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Key elements for nourishing the translational research environment

Hans-Dieter Volk[1,2,*], **Molly M. Stevens**[3], **David J. Mooney**[4], **David W. Grainger**[5], and **Georg N. Duda**[1,6]

[1]Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité - Universitätsmedizin Berlin, Germany

[2]Institute for Medical Immunology, Charité - Universitätsmedizin Berlin, Germany

[3]Department of Materials & Department of Bioengineering, Institute for Biomedical Engineering, Imperial College London, SW7 2AZ, London, UK

[4]Wyss Institute, Harvard School of Engineering and Applied Sciences, Cambridge, MA 02138, USA

[5]Department of Pharmaceutics and Pharmaceutical Chemistry, and Department of Bioengineering, University of Utah, Salt Lake City, UT 84112, USA

[6]Julius Wolff Institut, Charité - Universitätsmedizin Berlin, Germany

Seeking Nourishment

Biomedical innovations arising from academic settings often find their way to translation by chance: scouting by industry, personal relationships with academic and industrial key opinion leaders, or individual entrepreneurial efforts (forming spin-off companies), for example. Some say that this is to be expected because most academic biomedical research falls into the category of “discovery,” which includes extending general understandings of operational principles and biological mechanisms; in other words, basic research. Many investigators do apply this knowledge to addressing disease pathogenesis and developing therapeutics and medical devices (applied research). However, very few academic discoveries are appropriate to seriously consider translating.

Clinical development of new therapeutic strategies—from identifying lead candidates to their animal model and human safety and efficacy testing to their approval and final product release—is driven primarily by the biotech and pharmaceutical industries. Industry funds more life science research and development than all academic enterprises; worldwide, about US $200 billion—about US $90 billion alone in the United States—went to R&D in life science last year. About 70% of this R&D budget was invested by industry, 13% by academia (1, 2).

[*]To whom correspondence should be addressed: hans-dieter.volk@charite.de.

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Academic partners generally play a rather passive role during this translational process for drug and medical device development, restricted often to preclinical testing of device prototypes and drug lead candidates and limited clinical testing of new drug candidates in phase II/III trials. Furthermore, industry-driven developments frequently fail at late stages, owing partly to inadequate relationships with clinical scientists that result in critical deficiencies (inappropriate animal models, poor human adaptations of preclinical device designs, or inaccurate dosage scaling from preclinical to clinical studies).

Currently elevated socioeconomic pressures and trends toward more individualized therapies amplify the technical challenges for developing new therapies. In parallel, regulatory hurdles have increased in recent years; in addition to conventional therapeutic principles, such as small molecules, devices, and biologics, a new therapy class—the advanced therapy medicinal products (ATMPs), covering cell therapy, gene therapy, and tissue engineering—has been defined by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Similar discussions are ongoing for conventional medical devices as well as combination devices. Requirements for asserting safety to proceed into human trials have become more rigorous and complex, meaning more time and money are required to fulfill regulatory expectations. But money is drying up, too; industry and venture capital are pulling away from the high-risk, early-stage collaborations and partnerships with academia, reducing opportunities for successfully traversing the translational path.

As a result of the confusing translational agenda and accompanying mix of requirements and priorities, we in academia now experience an increasing discrepancy between general academic goals to discover and a more mature development of innovative therapeutic concepts from such knowledge toward application. Academicians are at the ill-defined crossroads of risk-taking, funding, translation, discovery, and professional advancement. As a result, efforts and resources are often wasted on misguided intentions and misunderstandings of what constitutes translation; what few, but select, qualified ideas are best translated; and who is qualified to do this important task. Infrastructure, expertise, and resources necessary to enable this process are often not present or poorly used.

In a consensus statement issued from the results of discussions at the recent Translate 2014! event in Berlin, Germany, a mindset that supports valid, efficient biomedical translation was forwarded (3). In that consensus, the authors asserted the need for a proper “well-oiled research infrastructure” that would vet and sort innovations, identify solutions to unmet clinical needs, and move the most promising technologies forward. Thus, a supply of essential infrastructure, expertise, and resources is requisite to “nourish” translational academic research through to clinical proof of mechanism (PoM) or proof of concept (PoC) (Fig. 1). Here, we attempt to identify important translational nourishment “checkpoints” associated with challenges in resources and structures needed to facilitate efficient and correct transitions from basic research to specific targeted applications through to their clinical validation.

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Step 1: Selecting translational projects

Because very few discoveries are appropriate for translation, a critical translational process is the first step of early-stage idea selection. If selection strategy is poor, this step can be exceedingly costly and wasteful. Proper selection of candidate projects among the plethora of projects claiming translational value is challenging. Technological feasibility, probability of success, intellectual property value, reasonable development costs and timelines to PoM and PoC, importance of the unmet medical need, requests from the end users (physicians), and clear regulatory requirements must all be considered carefully in this selection process.

Assessing the unmet medical need

Because they serve at the patient interface and often identify unmet needs, junior clinicians should be engaged early in translational development, including in the formal education and student training processes. Early exposure could involve research/clinical rotations and interdisciplinary training experiences that cross different medical and research fields. Such an introduction provides initial understanding to identify the underlying clinical needs and to assess them in the context of clinical practices, priorities, and preferences. Careful screening and scouting of the state-of-the-art approaches are important to recognize benchmarks for success in any given field. Early health technology assessments will help to identify current product and practical deficiencies and define the putative cost/value ratio related to addressing the unmet medical need.

Transforming basic knowledge into ideas and candidates for translation

As a primary source of discovery, basic scientists may be unaware of translational opportunities and their intrinsic challenges; thus, within an institution it is important to associate them with academic translational centers. This will also help to engage them in translational projects that require basic science—for example, clinical trials integrating mechanism-based research. An internal scouting system at academic centers can also help to identify promising basic research projects. Basic scientists should be involved in decision-making boards within academic translation centers (steering committees, technology assessment, and outcomes panels) and be extended professional and academic incentives to experience and engage in translational research.

Cutting-edge technologies from innovative fundamental ideas

Key issues in assessment of early-stage concepts for translation include technical feasibility, reasonable development costs, appropriate regulatory requirements and pathways, intellectual property scenarios, and freedom to operate. Early feasibility studies assessing these factors with each new technology are essential, as will be full analysis of manufacturing and regulatory hurdles to be faced later in the translational process.

Needs

A translational support structure at academic centers that critically evaluates the requirements for translating each concept is essential to better facilitate, streamline, and improve the selection processes. Such a support group should supply the following:

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An opportunity check (before start of translation): technological and financial feasibility assessments, analysis of targeted unmet medical needs, cost/value ratio of end product, advice on the therapy category for regulatory guidance, and putative industrial partners.

Risk assessment procedures: routine checks on project progress, new opportunities, and challenges arising over time that require a willingness to fail/explore multiple ideas in parallel.

Preregulatory support: identification of appropriate disease models and end points, study design and validation, and adequate documentation of preclinical work.

Core facilities: biomarker laboratories, good laboratory practice (GLP) animal research facilities, and good manufacturing practice (GMP) production.

Intellectual property support: prior art searches (including patent and product searches in databases), patenting strategies, freedom to operate analysis, and strategic patent advice/support.

Early health technology assessment (HTA): potential for payer reimbursement and cost-benefit analysis.

Partnering opportunities: academic and industry partners, including licensing models, return on investment (ROI) assessments, and reward based on assumption of risk.

Funding support for bridging basic to translational R&D mechanisms.

Acknowledgment of the value of translational research that does not result in technical publications, and ability to reward individuals who play substantial roles in translational teams and products.

Building these infrastructures requires long-term funding to hire capable, committed people experienced in technical innovation and to make the entire endeavor a “living concept” that all interested scientists at an academic center can be trained to appreciate and become involved with when appropriate and required.

Step 2: Clinically relevant *in vitro* and *in vivo* studies (preclinical PoC)

Approval for testing novel therapies in patients requires quality preclinical PoC studies as a key element

Most conventional in vitro and in vivo biomedical research experiments and study designs do not attain sufficient quality, precision, reproducibility, documentation, and clinical relevance or prediction to qualify as reliable preclinical support for human safety assessments. Preclinical studies are divided into two categories. The first is adequate preclinical disease models with high clinical relevance (validated, predictive models) that can be used for PoC comparable with planned clinical protocols and for biomarker validation. The second type of preclinical study involves in vitro and ex vivo testing on patient-derived material (tissues, biopsies, or blood) to validate targets and effects and to discover clinical parameters and biomarkers for risk or outcome stratification of patients. All

preclinical studies require adequate standardization, bioinformatics analyses, quality management, and documentation according to the Investigational New Drug/Investigational Medicinal Product Dossier guidelines for later submission to regulatory agencies such as FDA and EMA.

Needs

Preclinical studies are an important step for reducing risk from new developments moving from basic science toward clinical application. Academia can learn from the high levels of both standardization and documentation in industry-driven preclinical studies. There is a substantial need for public and private grant organizations to support this type of preclinical work because it is often less enticing than testing new ideas or entering early clinical trials. In this vein, young scientists should be incentivized to fully evaluate the translational potential of their ideas by advocating the value of making science tangibly useful.

On the other side, academic translational centers should exploit their relatively easy access to clinical data and patient samples. This requires the formation of (often project-related) multidisciplinary teams comprising physicians, engineers, and experts from translational support structures, as mentioned. It also requires high-level quality management systems for preclinical data surveys. An expert board of clinicians and basic scientists is highly useful for discussing the quality and relevance of preclinical in vitro and in vivo data before entering the next step of applying these data to initiate clinical trials.

Although key to translational efforts, such preclinical model development and patient sample analysis are more involved (regarding cost, effort, and time) than are the preliminary “novel” studies often reported by academicians in peer-reviewed literature. Moving too quickly past early model validation and patient relevance studies to the preclinical “efficacy” studies can produce false impressions of success for an early approach that is actually wasting valuable resources. It is better that ideas fail quickly and cheaply. Therefore, moving forward to mature phases of preclinical testing as suggested above requires careful selection of the project maturity and the type of potential product envisioned (from low to high risk): predicate versus new mode-of-action products. Each project will have different testing requirements and levels of evidence.

Step 3: Clinical PoM/PoC trials

Although fundamental progress that takes basic science findings forward toward application is frequently an important goal of the academic research mission, a complete and mature biomedical translational process must reach a clinical PoM or PoC at a clinical trials level to produce any benefit in human patients. To make this substantial commitment and investment requires a discerning vetting process that does not fall within the typical core expertise of biomedical academics. Clinical PoM/PoC is a key translational hurdle—and one most often left unattempted by basic researchers developing innovative new ideas. Vetting processes in translational pathways should both push the most promising ideas forward from discovery toward PoM/PoC while allowing distinct exits as early as possible in this process for those ideas that fail to approach or surmount this clinical hurdle.

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Because of financial and regulatory hurdles, the “first in human trial” is the most challenging translational step in an academic environment. However, investigator-driven studies can have more versatility as compared with classical industry-driven phase I/II study protocols. Key features that increase the value of investigator-driven trials include (i) highly selective and more flexible inclusion of “most appropriate” patients (patient subgroups) by specialized academic centers, (ii) observation of treated patients by experienced clinical experts, (iii) accompanying (biomarker) research and functional assessment, and (iv) greater freedom to explore combination therapies. Because safety is the key issue of early-stage clinical trials, adequate regulatory and clinical trial management is a precondition.

Determining the therapy category for regulatory processing

A therapy category recognized by prevailing regulatory authorities should be defined as early as possible (best case, at the preclinical project start) because this designation has a major impact on the feasibility and ultimate success of the translational project. Both regulatory and feasibility hurdles increase with the following sequence of therapy categories:

- Optimization of an approved therapy in the given indication.
- Off-label use of approved therapies in new indications (which requires new risk assessments and careful dosing).
- Biomarker-driven therapy by using approved drugs (secondary companion diagnostics for stratified therapy).
- Completely new therapies (need for complete preclinical studies, toxicology, phase I/IIa, for example).
- New therapies in patient subgroups based on biomarker profiles (companion diagnostics).

Regulatory hurdles

To jump the hurdles for obtaining all approvals needed for an investigator-initiated clinical trial, an adequate clinical development infrastructure is required. Different levels of approvals are needed for new trials: (i) study protocol approval by regulatory authorities (such as EMA or FDA)—recent changes in Europe now allow one multinational application by using the Voluntary Harmonisation Procedure; (ii) obtain manufacturing authorization (if the therapeutic product is produced by the academic centers themselves); (iii) obtain institutional review board (IRB) approval, ensure written informed consent from patients, and provide adequate insurance for the trial.

Accompanying biomarker studies

Aims of biomarker studies include identifying in vivo markers for safety, pharmacokinetics/pharmacodynamics, early therapeutic responsiveness, patient stratification, and nonresponder profiles to identify new targets. Such biomarker research is the basis for improved understanding of the therapeutic mode of action, reasons for non- or low response, and criteria for producing success or failure benchmarks or clinical trial end points, allowing more rational, iterative improvements for new or next-step approaches.

Whereas the first three points listed above (in “therapy category”) are reasonable for experienced academic medical research centers, introduction of completely new therapies with or without companion diagnostics is currently very challenging. However, the increasing availability of academic and contract research organization (CRO)–based GMP-certified laboratories for manufacturing biologics and ATMPs (e.g., gene therapy, cell therapy, tissue engineering) for clinical studies as required by regulatory authorities opens new opportunities for these academic translational centers to enable and direct even more complex, innovative translational research goals, including completely new therapeutic approaches.

Step 4: Refined translation – iterative improvements

The commonly used one-way path from phase I to eventual approval and commercialization has several limitations because after confirming safety, it focuses on asserting the statistical power of efficacy only. Hence, therapies can be approved even if many patients are nonresponders. Additionally, a statistical failure frequently kills the project—a costly end point occurring far too often at late stage. Insight into clinical trial designs that allow candidate approaches to fail earlier at reduced expense or to modify trial designs to obtain less risky end points would improve efficiency in translation. Opportunities for moving back and forth during less costly, early phases of clinical development along the translational path in an iterative, flexible way are very useful before moving forward into the late-stage development. The capacity to do such early, iterative risk reduction is an essential advantage of academic-based translational research approaches. This flexibility also helps to direct more basic academic research toward mechanisms-oriented studies.

A “refined translation” process can be a facile iterative strategy going from “bed” back to “bench” and forth again to bed. This process can dynamically respond to improve the original concept after a deep analysis of initial PoM/PoC trials informed by early patient data and allow performance of the next steps in clinical development with improved approaches, focus, trial designs, and refined clinical end points.

Analyzing data from early PoM/PoC clinical trials in detail, in particular from accompanying biomarker and clinical phenotyping studies, provides valuable opportunities to obtain important insights about trial failure in general or in individual patients (nonresponders). Basic science and technological investigations test the hypothesis, inform therapeutic metrics, improve the candidate pipeline, and bolster revised preclinical PoC studies. Although perhaps considered “iterative improvement,” inclusion of basic science in refined translation can better inform the second generation of PoM/PoC clinical trials. This next generation could feature a new design to verify the improvements, uncover new therapeutic approaches, and help to decide whether the approach or technology is ready to move forward to late clinical development (or go back for another iterative translational cycle).

Need

Reliable performance of investigator-driven early clinical PoM/PoC trials requires mature translational infrastructure and resources dedicated to covering regulatory aspects; patient

monitoring; safety management; GMP manufacturing; bioinformatics; biomarker development, validation, and studies; and multidisciplinary groups of basic and clinical scientists. Because independent structures within single clinics or institutes are not typically very cost-effective and professionally oriented toward translation, academic institutions offering infrastructure with modern interdisciplinary clinical research units have a great advantage.

Conclusions

The model proposed here for a complete, comprehensive formalized translational research process that runs through all clinical phases, including the promising option of a refined internal translational process, requires long-term vision, expertise, and investment. These are required to recognize, acquire, and build key processes and capabilities, infrastructure, and resources that together nourish the translational research process while emphasizing strategy, efficiency, and careful decision-making. Academic translational centers that support multidisciplinary research, translational activities, and dovetailed educational programs may be able to optimize structures along our guidelines to improve translational research. However, development of this capability also needs leadership and committed attitudes that overcome the many diverse challenges in funding long-lasting structures and providing incentives for translational research (1). The academic performance metrics require adjustments to reward those who pursue less elegant but more impactful research routes that lead—at substantial risk of failure—to patient quality-of-life improvements. In addition, collaborations between academia, biotech, and pharma industrial partners (4) must be facilitated at early development stages to produce new levels of interactions and access to mutual, shared expertise.

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One-sentence summary

Translation in an academic environment requires a support system—people, goals, models, partnerships, and infrastructures—that will push promising basic science and technology projects forward into the clinic.

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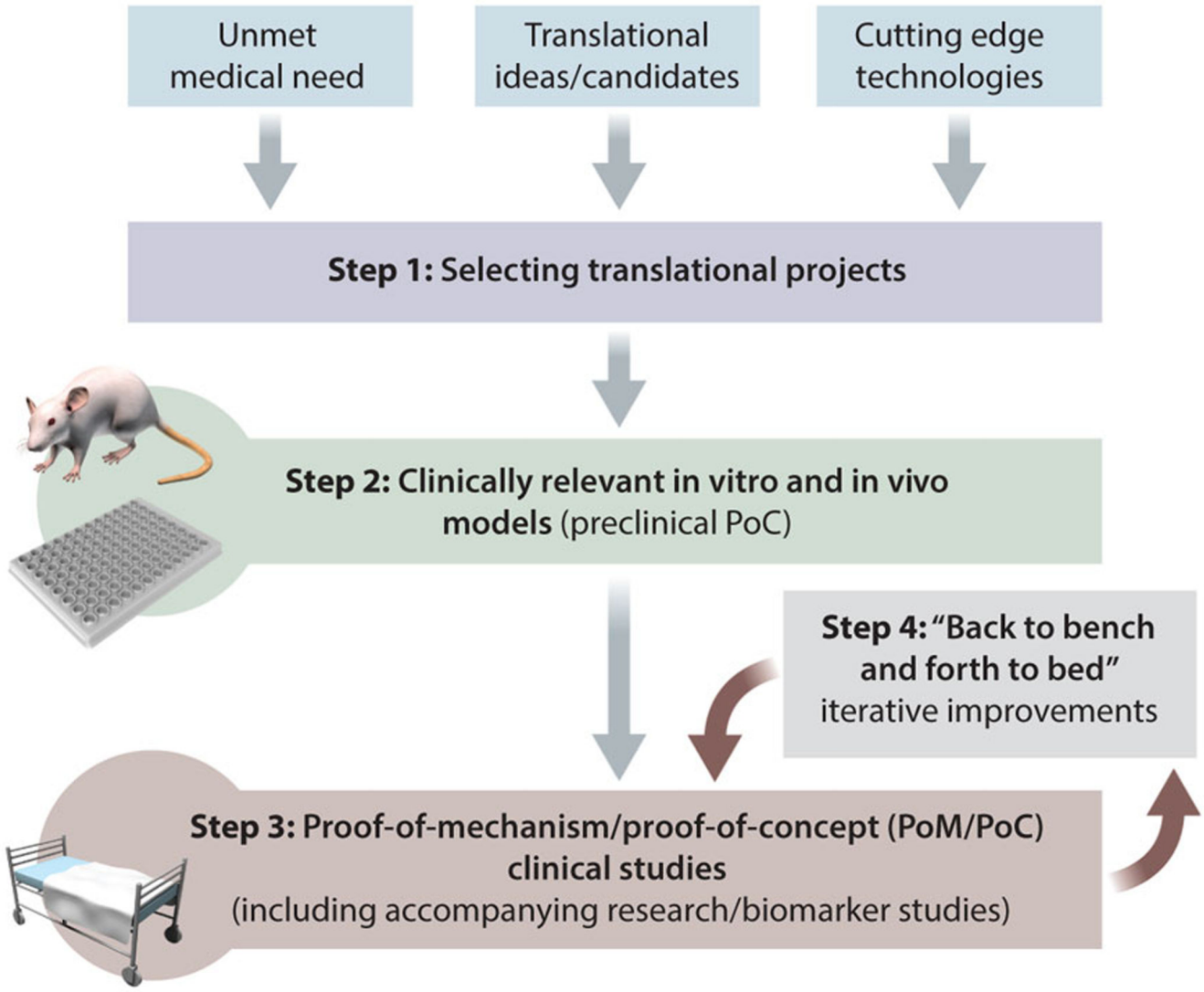

Figure 1. The nature of nurture.

Following the mandates identified by accurately assessing unmet clinical needs, the most appropriate translational approaches to address these needs are advanced to candidacy. Validation of the strategy with judicious, proven preclinical models, validation criteria, and markers is critical to achieve confident proof of concept prior to clinical testing. Clinical performance might be further optimized by iterative returns to modified bench prototypes, new preclinical testing, and improvements to aid other important commercial factors, including manufacturing, packaging and sterilization.