PART ONE

BIOMARKERS IN DRUG DISCOVERY

1

THE IMPORTANCE OF BIOMARKERS IN TRANSLATIONAL MEDICINE

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1.1 INTRODUCTION

The new millennium was to have ushered in a bright new era of drug discovery. The unraveling of the human genome would provide a host of new therapeutic gene targets to treat debilitating diseases (1). The rest of the "omics" (proteomics, metabonomics, and transcriptomics) would provide additional insights on these targets and methods to assess drug effects early in the development process (2, 3). New therapeutic modalities (sRNAi, therapeutic proteins, and vaccines) would allow us to treat diseases, such as Alzheimer's disease, that up until now have eluded our best efforts. This was an engaging vision of the future.

What the new millennium has brought so far is steadily decreasing R&D productivity in the pharmaceutical industry. In 2007, only 16 new chemical entities were approved, compared to the 27 approved in 2000 by the U.S. Food and Drug Administration. The success rate for drugs in phase II proof of concept (POC) testing is at 20% or less (4). At the same time, the cost of bringing a new medicine to the market is approaching US$1.7 billion (5). There have also been several high profile withdrawals of products from the market for safety concerns, most notably rofecoxib (VIOXX® Tablets). This is hardly the vision conjured by mapping the human genome.

The key to addressing these issues and realizing the bright future for drug development is to assess, as early as possible, the properties (good and bad) of a potential target for intervention in a disease process and therapeutic modalities against that target. On the basis of these data, one must make a decision

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whether to devote resources (private or public) to the development of that particular agent. The challenge is to do this with limited resources and with less than a 100% certain answer. By making early decisions on compounds and targets, we can then assess more targets/treatments for potential benefit and devote our limited resources to those that show the most promise. Traditional drug development paradigms have relied on large and prolonged studies to make go/no go decisions on new therapeutics. For example, a definitive answer on the utility of a disease-modifying agent for rheumatoid arthritis requires the assessment of the progression of joint narrowing and erosion by radiography (6). For Alzheimer's disease, long-term studies are necessary to establish a disease-modifying effect (7). How then do we get an answer within 3 months (or less) in 100 patients (or less) that an investigational treatment for these treatments is likely to be of therapeutic benefit and warrant the resources necessary for continued development?

Translational medicine has been proposed as the answer to the above question, and biomarkers are critical to the successful translation of findings in pharmacological studies in animals to therapeutic benefit in humans. The purpose of this chapter is to examine the integral role that biomarkers play in translational medicine and the development of new medicines. We examine successful applications of biomarkers to speed drug development and discuss examples where the lack of biomarkers has led to repeated failure in drug development. Finally, we discuss some future directions in biomarker research that can enhance drug development.

1.2 TRANSLATIONAL MEDICINE AND BIOMARKERS—SOME USEFUL DEFINITIONS

In any discussion on biomarkers, it is important that it is clear exactly what is being discussed. For example, the question, "Is your company working on biomarkers?" can be difficult to answer. Is the questioner referring to biomarkers for use in translational medicine and early decision making during drug development? Or rather, does the question really relate to a company's development of diagnostic tests to use when a drug is approved? Thus, the various definitions of translational medicine and biomarkers should be clearly understood in order to promote advancement in these areas.

Littman et al. (8) state that "The question of how to define translational research remains unresolved and controversial." They also provide a table (Box 1.1) that describes the areas that define translational research. The FDA Critical Path Initiative (9) describes translational research as being concerned with "moving basic discoveries from concept to clinical evaluation." The interesting part of this definition is that it is unidirectional from test tube to animal to human. Equally important is the back translation of clinical observations that may elucidate important insights into human disease, which drive further basic research aimed at new therapies (10).

Box 1.1 GOALS AND AREAS DEFINING TRANSLATION RESEARCH

Goals
The establishment of guidelines for drug development or for the identification and validation of clinically valid biomarkers.
Experimental nonhuman and nonclinical studies conducted with the intent of developing principles for discovery of new therapeutic strategies.
Clinical investigations that provide the biological foundation for the development of improved therapies.
Any clinical trial initiated with the above goals.
Basic science studies that define the biological effects of therapeutics in humans.

Source: Reproduced with permission from Littman BH, Di Mario L, Plebani M, Marincola M, *Clinical Science*, 2007;112:217–227 (8). This table was adapted from Mankoff SP, Brander C, Ferrone S and Marincola FM (2004), *J Transl Med* 2, 14, published by BioMed Central Ltd (9).

The NIH Biomarkers Definition Working Group (11) defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention." This is a relatively broad definition of a biomarker, which would include widely disparate methodologies such as FDG-PET, cognitive test batteries, gene expression, protein expression, and biochemical measures under the realm of biomarkers. The same group identified several uses for biomarkers, including diagnosis of disease, a tool for staging disease, and indicator of disease prognosis, or for prediction and monitoring of a clinical response to treatment. Translating these uses to drug development, biomarkers can be used to select which patients should be treated or to monitor beneficial and harmful effects of a medication. Implicit (but often forgotten) in the use of biomarkers in drug development is that they should be decision making; data obtained should affect either the conduct of a protocol or a development program.

In any discussion of biomarkers, one must differentiate between biomarkers and surrogate markers. The NIH group also defined a subset of biomarkers, the surrogate endpoint, as "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. In this sense, substitute is generally considered to mean substitute in a regulatory sense for a clinical endpoint." Classical surrogate endpoints are arterial blood pressure reduction as a surrogate for reduced stroke and cardiovascular mortality, LDL-cholesterol reduction for reduced cardiovascular mortality, and prolonged QT interval as a reflection of risk of sudden cardiac

death due to torsades de pointes. In this chapter, we deal with biomarkers in the broadest sense of their use, and do not focus on the development of biomarkers as potential surrogate endpoints.

In developing and using biomarkers, one can use various classification systems. One is related to the type of information that the biomarker provides. According to this, a biomarker can be classified as a target, mechanism, or outcome biomarker (12). A target biomarker measures the interaction of a drug with a target receptor. A common example is measuring the binding of an atypical antipsychotic drug to D2 receptors in the brain using positron emission tomography of a ^{11}C-labeled ligand. A mechanism biomarker measures a physiological, biochemical, genomic, or behavioral change that occurs downstream from the target. Examples would be glucose lowering for a diabetes drug, decreased target phosphorylation after a kinase inhibitor, or sedation after the administration of a benzodiazepine. Outcome biomarkers are those that relate to the efficacy/toxicity of a compound, such as viral load as a function of survival benefit for anti-HIV therapy.

One can also consider the linkage between biomarker effects and clinical outcome (13). For example, mydriasis may be an excellent indication of the activity of a norepinephrine reuptake inhibitor (mechanistic biomarker), but it is not necessarily an indicator of potential efficacy in depression (14). On the other hand, occupancy at the D2 receptor, as measured by PET for an antipsychotic (target biomarker), is very closely related to efficacy for this class of compound (15). Thus, the linkage with outcome, as well as the type of biomarker, should be considered when assessing the ultimate utility of a biomarker.

The terms *validation* and *qualification* in relation to biomarker development also cause confusion. Wagner (16) defines validation as "The fit-for-purpose process of assessing the assay and its measurement performance characteristics, determining the range of conditions under which the assay will give reproducible and accurate data." Qualification is defined by Wagner as "The fit-for-purpose evidentiary process linking a biomarker with biological processes and clinical endpoints." The key phrase in both definitions is "fit-for-purpose." The rigor around validation and qualification should be dependent on the use of a biomarker and the decision that it will drive. The rigor around the validation and qualification of a biomarker used to assess whether a compound continues in development may be much less than that for a biomarker used to determine whether a particular patient should be treated with a particular compound. Fit-for-purpose thus means that the assay and its relevance to therapy are sufficient to drive the decision for which they are being developed.

1.3 BIOMARKERS: THE ROSETTA STONE OF TRANSLATIONAL MEDICINE

The term *translational medicine* suggests that we are translating "something" in animals to "something" in humans. During drug development, this would be

translation of activity in an animal model of disease to activity in the human disease with great fidelity. Unfortunately, this is not a common occurrence in drug development. Perel et al. (17) systematically reviewed the concordance between animal and human data for six disease areas. Table 1.1 describes the areas reviewed, the number of animal studies reviewed, and the methodological aspects of these studies. Three of the interventions showed concordance in outcomes between animal and human studies (thrombolysis for acute ischemic stroke, bisphonates for osteoporosis, and antenatal corticosteroids), and three did not. In the case of antifibrinolytics for hemorrhage, animal models yielded no reliable data, while clinical trails showed clear benefit. In general, the study designs of the animal studies were poor, generally lacking in randomized treatment allocation or blinding of the allocation or the assessor. Thus, there is substantial room for positive bias in the assessment of the results in these animal studies. There was, however, no correlation between the quality of the experiments and the concordance between animal and human studies.

Irrespective of methodological considerations, there are often differences between human disease and disease models in animals (18). If one considers acute ischemic stroke, many drugs have been studied in animals and humans, and only one, tissue plasminogen-activating factor, has been found to be efficacious and is in clinical use. In the neurological trauma arena, many animal studies are conducted in healthy animals, free of the comorbidities (diabetes, high blood pressure, etc.) that would be present in an elderly patient with an acute ischemic stroke. In addition, genetic homogeneity with a rat strain does not reflect the genetic heterogeneity in the human patient population. Outcome measures in rodents (infarct size) do not reflect relevant outcome measures in humans (functional disability). Animal models, where therapeutic interventions

TABLE 1.1 Quality of Animal Studies Used to Predict Efficacy in Several Disease Indications

Intervention	Random Allocation to Group	Adequate Allocation Concealment	Blinded Assessment of Outcome
Corticosteroids for traumatic head injury ($n = 17$)	2 (12)	3 (18)	3 (18)
Antifibrinolytic agents ($n = 8$)	3 (38)	0	4 (50)
Thrombolysis for acute ischemic stroke ($n = 113$)	43 (38)	23 (20)	24 (21)
Tirilazad for acute ischemic stroke ($n = 18$)	12 (67)	1 (8)	13 (72)
Antenatal corticosteroids ($n = 56$)	14 (25)	0	3 (5)
Bisphonates ($n = 16$)	5 (31)	0	0

Values are number of studies (percentages of total).

Source: Adapted with permission from BMJ Publishing Group Ltd. Comparison of treatment effects between animal experiments and clinical trials: systematic review. Perel P, Roberts I, Sena E et al. *BMJ*, Volume 334, p 197, Copyright 2007 (17).

may be administered before or shortly after a neurological insult, may not be reflective of therapy in humans that will not begin for hours after neurological insult. While these examples are specific to the area of stroke and neurotrauma, similar results are seen across multiple therapeutic areas.

Disease models in animals themselves rarely reflect the human disease in total. Disease models generally reflect some aspect of the human disease. For example, some depression models in animals reflect the learned helplessness typical of human depression, while other models address the cognitive deficits seen in human depression (19). Separate transgenic mouse models in Alzheimers disease have been developed to address abnormalities in β-amyloid protein, tau-protein, and pre-senilin (20), which are commonly found together in the human disease. In many cases then, animal models are set up to reflect certain pathways in human disease, rather than the disease per se. Both disease models and pharmacology models in animals may be used in translation to humans, as shown in Figure 1.1, but both pathways require biomarkers for successful translation (21).

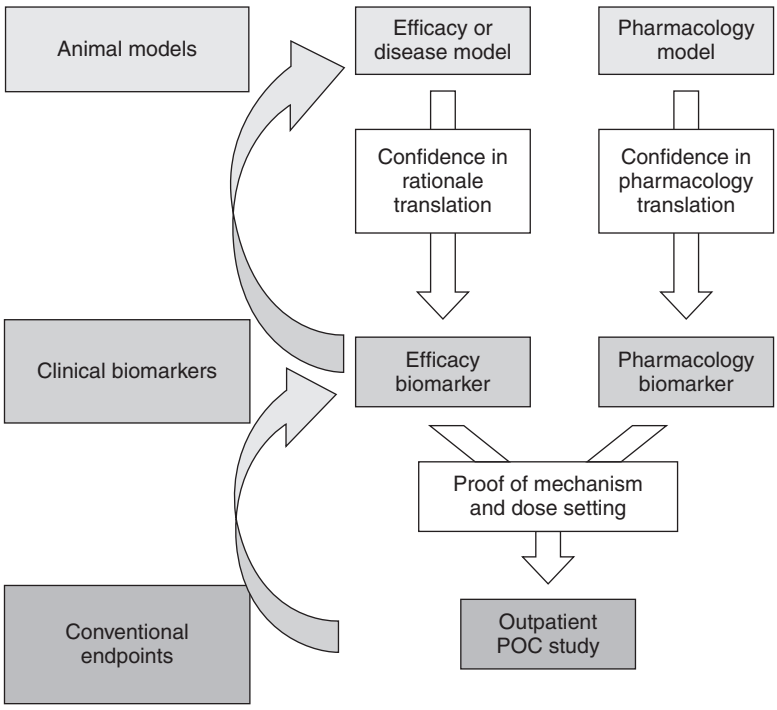

FIGURE 1.1 Linked animal models and clinical biomarkers can be used to confirm translation of preclinical efficacy and pharmacology to clinical effects. Clinical measures are used to set dose range and optimize the design of outpatient studies. *Source:* Reprinted from *Drug Discovery Today*, Volume 12, Sultana SR, Roblin D, O'Connell D, pp. 419–425, Copyright 2007, with permission from Elsevier.

The development of translatable biomarkers is still an evolving field, but there are several examples available. Cardiac troponin has been shown to be indicative of cardiac injury in both animals and humans, so that there is high confidence that the increases in cardiac troponin in animals seen in preclinical drug testing would also be seen in humans (22). As such it is a valuable screening tool. Imaging techniques such as PET for receptor occupancy or fMRI have been useful in the development of antischizophrenic compounds (21). Other soluble biomarkers, such as cyclic GMP, can reflect the pharmacology of agents such as the neuroendopeptidase inhibitor and PDE-5 inhibitors in both animals and humans (21).

Target and mechanism biomarkers that would be translatable from animals to humans are absolutely essential to answer key questions during the early development process. These questions are as follows:

1. Does the drug hit the intended target in humans?
2. Does the drug exhibit the intended pharmacology in humans?
3. What is the relationship between pharmacokinetics and pharmacodynamics in humans?
4. What doses/drug concentrations are appropriate for initial studies in patients to more fully explore the efficacy of the compound? Can these be achieved within the tolerable dose range for the compound in humans?

For novel compounds, positive answers to all of these questions are needed to assure that we adequately test the hypothesis that modulating the target mechanism in humans has beneficial effects on a disease process. While this conclusion is intuitive, large scale development programs have been conducted in the absence of this information.

1.4 DRUG DEVELOPMENT WITHOUT BIOMARKERS—AN EMPTY EXPERIENCE

Tirilazad mesylate (Tirilazad, Fig. 1.2) is a 21-aminsteroid compound that was developed as a free radical scavenger and antioxidant for the treatment of acute neurological trauma (23). Tirilazad was studied in the treatment of head injury, ischemic stroke, spinal cord injury, and aneurismal subarachnoid hemorrhage and was approved in several countries for the treatment of subarachnoid hemorrhage.

Tirilazad was designed to prevent lipid peroxidation following the generation of free radicals due to the initial tissue damage following a neurological insult. A variety of treatment paradigms in preclinical models were utilized for tirilazad, ranging from single-dose administration following head trauma in mice to administration for 6 days in a canine model of subarachnoid hemorrhage (23). These paradigms were designed to cover the time of penumbral neurological damage that could occur after the initial insult. All of these studies had several characteristics in common. Neurological outcome measures (motor scores,

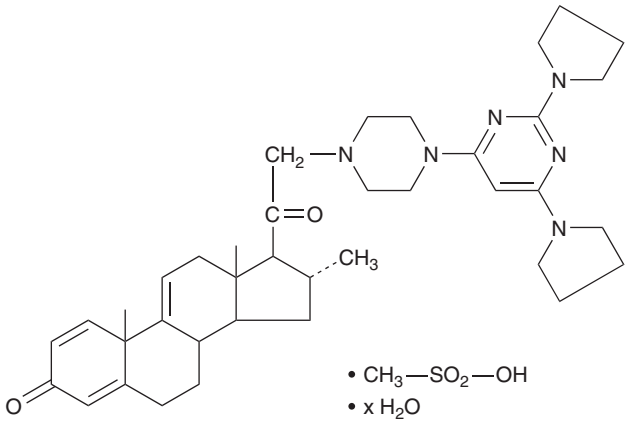

FIGURE 1.2 Structure of tirilazad mesylate.

evoked potentials) or local morphologic/biochemical measures (infarct size, middle cerebral artery vasospasm, lipid peroxide levels, etc.) were the key endpoints for these studies. With the exception of attempts to evaluate the sparing of antioxidant vitamins (vitamins C and E) peripherally by tirilazad (24), neither circulating biomarkers nor circulating or brain levels of tirilazad were measured as part of these studies. Dosing was based on body weight (mg/kg), and exposure was not compared across animal species.

On the basis of the data available in animals and humans, how would we answer the questions outlined in the previous section?

1. Does the drug hit the intended target in humans? We do not know. No assessments of brain uptake of tirilazad were performed in humans.
2. Does the drug exhibit the intended pharmacology in humans? We do not know. Tirilazad elicited no overt pharmacology in early clinical trials.
3. What is the relationship between pharmacokinetics and pharmacodynamics in humans? We do not know. No biomarkers were available to measure tirilazad activity, and there was no correlation between tirilazad dose or exposure and efficacy in humans.
4. What doses/target drug concentrations are appropriate for initial studies in patients to more fully explore the efficacy of the compound? Can these be achieved within the tolerable dose range for the compound in humans? We do not know. The only extrapolation that could be made between animals and humans was based on dose/body weight, not exposure.

Studies of tirilazad in the treatment of head trauma, ischemic stroke, and spinal cord injury failed to show efficacy, and some studies showed worsening of outcome relative to placebo (25–28). Initial studies of tirilazad for the treatment

of aneurysmal subarachnoid hemorrhage at a dose of 6 mg/kg/day showed some benefit in men, but not in women (29, 30). On the basis of pharmacokinetic data, premenopausal women showed higher clearance and lower plasma concentrations of tirilazad (31); two additional large studies were conducted in female SAH patients at a dose of 15 mg/kg/day (32, 33). Results from these studies did not show a general benefit of tirilazad in women.

After several thousand patients were treated with tirilazad, what was learned? There remain two possibilities. Either tirilazad is ineffective for the treatment of neurological trauma in humans or the trials that were conducted were sufficiently flawed (wrong dose, imbalance in groups in normal medical care, wrong patient groups, etc.) that the effects of tirilazad could not be seen in these patient groups (23). The available data do not allow a determination of which hypothesis is correct.

1.5 BIOMARKER TRANSLATION SUCCESS STORIES

While the lack of a translatable biomarker impedes the development of new medicines and reduces the probability of ultimate success, the availability of these biomarkers allows early assessment of therapeutic potential and can speed clinical development. The latter situation is described in two case studies that illustrate the power of translatable biomarkers in drug development.

1.5.1 Sunitinib

Various receptor tyrosine kinases (RTKs) and their receptors are overexpressed in different tumor types and contribute to tumor growth and survival. For example, vascular endothelial growth factor (VEGF) receptors are important in melanoma, platelet derived growth factor (PDGF) receptors are key in gliomas, stem cell factor receptors (KIT) are overexpressed in gastrointestinal stromal tumors (GIST), and Fms-like tyrosine kinase-3 (FLT3) receptor is deregulated in acute myelogenous leukemia (AML) (34). Sunitinib (SU11248, SUTENT® capsules) (Fig. 1.3) was designed as a potent inhibitor of these receptor kinase receptors. *In vitro* and *in vivo* measures (in mouse xenograft models) of VEGFR2, PDGF2, and FLT3 along with plasma concentration determinations in animals allowed robust PK/PD analysis that suggested that plasma concentrations in the range of 50–100 ng/ml were effective in various tumor types. The knowledge of overexpression in various tumor types and the PK/PD relationships based on markers of receptor inhibition allowed rapid identification of the doses that would be effective in phase I studies in humans and selection of indications and patients for early clinical evaluations in oncology patients. The initial three indications studied, AML, GIST, and renal cell carcinoma, were selected because sunitinib was active against the kinase targets that are overexpressed in these tumors.

On the basis of the observed *in vitro* and *in vivo* inhibition of FLT3 by sunitinib, a phase I single-dose, dose-escalation study was conducted in AML patients (35) with FLT3 inhibition as the primary endpoint. Twenty-nine patients received

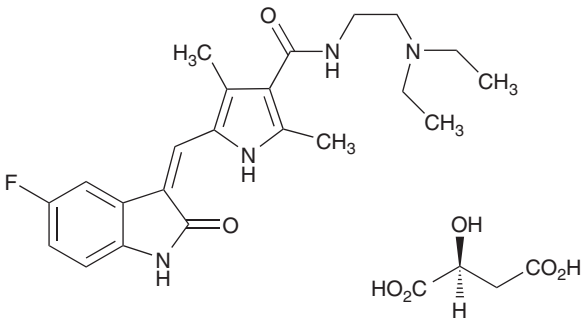

FIGURE 1.3 Structure of sunitinib malate.

single doses of sunitinib from 50 to 350 mg. Plasma sunitinib concentrations and plasma concentrations of SU-12662, an active metabolite, were determined serially after dosing. Likewise, FLT3 phosphorylation was measured at various times after dosing. Subjects were genoptyped for major FLT3 kinase mutations, with FLT3-ITD being associated with a negative prognosis in AML (36). Figure 1.4 shows FLT3 phosphorylation as a function of time after sunitinib dosing. Figure 1.5 shows the correlation between plasma C_{max} of active species (sunitinib and Su-12662) and FLT3 phosphorylation, as well as the correlation of time above 100 ng/ml and FLT phosphorylation. In patients with wild-type FLT3, strong inhibition ($> 50\%$) of FLT3 was associated with $C_{max} > 100$ ng/ml (consistent with experiments in animal xenograft experiments noted above)

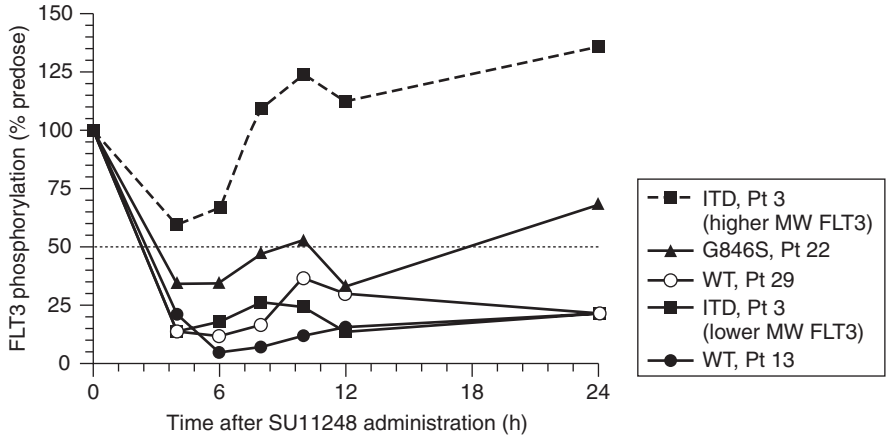

FIGURE 1.4 FLT3 phosphorylation as a percentage of predose values following administration of SU 11248 to AML patients. Points below the dotted line represent strong inhibition of FLT3 phosphorylation. Data from representative subjects are shown. *Source:* Reprinted with permission from the American Association for Cancer Research, *Clinical Cancer Research*, Volume 9, O'Farrell A-M, Foran JM, Fiedler W, et al., pp. 5465–5476, Copyright 2003.

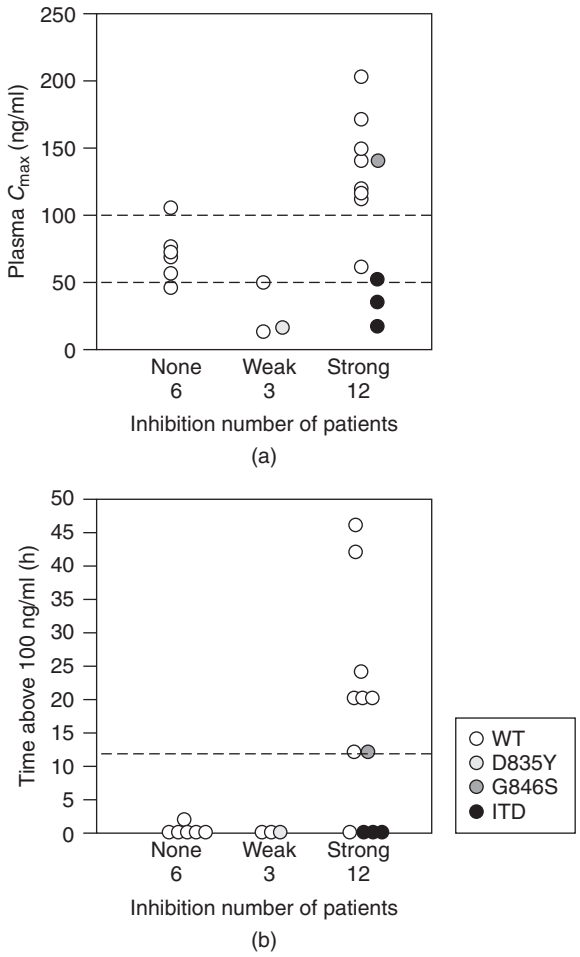

FIGURE 1.5 PK/PD analysis of FLT3 phosphorylation. Plasma C_{max} (combined SU11248 and SU12662; (a) and time exceeding the target plasma concentration of 100 ng/ml (b) are shown for each patient, grouped according to degree of FLT3 inhibition, and color coded based on FLT3 genotype. *Source:* Reprinted with permission from the American Association for Cancer Research, *Clinical Cancer Research*, Volume 9, O'Farrell A-M, Foran JM, Fiedler W, et al., pp 5465–5476, Copyright 2003.

and >10 h above 100 ng/ml of the combined active species in plasma. Interestingly, strong inhibition of FLT3 phosphorylation was observed in patients with ITD mutation. This initial study showed clear modulation of the target biomarker (FLT3 phosphorylation) in humans, and this biomarker was used to establish an effective concentration in AML patients, which was similar to that shown in animal models for AML and other tumor types. The results of this innovative experiment and the use of biomarkers helped to set the stage for future development of sunitinib.

An initial phase I/II trial in GIST patients provides another illustration of the utility of biomarkers in development. In this study (37), 97 patients with GIST were treated with sunitinib using one of three on/off treatment cycles (2 weeks on/1 week off, 2 weeks on/2 weeks off, or 4 weeks on/2 weeks off). Seventy-five of the 96 subjects underwent PET scanning with FDG-PET at baseline, on day 7 of the first cycle, at the end of the first cycle off drug, and during a subsequent cycle while on drug. FDG-PET is a measure of glucose uptake and indicative of metabolic activity in the tumor; decreased tumor activity by this measure has been shown to reflect clinical benefit (37). As such, FDG-PET is a mechanism and outcome biomarker. Figure 1.6 shows the response in one patient, with reduction in tumor activity within 7 days after starting dosing, return of tumor activity in the first off cycle, and continuing reduction in tumor activity during cycle 2. Using a measure of activity, the maximal standardized uptake value (SUV_{max}) for statistical analysis, similar behavior was seen across the cohort that completed all four scans (Table 1.2). Utilizing PET scanning, rapid objective assessment of response was obtained in this study, which set the stage for continued development of the compound.

What then was the implication of the use of biomarkers to drive the development program for sunitinib? The first dose of this drug was administered to a human in 2000, and the product was approved for marketing in the United States in 2006 for the treatment of GIST and renal cell carcinoma.

1.5.2 Maraviroc

In addition to the CD4 receptor being necessary for HIV-1 entry into T cells, more recently, the CCR5 and CXCR4 have been found to be coreceptors needed for HIV-1 entry into cells. The observation that homozygotes for a 32-bp deletion in CCR5 showed natural resistance to HIV-1 and that heterozygotes had a longer disease progression time sparked the development of CCR5 inhibitors for the treatment of HIV infection (38). Maraviroc (UK-427,857, CELSENTRI® Tablets, SELZENTRY® Tablets) (Fig. 1.7) is the first CCR5 receptor antagonist to be approved for HIV infection. Like sunitib, the clinical development and approval of maraviroc was rapid, with initial human dosing commencing in 2001 and approval gained in 2007. Also, like sunitinib, biomarkers played a key role in accelerating development.

An initial phase IIa study with maraviroc was conducted in HIV-infected volunteers who received placebo, 25 mg QD, 50 mg BID, 100 mg BID, and 300 mg BID maraviroc for 10 days. (39, 40) CCR5 receptor occupancy (target biomarker) and viral load (outcome biomarker) were the key measures in this study. Maraviroc reduced viral load as a function of time, with mean reductions >1.0 $\log_{10}$ observed at the 100 and 300 mg BID doses (Table 1.3). Doses at or above 100 mg resulted in $>80\%$ CCR5 receptor occupancy. The results from this study, in addition to previously developed HIV-1 disease model (Fig. 1.8) (41), were used to construct a PK/PD model for viral load that was used to predict the efficacy of three additional dosing regimens of maraviroc, which were subsequently studied (39, 40). The model predictions for these dosing regimens, as

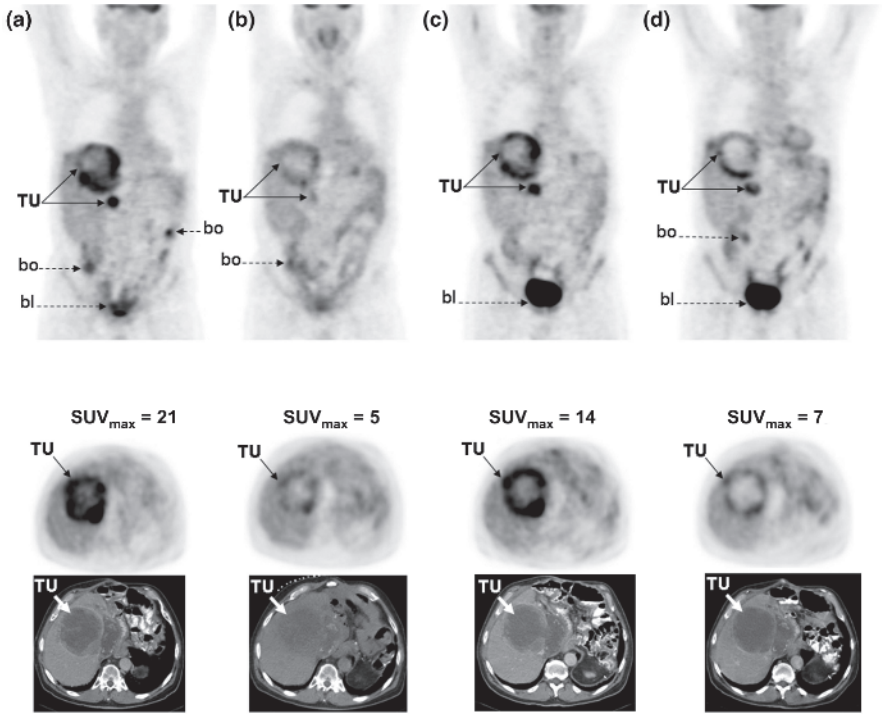

FIGURE 1.6 Coronal (top), axial (middle) FDG-PET slices, and corresponding axial CT slices (bottom) in a patient with GIST metastatic to the liver and anterior abdomen (solid arrows, TU) before sunitinib therapy (a, baseline), during cycle 1 (b), at the end of the resting period before cycle 2 (c, off treatment), and during cycle 4 (d). Physiologic uptake of FDG is seen in the bowel (dotted arrows, bo), and in the urinary bladder (dotted arrows, bl). The baseline FDG-PET (a) shows a large FDG-avid mass with a necrotic center in the liver and a SUV_{max} of 21, and a smaller mass in the anterior abdomen reflecting intense tumor glycolytic activity (solid arrows, TU). A marked decrease in glycolytic activity is noted in both tumor masses (solid arrows, TU) as early as 1 week following treatment with sunitinib during cycle 1 (b). The SUV_{max} of the liver lesion has decreased to 5. Note that the rebound in Glycolytic tumor activity in both masses (solid arrows, TU), as reflected by intense FDG uptake and an increase in the SUV_{max} of the liver lesion to 14, at the end of the resting period before the next cycle of sunitinib (c). During subsequent cycles of sunitinib therapy, a decrease in tumor metabolic activity is again observed (d, cycle 4). The SUV_{max} of the liver lesion has decreased to 7 during cycle 4. Note that the size of the hepatic lesion does not significantly change on the corresponding CTs obtained at the same time points (bottom, white arrows, TU). *Source:* Courtesy of Annick D. Van den Abbeele, MD and Iryna Rastarhuyeva, MD, Dana-Farber Cancer Institute, Boston, MA.

TABLE 1.2 Maximum Standardized Uptake Values (SUV_{max}) for FDG-PET Following the Administration of Several Cycles of Sunitinib in Patients ($n = 74$) with Imatinib-Resistant Gastrointestinal Stromal Tumors[a]

FDG-PET Scan	Baseline	After 7 days treatment in Cycle 1	At the end of first period off drug	During Cycle 4
SUVmax (Standard error)	9.7 (0.6)	5.6 (0.6)	8.0 (0.6)	5.1 (0.5)
Absolute difference in mean log SUVmax from prior scan (95% Confidence interval)		0.32 (0.25–0.39)	0.21 (0.14–0.28)	0.22 (0.15–0.30)

[a]Ref. 37.

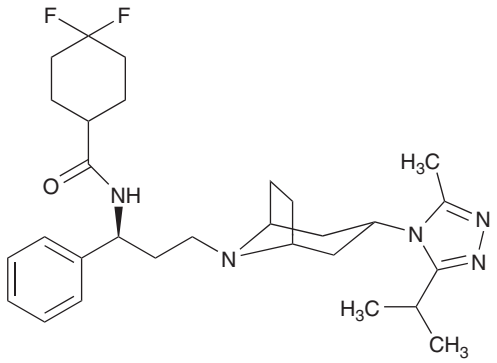

FIGURE 1.7 Structure of maraviroc.

TABLE 1.3 Mean (Range) of HIV-1 RNA log_{10} Declines after 11 Days of Maraviroc Therapy in Patients[a]

Maraviroc Dose	Mean (Range) HIV-1 RNA log_{10} Decline
Placebo	0.02 (−0.45 to 0.56)
25 mg QD	− 0.43 (−1.08 to 0.02)
50 mg BID	− 0.66 (−1.37 to 0.40)
100 mg BID	−1.42 (−1.84 to −1.04)
300 mg BID	−1.60 (−2.42 to −0.78)

[a]Ref. 40.

well as the observed values, are shown in Table 1.4. The model predicted the behavior of these new dosing regimens administered over a 10-day period very well. On the basis of clinical trial simulations using this drug and disease model (based on the viral load biomarker), the two phase IIb/III trials that were conducted with maraviroc utilized doses of 300 mg/day or 300 mg twice daily, with

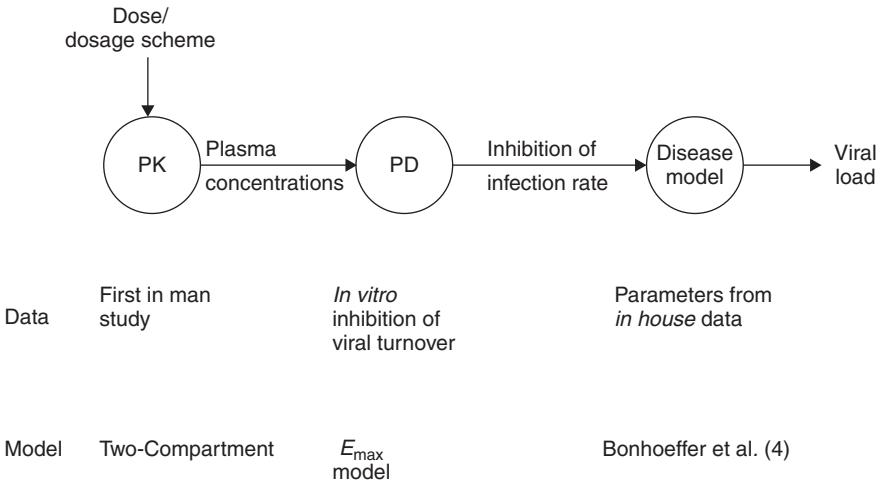

FIGURE 1.8 Schematic representation of pharmacokinetic (PK)-pharmacodynamic (PD)-disease model for an antiretroviral drug. E_{max}, Maximum effect. *Source:* Reprinted by permission from Macmillan Publishers Ltd: *Clinical Pharmacology and Therapeutics*, Rosario MC, Jacqmin P, Dorr P, van der Ryst E, Hitchcock C. A pharmacokinetic-pharmacodynamic disease model to predict in vivo antiviral activity of maraviroc, 78:508–519, Copyright 2005.

TABLE 1.4 Performance of Model in Predicting HIV-1 RNA $\log_{10}$ Declines after 11 Days of Therapy for New Maraviroc Dosing Regimens[a]

Maraviroc Dosing Regimen	Observed Mean (Range)	Predicted Median (90% Confidence Interval)
150 mg bid fasted	−1.45 (−1.71 to 0.90)	−1.30 (−1.67 to −0.82)
150 mg BID fed	−1.34 (−1.79 to −0.51)	−1.12 (−1.52 to −0.58)
100 mg QD	−1.13 (−1.70 to −0.43)	−0.81 (−1.32 to −0.32)
300 mg QD	−1.35 (−1.62 to −0.95)	−1.30 (−1.76 to −0.83)

[a]Ref. 40.

subjects receiving a CYP3A4 inhibitor receiving a dose of 150 mg twice daily (42). This resulted in a streamlined program that supported the rapid development and approval of this new medicine.

1.6 THE PATH FORWARD

In this chapter, examples of the perils of drug development without biomarkers and the use of biomarkers to speed development have been presented. What must happen so that the successes seen in some therapeutic areas may be expanded to others?

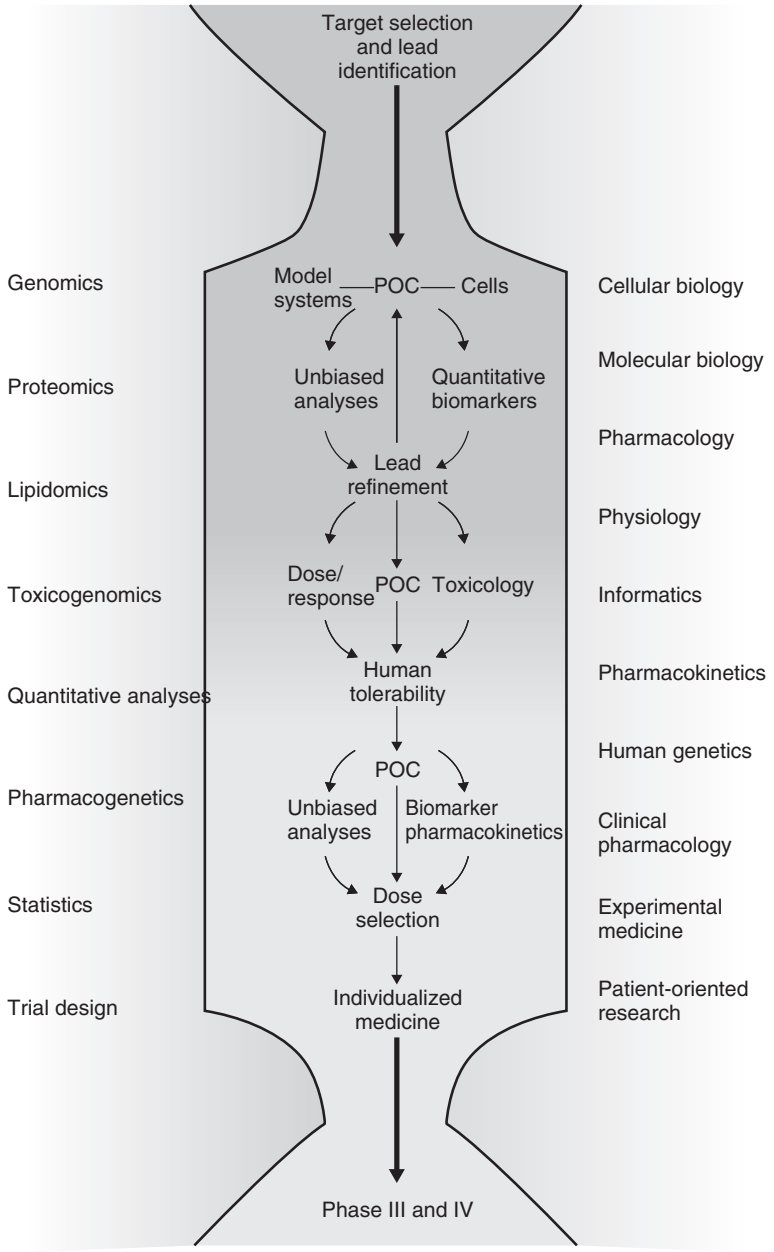

FIGURE 1.9 The spectrum of translational medicine and therapeutics. The translational space imposed on the process of drug development is defined as stretching from proof of concept (POC) in cells and model systems to completion of studies of drug mechanism and variability of response, which afford a basis for individualized dose selection. The conventional disciplines that are drawn on as one progress through the translational channel are indicated. *Source:* Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews in Drug Discovery*, Fitzgerald GA. Anticipating change in drug development: the emerging era of translational medicine and therapeutics, 4(10): pp. 815–818, Copyright 2005.

To speed decision making in drug development, biomarkers should focus on the aspects of a disease model that can most readily be translated between animals and man—disease pathways and drug pharmacology. Efficacy outcomes are difficult to translate between animals and humans, which is reflected in the current lack of confidence in animal models. Development of translational biomarkers relevant to disease pathways and drug pharmacology must begin when a promising new therapeutic target is identified. These biomarkers should also be developed with a fit-for-purpose mind set. Initially, we want them for decision making in drug development. The biomarker in question may some day be a diagnostic tool or a surrogate biomarker, but its initial development should reflect the limited use for which it is intended.

Since biomarkers are intended to be decision making, all of the stake holders in the decision should be involved in their development. Thus, in addition to the biologists, pharmacologists, and analytical experts needed to identify and quantify biomarkers, a host of others are involved in the analyses and optimal use of these data. Fitzgerald (43) provides an excellent summary of the cross-discipline nature of translational medicine and biomarker development (Fig. 1.9).

Finally, we have to actually use biomarkers, or lack thereof, for decision making. Those who guide drug development decisions must have the fortitude to forego the development of drugs for which there are no biomarkers available and no way to determine whether the drug will actually test the hypothesis regarding a molecular target. They must also be willing to abandon programs early for drugs that do not show the degree of biomarker modulation necessary to justify continued development. Likewise, they must be willing to use the data from fit-for-purpose biomarkers to inform dose selection, patient selection, and other protocol and program design decisions to speed drug development. These further examples of success will further increase the confidence in biomarkers and allow us to move toward the future vision of drug development and patient care conjured by the mapping of the human genome.

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