CellPress

Opinion

Strategies for Derisking Translational Processes for Biomedical Technologies

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Inefficient translational processes for technology-oriented biomedical research have led to some prominent and frequent failures in the development of many leading drug candidates, several designated investigational drugs, and some medical devices, as well as documented patient harm and postmarket product withdrawals. Derisking this process, particularly in the early stages, should increase translational efficiency and streamline resource utilization, especially in an academic setting. In this opinion article, we identify a 12-step guideline for reducing risks typically associated with translating medical technologies as they move toward prototypes, preclinical proof of concept, and possible clinical testing. Integrating the described 12-step process should prove valuable for improving how early-stage academic biomedical concepts are cultivated, culled, and manicured toward intended clinical applications.

The Need for Derisking Approaches in Translational Research

Translational biomedical research–the bridging of basic research breakthroughs to transform new therapeutic strategies into market applications–is a failure-prone process. The pharmaceutical industry has focused recently on reducing the recognized risks of advancing scientific discoveries into treatments through partnering with emerging commercial technologies and with academia, to collect as much evidence on potential drug or device candidates as possible during the *in vitro* and preclinical testing stages, an approach known as derisking. However, considerable heterogeneity in translational processes among researchers, especially in academia, limits data interpretability [1]. Moreover, global financing of biomedical and life science research is increasingly scrutinized for inefficient resource utilization, strategic mistakes, and mismanagement in producing health benefits [2,3]. Importantly, industries are also stymied by inefficiencies and risks inherent in their own innovation processes [4]. Therefore, carefully designed derisking strategies should be implemented, especially in academia, to improve translational research practices and contribute more efficiently and reliably to clinical success for both novel therapeutics and medical devices.

We propose a 12-step guideline for reducing risks typically associated with translating biomedical technologies. Figure 1 (Key Figure) describes the 'success cascade' that funnels many new life science early-stage (and often academic) innovations into translational processes and selects those best suited to move forward toward biomedical applications in further stages, often in partnerships with industrial sponsors.

I: Plan a Success Strategy in Translational Biomedical Research

(i) 'Initiate closer interactions early in the process between basic research and clinical/business development groups, both within the research endeavor and between industry and academia

Trends

Industrial strategies including realistic assessments of users, markets, regulations, reimbursements, and manufacturing strategies are being adopted more often in academic biomedical translation.

In vivo complexities that radically impact new drug and device stability, safety, and efficacy are appreciated sooner (e.g., if a new molecular entity is rapidly degraded in blood, its *in vitro* efficacy may be irrelevant and misleading).

Biomarker development emphasizes discovery over clinical utility because validation is difficult and expensive: only 19 approved drugs have companion diagnostics.

Robust electronic patient records, device registries that capture essential safety, and efficacy signals across patient populations are increasingly implemented.

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Key Figure

The 'Success Cascade' of the Translational Research Pipeline in Biomedical Innovations

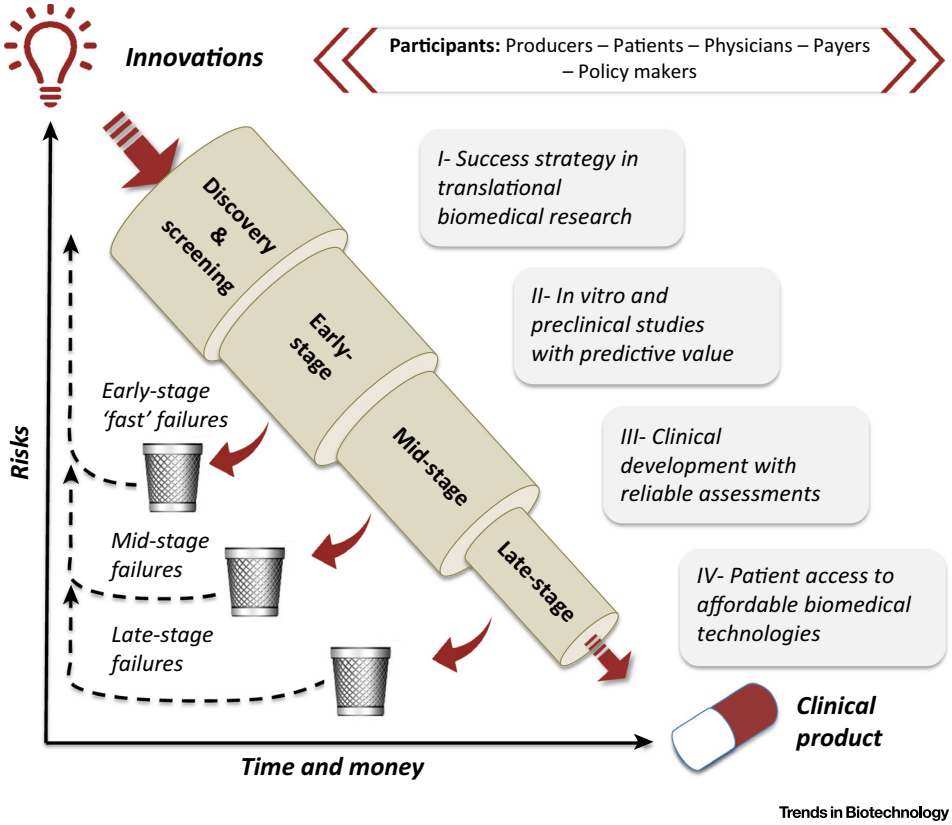

Figure 1. The cascade illustrates the different stages of derisking biomedical innovations as they proceed toward technology validation and possible product development. For the discovery and development of new biomedical technologies, planning a successful translational process is critical through having the right interdisciplinary partnerships, a milestone strategy, and the necessary intellectual property assessment. Early-stage development is then largely judged on the predictive value of the *in vitro* and preclinical outcomes. Failures at this stage can be discarded or recycled back for iterative improvements and reintroduction into the pipeline. Mid-stage 'culling' of candidates' failures produces similar recycling, and selection of best candidates to proceed further to late-stage development is based on the outcome of a well-thought clinical development criteria, including smart clinical trial designs, profound benefit–risk assessment strategy, and the use of validated biomarkers if appropriate. Late failures may still be recyclable but are costly. Final prototype developments proceed with confidence toward market adoption if adequate market motivators (accelerated regulatory pathways, tailored business models, and a patient-centric approach) are utilized. Participants include all of the stakeholder partners in translational research: producers, physicians, patients, policy makers, and payers.

partners'. Early market assessments of clinical needs and appropriate product targets should be a primary focus of any translational process. While unconventional for academic settings, this effort should be combined with a careful assessment of regulatory strategy governing eventual product approval. This approach fine-tunes preclinical and basic research hypotheses earlier in the process to provide a clearer path to a suitable clinical solution [5]. Such early interactions should also consider patient advocacy groups that are becoming increasingly important stakeholders in translational processes. For instance, the Cystic Fibrosis Foundation helped fund

Glossary

Biomarkers: key defining biologically derived molecules or signals used to validate relationships between underlying genetic or biochemical variables in patient populations to discriminate therapy responders from nonresponders.
Breakthrough therapy designation: a US regulatory status offering expedited regulatory review for new therapies targeting life-threatening conditions where preliminary clinical data demonstrate substantial improvements over existing therapies.
CTL019: immunotherapeutic product formed from autologous T cells exogenously transfected with lentiviral vectors delivering genes to express CART-19 (cancer antigen-binding domain targeting CD19 and linked to CD3ζ/CD137 immunostimulatory domains).
Ectopic tumor xenografts: tumorigenic cells or tissue transplanted across different species and placed within host tissue unrelated to tumor origin.
Gene-editing technologies: molecular technologies that enable precise manipulation of genomic nucleic acids to change genetic content and genotype.
Generating Antibiotic Incentives Now: new US incentives for developing novel antibiotics in the form of priority regulatory review with extended market exclusivity for the new drug. Generating Antibiotic Incentives Now-classified drugs are called qualified infectious disease products.
Immunogenicity risk: potential adverse host immunologically response (anaphylaxis, antibody reactivity, and cytokine release syndrome) related to protein-based therapeutics.
New chemical entity: a unique therapeutic chemical not previously authorized by a regulatory agency. New chemical entity status is granted upon approval of the new drug application and provides extended market exclusivity.
New drug application: key US regulatory document collating data from preclinical and clinical studies of an Investigational New Drug required to request and receive US regulatory approval to market a new drug.
Organoid: a three-dimensional tissue grown *in vitro* from progenitor cells or

research that led to the approval of Kalydeco in 2012 and secured $3.3 billion in licensing fees from Vertex Pharmaceuticals (USA). The Foundation now has significant capital to fund future research and has also demonstrated how a patient advocacy group can play a central role in shaping future drug development. While not every advocacy group is capable of financing research, they can help identify needs and guide product focus as equally important partners in the translational process.

(ii) 'Implement a valid evidence-based decision-making strategy in order to best select candidate approaches for further development'. Typically, academic settings are not prepared to use milestone-driven strategies that include criteria for go/no-go decisions. Milestone-driven projects have accompanying checkpoints and clearly defined time frames for investigators guiding different stages of the translational process. For instance, investigators should check and ensure the availability of clinical-grade materials and reagents used in product manufacturing before initiating clinical trials to avoid changes to manufacturing protocols at later stages. Decision strategies should therefore integrate the best available research evidence that better informs academic institutions as to when and how to efficiently allocate their scarce resources, facilitating a route for early-stage products to 'fail faster' in order to eliminate weak or costly prospects from the candidate pipeline. However, early-stage culling should be done with extreme caution, as many candidates may show efficacy only after modifying outcome measures or integrating suitable **biomarkers** (see Glossary) into their clinical testing. Efficient translational research, therefore, depends on concentrating resources on targets most likely to succeed, while balancing risks of discarding potentially valuable candidate therapeutics and device prototypes too early in their development process.

(iii) 'Certify that intellectual property surrounding the technology is secure and managed appropriately for confident freedom to operate, exclusivity in the marketplace, and licensing to commercial partners'. While academia is prone to invent, less attention is paid to producing effective protection and asserting 'freedom to operate'. The overwhelming academic motivation to publish data quickly and control the exchange of their research results freely collides with essential requirements to assess, select, and protect intellectual property (IP) [6]. As IP ownership guarantees technology exclusivity, no commercial efforts can be mounted to translate an innovation where exclusivity in the marketplace is compromised. The first public disclosure of data starts an immutable timetable for patent protection, and if executed in an uncoordinated way, an inventor's own statement in presentations or publications can be held as prior art against one's own invention and therefore thwart patenting. Therefore, a clear patent strategy is necessary to ensure a successful licensing arrangement between an academic institution and a company [7]. Because patent prosecution is an expensive proposition, particularly when international patents are sought, the IP strategy must be custom tailored to specific markets with an appreciation of the regional standard of care, prevailing clinical cultures, health-care economics, and competitive landscape.

II: Enhance Rigor and Increase the Predictive Value of *In Vitro* and Preclinical Studies

(iv) 'Develop *in vitro* models that better describe and predict *in vivo* preclinical outcomes'. Basic science is prone to use existing, available model test systems without validating their reliability toward predictive metrics in preclinical scenarios. Despite published claims for 'new' models, this limitation remains a curtailing pitfall for decades for several classes of new biomedical technologies. 'New' is not 'better' until validation is shown, and validation is tedious and expensive (and hence, rarely proven). Validation is used to assert predictive value of an *in vitro* model (i.e., correlation between *in vitro* and *in vivo* observations) using defined performance criteria independent of those used to construct such models [8]. Developing a solid strategy across early benchtop test systems to accurately predict *in vivo* performance helps to select only

organelles that recapitulates organlike functions.
Organ-on-a-chip: an *in vitro* miniature device that maintains living cells or functional tissue slices used for drug screening and human organ developmental studies.
Programmed death 1: a critical T lymphocyte checkpoint protein receptor that prevents attack on other cells. Programmed death ligand 1, presented by tumor cells, inactivates these immune checkpoints to permit tumors to undergo immune escape.
PRIority MEdicines scheme: European Medicines Agency (EMA) prioritization initiative to support drug development that target unmet medical needs by offering early dialog and scientific advice to expedite the development process.
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: lipid-lowering monoclonal antibodies that block PCSK9, an enzyme involved in lipoprotein metabolism.
Two-dimensional monocultured cell technologies: approaches that use flat, rigid plastic substrates specialized for monolayer cell culture of single cell types not resembling natural three-dimensional cell native growth conditions.

the best candidates for testing in preclinical animal models and subsequently in human conditions. Beyond 'classical' **two-dimensional monocultured cell technologies**, novel approaches include three-dimensional cell cocultures [9], **organoid** systems [10,11], and **gene-editing technologies** [12]. Importantly, whenever possible, qualified human cell sources originating from diseased patients with knowledge on their medical history should be exploited in test models and monitored via phenotype or validated biomarkers throughout the test duration [13]. While elucidating mechanisms of action is attractive at early stages, efficacy should remain the translational priority so that costs and time associated with future *in vivo* testing are warranted.

(v) 'Assess the availability of suitable preclinical animal models'. This step presumes that predictive disease models exist, but this is not always the case. Some diseases have no or poorly predictive *in vivo* models available (e.g., autism, stroke, Type I diabetes, glioma, osteoarthritis, osteoporosis, implant infection) yet demand therapeutic innovations. As investigating these technical limitations is important [14], the unavailability of suitable *in vivo* models should not necessarily hinder innovation. Exploitation of human tissue for diverse *in vitro* research uses is an increasingly recognized alternative to animal experiments. For instance, several *in vitro* tissuelike microsystems (e.g., **organs-on-a-chip**) have reported abilities to exhibit appropriate human drug pharmacologies [10,11]. However, regulators may only accept alternatives to animal tests for prediction of organ-specific toxicity if newly proposed *in vitro* human tissue models provide equivalent if not superior evidence, while accounting for interindividual human variability in data interpretation. Moreover, regulators may specify the use of *in vitro* human tissue models not as a replacement for, but as a tool to aid in, selecting the most appropriate animal species for pharmacological and toxicological studies (i.e., comparing drug toxicological profiles generated in human and animal hepatocytes [15]). Therefore, it appears essential to include regulatory agencies as early as possible in discussions that could save considerable time and resources during product development processes.

(vi) 'Use appropriate study designs for required preclinical *in vivo* animal testing that simulates actual product use in the relevant clinical context' (Box 1). This strategy seeks to improve the evidence base of preclinical disease modeling by enhancing study quality, robustness, and validity (internal, external, construct), and hence abilities to better predict clinical efficacy [16]. Improvements include prudent selection and research justification of appropriate models to assert efficacy [17]; reducing impacts from bias (by randomizing, blinding, and publication of negative results, among other measures); increasing statistical power (thereby reducing the number of false positives) [18], improving the quality of reporting of both *in vivo* methods and results [19]; conducting international, randomized and controlled preclinical trials; and performing systematic reviews and meta-analyses of preclinical studies before venturing into clinical trials. Inappropriate, poorly validated, or inadequate models to test new therapies (i.e., scaling drug dosing allometrically to rodents or using **ectopic tumor xenografts** or medical device

Box 1. Aligning Preclinical and Clinical Trial Designs.

Well-recognized inconsistencies in translating results from abundant murine disease models to predict human clinical treatment outcomes often are used to justify developing new preclinical models that better recapitulate disease biology and response criteria, and that more closely align the mouse and human conditions. While this criticism is most commonly directed to translational cancer therapeutics, with diverse murine models available [33], analogous deficiencies are prominent across all aspects of drug and medical device innovation [14,17,29]. Recently, the concept of 'coclinical trials' testing drug efficacy in parallel in humans and mice has been introduced [34]. These trials require that the animal model mirrors the human counterpart as closely as possible and that study designs for both species are strictly aligned. New preclinical strategies, including the improvement of sophisticated mouse models and coclinical study designs, are increasingly used to augment the predictive value of animal-based translational cancer research [35]. Recent cancer therapy meta-analysis shows how divergent mouse and human clinical outcomes can be for experimental therapeutics [36].

implants in rodent tissues) are used all too often. Additionally, inadequate links between *in vivo* testing, product prototypes, and most marketable indications for a product can require new rounds of animal testing, invoking substantial costs and delays with ripple effects throughout the entire product development cycle including compromised patent life, technology value, and its attractiveness to commercial partners.

III: Design a Clinical Development Program That Provides Reliable Assessments

(vii) 'Validate newly discovered biomarkers for their translational value in definitive diagnosis and monitoring of human diseases, and evidence of therapeutic progress'. Biomarkers may facilitate accelerated approval processes when employed as surrogate end points for serious conditions and rare diseases [20]. Indeed, the US Congress passed legislation as part of the Food and Drug Administration (FDA) and Innovation Act of 2012 (FDASIA 2012) that encourages use of surrogate end points and other advanced scientific tools to support accelerated approvals. Moreover, the European Medicines Agency (EMA) provides opinions on qualifying biomarker use to indicate the acceptability for using specific biomarkers in pharmaceutical research and development. Using validated biomarkers to reliably identify drug responders nested within broader patient populations allows a clinical trial to specifically interrogate the responder pool for safety and efficacy [21]. This approach focuses on trial resources, delineates target populations for therapies, and helps to limit enrollment with statistical powering, saving time and money. As an example, the Yale Lung Cancer Consortium identifies and catalogs individuals with genetic markers associated with specific lung cancer types. The ultimate goal is to connect patients carrying certain mutations to clinical trials for medicines targeted to correlated types of lung cancers, thus facilitating access to investigational drugs and also improving the likelihood of success by focusing on potential responders.

(viii) 'Improve clinical trial designs and select clearly measurable outcomes for clinical assessments' (Box 2). While outcome measures are easily identified in most preclinical models, their corresponding correlates in later clinical study designs might not be so easily achievable.

Box 2. Designing and Implementing Clinical Trials.

Typically, conventional clinical trial methodologies are applied to traditional Phase I–III clinical trial designs, conduct, and outcomes analysis. Appropriate trial designs must consider sufficiently large sample sizes and statistical powering, as well as including methods for minimizing bias in order for results to be reliably interpreted. Designs must include defined outcomes that can be clinically and reliably measured to distinguish changes and effects, and to define 'success' via comparing baseline values with 'treatment-produced' values for outcomes. The randomized, parallel-group controlled clinical trial design is generally considered the gold standard. Some trials, however, including rare diseases with very low incidence/prevalence, individually tailored therapies, and specific trial populations, have difficulties utilizing this conventional trial design. Nevertheless, requirements for small trials are identical to those for larger trials: their design and analysis must enable a reasonable measure of treatment effect to be statistically asserted [37].

Many validated clinical trial design alternatives to conventional Phase I–III designs have been considered [37,38]. Each trial design provides both advantages and limitations. Selecting the most appropriate design is not a trivial decision, and for a given situation, several designs could be justified. Adaptive designs in particular are considered especially attractive for certain trial situations [39]. Such adaptive designs provide unique opportunities to modify or redesign trials in real time during study conduct without undermining trial validity and integrity. Trial adaptations include early stopping (futility, early rejection), sample size reassessment, treatment allocation ratios, treatment arms (dropping, adding arms), hypotheses (i.e., noninferiority vs. superiority), population (inclusion/exclusion criteria, subgroups), test statistics, and combining trials/treatment phases (i.e., adaptive seamless designs). This dynamic option engenders related concerns that significant redistributions in targeted patient populations can occur with increasing adaptations, creating bias and violating preservation of the overall Type I error rate. Generally, adaptive trial results also can suffer from reliability and intrinsic interpretation difficulties. A recent US Food and Drug Administration draft guidance informing adaptive clinical trial designs for medical devices requires prospective adaptive designs to be based on information collected within the study, with or without formal statistical hypothesis testing (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446729.pdf).

Even established clinical outcome measures have sometimes been developed decades ago (e.g., implant failure in joint replacement surgery) and do not necessarily reflect the current innovation process and patient expectation (e.g., early and full functional recovery), leading to long follow-up times and high costs to demonstrate benefits. Clinical studies for predefined translational approaches should integrate smart study designs that provide primary support for effectiveness, and is aligned with clinical end points relevant to patients, providers, and payers, and that benefit health-care systems [22]. For instance, small first-in-human studies, sometimes called Phase 0 trials, may be valuable to gather preliminary data on a drug's pharmacokinetic/pharmacodynamic profile and demonstrate drug-target effects in cases where preclinical data might be misleading, prior to a Phase 1 trial [23]. Such goals can be achieved by including infrastructure for clinical trials and translational research capacity into academic centers to provide the needed expertise. These clinical research units are recommended to be involved at the preclinical research stages to avoid issues in translating preclinical data into appropriate clinical protocols. Most importantly, for academic centers lacking dedicated translational infrastructures, extending collaboration between preclinical and clinical research groups is required to transition drug development processes and enforce an open culture of shared innovation and knowledge exchange. Several large pharmaceutical companies are now supporting this paradigm shift while maintaining sufficient levels of profitability and competitive advantages [24].

(ix) 'Adopt a profound benefit–risk assessment strategy in clinical testing to decide if the balance is acceptable to justify product development'. A challenge to developing biologics and cell-based products is establishing **immunogenicity risk** assessment plans tailored to a specific product while satisfying regulatory expectations for product registration [25]. Nevertheless, investigational therapies that offer favorable risk–benefit profiles for treating serious, life-threatening conditions can offset the high levels of technology novelty or project complexity required for development. For example, the potential benefits of a provocative, personalized cellular therapy (**CTL019**), where patients' own T cells were reprogrammed externally to treat their acute lymphoblastic leukemia, outweighed the risks of pursuing this unprecedented investigational approach. This innovation was pioneered by an academic research team supported by considerable biomedical infrastructure at the University of Pennsylvania (USA). The initial clinical trial was profoundly successful, demonstrating 90% remission rates in liquid tumors [26]. Evidently, the risk–benefit assessment paid off in this case. Subsequently, CTL019 was granted regulatory privilege and attracted further major investment by a commercial partner, Novartis. Clearly, validation of a new innovative therapeutic approach that identifies new opportunities, like CTL019, or current successes in targeting tumor checkpoint **programmed death 1 (PD-1)**, or moving beyond statin-based cholesterol control with **proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors** to prevent cardiovascular events [27], all carry greater risks than developing incremental analogous candidates in existing mechanistic drug classes, but they may also be significantly more impacting and offer attractive market exclusivity, offsetting risk and incentivizing their development.

IV: Ensure Patient Access to Affordable Novel Biomedical Technologies

(x) 'Navigate the regulatory maze and utilize the most appropriate regulatory framework for drug development'. Ongoing initiatives supported by US FDA and EMA aim to improve and expedite drug development processes while maintaining highest levels of safety (Box 3). Such 'fast tracking' initiatives are expected to shave years off of clinical development timelines and change drug R&D economics, especially for innovative therapies, reducing risk for commercialization decisions.

(xi) 'Establish a patient-centered approach to clinical testing, with increased emphasis on satisfying patients' needs while considering their views on adverse event risks, side effects, treatment responses, and quality of life benefits' (Box 4). Historically, patients have merely been

Box 3. Initiatives by Regulatory Agencies to Speed Up Drug Development Processes.

The US Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) introduced the **breakthrough therapy designation (BTD)** to expedite development and review of new drugs targeting serious or life-threatening conditions. BTD applications must receive FDA response within 60 days, providing a key indicator for future regulatory hurdles. Once FDA designated as BTD, candidates must satisfy fewer requirements than traditional new therapeutics. The drug sponsor must provide preliminary clinical evidence demonstrating that the drug may substantially improve at least one clinically significant end point over available therapy [40]. In 2013, 11% of FDA-approved new molecular entities were designated BTD, increasing to 22% in 2014. The FDASIA also authorized an alternative pathway to market for medical devices: the 'direct *de novo*' process, streamlining the review of novel low- to moderate-risk devices (Class I or II) for which no clear predicate device exists. This is limited to non-Class III devices or to where cited predicates have not required a premarket approval (PMA). Significantly, implanted medical devices are excluded. The FDASIA also contained new authorization under the '**Generating Antibiotic Incentives Now' (GAIN)** legislation to provide new pathways to improve the speed of regulatory review for new antibiotic strategies directed at addressing antibiotic-resistance issues. The GAIN Act grants an additional 5 years of marketing exclusivity upon **new drug application** approval for drug products designated by FDA as qualified infectious disease product (QIDP). Thus, for QIDPs, the periods of 5-year **new chemical entity** exclusivity, 3-year new clinical investigation exclusivity, and 7-year orphan drug exclusivity now become 10, 8, and 12 years, respectively. To date, five QIDP-designated antimicrobial drug products have been approved. Similarly, European Medicines Agency already established the 'accelerated assessment' procedure eligible for marketing authorization to applicants developing a medicinal product expected to be of major public health interest. In addition, the Agency launched the **PRIority MEdicines scheme** in 2016, aiming to support development of new therapeutic approaches that target unmet medical needs. This voluntary scheme provides possibilities for early dialog between regulators and developers to optimize generation of robust data and enable accelerated assessment of the marketing authorization applications. Moreover, the recently adopted clinical trial regulation in the EU aims to improve harmonization and increase transparency of clinical research practices [41].

involved as medical research participants, engaged little beyond passively receiving therapies, devices, and procedures. This paradigm limits their input where many possible, more valuable and informative roles might be encouraged to provide new input and perspectives on a given approach. Patient organizations and advocacy groups can be specifically helpful in this aspect but are infrequently included by academic settings. Better including patients is particularly important for novel therapeutic strategies, such as cell and gene therapies, where high levels of uncertainty surround their modes of action [28]. Patient input can begin to influence clinical trial designs, their end points and outcomes, and risk–benefit assessments.

(xii) 'Initiate discussions with payers on health technology assessment and product reimbursement strategies'. Analogous to the entire translational process, cooperation among diverse groups of stakeholders, including research sponsors (industry, academia, government,

Box 4. Potential Improvements to Active Patient Participation in Clinical Research and Enhanced Value and Sense of Worth in Clinical Trials.

(i) Using patient input to improve clinical trial designs: soliciting direct patient involvement in trial design can enhance patient recruitment, protocol adherence, retention, and guide trial design relevance and tolerability.
(ii) Expanding and diversifying enrollments in clinical trials: the current trial system using study volunteers from nonrepresentative patient groups must transition to substantially larger, diversified, and broadly representative study populations better representing those for whom results are medically relevant. Expanded volunteer recruitment into trials enhances their speed, reduces trial costs, and improves the general value of outcomes, better assessing risk–benefit and providing improved treatments to patients more rapidly. Public awareness of the clinical trial process and its societal value must be improved by educating the public about clinical research and actively dispelling common misperceptions.
(iii) Collecting patient-reported outcomes: objectively measured outcomes data are currently collected in trials, neglecting the most important outcome provided directly by patients, those reflecting how they feel (physically, emotionally) after receiving a medical intervention.
(iv) Performing patient-informed risk–benefit assessments: regulatory assessments of new therapies emphasize 'safety' as the paramount value; a safe technology is intuitively described as one that 'causes no undue harm'. 'Safety' represents a value judgment of the acceptability of risk of exposure to harm. Nonetheless, all therapies have some inherent risks of adverse events. Hence, a regulatory safety mandate is not an absolute criterion, but rather the relative acceptability of the safety profile of a medical intervention in the context of its potential benefits. Patients can provide unique and extremely valuable perspectives on impacts and relative values of various demonstrated benefits and risks.

nonprofit organizations, and patient advocates), clinical investigators, patients, payers, physicians, and regulators, is necessary to effectively pursue product development processes to market [29]. However, various stakeholders tend to initiate, for example, drug development programs for wide ranging and divergent purposes, some not directed at the question most often asked by payers or patients: 'Which treatment option is the most cost effective?' Most importantly, negotiating insurance reimbursement is often critical and missed by early-stage technology developers, particularly in academia, resulting in products with multiple, expensive components that drive up costs of goods sold not commensurate with value that each component contributes. To overcome this hurdle retrospectively, many companies enlist insurance company representatives to report newest requirements for reimbursement and discuss specific product development options. This strategy would be more effective when considered prospectively: to inform a health economic analysis essential for adequate business planning, and to establish pricing ranges reflecting the market. Moreover, developers should always be invested in refining their manufacturing processes to reduce costs [30] and implementing robust plans to improve reimbursement strategies, especially for novel therapeutic technologies [31]. Although production costs hugely impact pricing strategies for novel therapeutics, specifically new cell and gene therapies [30,31], developers are increasingly justifying their extraordinarily high pricing on improved levels of clinical efficacy achievable with these therapeutic modalities (e.g., value-based medicine) [32]. However, this strategy has failed to promote market adoption, as shown by Glybera, the million Euro gene therapy, and Provenge, Dendreon's immunotherapy drug costing approximately $23,000/month to provide 4.1 months of life extension. Instead, prices should reasonably recapture development costs while remaining affordable to patients and payers, and suitably incentivizing innovation over risks [30,31].

Concluding Remarks

As most research budgets are constrained, conserving resources to focus and coordinate translational efforts on best practices that avoid inefficiencies, losses, costly product failures, and 'red herrings' in new product development is critical. Many basic research approaches currently fail far too late in their development, maintaining a high-risk, high-cost liability over multiple developmental stages. Producing efficient processes that respect the ultimate needs of the industrial sector to remove weak technologies more rapidly and reliably, while selecting only the best prospects to move forward toward market is optimal. Although not always applicable, the 'fail faster' philosophy now pervasive in pharmaceutical industry should be considered in academic institutions pursuing translational research activities in early stages. This strategy should integrate and prioritize the different, relevant components of the 12-step guideline outlined here across early-, mid-, and late-stage translational processes for each case (i.e., new drug candidates might emphasize or select these steps differently than device innovations). This process emulates characteristics of industrial development strategies but within the distinct academic environment where scientific and scholarly priorities can be orthogonal to industry best practices to 'get to market'. While several open questions remain (see Outstanding Questions), adherence to these derisking principles in academic settings should increase chances for translational success while reducing research waste and expediting development timelines. As in all optimization protocols, further prospective research is warranted to verify the impact of these principles in practice, and to continue refining best translational mechanisms for biomedical technologies.

Outstanding Questions

What factors contribute to the poor translation of animal model outcomes to clinical practice: the suitability of the models themselves, the low predictive value of the models in evaluating efficacy of new drug candidates, the animal testing of product prototypes is not proceeding under appropriate quality standards, or the level of knowledge about the physiological and pathological characteristics of the disease?

How can patient advocacy groups promote the concept of 'mutual ownership', empowering patients to contribute to the clinical trials or research process for their own benefit and the benefit of others requiring similar care?

How can top–down selection of projects and priorities in academic translational research seek the earliest possible indication suggesting that a therapeutic candidate's performance does not warrant further and expensive experimental pursuit in development?

How can we obtain or adapt valid parameters useful in assessing reimbursement strategies for novel and orphan products; who is paying and what governs the market price?

What is the best way to balance the risk–benefit problem wherein a product may get approved based in part on biomarker evidence but where the ultimate clinical benefit might not be realized postmarketing in larger patient populations, possibly resulting in product withdrawal?

How can we capitalize on the benefits of big data in order to gain more translational breakthroughs?

How should we change the mind-set of academic institutions where publication strategy would support academic career development and knowledge dissemination while respecting intellectual property protection, careful assessment of global patenting costs necessary to ensure technology value preservation, and attraction of resources required to bring a product to market?

What is the best way to marry long-term, slow, inefficient basic research discovery foundations with short-term quarterly market expectations and performance goals for most companies?

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