Translational Medicine: History, Principles, and Application in Drug Development
What is translational medicine? This discipline, although defined differently by various groups in academia, regulatory institutions, and industry, shares the fundamental vision of translational medicine, which is to efficiently and effectively translate basic scientific findings relevant to human disease into knowledge that benefits patients. Pfizer was one of the first pharmaceutical companies to embrace experimental medicine and translational medicine as a recognized discipline within the sphere of early drug development, and this author was intimately involved in the evolution of this discipline since its inception at this company. This chapter therefore describes the significance, role, and practice of translational medicine in drug development from a Pfizer perspective, although the concepts are considered to be widely applicable to drug development at any academic, public, or private institution. At Pfizer, translational medicine was defined as "the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies, and study designs to improve confidence in human drug targets and increase confidence in drug candidates, understand the therapeutic index in humans, enhance cost-effective decision making in exploratory development, and increase success in Phase 2 leading to a sustainable pipeline of new products." Because this book focuses on drug development, this will be the definition for the purposes of this chapter.

In the late 1980s and early 1990s, pharmaceutical companies were rapidly adopting a drug discovery strategy that depended on selecting drug targets based on what was known about key pathways important in disease expression, enzymes that catalyzed rate-limiting steps along the pathway, or cellular receptors that were ligated by important relevant mediators. After these targets were selected, chemical libraries were screened for leads that modulated the activity of these pathways. These chemical leads were optimized into new chemical entities (NCEs) and progressed into in vitro and in vivo biological testing to confirm their druglike properties. This drug discovery strategy and its associated activities were quite different from earlier methods that directly screened NCEs or naturally occurring
Fig. 1.1a
The remit of translational medicine during drug development.

Translational Medicine

Three hypotheses tested in humans during drug development.

- POM: Pharmacology can be safely expressed in humans
- POC: Pharmacology translates into benefit to patients
- Patient benefit is commercially attractive

substances for efficacy in animal disease models. It was thought that knowing the drug’s target and mechanism of action and having a scientific rationale for efficacy and safety from the beginning would increase the success rate for drug discovery. The new approach resulted in fuller pipelines that stretched resources, and companies needed to develop a strategy for identifying the compounds with the greatest probability of developmental success ("winners") and those less likely to be successful ("losers") as early as possible. To execute this new strategy, pharmaceutical companies formed “experimental medicine” organizations, the primary mission of which was to demonstrate that a drug was safe and active on its target in humans (defined as proof of mechanism or POM) and to determine whether this expression of pharmacology translated into meaningful efficacy in patients (defined as proof of concept or POC). Within the pharmaceutical industry, it was these groups of clinician–scientists that developed and refined their translational skills and evolved into translational medicine groups. Their role often involved the translation of biomarkers from the laboratory into the clinic using transparent criteria for qualification and validation for a specific decision-making purpose such as POM and POC (Figure 1.1a).

Compared with experimental medicine, however, translational medicine groups began to work further upstream in the drug discovery and development process. Experimental medicine groups generally did not have any responsibility for drug projects prior to identification of the drug candidate or, in some cases, prior to the first in human (FIH) studies. Translational medicine groups, in contrast, became involved in all early phases of drug discovery from target identification forward. They often conducted studies in patient populations to increase confidence in drug targets or test the translatability of biomarkers from preclinical models to humans in parallel with the early stages of drug discovery in the laboratory. The frequent failure of animal models to predict efficacy in humans led to a more cost-effective and efficient strategy to get drug candidates to humans earlier to aid target selection and optimize candidate selection because humans were recognized as the “ultimate model
I.1. Biomarkers in Drug Development: A Common Understanding

In 2003 at Pfizer, different groups and individuals focusing on different stages and disciplines of drug development, including discovery, toxicology, biomarker development, clinical research, translational medicine, and drug metabolism, had different understandings of what biomarkers were, how they could be used, and how they were validated or qualified. To move translational research objectives forward and achieve universal buy-in for the use of biomarkers for development decisions, it was important to develop a common lexicon. Leaders of these various disciplines not only wanted to accomplish this for Pfizer, but they also wanted to do this for the drug development community as a whole. The following definitions were agreed on and used in many internal and external communications and presentations.

**Biomarker:** A characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (consistent with the National Institutes of Health [NIH] Workshop definition).

**Diagnostic:** A biomarker that has clinical applicability for patient management (e.g., in diagnosis, in identification of a subpopulation of patients who would benefit most from a drug or suffer adverse events from a drug, to aid dose selection).

**Surrogate end point:** A biomarker accepted by regulatory agencies as a substitute for a standard clinical endpoint for drug approval (e.g., organism" (Figure 1.1b). This strategy was supported by the U.S. Food and Drug Administration (FDA) in the United States through the exploratory investigational new drug (IND) mechanism and subsequently in the European Union (EU) through the exploratory Clinical Trials Application (CTA) mechanism.

This chapter will focus on the role of translational medicine groups in the pharmaceutical industry, how their work supports the aforementioned decision-making strategies, and how these strategies may undergo subsequent change as we embark on an era of personalized medicine.

**Biomarker Types and Linkage to Outcome:** Every biomarker could be defined based on two parameters: its type and its degree of linkage to efficacy or safety outcomes in humans. Three types of biomarkers were defined:

**Target Biomarker:** Measures physical or biological interactions with the molecular target (e.g., positron emission tomography [PET] ligand demonstration of receptor occupancy, measurement of enzyme inhibition, measure of receptor blockade).

**Mechanism Biomarker:** Measures a biological effect presumed to be downstream of the target. For example, the biomarker may be physiological (e.g., blood flow), biochemical (e.g., change in downstream substrate turnover), behavioral (reaction time), genetic (e.g., change in gene expression), or proteomic (e.g., change in protein profile in tissues or biofluids).

**Outcome Biomarker:** Substitutes for a clinical outcome measure that is independent of the mechanism or target of a compound or predicts an outcome of a disease or toxicity following treatment.

**Linkage to Outcomes:** This second dimension for describing a biomarker refers to its linkage to human efficacy or safety outcomes. The linkage is labeled low, medium, or high based on the following definitions:

- **Low** = There is no consistent information on the linkage of biomarker change to efficacy or safety outcomes in humans. Linkage to outcomes in animal models may exist.

- **Medium** = Biomarker differences are associated with efficacy or safety outcome data in humans but have not been reproducibly demonstrated in clinical studies.

- **High** = Biomarker differences have been reproducibly demonstrated to be correlated with disease efficacy or safety outcomes in two or more longitudinal studies in humans.

Examples of how biomarkers were classified using this system are provided in Figure 1.2.
The process of achieving acceptance of the validity of biomarker data for decision making also required a common understanding of the definition and requirements for validation or qualification, including the following:

**Validation:** Characterization of the biomarker that confirms its fitness for a specific purpose. The degree of rigor required varies with the purpose but always requires organizational agreement. This has more recently been termed “qualification.”

**Technical Validation:** The process of selecting all technical attributes required to demonstrate fitness for the purpose, setting appropriate performance requirements for each attribute, and evaluating the biomarker against these requirements. Examples of some of the elements of the technical evaluation process that may be required are demonstrations of selectivity and specificity, accuracy, precision, responsiveness to pharmacology or disease, and robustness of all necessary procedures and assay steps under conditions similar to those that will be encountered in use (e.g., in a clinical methods study, storage, stability, and matrix effects are considered).

**Note:** The term “clinical validation” is not recommended because it is included in the linkage to outcome dimension of this biomarker classification. Full clinical validation such as may be required to achieve surrogate endpoint status can be viewed as meeting the criteria for high linkage to outcome, but for many purposes this degree of validation is not required.

**Biomarker Translation:** The activities needed to ensure that the biomarker (assay and underlying biology) is valid between preclinical species, between preclinical species and humans, or both.

Refer to Chapter 8 for additional information on the process of biomarker qualification.

The roles of biomarkers in drug development relate to their ability to be translated to humans from preclinical models to define criteria for POM, to measure pharmacodynamic (PD) activity in animals and humans for purposes of dose selection and pharmacokinetic (PK) – PD modeling and simulation, to substitute for efficacy and safety clinical endpoints in defining POC, to select appropriate populations of subjects for a clinical trial, and to predict clinical outcomes. These uses will be discussed later in this chapter.

### 1.2. Pharmacology: Testing the Target (POM)

If preclinical data on compounds and predictions of efficacious doses in humans were 100% accurate, new compounds could simply undergo...
Phase 1 testing for pharmacokinetics and safety (on completion of toxicological testing) and then be evaluated in appropriately powered Phase 2 trials with a high probability of success. Across the industry, however, success rates in Phase 2 decisions have decreased to half their level in the early 1990s (Figure 1.3).\(^5\) The most common reason for failure in Phase 2 in the 1990s was lack of efficacy, and the failure rate for unprecedented mechanisms (i.e., new mechanisms) is considerably higher than the industry average.\(^6\) Why is this the case, and how did the industry respond?

There are many areas of uncertainty regarding the translation of preclinical pharmacology data to humans. The simplistic strategy of accepting the validity of predicted efficacious doses or drug exposure and performing large Phase 2 trials after they are achieved could be the fastest route to Phase 3, but it leaves many unanswered questions when it is not successful. What do you do next if the drug fails to achieve an efficacy signal? Is the molecular target still valid? Has the mechanism been fully tested? Has the target been fully engaged? Do we just need a more potent NCE or one with better (higher or longer) exposure? In fact, this was the situation in which many companies found themselves during the late 1990s as failure rates in Phase 2 doubled (Figure 1.3). These questions cannot rationally be answered unless we know whether the drug actually expressed its intended pharmacology as a result of modulating the drug target.

Translational medicine groups addressed this issue by developing clinical experimental methods and biomarkers that could be used to evaluate the pharmacological activity of drug candidates in Phase 1 studies, usually in the FIH or first multiple-dose Phase 1 study. These methods and biomarkers are translated from preclinical animal or in-vitro studies to humans to confirm that a compound is active on its target and expresses its mechanism of action. As defined earlier in this chapter, these may be target biomarkers if they directly measure drug–target interactions (e.g., receptor occupancy using a PET ligand) or mechanism biomarkers if they measure downstream consequences of target modulation. Criteria for moving forward into Phase 2 are based on the translation of preclinical results and
defined as POM. This process is illustrated in Figure 1.4. In general, the POM biomarker criteria are based on a similar biomarker signal in animals that resulted in downstream outcomes in disease models. Although efficacy in preclinical disease models often does not translate into efficacy in the human disease, efficacy in the animal disease model is a result of the compound’s pharmacology and is a downstream outcome. Because most companies would not be advancing the drug candidate if it did not have efficacy in an animal disease model, using the model to help define POM is both logical and acceptable. Figure 1.5 illustrates how POM criteria are translated to humans and describes the principles for creating these criteria. In all cases, the clinical methods, biomarkers, and “doability” in the setting of a clinical trial must be validated to a level at which all stakeholders agree to use the results for the POM decision.

The process of validation or qualification can be illustrated using the example of an ultraviolet light type B (UVB) skin irradiation challenge model for a p38 mitogen-activated protein (MAP) kinase inhibitor program for rheumatoid arthritis (RA) that was developed at Pfizer. The validation plan included the following steps:

- Technically validate all biochemical assays using murine and human skin biopsies;
- Evaluate these endpoints in hairless mice after exposure to UVB irradiation and determine the effect of the p38 inhibitor;
- Confirm UVB effects on the same endpoints in human skin;
- Evaluate reproducibility of UVB-induced changes in humans to determine sample size for a Phase 1 clinical study; and
- Benchmark the changes seen with murine p38 inhibition in skin with the efficacy outcomes in a collagen-induced arthritis disease model.
Figure 1.6 summarizes the outcome of these efforts. Here the downstream mechanism biomarkers are biochemical, and the model could be performed in healthy volunteers during the course of a Phase 1, single-dose trial. The drug candidate’s level of inhibition of UVB-induced murine responses downstream of p38 MAP kinase at a dose and exposure that had efficacy in the collagen arthritis model is the level of inhibition needed for POM in humans using the same skin model. The same model could be used for compound differentiation or optimization either in the preclinical phase or in humans through modeling of drug exposure and pharmacodynamic response relationships (PK/PD modeling) and simulation.

As described earlier in the text, mechanism biomarkers do not necessarily have to be biochemical. For some mechanisms and indications, POM criteria may require confirmation of drug activity in a target population using a translated behavioral biomarker rather than a biochemical endpoint. For example, Figure 1.7 describes how POM was defined and achieved for an anorectic agent being developed for obesity. Here reduced...
1.2. Pharmacology: Testing the Target (POM)

Table 1.1. Examples of POM Using Biomarkers Translated from Preclinical Models

| Inflammation/Immunology: Flow cytometry for changes in cell surface activation markers, intracellular biomarkers (cytokines, etc.); lymphocyte subpopulation changes; pathway-relevant gene expression changes (blood, tissue); endotoxin challenge models; skin challenge models; direct measurement of mediators in serum or urine; immunization models |
| Obesity programs: Food intake and energy balance |
| ADHD: Cognitive effects, functional imaging |
| Osteoporosis: Bone biomarkers |
| Psychotherapeutic programs: PET receptor occupancy |
| Oncology programs: Angiogenesis biomarkers (dce-MRI, vessel density), tyrosine kinase inhibition (target phosphorylation), metabolic response (FDG-PET) |
| Atherosclerosis: Lipids, inflammation biomarkers |

POM decision criteria are derived from the biomarker change associated with desired downstream outcomes in animal models that are translated to humans for POM decisions.

dce-MRI: dynamic contrast-enhanced magnetic resonance imaging.
FDG-PET: Fluorodeoxyglucose positron emission tomography.

food consumption was validated as a mechanism biomarker and translated from a mouse model to humans. Other examples of POM for various types of projects are listed in Table 1.1.

What if POM is for a compound whose target is nonhuman and instead belongs to a pathogen? Antiviral agents and antibiotics usually target molecules that are coded for by the genome of the pathogen. Frequently, the preclinical work for antiviral agents includes the development of an