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Solving the Lost in Translation Problem: Improving the Effectiveness of Translational Research

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Abstract

Translational research frequently fails to replicate in the clinic what has been demonstrated in the laboratory. This has been true for neuroprotection in the central nervous system, neuroprotection in glaucoma, as well as many other areas of medicine. Two fundamental reasons for this “Lost in Translation” problem are the “Butterfly Effect” (chaotic behavior of many animal models) and the “Two Cultures” problem (differences between the methodologies for preclinical and clinical research). We propose several strategies to deal with these issues, including the use of ensembles of animal models, adding intraocular pressure lowering to neuroprotection studies, changing the way in which preclinical research is done, and increasing interactions between the preclinical and clinical teams.

Introduction

Glaucoma translational research has a Jekyll/Hyde character. On the one hand, the use of animals for developing drugs or surgical devices that lower intraocular pressure (IOP), the only proven therapy in glaucoma, has been enormously successful. Although there are some exceptions, e.g. the minimal IOP lowering with the β-antagonist timolol in the rabbit [1], the vast majority of IOP lowering therapies work well in both animals and humans. On the other hand, the translation of neuroprotection therapies from the animal to humans has been fraught with problems. The two largest clinical trials in ophthalmology studied the N-methyl-D-aspartate receptor antagonist memantine in open angle glaucoma, and failed to show efficacy on the primary outcome measure(s) [2,3]. A smaller trial in acute angle closure glaucoma did not show efficacy with the α_2 agonist brimonidine [4], while another small trial of brimonidine in open angle glaucoma showed a marginal effect on contrast sensitivity but not visual fields, the primary endpoint considered most important by the United States Food and Drug Administration (FDA) [5]. In fact, the only clinical trial to show an effect consistent with neuroprotection in glaucoma was the Low-Pressure Glaucoma Treatment Study [6], and even that study did not definitively prove neuroprotection [7].

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There are several reasons why translational research in glaucoma is difficult. The most important are: (1) differences in the retina/disk/optic nerve between animals and humans; (2) differences in etiology of disease between glaucoma animal models and patients with glaucoma; and (3) differences in study design and statistical analysis between preclinical and clinical studies. Furthermore, the dose, scale and timing of intervention, methods and end-points, age of study groups, and absence versus presence of IOP-lowering treatment represent major differences in study design between preclinical and clinical glaucoma studies. Many of these features have been discussed in recent reviews [8,9].

Beyond these glaucoma-specific issues, there is a wider problem in translating animal studies to the clinic, which is seen across most areas of medical research. The reasons for this “Lost in Translation” problem have been discussed previously [10], and there are three specific problems underlying most translational research that can be delineated. The first is the “Butterfly Effect,” the fact that small differences in the details of an animal model often lead to vast differences in results, a sign of chaotic behavior. The second is the “Princess and the Pea” problem, and is based on the common finding that there is increased variability in effect size as studies transition from biochemistry to tissue culture to animal studies to human studies. This is contrary to the expectation that the effect size would remain the same, in the same way that a pea indenting the bottom of a stack of mattresses would indent the princess to the same extent. The third is the “Two Cultures” effect, where differences between the cultures of preclinical and clinical research lead to translational problems.

Much of the difficulty with translational research is inherent in the structure of how it is performed, and is not amenable to easy solutions. In this review, we provide a framework for improving the effectiveness of the translational process, using recent examples from the literature along with new models and constructs. We focus on the Butterfly Effect and the Two Culture Problem because they are more amenable to solutions. Although we discuss glaucoma as a target, many of the proposed methods are equally applicable to other fields of biomedical research.

Taming chaos

A butterfly in Brazil and a tornado in Texas

Small differences in animal model designs can lead to large differences in effect size of therapeutics. In the area of experimental glaucoma, an example is the difference between the episcleral vein cautery model and the hypertonic saline aqueous vein sclerosis model. These differences (among others) led to one study showing neuroprotective efficacy of 2-aminoguanidine [11] and another showing the opposite [12]. Another example is the difference between optic nerve crush and optic nerve transection, which may have been the reason why one group found neuroprotection with glatiramer acetate [13] and another group showed the opposite [14]. The sensitivity to what might seem to be minor differences in model design is reminiscent of chaos theory, where small differences in initial conditions or model parameters leads to large differences in results.

To deal with this, we suggest that the strategies used by meteorologists in dealing with the chaos inherent in forecasting weather can be applied to translational research [15]. Meteorological models are considered robust when minor perturbations in initial conditions lead to minor perturbations in the predicted weather. A process of theme and variations is used to produce an ensemble of weather predictions, each corresponding to an equal number of perturbed initial states. The more similar the predictions, the more stable the model. Even more advanced methods for dealing with the difficulties of weather prediction have been developed over the last decade [16], and a recent review is accessible to the non-meteorologist [17].

Analogously, in translational research the characteristics of each model can be systematically varied in several dimensions. If the therapy remains efficacious despite changing the species, the method of inducing disease, the degree of injury, and other factors, it is more likely to translate to human patients than a therapy that behaves unstably. These approaches are those of systems biology, and there is precedent for their use in biology, e.g. translation initiation in eukaryotes [18] and differentiation of HL-60 cells [19]. Below we discuss recent advances in applying ensemble theory to glaucoma models, based on the concept that preclinical testing of drugs in more than one animal model increases the likelihood of successful translation to the clinic.

Ensembles of multiple glaucoma models

Although the cause of glaucoma is still unknown, elevated IOP and aging are the major risk factors. It is unclear how these and several other risk factors (e.g. heredity, race, myopia, etc.) cause neuronal death in glaucoma, with likely mechanisms including biomechanical stress, neurotrophin deprivation, excitotoxicity, autoimmunity, glial cell activation and inflammation, changes in blood supply and nutrition, mitochondrial dysfunction, protein misfolding, and changes in RGC survival pathways [20,21]. Whether any of these mechanisms act upstream, in parallel, or downstream of elevated IOP is unclear. The fact that there is a significant prevalence of elevated IOP without evidence of optic nerve degeneration suggests that ocular hypertension is not the sole critical factor for glaucoma. In patients with so-called normal-tension glaucoma (IOP in the “normal” range but clinically evident optic neuropathy), it is possible that undetected IOP elevations (spikes) contribute to the degeneration of the optic nerve. In humans, glaucoma is likely to be a multi-factorial disease shaped by complex genes and environmental conditions [20,22] that lead to activation of combinations of molecular pathways, resulting in a patient population of heterogeneous etiology.

In contrast to the complex nature of human glaucoma, in preclinical studies an animal model of glaucoma is created using the same unifactorial methodology in every animal. The outcome is a group of fairly homogeneous animals compared to human patients. Not surprisingly, if a drug is proven to be effective in an animal glaucoma model with homogeneous etiology, the same drug might not work in human glaucoma patients with heterogeneous etiology [8]. One solution is to test drugs in preclinical studies in different animal models of glaucoma. Ideally these are created via different interventions, analogous to the multiple mechanisms that contribute to RGC pathology in humans. If a drug demonstrates efficacy in different animal models of glaucoma induced via mechanisms similar to those seen in humans, it is more likely that such a drug would show efficacy in clinical trials of glaucoma patients with heterogeneous etiologies.

The ensemble approach is limited by the availability of glaucoma models, making it important to develop animal models in which the induction of the optic neuropathy mimics one or more mechanisms and risk factors seen in the human disease. It would also be helpful if glaucoma models could be generated based on use of a combination of mechanisms. Below, we critically discuss some of the current available animal models of glaucoma and related optic neuropathies for preclinical studies.

Sustained elevation of IOP—The rat is currently the most commonly used animal for experimental glaucoma in preclinical studies of glaucoma neuroprotection. There are two well-established and widely-used experimental models in the rat for inducing chronic elevation of IOP, the major risk factor for human glaucoma (reviewed in [23]). In both animal models, aqueous humor outflow pathways are targeted to damage the anterior chamber conventional outflow pathway of the eye. In these models, injury to outflow is

induced either by injecting hypertonic saline into the episcleral veins in the Brown Norway rat [24] or laser treatment of limbal or trabecular tissues in non-pigmented rats [25,26].

Many other species are used for IOP-related glaucoma models, including genetic models in the mouse [27,28], interventional models in the mouse [29–31] and pig [32], and spontaneous glaucoma in the cat [33]. The IOP-dependent animal model most similar to human glaucoma is with laser destruction of a portion of the trabecular meshwork in the non-human primate [34], usually the rhesus or cynomolgus monkey.

Induction of an autoimmune response involving the optic nerve head—In some patients with normal-tension glaucoma, the serum levels of autoantibodies against small heat shock proteins (HSP) are elevated [35]. Correspondingly, the expression of HSP27 and HSP60 are upregulated in postmortem glaucomatous human retinas [36]. These findings led to the development of a model of experimental autoimmune glaucoma in the Lewis rat by immunization with HSP27 and HSP60. This activates T-cells in the retina and results in significant RGC loss [37].

Induction of glial activation and inflammation—Levels of the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) and its death receptor TNFR1 are elevated in glial cells in the retina [38] and optic nerve head in postmortem glaucomatous human eyes [39]. Increased levels of TNF-α are also observed in the aqueous humor of glaucoma patients [40]. There is growing evidence demonstrating that TNF-α signaling is involved in the neurodegeneration process in glaucoma [41]. Consistent with these findings, a single intravitreal injection of TNF-α in mice results in activation of microglia, loss of oligodendrocytes in the optic nerve, and loss of RGCs, despite normal levels of IOP [42]. In mice with laser-induced ocular hypertension, blocking the TNF-α protein or deleting its gene fully rescues the loss of oligodendrocytes and RGC [42]. The expression of membrane-bound full-length FasL, most likely on activated microglia, is critical for the TNF-α–induced loss of RGC in mice [43].

Ischemia to the optic nerve head—There is a strong association of alterations in retinal and optic nerve head perfusion, autoregulation, and vascular reactivity in patients with glaucoma, but it has been difficult to tease out how many of the measured changes are the cause of the glaucomatous process and how many are the result. Several of the critical issues in vascular reactivity have recently been reviewed by Venkataraman and colleagues [44]. The use of models to study ischemia in glaucoma has been challenging. For example, retinal vascular occlusion or elevation of the IOP above the central retinal artery systolic pressure causes ischemia to the inner retina, RGC death, and consequent optic atrophy. However, the morphological features of the resulting pale disc are grossly different from the cupping seen in glaucomatous optic neuropathy. A more appropriate model is ischemia to the optic nerve head, and this has been studied by several groups. One method is chronic delivery of the vasoconstrictive protein endothelin-1 via osmotic minipump to the optic nerve head. This results in an optic neuropathy when performed in non-human primates [45], rabbits [46], and rats [47], but the degree of excavation and development of atrophy do not mimic the absence of pallor and severe excavation seen in human glaucoma. Another method is the laser of the optic nerve head of rats [48], mice [49], or non-human primates [50] after infusion of the photosensitizer Rose Bengal, resulting in an ischemic optic neuropathy, but this causes a type of anterior ischemic optic neuropathy with acute disc edema, followed by primarily optic atrophy without glaucomatous cupping.

Models focusing on mechanisms of RGC death signaling—A tremendous amount is known about the steps leading to axon injury and RGC death in glaucoma, summarized in

two recent and comprehensive reviews [51,52]. Some of these mechanisms are biomechanical stress, neurotrophin deprivation, excitotoxicity, mitochondrial dysfunction, protein misfolding, superoxide signaling, and redox modulation, and other changes in RGC survival pathways. For each of them there are models that can address the specific mechanism, but it does not mean that the model itself causes a glaucoma phenotype. For example, redox modulation is associated with the RGC axonal injury response [53], but it does not mean that animals with excessive levels of reactive oxygen species (e.g. superoxide dismutase-1 knockout mice) have glaucomatous discs [54]. Similarly, although RGC axonal injury involves a complex interplay between NMDA receptors activating NF-κB in retinal Müller cells, TNF-α secretion, and increasing Ca^{++}-permeable AMPA receptors on RGCs, the use of glutamate or NMDA as excitotoxic agents results in optic atrophy without glaucomatous cupping.

Bridging the two cultures

Applying clinical research processes to preclinical research

Another approach to improving the quality of translational medicine is to make the process of animal research more like human research. The reinforcement structure that rewards milestones in pharmaceutical and device companies produces a remarkably powerful momentum for continuing development of a treatment despite accrual of evidence that it may not be provable in humans. The prospect of dismantling whole teams of scientists committed to an approach is daunting, especially when unmasked phase I or phase II studies appear to show some efficacy. Yet if the same rigor that is used by regulatory agencies for pivotal studies is also applied by scientists throughout the late preclinical and early clinical stages, it is less likely that time and money will be invested chasing false trails. Borrowing techniques of systematic reviews and the “futility” and “stopping” rules used in clinical trials and applying them to preclinical research has been valuable when done retroactively [55,56]. Identical measures could be used prospectively for assessing and improving the design of animal studies, including greater emphasis on sample size calculations, strict randomization to intervention groups, and intention-to-treat analyses. Computerized, automated collection of observations, scoring, and other data should be maximized in preclinical studies to decrease human error, bias, and personal differences in data collection. The same approach might be practical for clinical studies where there is potential for subjectivity or variability, e.g. assessment of intraocular pressure, visual acuity, etc.

Interaction of IOP-lowering and neuroprotection

The study design of animal research can also be made more similar to that of human research. For example, subjects in clinical trials of neuroprotection are usually also treated with IOP-lowering drugs. This is done for ethical reasons, because at present IOP lowering is the only treatment proven to reduce the progression of visual field loss in glaucoma. With IOP-lowering treatment, the risk of visual field progression is roughly half of that without treatment [57,58]. For the neuroprotective effect of a compound to be detected in glaucoma clinical trials, the disease progression rate should be further diminished to a level lower than that achieved by IOP-lowering alone [9]. This smaller window for detecting a reduction in glaucoma progression makes it much more difficult to assess the neuroprotective effect of compounds in clinical trials.

We suggest one strategy to mitigate this problem is to test neuroprotective drugs in experimental models of glaucoma where the animals are also treated with clinically relevant IOP-lowering agents. A sample preclinical study design would include two negative-control vehicle groups, one with and one without an IOP-lowering treatment, and two test groups of the putative neuroprotective agent, one with and one without IOP-lowering. The comparison

between the test and negative control groups without the IOP-lowering treatment would demonstrate the full efficacy of the neuroprotective compound. The difference between the two negative control groups (with and without IOP-lowering treatment) would provide information about the effect of the IOP-lowering treatment alone on disease progression. Comparison of the test and negative control groups with the IOP-lowering treatment would give the proportion of detectable reduction in disease progression achieved by neuroprotection beyond that achieved by IOP-lowering. Such preclinical study designs would better predict the outcome of subsequent clinical trials. If the neuroprotective effect of a compound is to be detected in clinical trials of patients, then a robust effect in preclinical studies should be seen when it is studied in the presence of IOP lowering. If this cannot be observed in animal studies, which are less variable than clinical studies (the "Princess and the Pea" problem), then it is unlikely that a clinical trial will show efficacy.

Another advantage of including IOP lowering in preclinical studies of neuroprotection is to detect synergistic or antagonistic interactions that may be relevant to subsequent clinical studies. A wide variety of IOP-lowering drugs should be assessed to ensure that unexpected findings do not become apparent in more expensive and lengthy clinical trials.

Humanizing animal models

A different approach to making animal research more like clinical research is to make the subjects of animal research, i.e. animals, more like humans. An example from another area of biomedical research is the use of immunodeficient mice engrafted with human islet cells for the study of diabetes [59] and other diseases [60]. These humanized mice represent a stepping stone between the animal model and human subject. Although this has not yet been done in glaucoma, as we learn more about its pathophysiology it is possible that there may be value in humanizing selected tissues, e.g. the outflow pathways, the optic nerve head, the RGC, glia, connective tissues, the sclera, and other targets. An alternate approach is the use of non-human primate models earlier in the preclinical process [61], although this has its own set of structural and ethical difficulties.

Increasing Interactions Between the Two Cultures

The culture of preclinical research can differ fundamentally from that of clinical research [10]. In addition, there is usually a disconnection between the preclinical and clinical teams during drug development. We suggest that increasing interactions between the preclinical and clinical teams is another way to improve translational research, including that in glaucoma. A better communication could be established between the preclinical scientists and the clinical trialists to discuss, compare and improve consistency in preclinical and clinical study designs (e.g. methods, instruments, training of personnel, study groups, study duration, end-points, statistical analysis, etc.).

For example, almost all preclinical studies in glaucoma use structural measures such as RGC cell body or axon counts as the endpoints, and occasionally electrophysiological functional measures. On the other hand, clinical trials that could lead to approval of a neuroprotective therapy usually involve a functional measurement as the primary endpoint. Surprisingly, there is usually minimal interaction between the scientists who assess neuroprotection in the laboratory, e.g. of retrograde labeled RGCs in retinal whole mounts, with those designing clinical trials, where specifics of the visual field assessment are critical. Improving such interactions may lead to unanticipated insights between the teams.

Other Methods for Improving Translational Efficacy

The phase 0 study is one where receptor binding, mechanism of action, pharmacodynamics, pharmacokinetics, or other biologic principles are studied in humans using microdoses of

drug [62,63]. A phase 0 study is carried out without any therapeutic intent, given the small amount of drug administered. Such Phase 0 studies are most commonly used in cancer research, to test whether the biological mechanism seen in animals can be affected by the treatment at a very low dose in a human. This approach can be applied to any clinical study in which a biological mechanism can be identified and the effect of treatment on the mechanism assayed. Such studies should be considered a more vital component in improving the translational research process than at present. An approach to improving translation efficiency in glaucoma would be the use of very early clinical studies such as phase 0 studies as tests of biological efficacy in humans. This is best done with a biomarker that could be highly sensitive to small concentrations of a neuroprotective agent, e.g. confocal scanning laser ophthalmoscopy of RGC death and injury [64,65] or early axonal injury [66].

Finally, we propose increased focusing on what we call phase –1 studies, a.k.a. the individual case report or small case series, in which the clinician notes an unexpected positive response to a drug used for another purpose [67]. Knowledge of a biological mechanism found in a disease can be employed to find new therapies, e.g. aberrant activation of Bcr-Abl tyrosine kinase in chronic myelocytic leukemia, which led to the development of the highly effective kinase inhibitor imatinib. Such bedside-to-bench observations in human disease can help focus the direction of animal research, which in turn will improve the translational process because they are already known to be associated with a clinical endpoint.

Conclusions

Translational research is not easy. This is especially true in neuroprotection, and even more so in glaucoma neuroprotection. We suggest that methodological changes in how animal models are used (particularly the use of ensembles of models), how experiments are designed and carried out, and how preclinical and clinical teams work together, can help solve this “Lost in Translation” problem and increase the likelihood that therapies can be translated from the laboratory to the clinic.

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Highlights

- One problem with translational research is caused by models behaving chaotically.
- One solution is to use ensembles of models, similar to how weather is predicted.
- A second problem is that the preclinical and clinical cultures can be far apart.
- A solution is to make the process of animal research more like clinical research.