

Lost in translation: barriers to implementing clinical immunotherapeutics for autoimmunity

Matthias G. von Herrath and Gerald T. Nepom

Induction of selective, autoantigen-specific tolerance is the “holy grail” for the treatment and prevention of autoimmune diseases. Despite successes in many differential murine models, rational and efficient translation to the clinic has been difficult. During the 5th Annual Federation of Clinical Immunological Societies (FOCIS) Meeting, May 12–16, 2005, in Boston, MA, a Kirin-sponsored “Ideashop” was convened to discuss this theme amongst scientists, clinicians, industry partners, and funding agencies.

The major barriers delaying the translation of basic research that were articulated in the workshop were not the remaining gaps in scientific knowledge, but rather cultural and communication gaps in a field that has long been oriented toward fundamental discovery research, and in which the new era of “interventional immunology” is in its infancy. Here, we discuss the various problems facing the field, including the difficulty in translating animal models to human intervention trials, and delineate a possible roadmap for success.

Exciting observations; then what?

A translational roadmap for a vast majority of the discovery-oriented immunology research community is currently uncharted and thus nearly impossible to follow. Researchers in academia are woefully unprepared and untrained for the complex, arduous, and difficult process of translating basic immunology to the clinic, as trainees are taught to focus on scientific discovery. The academic immunology research community has been successful in creating the infrastructure to nurture and reward discovery research. However, upon making a discovery with therapeutic potential, it is rare for an academic investigator to think about or

have access to the resources necessary to nurture translational opportunities. Most senior immunologists can cite examples of lost opportunities in which potential clinical advances were derailed by a failure to pursue early partnerships with industry and legal experts, or by unskilled negotiations that created unnecessarily complicated agreements or royalty arrangements and hindered progress. Yet knowledge of the legal parameters involved in these collaborative ventures is only one piece of the puzzle. It is perhaps more important to develop a culture in which translational goals are a priority, so that the motivation to seek out clinical colleagues, to reach fair compromises between academic, industrial, and regulatory entities, and to establish a collegial relationship with institutional intellectual property officers is a reasonable expectation, rather than a rare exception.

Is “academic R&D” an oxymoron?

Academic institutes are not well-suited for the collaborative therapeutic development that is needed for translational research in autoimmunity. The key issues are well-illustrated by attempts to induce antigen-specific tolerance in patients with type 1 diabetes. The major work in this area is underwritten by the National Institutes of Health (NIH) and nongovernment organizations such as the Juvenile Diabetes Research Foundation (JDRF), with a relative absence of industry support. As a consequence, the approaches are largely investigator initi-

ated and are sometimes uncoordinated, with no overarching prioritization. Grants of short duration (typically 3 years) that are reviewed by discovery-oriented basic investigators are simply not adequate, as it may take 5 years or more to apply ideas from mouse models to testing in humans. Yet short-term grants remain the principal mechanism for funding investigator-initiated translational work. Several important attempts are underway to address this fundamental problem, including a new prioritization review system within the TrialNet consortium (<http://www.niddk.nih.gov/fund/diabetesspecialfunds>) sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, a strategic planning process within the Immune Tolerance Network, and a refocusing of the funding portfolio of the JDRF toward applied research goals. Nevertheless, allocating scarce research funds for infrastructure at the expense of basic research continues to be unpalatable for a field in which industry partners—the traditional source for clinical trials and product development—have not materialized.

It is also fair to ask whether academically directed clinical research is the best approach. Some therapeutic avenues, such as cell-based therapies, are inherently expensive and would benefit from industrial partnerships that could help cover early development costs. Industry is also generally more efficient in dealing with the regulatory issues that surround clinical trials. In the case of diabetes immunotherapy, complicated quality of life issues also arise, as the short-term benefits of replacing insulin therapy are currently used as a clinical endpoint, whereas the real medical benefit lies in the prospect of decreasing long-term diabetic complications. These and other complex issues necessitate close interactions with the Food

M.G.v.H. is at La Jolla Institute for Allergy and Immunology, San Diego, CA 92109.

G.T.N. is at Benaroya Research Institute at Virginia Mason, Seattle, WA 98101.

CORRESPONDENCE

M.G.v.H.: Matthias@liai.org

and Drug Association (FDA) and other regulators during trial development—interactions not known to be a strong suit for most academic investigators. A specific issue for immune-based interventions and tolerance induction in autoimmunity is the need to develop surrogate markers for therapeutic efficacy (which again requires FDA involvement) in order to optimize assays to measure alterations of autoimmune responses in blood samples and to define the clinical indicators of successful or deleterious outcomes. How many academic immunologists think about (or are even aware of) these issues? It will therefore be important to allocate funds to create infrastructure within academic institutes to facilitate interactions with regulatory bodies.

Are animal models letting us down?

The historical hand-off juncture between basic and clinical immunology has been the demonstration of therapeutic efficacy in animal models of autoimmunity. But in many animal models, translating these findings to humans may be a huge leap for clinicians. One problem is that cells traveling within the human blood, which is our main source of readily accessible autoantigen-specific immune cells, might not accurately reflect the events taking place in a given autoimmune target organ, such as the brain or pancreatic islets of Langerhans. This simple observation pinpoints an important problem with our scientific approach. When studying animal models, we generally recover cells from organs and tissues that we think will provide the most reliable answer to the question asked. In the case of diabetes, these include the pancreatic draining lymph node, the islet cells themselves and sometimes the spleen—all sites that are not readily accessible in humans. Although this strategy gives us good answers in animal models, it misses a crucial step in translating the discovered mechanistic insight to clinical trials: how to test for the establishment of the same protective mechanism, such as the development of antigen-specific tolerance, in humans. For example, the deletion of aggressive T cells or induction

of regulatory T (T_{reg}) cells—commonly used approaches for ameliorating autoimmunity in mice—is reflected in the lymph nodes or spleen but not in the peripheral blood of rodents, suggesting that monitoring peripheral circulating cell populations in humans might not be fruitful.

Another difficulty that arises in the design and monitoring of clinical trials is determining the correct antigen dose for therapies, which cannot necessarily be “scaled up” directly from mouse to human. In a recent diabetes prevention trial (1), oral insulin was given to prediabetic patients based on overwhelming evidence from animal models that oral insulin can induce T_{reg} cells that suppress aggressive antiislet responses in the pancreatic lymph node and thus prevent disease. It was clear that, in mice, this autoantigen-induced suppressive effect was dose dependent, as very low or very high oral insulin dosages did not have the desired effect (2,3). When designing the human trial, the investigators were faced with the difficult question of how to translate a rather large insulin dose (1 mg p.o. 2×/week) in the mouse for human application. They chose to emphasize safety rather than simply scale up from the animal model—a cautious and logical choice—and used a comparatively low dose (7.5 mg), based on gut size and body weight. Interestingly, a partial response reflected by delayed disease progression was noted only in a subgroup of patients who already had significant signs of antiislet autoimmunity (as assessed by autoantibodies). Since we have no reliable way to correlate a given stage in the development of autoimmunity in animal models to the course of human diabetes, there is really no straightforward way to apply the enormous body of animal data to the rational determination of antigen dose in future human trials.

Another example of the difficulty in translating antigen-specific approaches from mice to humans is the failed clinical trials using altered peptide ligands of myelin basic protein (MBP) in patients with multiple sclerosis. The peptides chosen for the human thera-

peutics were based on inbred mouse models of experimental autoimmune encephalomyelitis, in which disease is induced by MBP peptide administration. The human trial was quickly terminated when it became evident that some patients were responding to the peptide as an agonist, with deleterious clinical consequences (4,5). In retrospect, this adverse response might have been predicted if human *in vitro* studies using polyclonal cell populations or mouse studies using genetically diverse animal models had been performed, rather than relying on a single animal model. Indeed, the genetic diversity among human subjects may necessitate individual predictive testing of peptide responsiveness, analogous to provocative allergen testing before desensitization therapy, as a necessary component of future trials. In this manner, it may be possible to distinguish which patients are likely to have a deleterious response to the peptide therapeutic (such as an agonist response or augmentation of autoaggressive type 1 helper or cytotoxic T cell responses), and which patients are likely to benefit from such treatment.

Inbred animals: multiple copies of one individual

Human genetic diversity is another monster in the immunological closet, which is becoming hard to ignore. The more we know about the impact of genetic diversity on immune function, the more variable phenotypes we begin to recognize, even among subjects with the same clinical diagnosis. Yet most animal models of autoimmunity use a very small number of highly inbred mouse strains. Type 1 diabetes research is a flagrant example of this, as it is heavily reliant on the nonobese diabetic (NOD) mouse model, despite the fact that the NOD strain has a number of unique immunological defects (6) that are not found in other mouse strains and likely not in most human patients with diabetes, either. Clinical immunologists would be reluctant to draw major conclusions based on the study of a single individual, but basic immunologists do this routinely by

testing what are essentially multiple copies of a single animal.

How can we increase the confidence of translating from mouse to man? It is impossible to argue with the major insights into antigen-specific tolerance that have been gained from testing in well-defined inbred mouse models of autoimmunity. However, we may need to acknowledge a new set of criteria for translation, in which validation of a finding made in genetically diverse models is a required component (7). Genetically diverse models will not only be critical for assessing disease manifestations themselves, but will be even more important for evaluating the response to a particular therapy. An alternative approach that offers some possibilities for modeling human genetic diversity is the utilization of partially humanized mice (8,9,10). Even in these models, however, there are limitations to the diversity that can be modeled. For example, autoimmune disease models in human HLA-transgenic mice show major differences in antigen epitope recognition by T cells and in disease penetrance, depending on whether they express a single HLA molecule or two different HLA molecules. Since every human expresses between 8 and 12 HLA molecules, it is doubtful whether it will be possible to create an animal model that faithfully represents this important immunologic control element. Human TCR transgenic mice are useful for recapitulating a particular human T cell response. However, these mice can still be seen as multiple copies of a single genetic individual, and findings in these mice are not likely to be translate into useful immunotherapies for the human population in general. Indeed, is it too uncomfortable to ask whether, in some cases, *in vitro* human studies are more likely to be informative than *in vivo* mouse work? If no mouse model is perfect, at what point is it no longer cost effective to utilize scarce resources to create additional mouse models? Rather, important and promising observations made in mouse models could be solidified by proof-of-principle *in vitro* studies using human blood cells.

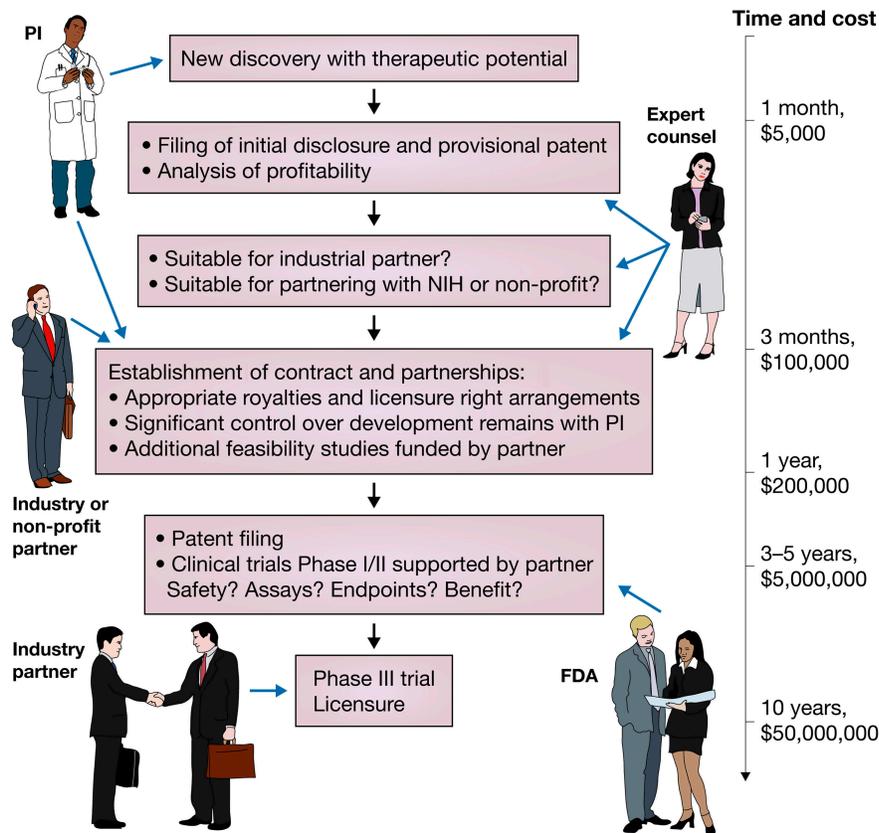


Figure 1. A translational roadmap for academic researchers.

This strategy might also have an added benefit if the goal is the induction of antigen-specific regulation or tolerance. As we are still in the process of establishing reliable *in vitro* assays that accurately reflect the induction of antigen-specific tolerance *in vivo*, such investigations might be a useful step in reaching this goal.

Opportunity for substantial change?

Some of the structural barriers to translational research are deeply entrenched in the academic system, and are beyond the scope of this discussion, which is centered on immunologic tolerance. Tenure, promotion, and funding decisions that constrain the training and performance of translational and clinical immunologists are certainly issues needing redress. However, with respect to the opportunities that now exist in the immunological community, we are blessed with a large array of potential immunotherapeutic strategies that are in need of testing and translation (11). Substantial changes need to be made if

we are to avoid a piecemeal approach in the near term, and failed or lost therapeutic opportunities in the future. Some initiatives are now underway, such as the FOCIS Centers of Excellence program, which provides a structure in which translational and clinical immunologists at collaborating institutions can self-organize in order to garner local resources more effectively. Consortia such as the immune tolerance network and Trialnet have a key role to play on the national level, where firm NIH support is essential. Constructing a useful translational roadmap for academic researchers to follow, like that proposed in Fig. 1, will require a substantial effort that is compelled by the prospect of therapeutic interventions in a vast array of human diseases. Immediately after a new discovery has been made, it will be essential for the academic institute to support a rapid evaluation of its therapeutic potential and the securing of intellectual property. Even at this early stage, designated skilled officials should

contact potential industry partners and establish relationships that will be crucial for translating the invention to the clinic. Indeed, academics and industry have diverging goals for follow-up experimentation (mechanistic insights and publications versus toxicology, safety, and reproducibility), and financing will be needed to satisfy both groups. We also believe that the individual investigator should remain involved throughout the discovery and development process and that industry partners must accept the possibility that the new intervention may have undesirable as well as desirable effects.

The potential impact of immunologic therapies on human health is enormous, and the opportunity to advance our knowledge of immunology in concert with clinical experience is equally large. For this vision of interventional immunology to realize its full potential, however, a smoother path for academic scientists aspiring to translational goals is needed. All parts of this enterprise—funding agencies, regulators, investigators, industry, and aca-

dem institutions—need to recognize that the cost of lost opportunity is high.

The authors are grateful for the generous support for the Kirin Ideashop series by Kirin Pharmaceuticals. In addition, we especially thank Eli Sercarz, who initiated this forum several years ago.

REFERENCES

1. Diabetes Prevention Trial—Type 1 Diabetes Study Group. 2002. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N. Engl. J. Med.* 346:1685–1691.
2. Bregenholt, S., M. Wang, T. Wolfe, A. Hughes, L. Baerentzen, T. Dyrberg, M.G. von Herrath, and J.S. Petersen. 2003. The cholera toxin B subunit is a mucosal adjuvant for oral tolerance induction in type 1 diabetes. *Scand. J. Immunol.* 57(5):432–438.
3. Bergerot, I., N. Fabien, A. Mayer, and C. Thivolet. 1996. Active suppression of diabetes after oral administration of insulin is determined by antigen dosage. *Ann. NY Acad. Sci.* 778:362–367.
4. Bielekova, B., B. Goodwin, N. Richert, I. Cortese, T. Kondo, G. Afshar, B. Gran, J. Eaton, J. Antel, J.A. Frank, et al. 2000. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83–99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. *Nat. Med.* 6(10):1167–1175.
5. Kappos, L., G. Comi, H. Panitch, J. Oger, J. Antel, P. Conlon, and L. Steinman. 2000. Induction of a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. The Altered Peptide Ligand in Relapsing MS Study Group. *Nat. Med.* 6(10):1176–1182.
6. Anderson, M.S., and J.A. Bluestone. 2005. The NOD mouse: a model of immune dysregulation. *Annu. Rev. Immunol.* 23:447–485.
7. Lam-Tse, W.K., A. Lernmark, and H.A. Drexhage. 2002. Animal models of endocrine/organ-specific autoimmune diseases: do they really help us to understand human autoimmunity? *Springer Semin. Immunopathol.* 24(3):297–321.
8. Roep, B.O., M. Atkinson, and M. von Herrath. 2004. Satisfaction (not) guaranteed: re-evaluating the use of animal models of type 1 diabetes. *Nat. Rev. Immunol.* 4(12):989–997.
9. Mestas, J., and C.C. Hughes. 2004. Of mice and not men: differences between mouse and human immunology. *J. Immunol.* 172(5):2731–2738.
10. Gregersen, J.W., S. Holmes, and L. Fugger. 2004. Humanized animal models for autoimmune diseases. *Tissue Antigens.* 63(5):383–394.
11. Feldmann, M., and L. Steinman. 2005. Design of effective immunotherapy for human autoimmunity. *Nature.* 435(7042):612–619.