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Introduction and Definitions

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1.1. What Is Translational Medicine?

The definition found in Wikipedia (2007), an online encyclopedia, is as follows:

> Translational medicine is a branch of medical research that attempts to more directly connect basic research to patient care. Translational medicine is growing in importance in the healthcare industry, and is a term whose precise definition is in flux. In the case of drug discovery and development, translational medicine typically refers to the "translation" of basic research into real therapies for real patients. The emphasis is on the linkage between the laboratory and the patient's bedside, without a real disconnect. This is often called the "bench to bedside" definition.
>
> Translational medicine can also have a much broader definition, referring to the development and application of new technologies in a patient driven environment – where the emphasis is on early patient testing and evaluation. In modern healthcare, we are seeing a move to a more open, patient driven research process, and the embrace of a more research driven clinical practice of medicine.

Although this attempt at a definition is probably the most accurate one at present, a simpler definition may serve the purpose even better: Translational medicine describes the transition of in vitro and experimental animal research to human applications (Figure 1.1, Plate 1).

Other names for the same entity are "experimental medicine," "discovery medicine," or "clinical discovery." Translational medicine shares major aspects of clinical pharmacology when it relates to drugs, as early clinical trials are major components of translational processes.

The need to develop this discipline reflects the cleft that has been brought about by the separation of medical teaching and pharmaceutical research into preclinical and clinical categories. Bridging this gap is crucial to success in curing diseases in humans. It is obvious that the term is born out of a situation

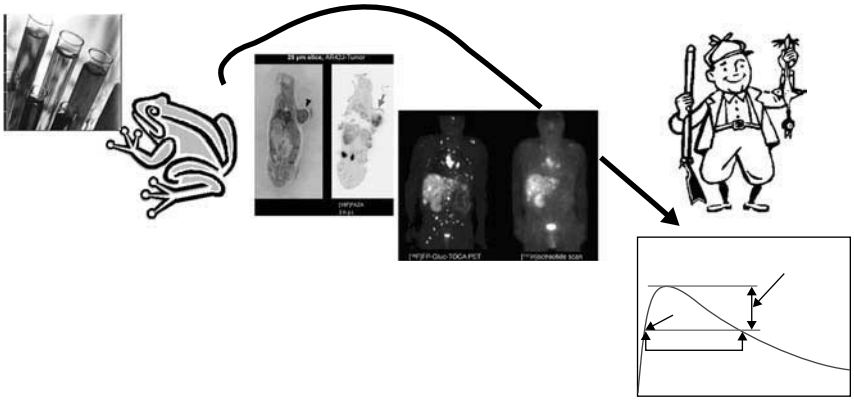

Fig. 1.1
The main aspects of translational medicine: biomarkers as major tools for the transition from test tube or animal experiments to human trials, with imaging as a major biomarker subset (from Wehling 2006, reprinted by kind permission from Springer Science and Business Media).

in which the transition – the prediction or extrapolation, respectively – from basic findings to human findings has been disappointing. This difficulty is simply a reflection of the differences among in vitro conditions (e.g., cell cultures or test tube experiments), the wide variety of animal species, and, finally, humans. For example, cell cultures of vascular smooth muscle cells are artificial, as they only grow in the presence of serum (e.g., fetal calf serum). In contrast, while in vivo, nature does everything to ensure that vascular smooth muscle cells do not encounter serum; endothelium protects them against it. If the cells become damaged and are exposed to serum, all types of vascular pathology commence: hypertrophy, hyperplasia, de-differentiation, inflammation, and finally atherosclerosis. It is very conceivable that results from vascular smooth muscle cells in culture may not reflect even basal physiological in vivo conditions, and projections from such experiments into human pathology may be fruitless or misleading, especially as cells change their phenotypes with increasing culture time or passage numbers (Chamley-Campbell, Campbell, and Ross 1979).

Such artifacts can only raise hypotheses that may or may not be corroborated in animal or, finally, human experiments. The artifact character of test tube systems is obvious, and differences among species are profound at both the genotype and phenotype levels, so no one is surprised if an intervention works in one species but not another. Although morphine is a strong emetic in dogs, it does not have this effect in rats. It is apparent that this variability applies even more when dealing with human diseases, which may or may not have any correlates in animal models. This especially concerns neuropathologic diseases for which animal models are either lacking or misleading (e.g., psychiatric diseases such as schizophrenia).

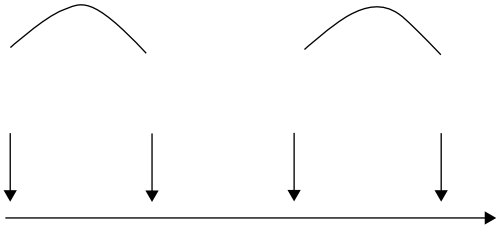

Fig. 1.2
Scheme depicting the two principal transition zones for translation of projects such as drugs: From preclinical development (target discovery) to clinical development is the primary translation, and from market approval to real-life patient care is the secondary translation.

Thus, the difficulty of predicting the beneficial or toxic effects of drugs or medicinal devices, or the accuracy and value of diagnostic tests, is a major problem that prevents innovations from being useful for treating human diseases. From this end, the following is an operational definition of translational medicine: By optimization of predictive processes from preclinical to clinical stages, translational medicine aims at improving the innovative yield of biomedical research in terms of patient treatment amelioration.

1.1.1. Primary Translation versus Secondary Translation

In the definitions mentioned previously, the focus is clearly concentrated on translation in development courses from preclinical to clinical stages, in particular as applied to the development of new drugs. These developments would bring innovation to the patients who receive the new drug, test, or device. It seems odd to underline that some patients may receive the innovation and, thus, benefit from it, while others may not. However, there is yet another gap that prevents innovations from flourishing to their full potential. Even if innovative drugs have changed clinical guidelines and rules and thus been undoubtedly proven to represent beneficial options to suitable patients, they may not be applied in what is commonly termed "real life."

Undertreatment may result from ignorance, budget restrictions, or patient or doctor noncompliance and often has severe socioeconomic implications: Though potentially correctable in all patients, arterial hypertension is only treated to guideline targets in 20–50% of patients (Boersma et al. 2003); LDL-cholesterol in cardiovascular high-risk patients is at target levels in 12–60% of patients (Böhler et al. 2007). This means that innovations that have successfully passed all translational hurdles in the developmental process from bench to bedside still may not reach the patients at large, as there is a second barrier between guideline recommendations and real-life medicine (Figure 1.2).

This translational aspect of innovation is sometimes called *secondary translation* (as opposed to the developmental primary translation). Because problems in secondary translation mainly reflect insufficiency at the level of

patient care, socioeconomic structures, education and society, and habits, the scientific challenge is secondary to social and political tasks and obligations. Therefore, this textbook book is entirely devoted to the scientific aspects of primary translation and does not deal with secondary translation, though its impact on patient care may also be crucial.

1.1.2. The Scope of Translational Medicine, Its Remits, and Why We Need It

As described previously, the main feature of translational medicine is the bridging function between preclinical and clinical research. It aims at answering the simple but tremendously important question, if a drug *X* works in rats, rabbits, and even monkeys, how likely is it that it will be beneficial to humans? Historically, how did this simple and straightforward question, which is naturally inherent to all drug development processes, become of prime relevance in biomedical research?

If all drug, device, or test development components were closely connected within a common structure, the necessity to develop this discipline would probably not have become apparent. As it stands now, however, the new emphasis on translational medicine reflects the wide and strict separation of biomedical research into preclinical and clinical issues, a situation best illustrated by the acronym "R&D," which is used in pharmaceutical companies to describe their active investments into science as opposed to marketing. "R" stands for research, which largely means preclinical drug discovery, and "D" stands for development, which is largely identical to clinical drug development. It is obvious that even the words behind "R&D" arbitrarily divide things that share a lot of similarities: clinical development and clinical research are very congruent terms, and compounds are *developed* within the preclinical environment, for example, from the lead identification (LI) stage to the lead optimization (LO) stage.

In the drug industry, the drug discovery and development process follows a linear stage progression; a major organizational transition occurs when a candidate drug is delivered from discovery (R) to clinical development (D), which is synonymous with trials in humans. When this happens, it is often said that the discovery department has "thrown a compound over the fence." This ironic or cynical expression exposes the main concern in this context: clinical issues – that is, the human dimension of a drug project – are not properly and prospectively addressed in the early stages of preclinical discovery or even at the level of target identification or validation. Clinical researchers are then surprised or even upset by what has been sent to be developed in humans. A chemical that had been shaped years earlier with too little or no clinical input or projections may turn out to be impractical for swallowing (e.g., the compound dose may be too large or measured in grams instead of milligrams) or may quickly prove to be too short-lived, requiring multiple dosing schemes that are far out of scope in many therapeutic areas.

Why is this interface problem relevant? Bridging this divide or improving the interface performance is a major prerequisite for success if laboratory or

animal data are to finally lead to treatment of diseases in humans. There is an old dispute over free and basic sciences versus applied sciences, and universities in particular take pride in being independent and free in their choice of research areas and scientific strategies. This *l'art-pour-l'art* approach is thought to still yield "useful" discoveries – namely by serendipity or simply by chance findings. Even worse, it is thought that big, applicable discoveries can only flourish in unrestricted, free scientific settings.

Unfortunately, drug discovery and development has to assume that a restricted, structured, and therapy-driven process is the only way to cope with modern standards of drug approval requirements. Chance findings may trigger the initial steps of drug discovery, but those are rare in clinical stages. (One famous exception is sildenafil, which had been clinically developed as antianginal agent when its effects on erectile function were incidentally discovered.) The typical R&D process has to rely on projections across this interface, and, thus, it has to focus its early discovery stages on later applications, that is, the treatment of human disease.

This implies that "throwing a drug over the fence" is not optimal if the final output is to be measured in terms of the number of approved new drugs being sold on the market. Unfortunately, output *is* in fact the major concern: complaints about this interface problem have largely been driven by the widening gap between surging R&D costs and the steadily and dramatically decreasing output of drugs from shrinking pipelines (Figure 1.3, Plate 2).

Shrinkage correlates with high late-stage attrition rates, meaning that many drug projects die after billions of dollars and 5–10 years of investment. This attrition problem particularly applies to expensive clinical phase IIb trials and especially phase III trials. Attrition can be largely attributed to the inability to predict

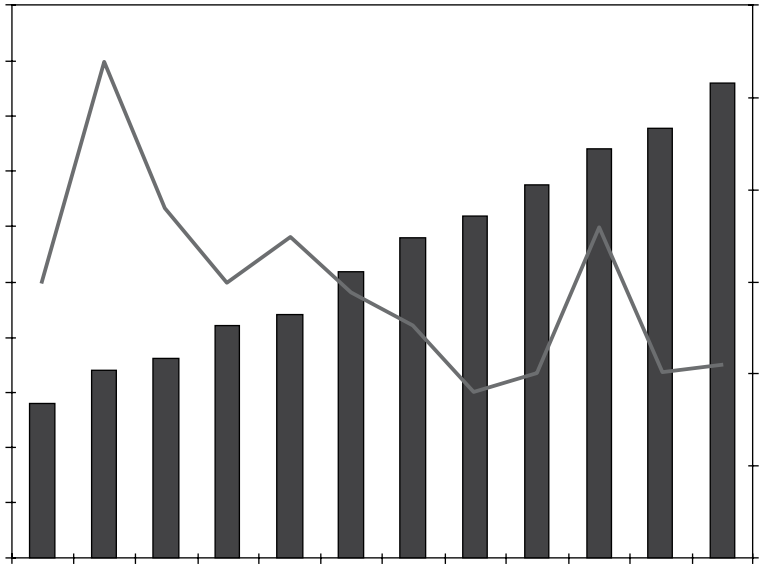

Fig. 1.3
Increasing R&D costs (bars, left ordinate) versus decline in the number of new drug approvals (line, right ordinate) (compiled from FDA data).

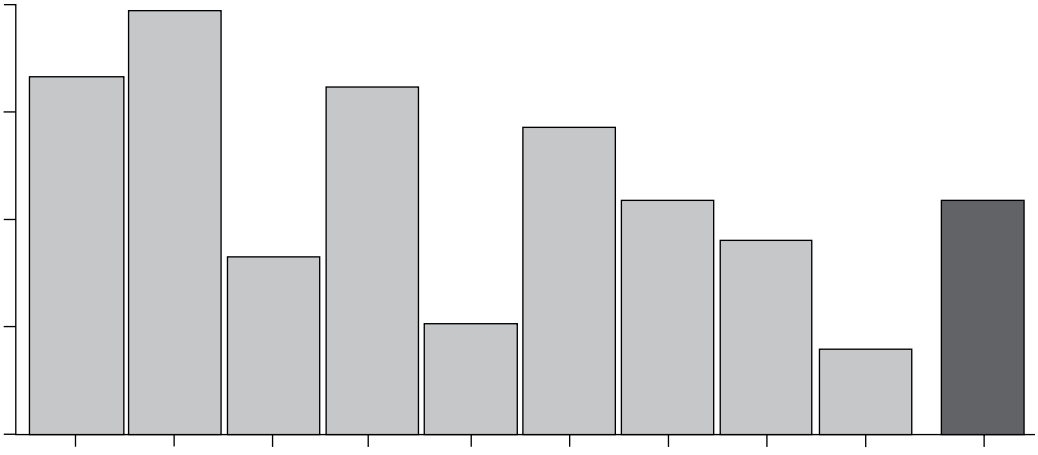

Fig. 1.4
Success rates from first-in-humans to registration (from Trusheim, Berndt, and Douglas 2007, reprinted by permission from Macmillan Publishers Ltd: *Nature Rev Drug Discov*, 3: 711–715, © 2004).

the efficacy and/or safety of a new candidate drug from in vitro, animal, or early human data. From 1991 to 2000, only 11% of all drugs delivered to humans for the first time were successfully registered (Figure 1.4).

It is obvious that there are huge differences among therapeutic areas; for example, success rates in central nervous system (CNS) or oncology drugs are particularly low (7 or 5% versus a 20% success rate in cardiovascular drugs). This means that in CNS only 1 out of about every 14 compounds that have passed all hurdles to be applied to humans for the first time will ever reach the market and, thus, the patient. In more than 30% of cases, attrition was related to either clinical safety or toxicology, just fewer than 30% were efficacy-related, and the remainder were caused by portfolio considerations and other reasons (Figure 1.5) (Kola and Landis 2004). Attrition caused by portfolio considerations means that the company producing the project has lost interest in it because, for example, a competitor has reached related goals before the project was finished and thus the project no longer has a unique selling position.

Late-stage attrition is a problem for all large companies, and lack of innovation is a major reason for the recent stagnation in progress in the treatment of major diseases. If the tremendous costs of drug development continue to rise, companies may resort to concentrating on the relatively safe "me-too" approach. This approach aims at minimally altered compounds that are patentable but resemble their congeners as much as possible in terms of efficacy and safety. These compounds are (sometimes erroneously) thought to be without pharmaceutical risk; their main disadvantage is the fact that they are not innovative.

Thus, tackling the translational challenges in the R&D process may become essential to the struggle for the survival of the pharmaceutical industry in an increasingly adverse environment. This adverse environment includes reduced remunerations for smaller innovative gains (such as those made by the aforementioned "me-too" compounds) and ethical issues that continuously undermine the reputation of the drug industry, which is now seen as similar to the

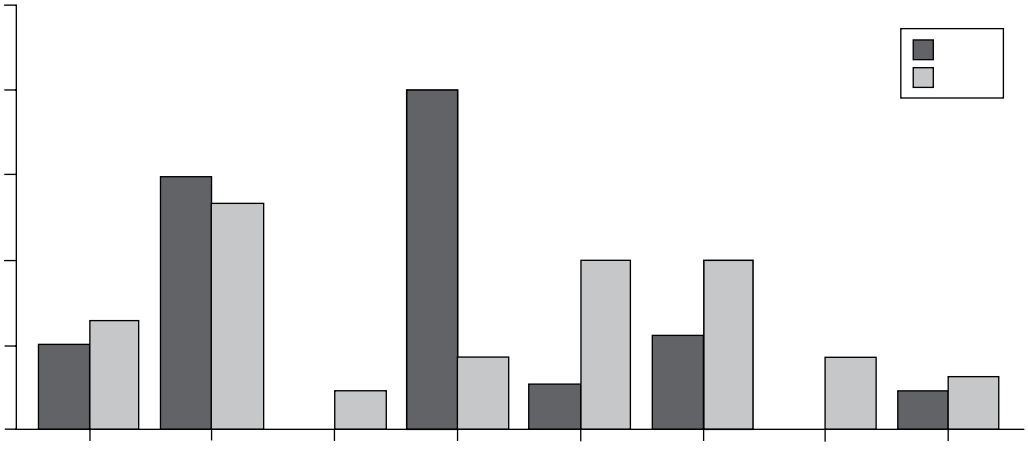

Fig. 1.5
Main reasons for termination of drug development – for "wasted investment," 1991–2000 (from Kola and Landis 2004, reprinted by permission from Macmillan Publishers Ltd: *Nature Rev Drug Discov*, 3: 711–715, © 2004).

reputations of the oil and tobacco industries (Harris Interactive 2006). Thus, translational medicine, if successfully applied, appears to be an important remedy for improving the ethical (i.e., patient-oriented) and financial success of the R&D process. It could also help the battered reputation of the drug industry by improving the treatment of major diseases.

It is important to note that translational medicine problems do not only pertain to drug industry; they are inherent to all developmental biomedical processes and include device and diagnostic tool development as well. They also exist in academia, in which translation is not the primary goal of research; at least it is not perceived as such. However, in academia there is also growing awareness of the fact that public funding of expensive biomedical research will not continue forever if this funding is not seen to lead to patient-oriented results. Thus, academic research utilizes this phraseology increasingly as well.

It is obvious that the persistence of the low-output syndrome in terms of true medical innovations is a threat to the existence of

- Big pharmaceutical companies (known collectively as "big pharma"): Big pharmaceutical companies are laying off tens of thousands of people. For example, Pfizer laid off 10,000 in 2007. It is assumed or feared that 30–50% of all jobs in big pharma R&D will be axed within the next 5–10 years.
- Academia: Taxpayers will not tolerate expenditures of billions of dollars or Euros without measurable treatment improvement; the U.S. parliament has asked researchers what happened to the $100 billion invested into cancer research from the mid-1980s to mid-1990s in terms of measurable outcome.
- Society: If biomedical research does not improve its utility and create an impressive track record of substantial innovations, biomedical research will be marginalized in the competition for resources, as environmental changes, such as climate or energy catastrophes, create tremendous challenges to humankind. In the future, medicine may become static, executed by robots fed by old algorithms, and progress may become a term of the past.

Table 1.1 Main remits of translational medicine.

- Target investigation and target validation in humans
- Early evaluation of efficacy and safety using biomarkers in humans
- Use of the intact living human as the ultimate screening test system

1.1.3. What Translational Medicine Can and Cannot Do

Proponents of translation medicine feel that the high attrition rate can be ameliorated by the main remits of translational medicine as illustrated in Table 1.1. The first goal is target identification and validation in humans. Identification has already been achieved by the human genome project, which literally identified all genes in the human body. Thus, validation of known genes is the next task.

Genetics is one of the most powerful tools in this regard, because it tests

- Disease association genes
- Normal alleles
- Mutant genes, especially in oncology
- BCRabl (Imatinib)

To this end, we must ask and attempt to answer the following questions:

- In general, does the target at least exist in the target cell or tissue, or is expression low or undetectable?
- Is it dysregulated in diseased tissues?
  - Functional genomics, for example, Her2neu expression (trastuzumab)

Another approach utilizes test or probe molecules:

- Can we test the hypothesis with a probe molecule?
  - Using a substandard candidate drug or the side effects of a drug used for something else
  - Monoclonal antibodies
  - Antisense technology
- Has someone else tested the hypothesis?
  - Antegrin for VLA4 antagonists in multiple sclerosis

This is just a small fraction of the possible target validation or identification approaches. The basic principle is the early testing of human evidence at a preclinical stage of the drug development process. The reverse could be true as well: knowledge of the side effects of drugs can be utilized to discover new drugs by exposing this side effect as a major effect. Minoxidil was developed as an anti–hair loss agent until its ability to lower blood pressure was clinically detected. Although this *reverse pharmacology* approach has been utilized to

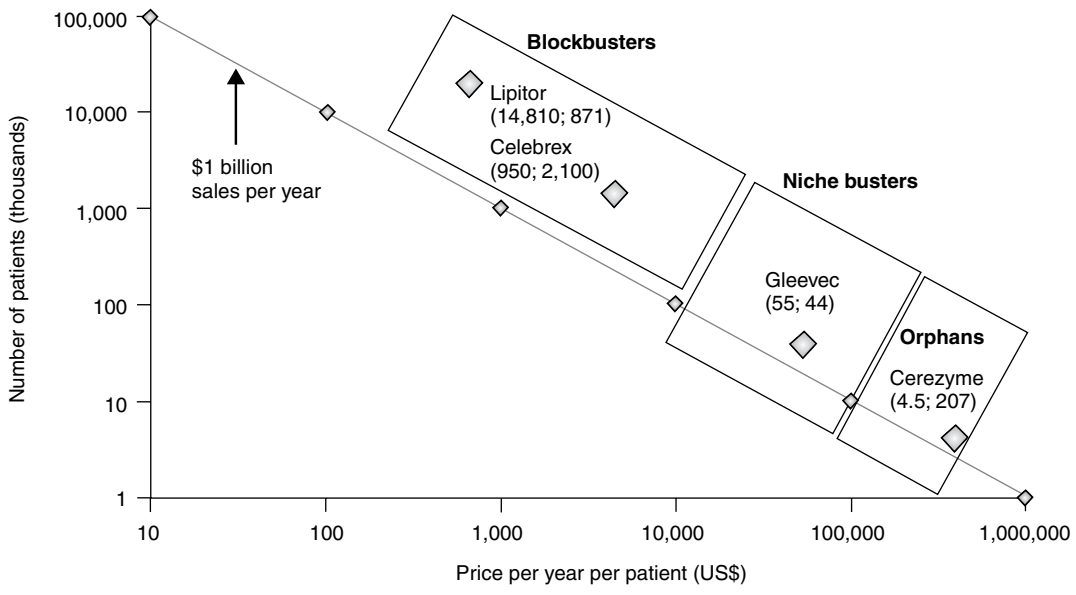

Fig. 1.6
From blockbuster to niche-buster: Even the latter can generate billions of dollars of revenue if profiled by personalized medicine approaches and if they are highly effective and highly prized (from Trusheim et al. 2007, reprinted by permission from Macmillan Publishers Ltd: *Nature Rev Drug Discov*, 6[4]: 287–293, © 2007).

find pure blood pressure drugs and pure anti–hair loss drugs, most attempts have failed so far. The principle, however – human target identification and validation with subsequent feedback into preclinical stages (see Chapter 2) – has been proven to be a successful strategy in general.

Another important focus in translational activities is on predicting as early as possible the safety and efficacy of a new compound in humans, mainly by the identification, development, and smart utilization of biomarkers. Several chapters of this book are devoted to biomarkers, which describe physiological, pathophysiological, and biological systems and the impact of interventions in those systems, including those of drugs. This is the most important translational work, and 80% of translational efforts are devoted to finding or developing the right biomarker to predict subsequent success across species, including humans. Biomarker work includes the smart design of the early clinical trials in which those experimental biomarkers are most suitably exploited. This work may also include the validation work necessary to establish the predictive value of novel biomarkers; thus it may include a developmental program (for the biomarker) that is embedded in the drug development program.

The remit of biomarker work goes far beyond early efficacy and safety prediction, but is increasingly seen as a necessary tool for profiling compounds to better fit the needs of individual patients. The fashionable term in this context is "personalized medicine," which is a term as old as drugs are. Renal drugs (excreted by kidneys) have always necessitated tests to assess kidney function and thus require personalized medicine; otherwise, poisoning in renal impairment is inevitable. The novelty in this regard is the use of profiling to achieve better matches between success rates (responder concentration) and thus increase cost-effectiveness. It is thought that this approach will save billions of U.S. dollars in revenue (Figure 1.6, Plate 3) when the blockbuster is new.

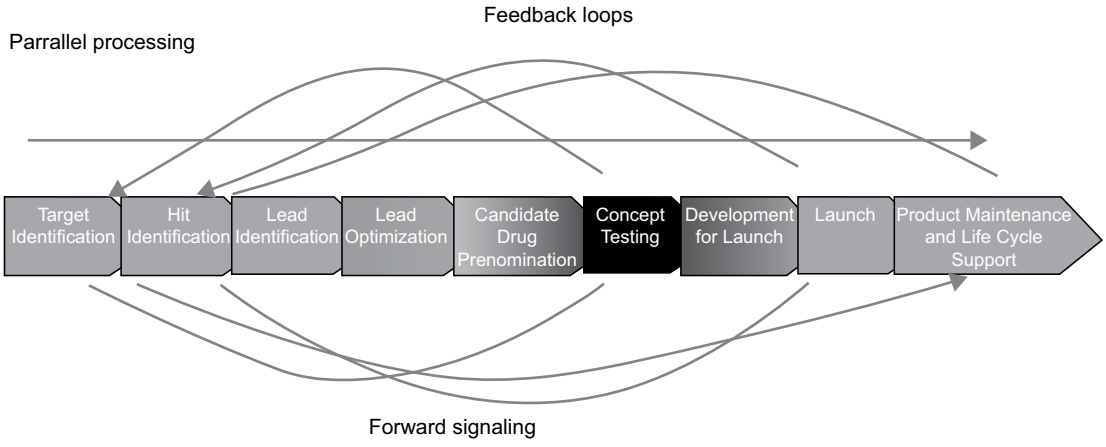

Fig. 1.7
The pseudo-linear model of drug development. Translational medicine creates forward-signaling loops and reverse-signaling loops, speeds up processes, and allows for parallel processing.

Another remit of translational medicine is its facilitation of early testing of principles in humans without directly aiming at the market development of the compound tested. These human trials are called exploratory trials, and they may involve experimental investigational new drugs (eINDs), which are compounds that are known to have shortcomings (e.g., a compound with a half-life that is too short for the compound to become a useful drug) but could be ideal test compounds to prove the basic hypothesis of efficacy in the ultimate test system, the human being. Such tests could validate the importance of, for example, a particular receptor in the human pathophysiology; could substantiate investment decisions; and could speed up developmental processes at early stages. Examples will be given in Chapter 4.

This short list of remits is incomplete, but it should demonstrate that the major tool of translational medicine is the early, intensive, and smart involvement of humans as the ultimate test system in discovery and development processes. Its scope reaches from straightforward translation power through reverse pharmacology to personalized medicine.

In an ideal world, translational medicine creates forward-signaling loops and reverse-signaling loops along the artificially linear development line of drugs (Figure 1.7, Plate 4). It can speed up the process, allow for parallel processing, and generate knowledge for other projects as well (e.g., generic biomarker tools and side effects as target starting points).

Translational medicine cannot replace the most expensive study – the pivotal phase III (safety) trial. However, it can increase the likelihood of success in phase III trials. It cannot invent new targets (all potential targets are gene-related and all genes have, meanwhile, been "invented" and described), but it can significantly help to assess the validity of targets and reduce lapses due to "unimportant" targets at the human level. For these reasons, translational medicine might be the key to preventing biomedical research and medicine from falling into oblivion because of transfer of funding to more successful areas of innovation such as energy and climate survival technologies.