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Perspective

How Clinical Development Can, and Should, Inform Translational Science

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There is an urgent need for preclinical translational efforts to be realized as breakthroughs in therapy for the many patients with life-altering conditions affecting the CNS. Despite intensive efforts, few transformative therapies have emerged, and many new potential therapies that looked promising in preclinical development have failed in the clinic. In this Perspective, we suggest that if preclinical scientists partner early with clinical scientists, they can begin to envision the pathway forward for their work through clinical trials. Options might include determining the populations to be treated, issues of dose selection, timing of intervention, duration of intervention, and the availability of biomarkers. In addition, understanding other factors that impact the likelihood that a proof-of-concept trial can be performed, as well as other critical issues, will altogether increase the attractiveness of the project to investors and partners and will also increase the likelihood that the intervention will succeed in the clinic.

Introduction

Basic science can be undertaken for a number of reasons, but increasingly there is a desire among translational neuroscientists to bring their discoveries to the clinic and ultimately to advance the health of people with diseases of the brain or nervous system. Laboratory scientists who make a discovery that leads to a breakthrough treatment or prevention of an otherwise untreatable condition can be immeasurably rewarded for their contributions. However, many neuroscientists have also experienced enormous disappointment when their promising intervention fails in clinical development. Such failures can negate years of effort and waste enormous expenditure of resources. Unfortunately, this type of failure is all too common among therapies for CNS diseases such as ALS, Alzheimer's disease, Parkinson's disease, and others (Benatar, 2007; Franco and Cedazo-Minguez, 2014; Katsuno et al., 2012). While all such failures cannot be prevented, some may be traced back to a lack of partnering between neuroscientists working on discoveries in the laboratory and clinical scientists who assess treatments in human disease. The worlds that these two types of scientists inhabit are both very complex. Both require years of specialized training. While the clinical scientist will rarely have the responsibility of worrying about how his or her work is translated back into the laboratory (although sometimes this happens), the laboratory scientist interested in clinical intervention should most certainly understand the concepts of the clinical development path.

The purpose of this article is to provide a "how to" for translational scientists and to outline some of the major issues that often lead to an inability to bring a big discovery across the translational divide. The authors include scientists working on both sides of the translation gap in the field of epilepsy. As a group, we have seen both successes and failures in the clinic, and in some cases the reasons for these have become evident, even if only in hindsight. Where possible, examples will be provided. Although these examples are mostly in the epilepsy field, we will be discussing issues that are generalizable to other areas of CNS therapy. We will not cover issues of lack of preclinical rigor. Whereas this is an extremely important reason for failure of translation, it is covered elsewhere in this issue.

Types of Therapeutic Intervention

Because the issues will vary based on the intent of the therapy, we will begin with a brief discussion of the three main areas of therapeutic intervention. These include symptomatic control, disease modification/cure, and disease prevention.

Control of Symptoms

Treatment for control of symptoms provides relief while the treatment is administered but does not alter the underlying disease or its course. Examples include seizure suppression in patients with epilepsy, symptomatic headache therapies, and improvement of memory in patients with Alzheimer's disease. Often many pathways are available for intervention, and there are animal models that translate reasonably well to the clinic, making high-throughput screening a possibility in some cases. Also, therapies may already exist for these purposes, and therefore the regulatory pathways are well understood. Translation of therapies for symptomatic control are probably the most likely to succeed, although even here there are pitfalls such as dose determination, safety assessment, and determining whether the treatment is better than existing treatments. All of these issues are addressed below.

Disease Modification/Cure

Disease modification comprises an alteration of the underlying pathophysiology before or after the disease has clinically manifested, leading to an improvement or change in progression of the disease or its comorbidities. Successful translation of a

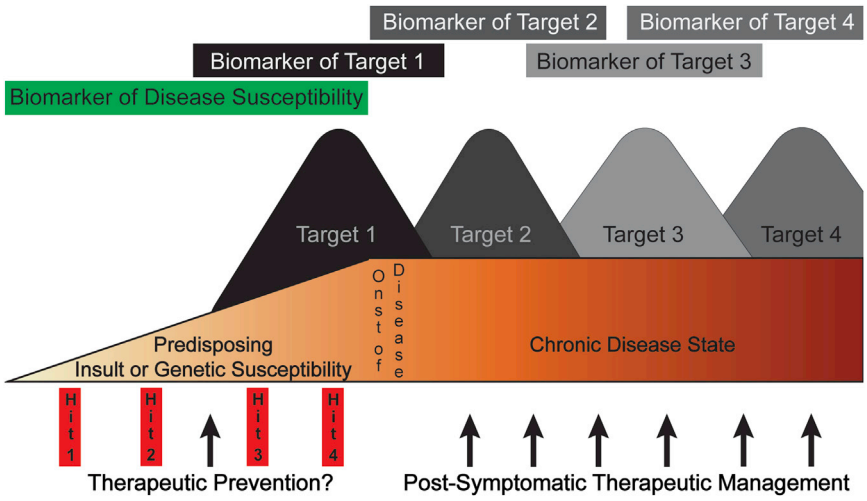

Figure 1. Schematic Representation of Disease Susceptibility, Risk Factors, and Progression, as Well as Avenues for Potential Therapeutic Prevention and Postsymptomatic Management

In general, diseases can be attributed to a predisposing insult or genetic susceptibility, which may or may not be exacerbated by multiple hits prior to disease onset. It is hypothesized that biomarkers of disease susceptibility and biomarkers of various contributors to the chronic disease state exist or can be identified for most clinical conditions.

disease-modifying intervention requires a more fundamental understanding of the underlying pathophysiology of the disease in question. This complete understanding will most often come as a result of cross-communication and collaboration between clinician and basic researcher. The translation of a disease-modifying treatment is often predicated on one of two scenarios. In scenario 1, clinical investigation of the human disease leads to identification of a fundamental mechanism of disease, and preclinical science identifies a way to modulate that mechanism. In this case, translation may fail because the mechanism identified was not essential in the disease pathophysiology, or the effect size of the intervention was not great enough, among other reasons. As an example, failures in clinical trials for both Alzheimer's disease and Parkinson's disease have potentially been due to a modest effect in large patient cohorts at diverse stages of the disease severity (Cedernaes et al., 2014; Pinna, 2014). It is possible that future successes in clinical trials for both of these disorders, e.g., amyloid beta-targeting antibodies for AD and adenosine A2 receptor antagonists for PD, may come through a better understanding of the role of that target in the disease pathology or better identification of relevant patient populations. In scenario 2, which is much more risky, an animal model of the disease has been created (e.g., the ALS mouse, the Alzheimer's prone mouse, etc.), and an intervention has been demonstrated to reduce or eliminate disease in the animal model. This scenario can be very enticing to a translational scientist, particularly when there is some apparent overlap between the pathology of the human disease and the pathology seen in the animal model. For example, a toxic gain-of-function mutation in chromosome 21, which codes for superoxide dismutase, produces ALS in both humans (familial ALS) and mice. Yet, therapies that slow progression of disease in the animal model have failed to impact human disease (Benatar, 2007). Unfortunately, disease modification/cure is intimately linked with mechanisms of development and progression of disease, and these have yet to be clearly determined to be comparable between animal models and human. Appropriate timing of intervention will also be a factor, and this is discussed below.

Disease Prevention

Disease prevention may be very straightforward in some cases, where the approach is to prevent the insult that produces disease from occurring (for example, antiplatelet agents to prevent recurrent stroke, motorcycle helmets to prevent traumatic brain injury). In almost every other scenario, this may be the most risky of all translational objectives. Outside of insult prevention, it is difficult to even think of a scenario in which such an approach has been successful in the CNS, presumably because most CNS diseases have complex pathophysiology and because most of the diseases (ALS, multiple sclerosis, and epilepsy, to name a few) are insidious in their origin. As can be seen in Figure 1, some mechanisms that promote disease initiation may be present even before the purported onset of the disease but may only be activated by a second or third hit. It may be very difficult to pinpoint the moment that disease becomes inevitable. Also, in essentially every case, a disease prevention therapy will be a first-in-class therapy, and issues related to this will be discussed below.

Is a Proposed Therapy Better than Existing Therapies?

In areas where therapies already exist (mostly therapies to control symptoms), there is still a potential for a breakthrough therapy if the novel therapy is demonstrated to be substantially better than existing therapies. The expectation that a therapy may represent a substantial advance may come from the fact that the drug works through a different mechanism than its predecessors or from evidence of improved benefit over currently available standards of care in an etiologically relevant animal model. In some neurological diseases, e.g., pain and epilepsy, numerous preclinical models exist with translational validity (Löscher, 2011), whereas in other disease states, e.g., ALS and stroke, the search continues for clinically validated animal models (Perrin, 2014).

Both scenarios carry challenges for the translation of revolutionary therapies. Epilepsy therapies can act as an example. On the one hand, ample models of acute and chronic seizures have benefited the patient with epilepsy by advancing treatments to the clinic for the symptomatic management of seizures. On the other hand, many years of testing in these models have ultimately demonstrated that they cannot be used to identify breakthrough therapies. The animal models routinely used, e.g., maximal electroshock (MES), do not substantially