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feature

Failure is an option: learning from unsuccessful proof-of-concept trials

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Recent statistics indicate that the attrition rates during drug development remain high. Lack of clinical efficacy has meanwhile become the most frequent cause for discontinuation of a drug development program. Consequently, attrition rates are highest in clinical Phase II, which usually includes the first evidence for pharmacodynamic action of the compound or, proof of concept. Interestingly, attrition is approximately 60–70% across a variety of therapeutic areas, including the central nervous system (where predictivity of animal models is usually low) and cardiovascular medicine (where animal models are considered to be more predictive). Obviously, the translation of animal data into clinical benefit remains suboptimal.

Recapitulating failures in proof-of-concept trials in the cardiovascular field despite promising experimental data, we have identified three important factors that determine the successful translation of preclinical research into clinical development: to test the right compound in the right model, using the right endpoint.

Introduction

The key role of the pharmaceutical industry is the transformation of molecules into medicines. In comparison to the many steps that are necessary to promote a new molecular entity toward its clinical use, the achievement of clinical proof of concept represents a giant leap along the value chain. It is this translation from efficacy in experimental animal models into clinical benefit that represents a key success factor for the pharmaceutical industry. Ironically, it is exactly this step that seems to be the most vulnerable in the drug development process. Recent statistics indicate that only a fraction of all compounds can demonstrate clinical efficacy in the target indication and successfully pass Phase II development [1]. An unsuccessful clinical trial is usually a missed opportunity to improve the standard of patient care. It also represents a substantial loss of money, reputation, and motivation for all stakeholders involved, regardless of whether the trial is sponsored by the pharmaceutical industry or the public.

Moreover, a clinical trial that is not based on the best available (experimental) evidence is regarded as unethical because it represents a waste of resources and exposes patients to risks that could be avoidable [2].

For many reasons, therefore, efforts should be directed toward improving the success rates of clinical trials. In order to improve the translational success rates in the future, it might be worthwhile to recapitulate previous failures and try to identify potential success factors. In an effort to do this, we have looked at a number of Phase II disappointments in the cardiovascular field from a translational medicine perspective. We found that Phase II proof-of-concept trials have failed when the decision to enter clinical development was based on preclinical experiments using the wrong compound, the wrong experimental model, or the wrong endpoint. The following examples illustrate the role of these three factors in modern drug development.

The wrong compound

In preclinical research, the most commonly used animal models are small rodents, particularly the mouse and the rat. Usually, one of these animal species is used to prove efficacy, test for potential side effects, analyze pharmacokinetics, and predict the human dose.

Vasopressin is one of the most potent endogenous vasoconstrictors [3]. On the basis of this property, interfering with vasopressin signaling has long been postulated to be an effective therapy for arterial hypertension [4]. In 1991, an

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orally active, non-peptide vasopressin subtype 1A receptor (V1A) antagonist was synthesized by researchers at Otsuka Pharmaceuticals [5]. The molecule, OPC-21268, exhibited K_i values of 100 nmol/l in binding studies using rat liver tissue, which is known to express a high level of the vasopressin receptor [5]. Because the vascular vasopressin 1A receptor subtype mediates vasoconstriction upon binding of vasopressin, OPC-21268 impressively blocked the vasopressin induced pressor responses in conscious rats [5]. The conclusion was straightforward: OPC-21268 could be a valuable new drug for hypertension, and numerous publications about the activity of OPC-21268 *in vitro* and *in vivo* were published in the following years. Up to 1999, at least 26 peer-reviewed articles were published describing beneficial properties of OPC-21268 under different conditions in rats. In parallel, the compound rapidly went into clinical testing: the Phase I results from 33 healthy subjects were published in 1993 revealing safety and tolerability at various doses [6]. On the basis of the hypothesis that activation of vasopressin V1A receptors contributes to renal dysfunction via contraction of glomerular efferent arterioles, two small studies were conducted in type 2 diabetic patients. Oral administration of OPC-21268 caused a significant decrease in urinary albumin excretion, suggesting that OPC-21268 may be useful for the treatment of diabetic nephropathy [7,8]. It was therefore a disappointment that, in a proof-of-concept study in patients with arterial hypertension, as well as in normotensive subjects, OPC-21268 did not affect systolic or diastolic blood pressure at all [9].

A careful analysis of published data reveals that the lack of blood pressure lowering activity of OPC-21268 in humans, compared with rodents, is subject to profound species differences with respect to the corresponding V1A receptors. When the cDNA of the human V1A receptor was cloned in 1994, an approximately 1000-fold lower binding affinity of OPC-21268 at the human, compared with the rat, receptor was found [10]. Similar observations were published in different experimental settings, such as human liver preparations [11], human internal mammary artery [12], human coronary artery [13], or human gastric artery [14]. In summarizing the available data from different pharmacological (i.e. smooth muscle contraction), biochemical (i.e. binding to tissue V1A receptors), and molecular biology (i.e. binding to recombinantly expressed human V1A receptor) studies, one can conclude that OPC-21268 is not an optimal compound to test the effect of a V1A receptor antagonist in humans.

It remains unclear why OPC-21268 caused any benefit in humans at all. Perhaps the initial positive data were just chance findings, triggered by relatively small group sizes. While Otsuka confirmed the discontinuation of OPC-21268, in the meantime the company has successfully developed a potent V2 receptor antagonist, tolvaptan, which has entered Phase III for treatment of hyponatremia and heart failure.

The wrong model

The pathophysiology of myocardial ischemia and reperfusion is one of the most topical areas of cardiovascular research. Interestingly, it also seems to be one of the most challenging areas for the pharmaceutical industry, because to date no compound has been approved for the protection from myocardial ischemia-reperfusion damage.

In view of the fact that there are approximately 865 000 myocardial infarctions per year in the USA alone [15], the medical need for a cardioprotective agent is enormous. During the past two decades, much progress has been made in characterizing the functional consequences of myocardial ischemia, which can range from transient dysfunction (or myocardial stunning [16]) and prolonged but reversible dysfunction (or myocardial hibernation [17]) to apoptosis and necrosis (or myocardial infarction). In addition to the damage brought about by the ischemia itself, it is now established that reperfusion can independently contribute to, and increase, the damage to the myocardium. Upon reperfusion, a cascade of intracellular ion changes takes place, where intracellular protons are replaced by sodium via the sodium proton exchanger 1 (NHE-1). Subsequently, the sodium ions are replaced by calcium, which can induce myocardial hypercontraction and tissue rupture [18].

On the basis of this concept, specific NHE-1 inhibitors were developed to interrupt this vicious circle and, thus, protect the myocardium from ischemia and/or reperfusion damage. A number of preclinical experiments had convincingly demonstrated dose-dependent reductions of myocardial infarct size in a variety of experimental models, including variations of species, anesthesia, or duration of ischemia, as well as using different compounds from several companies [19–21].

It came, therefore, as a surprise that, in the subsequent ESCAMI trial, the NHE-1 blocker eniporide did not produce a significant benefit in patients with acute myocardial infarction compared with placebo [22]. A close look at the published data from the animal experiments, however, reveals an important detail that could, at least partly, explain the failure of this Phase II trial. Pharmacological blockade of the NHE-1 was very effective when it was administered before the ischemic episode (i.e. in a prophylaxis setting). However, when the NHE-1 inhibitor was applied before reperfusion but after the beginning of the ischemia (intervention setting) treatment was much less effective [20,23]. In an acute myocardial infarction the ischemic episode is ongoing before any treatment can be initiated. Therefore, although acute myocardial infarction seemingly is the more frequent and potentially more attractive indication, the limited effect of NHE-1 inhibitors in the intervention compared with the prophylaxis setting substantially increased the risk of failure of eniporide in the ESCAMI trial. Interestingly, the competitor compound, cariporide, was profiled in a different way. In the GUARDIAN trial, cariporide proved to reduce myocardial infarctions in the subgroup where the compound was administered before a coronary artery bypass graft operation (i.e. in a pre-treatment or prophylactic situation with predictable reperfusion) [24]. Consistent with the animal experiments, there was no significant benefit in the other groups, where either a prophylactic treatment could not be applied (in the acute myocardial infarction setting) or when reperfusion could not be controlled (in high-risk coronary interventions). Unfortunately, despite confirmation of efficacy in a subsequent Phase III trial, the development of cariporide was discontinued because of an unexpected, and as yet unexplained, excess rate of strokes and deaths [25].

The wrong endpoint

The nitric oxide (NO) signaling pathway is one of the most important pathways in the cardiovascular system. In vascular smooth muscle cells NO activates the soluble guanylate cyclase, leading to an increase of cyclic GMP and vasodilatation. Employing this mechanism, NO-releasing molecules, the organic nitrates, are a standard of care for the treatment of angina pectoris as a result of their ability to reduce cardiac preload, leading to improved perfusion of ischemic myocardial areas, particularly its subendocardial layers. Unfortunately, the benefit of organic nitrates is limited by their side effects, such as headache, and by tachyphylaxis upon repetitive use. Therefore, several pharmaceutical companies started research programs in the mid-1980s aiming at mechanisms that would increase intracellular cGMP levels independently from NO. It emerged that pharmacological inhibition

of phosphodiesterase 5 (PDE5), an enzyme that degrades cGMP to its inactive form GMP, increases intracellular cGMP in vascular smooth muscle cells, and produces potent vasorelaxation. Consequently, PDE5 inhibitors were considered to become the new generation of anti-anginal drugs. In 1989, the compound UK-92 480 (later sildenafil) was identified as a potent and specific PDE5 inhibitor at Pfizer laboratories in the UK. The compound exhibited convincing pharmacological activity in preclinical models: it selectively increased cGMP levels in coronary vascular smooth muscle and produced synergistic effects with an NO donor in phenylephrine-contracted isolated rabbit aortic rings. In addition, the anti-aggregatory activity of sodium nitroprusside was potentiated by sildenafil on rabbit and human platelets [26]. On the basis of the experimental data in these models of vasomotion, sildenafil entered clinical trials for the treatment of angina pectoris in 1991. However, angina pectoris is a complex phenomenon and the pathophysiology is determined by a variety of factors, including the regional nature of the myocardial ischemia, the size and location of the ischemic area, and global hemodynamic parameters such as preload and afterload [27]. Animal models of regional myocardial ischemia can therefore be considered more predictive of the clinical situation, compared with vasodilation experiments in isolated vessels or the normal coronary circulation *in vivo*. We are not aware of any published preclinical studies on the effect of sildenafil in a model of regional myocardial ischemia that could have confirmed sildenafil's purported benefit in angina pectoris. Only later, when concerns came up that sildenafil might have adverse cardiovascular properties, were such studies published. In open-chest dogs sildenafil did not improve regional blood flow in the myocardium distal to a crucial coronary stenosis [28]. In combination with isosorbide dinitrate sildenafil even reduced systemic blood pressure and blood flow in stenotic coronary arteries [29]. In awake dogs with chronic coronary artery stenosis sildenafil, unlike the nitrates, did not improve endocardial blood flow during exercise induced myocardial ischemia [30]. Overall, while sildenafil was effective when vasodilation was used as an endpoint, it failed to demonstrate efficacy in the more adequate but more laborious models using regional myocardial ischemia as an endpoint.

In hindsight, bearing in mind the results from the animal models of regional myocardial ischemia, it is not surprising that the initial clinical performance of sildenafil in patients with coronary heart disease fell short of the expectations [31]. Unfortunately, the initial studies leading to the discontinuation of the development of sildenafil in angina pectoris are not published. However, additional trials were conducted after the launch of sildenafil as a treatment for erectile dysfunction. Several studies in men with and without coronary heart disease revealed either no relevant (or modest) effects of sildenafil on systemic hemodynamic parameters at rest or during exercise [32–34]. In patients with stable angina pectoris, sildenafil did not improve exercise tolerance or hemodynamic parameters [32]. In a randomized, placebo-controlled trial sildenafil had no effect on symptoms, exercise duration, or presence or extent of exercise-induced ischemia in men with stable angina pectoris [35,36]. Taken together, clinical trials demonstrated the safety of sildenafil in patients with coronary artery disease, but they also confirmed a lack of anti-ischemic effect, a finding that is consistent with the results from the animal models using myocardial ischemia as an endpoint.

It is an almost historical incident that, after the initial disappointments in patients with coronary artery disease, penile erections in volunteers during a 10-day Phase I study triggered the kick-off for the development of sildenafil as the first pharmacological treatment for erectile dysfunction [37] and, later, pulmonary arterial hypertension [27]. Thus, the ultimate success of this drug is a good example of the complexity of drug development and an excellent piece of serendipity for the researchers involved. Nevertheless, the failure of sildenafil in angina pectoris could have been avoided had the more predictive, albeit more complex, animal models been used.

Conclusions

In the pharmaceutical industry, translational medicine is about facilitating the communication between preclinical research and clinical development. Recent statistics indicate that particularly the clinical Phase II, or proof of concept, phase remains most susceptible to failure along the drug development process. The potential reasons for failures in Phase II trials are generally manifold. They include, but are not limited to, poor pharmacokinetics or limited bioavailability, lack of target validity in the human and insufficient clinical safety [1]. In addition to these traditional risks, attention has recently been drawn to the impact of bias during the research phase [38] and the selection of appropriate, homogeneous patient subgroups (responders) for the first clinical trials.

Frequently, the reasons for failure in Phase II trials are not obvious, and potentially involve a combination of different factors. An example for such a complex situation is – in our view – the recent failure of the inhibitor of the cholesteryl ester transfer protein (CETP), torcetrapib, for the treatment of dyslipidemia and atherosclerosis. The development of torcetrapib was discontinued owing to a lack of efficacy regarding major cardiac events in a large trial. In the ILLUMINATE trial, which was terminated prematurely, torcetrapib, according to its mode of action, evoked a substantial increase in high-density lipoprotein (HDL) cholesterol, but also significantly increased blood pressure [39]. While recent experimental data indicate that an increased blood pressure can be observed with torcetrapib, but not with other CETP inhibitors [40], the concept of HDL-targeted interventions for the treatment of atherosclerosis as such has been called into question [41]. Future trials with alternative CETP inhibitors will be able to answer the question whether the failure of torcetrapib was compound- or mechanism-related.

The examples given in this Feature article illustrate that failures of clinical development programs – among many other reasons – can arise from developing the wrong compound, from relying on data from the wrong experimental model or from using the wrong endpoint in experimental studies. Conversely, we postulate that in drug development, the meaning of translational medicine lies in testing the right compound in the right model, using the right endpoints (Box 1).

Taken together, it appears that failures in drug development can be avoided, at least in some cases, if research and development departments are more closely connected. In many cases, the business decision to take a drug development project into the clinic will involve a great deal of judgment. Usually, the potential clinical benefits and financial rewards will have to be balanced against the risks of failure for technical or scientific reasons. To some extent, greater efforts in preclinical research will increase the amount of preclinical data and allow a better estimation of the development risks. When taken seriously, translational medicine can help to identify

BOX 1

Key success factors for translation from research to development:

Right compound
Right model
Right endpoints

ineffective compounds earlier, to define a clinical target population more precisely and to guide the development of clinical candidates in a more stringent way. Thus, translational medicine has a concrete value: it can save the pharmaceutical industry unnecessary investments and avoid risks to volunteers and patients that arise from exposure to an ineffective and potentially dangerous drug.

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