline, some early scientific and management findings exist. Regarding R&D management process, the project teams reported that the *TxM Guide* question-based process helped identify evidence gaps and coordination issues, and prompted more systematic external environment scanning. For instance, 80% of the program leaders reported that the IDP was helpful and actively used by the team to translate the strategy into activities, as well as helping justify the resource needed to perform those activities. Importantly, they also noted that the *TxM Guide* forced true crossfunctional scientific planning and design rather than parallel function thinking.

As with most corporate cultural and mindset changes, senior leadership commitment to advocate and implement the changes has proven critical. Actions proving pivotal ranged from the integration of translational medicine into strategic company-wide communications as well as simplifying organizational structures at a high level to the practical structure of project review sessions to focus discussions on strategic questions. Investing the resources to perform the early TxM science while simultaneously advancing late-stage trials that have not had the benefits of such science remains a scientific and financial tension not fully resolved. However, what is clear is that project teams hold scientifically richer program strategy discussions and that the IDP/*TxM Guide* is rescuing senior leadership from detailed checklist reviews and restoring focus on scientific discussions for the most critical program decisions.

The *TxM Guide* has supported, gathered, and promoted best practices from around the company. In one example, a project team in exploratory development determined the PD efficacy relation using preclinical human-based evidence, which effectively provided the rationale for selecting the starting dose. Specifically, the Phase I clinical trial dosing design used human tumor mouse xenografts to estimate the extent and duration of target engagement required to generate meaningful tumor growth inhibition.

In another example (Box 2), the abituzumab oncology project team established the concentration profile for the monoclonal antibody required to saturate the target, without a reliable target modulation biomarker, through the use of a semimechanistic population PK model. Based on a PK simulation using a two-compartment model, the likelihood of achieving the predefined target occupancy levels during a dosing interval could be determined. Two doses for a Phase II study were then selected that achieved different levels of target saturation in the study. While biomarker evidence is highly preferred, the abituzumab experience demonstrated that PK modeling and simulation may provide a rational basis for supporting dose selection [10].

A reverse translational medicine example occurred within the Nanovacc cancer vaccine development program (Box 1). The optimization process for Nanovacc required a cyclical interaction among departments by which the program benefited from earlier vaccine encapsulation study experience and biological activity assay results. This back-translation sped up the process as well as set optimization stopping criteria. Nanovacc provides a tangible example of how the manufacturing, clinical, and regulatory experience gained from related prior programs improves the efficiency of a discovery phase project.

Finally, as described in Box 3 with a follicle-stimulating hormone receptor (FSHR) project, creative use of human cell models provided confidence early in the development process that a given lead series could be optimized. The duration and effect of a lead compound on the target was unknown; therefore, the required candidate drug target profile parameters to reach a suitable human dose level could not be defined. By establishing a PK/PD relation using human PK and *in vitro* potency profile for Gonal-f and validating this relation for the lead compound in rats using

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BOX 3

FSHR agonist

TxM strategic question(s)

DPLO; Dose & Drug: what are the optimization parameters to meet the candidate drug target profile and how much optimization is required? Does at least one lead series and/or antibody have the potential to deliver the essential attributes of the candidate drug target profile?

Impact example

Translational PK/PD modeling based on a human exposure–potency relation and rat *in vivo* PK/PD (oocytes count) to estimate the human dose range for an oral, small-molecule preclinical FSHR agonist, MSCx, using a marketed large molecule, recombinant FSH (human follitropin alfa; Gonal-f®, administered subcutaneously).

Impact

By establishing a PK/PD relation using Gonal-f, and validating this relation for an oral, small molecule, MSCx, optimization parameters were determined to meet suitable human dose levels for this hit series.

Background and context

FSHR is a G-protein-coupled receptor that binds FSH, a hormone essential for human fertility. FSHR is a highly validated target. It upregulates serum estradiol, a well-established biomarker for activation of FSHR. Merck Serono markets Gonal-f (follitropin alfa for injection), which is a large molecule that stimulates follicle development and maturation, and is used clinically for ovulation induction and assisted reproductive technologies. An oral FSHR agonist, MSCx, was developed by EMD Serono.

Project objectives

(i) Develop a PK/PD relation for MSCx based on the ratio of human exposure to Gonal-f at the therapeutic dose (150 IU at steady state) versus *in vitro* EC_{50} for estradiol release measured in human granulosa cells to understand the target activation needed for efficacy. The PK/PD relation was confirmed by a rat PD model using oocytes count as a marker; (ii) determine the distance of the current lead compound relative to the target maximum human dose of 100 mg four times daily, which was set up arbitrarily by the therapeutic area research unit to minimize any safety concern; and (iii) select the key parameters for optimization based on the distance to human dose and properties of the lead compound.

Outcome

A PK/PD relation was established for MSCx, and the optimization parameters target potency, log *P* value, and *in vivo* clearance to reach an effective dose in humans were determined. As a result, the hit series was declared as a lead series, because the work demonstrated that the lead series could be optimized during the lead optimization phase by improving potency, decreasing log *P* value, and decreasing *in vivo* clearance.

Key lessons

The duration and effect of the lead compound on the target was unknown during the hit optimization (HO) phase of the project; therefore, it was unknown how much optimization and what kind of CDTP was needed to reach a suitable human dose level. By establishing a PK/PD relation using human PK and *in vitro* potency profile for Gonal-f (Table I) and validating this relation for MSCx in rats using oocytes count as a biomarker (Figs I, II), the optimization parameters needed to reach an effective dose in humans were determined. It was found that a 100-fold increase in the exposure–potency relation was needed to achieve the desired human dose range. Based on the current structure–activity relation of the compound library, this was a realistic goal.

TABLE I

FSH.

Compound	Free EC_{50} (ng/ml)	Target concentration range (ng/ml) (free C_{ss}) for comparable efficacy to FSH	Free EC_{50}:free C_{ss} ratio
Human FSH (Gonal-f®)	17.75 (in human)	0.37–0.67 in human (observed, 150 IU SC)	48–26
MSCx	731 (in human)	15–28 in human (predicted)	48–26 (based on FSH ratio)
	1193 (in rat)	25–45 in rat (predicted)	48–26 (based on FSH ratio)

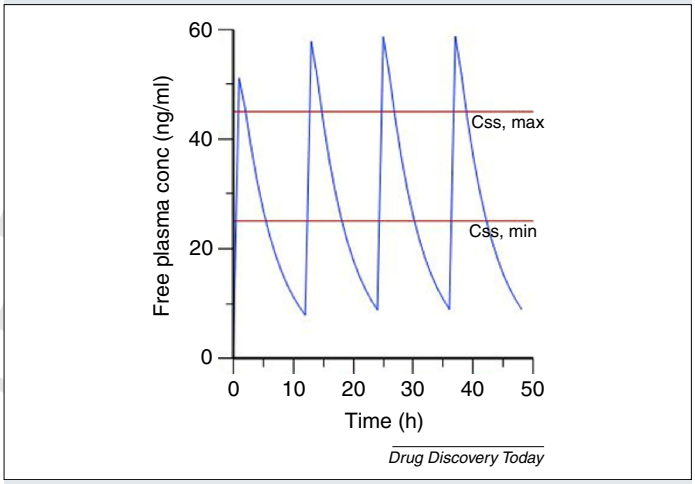

FIGURE I

Rat plasma concentration.

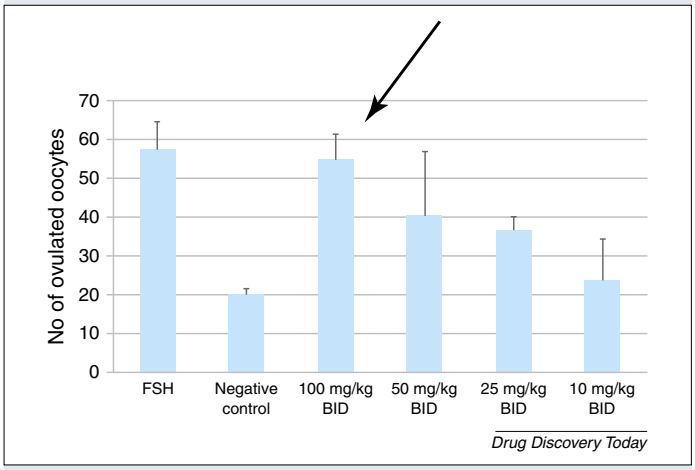

FIGURE II

Rat oocyte count as an efficacy biomarker. At 100 mg/kg twice daily (bid), efficacy observed for MSCx was comparable to the maximal efficacy induced by follicle-stimulating hormone (FSH) (arrow). Exposure above C_{ss}, min for at least 12 hours daily seems to be needed for comparable efficacy to. Q6

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oocytes count as a biomarker, it was found that a 100-fold increase in the exposure–potency relation was needed. Based on the current structure–activity relation of the compound library, this assessment concluded that achieving the potency goal was likely.

Future directions and concerns

As Merck continues to roll out the *TxM Guide* as project teams approach their next eligible decision points, we are addressing cultural, operational, and capability gaps. Translational medicine requires a mindset change, as noted by academia and industry alike [4,11]. We continue to evolve our training materials, expert team advisors, external partners, incentives, and feedback mechanisms. As we use the *TxM Guide*, we are working to develop better ways to visualize the achievements across multiple questions. Perhaps most importantly, we continue to evaluate the lessons learned from both successes and failures, and use those learnings to 'back-translate' into our *TxM Guide* and ongoing program IDPs.

Operationally, our experiences are highlighting the need for internal standards (when external standards do not exist) for the biomarker data from discovery through submission to enable data pooling across projects, which is essential to reverse translation. Doing so without stifling scientific creativity and adaptability to the specific needs of each program proves challenging.

The *TxM Guide* process has highlighted scientific capability gaps. Some areas, such as translational PK/PD biomarkers, are best addressed internally in the context of each candidate drug. However, many gaps also exist in community resources, particularly those regarding populations, disease attributes and natural history, validation of models to recapitulate human phenotypes, and platforms to rapidly develop models, simulations, biomarkers, and diagnostics.

We commend the disease foundation community for advancing many of these resources. Industry also has a role in supporting these efforts and in multiparty precompetitive consortia. We also encourage public funders to support long-term resources as well as project-based research. Too often, public resources from bioinformatics repositories to biobanks struggle to find reliable public funding support to the detriment of the entire community. We also strongly support strengthening data standards and methods transparency in scientific publications to enable results replication.

Answering the questions raised by the *TxM Guide* will require continued change in our mindset, with the tools we use, to the processes we employ and, increasingly, with the number, depth, and quality of the collaborations and consortia in which we participate as we strive to deliver more therapies rapidly, safely, and effectively to patients globally.

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