Published in final edited form as:

Nat Med. ; 18(1): 35–41. doi:10.1038/nm.2632.

Unraveling the autoimmune translational research process layer by layer

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Abstract

Autoimmune diseases have a complex etiology and despite great progress having been made in our comprehension of these disorders, there has been limited success in the development of approved medications based on these insights. Development of drugs and strategies for application in translational research and medicine are hampered by an inadequate molecular definition of the human autoimmune phenotype and the organizational models that are necessary to clarify this definition.

The autoimmune problem

Autoimmune diseases comprise a large number of disorders with varied pathogenesis that are currently characterized into more than 100 different types of probable syndromic conditions¹. Consequently, the global burden of these diseases is vast. In the United States alone, the American Autoimmune Related Diseases Association estimates that there are more than 50 million Americans afflicted with autoimmune diseases, as compared to heart disease and cancer, which are estimated to affect 81 million and 11 million Americans, respectively². Most of these autoimmune conditions are diseases of low prevalence, with the majority being associated with eight disorders: rheumatoid arthritis, type 1 diabetes mellitus, multiple sclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease and scleroderma.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Although the direct economic cost of the autoimmune diseases is difficult to determine given the varied and poorly characterized nature of the disorders involved, the US National Institutes of Allergy and Infectious Diseases estimates that this category of diseases correlates with an annual cost to the US healthcare system of more \$100 billion, not including the cost of uninsured individuals, which is estimated to be at least another \$25 billion per year according to the America Autoimmune Related Diseases Association². Given their idiopathic nature and the epidemiologic evidence of an increasing disease prevalence for many of these afflictions as a result of the effects of undefined environmental factors³, these costs are likely to continue to increase, emphasizing the importance of ongoing international efforts to define the mechanisms of disease and translate this knowledge into effective therapeutic agents. However, despite recent great strides in understanding the immunologic and genetic basis of these disorders, such as those made through genome wide association studies (GWASs)⁴, and major advances in deciphering some of the key environmental influences, discovered through studies of the commensal microbiota⁵, there has been limited progress in the development of new therapeutic agents that target this group of diseases (**Box 1** and **Fig. 1**). This commentary highlights some of the operational difficulties that may be responsible for this separation between scientific and clinical success.

What do translation and translational hurdles mean?

The operational description for transforming biology into an effective therapeutic agent as associated with translational research (or medicine) is borrowed from the manufacturing denotation of a ‘value-added chain’, as originally established by Michael Eugene Porter⁶. Within this connotation, translational medicine spans five sequential areas of activity, which highlight the discrete translational hurdles that must be overcome (**Fig. 2**)⁷. It is estimated that only 10–15% of therapeutic agents that enter a phase 1 clinical trial eventually become approved products, although this approval rate may be higher for recombinant proteins^{8–11}. As such, the transition from the late preclinical phases to phase 2 and 3 clinical trials has been coined the ‘valley of death’ and was identified as ‘critical-path research’ by the US Food and Drug Administration (FDA) in 2004 (ref. 12). This critical path is an arduous and expensive industrial process that may take as long as a decade and a total estimated development cost of \$1.2–1.3 billion per product, with two thirds of this cost being related to clinical development^{13,14}. There has therefore been an increasing focus on overcoming the challenges associated with these aspects of biomedical research (**Box 2** and **Fig. 2**), which have resulted in a variety of efforts at the US National Institutes of Health (NIH), such as the roadmap initiative¹⁵ and the development of the Clinical Science Translational Award program¹⁶, as well as efforts at the NIHR-funded Biomedical Research Centre¹⁷ in the UK, to confront the associated challenges.

Challenges for translating autoimmunity research to clinical practice

Defining the human autoimmune phenotype: from genes to environment

One of the greatest problems in translating therapies into clinical practice in autoimmunity are the numerous failures that have been the results of clinical trials¹⁸. Despite the rapid progress that has been made in understanding the immune system, most of the underlying

data has come from animal models, which necessarily only partially represent what is observed in humans^{19,20}. The use of an animal model is only as good as the question researchers ask of it. To compound this limitation, there exists no standardized definition of the normal human immune system, no comprehensive understanding of how this normal system is altered in autoimmune diseases and no understanding of the relationship between these immunophenotypic characteristics and either the genetic composition of the host or the environmental stimuli that either promote or protect from the development of autoimmunity. Hence, researchers in the various fields of autoimmune disease have continued to rely on descriptive classifications, just as they have usually been applied for decades, to guide the translational process—there is therefore an overarching need to further develop this understanding.

Because they are complex, autoimmune diseases result from variably interacting biologic pathways that are either unique to a specific organ system, such as epithelium-associated pathophysiologic processes²¹, or common to many conditions, such as the mechanisms and consequences of inappropriate immune deviation or lack of immune regulation^{22,23}. There is a need to complement disease modeling in animal studies with an increased understanding of biologic pathways in humans and how these pathways interact with each other, as well as the specific relationship of these pathways with disease phenotype. Developing and standardizing high-throughput, multi-parameter and comprehensive methodologies together with systems medicine will allow for a simultaneous analysis of the immune system in relation to the genetic and functional genomic composition of the host, the commensal bacteria present and other environmental factors²⁴.

Recent progress in the identification of the genetic variation in healthy humans and in individuals with autoimmune diseases by GWASs has been a noteworthy success²⁵. Through GWASs, over 1,500 genetic variants have been linked to more than 220 complex diseases, including a variety of autoimmune diseases, such as ankylosing spondylitis, asthma, Celiac disease, Crohn's disease, juvenile idiopathic arthritis, multiple sclerosis, primary sclerosing cholangitis, biliary cirrhosis, psoriasis, diabetes mellitus and ulcerative colitis⁴. In addition, nearly 150 immune-mediated diseases that are correctly classified as primary immunodeficiency diseases and that are often associated with autoimmunity have been molecularly defined²⁶. These definitions allow for the creation of a 'road map' of the genetic framework within which to incorporate standardized information about the human immune phenotype. By overlaying a similar comprehensive analysis of the environmental milieu, it is possible that three-dimensional 'connectivity maps' between the immune system, genotype and environment can be created (**Box 3**). If such information could be linked to electronic medical records—arguing for a standardization of these systems nationally and even internationally—it would allow for the analysis of the linkage between these biologic components, disease phenotype, development of knowledge in disease pathways and identification of surrogate markers. Accomplishing this ultimate goal will require large-scale methodologic, organizational and regulatory efforts aimed at bringing together consortia that are able to manage and analyze such dense collections of datasets.

Optimal usage of clinical tissue banks in autoimmune disease

Translational research and medicine in the field of autoimmunity will require new approaches to establishing durable and usable human tissue banks of high quality that are amenable to a wide range of analytic techniques. There is currently no standard of practice for establishing these types of collections; however, it is clear that certain principles of sample collection, data acquisition and integration of these data into clinical care are required, as has been previously suggested²⁷, for the efficient acquisition and competent use of these samples as they apply specifically to autoimmunity (**Fig. 3**). These three principles are a prerequisite for success in defining the human immune system associated with autoimmunity and must include standardized methods of tissue procurement coordinated with well-defined molecular and immunological techniques and electronic phenotypic databases, all of which must be under appropriately established quality control standards and undergo quality assessment analyses. In addition, these three processes—tissue acquisition, molecular analysis and integration with a phenotypic database—need to be linked in a temporal fashion to sequential samples taken from healthy and diseased individuals both before and after specific therapeutic interventions. This will allow for the creation of legacy samples for future characterization. Such efforts will require multidisciplinary teams of clinicians, basic scientists, clinical scientists and other individuals familiar with regulatory and biomedical technology issues. Notably, tissue banks and their required infrastructures must be both properly designed to align with current relevant hypotheses and built in a flexible way so as to allow for the testing of future hypotheses, as will surely arise during the course of pre-clinical and clinical therapeutic studies. A biobank of properly archived peripheral blood fractions (cellular and noncellular fractions that include DNA, RNA and protein) should be a basic requirement for inclusion, and the biobanks should aim to include clinically relevant samples of the diseased organ of interest when possible, additional plasma samples or both to assess surrogate markers that reflect the inflammation associated with that organ.

A crucial first goal of these efforts would be to redefine the annotation of autoimmune diseases. Autoimmune disease classifications are now almost entirely based on clinical manifestations, pathologic findings and a limited range of blood tests that monitor nonspecific markers of inflammation. However, there is an unmet need for the reclassification of almost all autoimmune diseases on the basis of different—and more appropriate—pathogenic principles: genotype, immune profiles, environmental composition, environmental disease-causing factors and responses to therapy. Understanding these criteria and their relationship to disease is key to better defining autoimmune diseases and ensuring the success of future clinical trials. It is hoped that this understanding will allow for smaller and more focused clinical studies, with all the attendant benefits regarding financial requirements and methodologic success (**Box 4**).

In the most extreme view, autoimmune diseases may be envisioned as a collection of orphan diseases that involve specific types of immune pathways and, consequently, the associated clinical responses to therapies. In addition, these pathways and their responsiveness to therapy may overlap across disease categories. Accomplishing a personalization of disease mechanisms must take into account two things: first, considerations that relate to defining

biologic pathways through the analysis of immune profiles, genotype, environmental composition and responses to therapy, and second, the operational need for accessing not only large cohorts of affected individuals but also equally large cohorts of healthy individuals. The power to identify genetic diversity, for example, clearly relies on an adequate sample size²⁸ and is supported by international efforts, such as consortia that encompass several autoimmune diseases, including multiple sclerosis, Crohn's disease, ulcerative colitis and rheumatoid arthritis, among others. A similar case can be made for the analysis of the human commensal microbiome, given the well-established variation in this microbiome observed among human subjects²⁹. Similarly, healthy clinical samples need to be accessible, and large-scale phenotyping efforts of healthy blood donors, such as those being done at the Cambridge Bioresource (<http://www.cambridgebioresource.org.uk/>) or the TWINS UK Bioresource (<http://www.twinsuk.ac.uk/>), should be pursued and should include materials for the analyses of genetics, immune phenotype and the composition of the commensal microbiota. Such resources would streamline the availability of healthy controls and provide a template for other studies worldwide.

Organizational models to enable translation in autoimmunity

Centers to integrate patient care, experimental research and manufacturing

The current approach to translational medicine has grown by random accretion over the past few decades; consequently, this process has resulted in 'functional silos' that are contained within academic medical centers, industry and government. Unfortunately, attempts to integrate these components across the various groups and industries have not yet yielded a harmonious architecture for an approach to translational medicine. One solution to this problem may be to establish forward-thinking, translational units (or centers) built *de novo* for this specific purpose that would allow standardized sample collection, data analysis and clinical study development that are suitable for translation in autoimmunity. Such a center would aim to create a real physical structure that has the necessary financial and human capital, integrated into a clinical setting, capable of both translational investigation and the education of translational investigators, and this center must be able to negotiate the private-public interface. The NIHR-funded Biomedical Research Centre at Guy's and St. Thomas' Hospital in London exemplifies this model by bringing together all these elements in a single physical space, allowing for the preclinical and clinical activities that are required for translational activities in autoimmunity and experimental medicine and serves as a case study (**Fig. 4**)¹⁷.

An additional key feature of the Biomedical Research Centre is its integration with other immunology centers in Europe, such as the Pasteur Institute, centers in Oxford, Cambridge and Heidelberg, the Karolinska Institute, the Academic Medical Center Amsterdam and the Curie Institute, under the Federation of Clinical Immunology Center's of Excellence umbrella, as well as with other activities taking place in the United States, including those at the NIH U19 Translational Immunology centers. The development of similar types of models is underway in the United States through the Clinical Translational Science Award (CTSA) program at the NIH, which, once complete, will fund 62 centers at a cost of \$500 million per year by 2012 (ref. 30). Although the CTSA is currently mostly focused on

education and facilitating translational medicine, there is also a need for true functional translational units that are able to take advantage of both the roadmap initiatives of the NIH, the anticipated National Center for the Advancement of Translational Science that is currently under development (see below) and other private sector events that are occurring in the community between academia and industry¹⁶. The Biomedical Research Centre at Guy's and St. Thomas' Hospital and the Clinical Center at the NIH, which received a 2011 Lasker Award as a model for how translational research should be undertaken, might serve as templates for CTSA structures in the United States and elsewhere³¹. A comparison between UK and US strategies for translational research has recently been published that highlights some of these similarities³².

Enhancing academia-industry relationships

There are numerous challenges associated with critical path research: characterization of the safety of new molecular entities and devices, development of the medical utility of an agent and production of the agent at an industrial scale (**Fig. 2**). Therefore, once a target is identified through basic and applied research, typically within academia, and the basis for a new molecular target or entity is defined, efforts must be undertaken to determine the potential clinical utility of the molecule, refine the applicable properties of this molecule (pharmacokinetics, pharmacodynamics, toxicology, production and characterization) and validate its therapeutic potential in preclinical animal models. A variety of non-academic disciplines are necessary during these stages, such as chemistry, toxicology, pharmacology, drug delivery and formulation, general manufacturing production of therapeutic materials and expertise in intellectual property and regulatory issues. Inadequate access to non-academic experts in these areas poses a challenge to the success of the translational process. Thus, even in the early stages of translation, there is a need for better interactions between investigators and individuals associated with the commercial side of translation; in fact, one of the best predictors of success in the clinical development of a promising idea is the early involvement of industry³³. All stakeholders will therefore benefit from defining ways to encourage such interactions as early as possible in the translation process.

However, as recently discussed^{34,35}, there are many organizational challenges involved in these interactions. For instance, the cultures within academia and industry are distinct. The former is characterized by a relative lack of structures and systems that promote team-work or incentives to develop careers in translational medicine, whereas the latter—although less appropriate for early basic and applied discovery within a clinical framework—is organized based on skills and structures that are amenable to large-scale team-based activities. In the absence of a clear model to integrate the beneficial aspects of each of these cultures, pharmaceutical companies and private foundations have tried to provide some leadership by creating multidimensional, institutional reservations, such as the Basel Institute, the Roche Institute and the DNAX Research Institute, many of which have had autoimmunity as a major focus. Some of these attempts failed arguably at least in part because of a lack of integration into the clinical, academic setting.

More recently, pharmaceutical companies have increasingly been establishing more forth-right means of bringing academia and industry together at a small scale to promote direct

clinically oriented interactions. An excellent example of this is Pfizer Pharmaceuticals, which has established collaborations with Harvard Medical School, the University of Pennsylvania, the University of California San Francisco and Scripps to allow for immediate interactions and bidirectional intellectual contributions between academia and industry with a limited amount of financial support in specific projects³⁶. Nevertheless, these associations must still be considered ‘arms-length’ relationships that are constraining in the absence of more firm means of integration.

In a similar manner, the US government as well as governments in Europe are promoting the large-scale translational efforts that are required to bridge the research and development that are necessary for translational medicine to be successful. The NIH has shown efforts to define a road map to facilitate the necessary infrastructure and organizational changes. Thus, the reorganization of clinical research centers around the United States through CTSA programs and a proposal to develop a National Center for the Advancement of Therapeutics will support therapeutic target validation, chemistry, virtual drug design, preclinical toxicology, biomarkers, efficacy testing, phase 0 clinical trials with smaller numbers of patients, methods to rescue and repurpose medicines, facilitation of clinical trial design and additional support for post-marketing research^{15,16}. The UK Department of Health through the NIHR will spend up to £775 million over 5 years for translational research. In Europe, the Innovative Medicines Initiative has committed two billion Euros over 10 years to translational medicine^{37,38}. This pan-European initiative proposes to focus on brain disorders, metabolic diseases, infectious diseases, inflammatory diseases and cancer. This endeavor will involve approximately half a dozen pharmaceutical companies and a dozen universities throughout Europe that are proposed to join together to coordinately resolve some of the challenges discussed above, such as determining approaches to standardize sample collection and the establishment of preclinical models.

Finally, it has been argued that the creation of ‘stealth teams’ is needed. These groups, which are driven by nonprofit organizations, consist of small, flexible teams of academic investigators together with experts in the legal profession and in intellectual property, as well as participants from the NIH, FDA, insurance companies, pharmaceutical companies and other sources of potential funding³⁴. Although these teams may be especially crucial in the translation of orphan diseases, they have broad utility to autoimmunity diseases overall and are patient-centered initiatives.

In general, all of these approaches have the common goal of seeking a means to improve the operational relationships among the entire set of stakeholders involved in translational medicine. These approaches should be expanded on, with consideration being given to even bolder approaches.

The capital necessary for translation in autoimmunity

Effective translational research and medicine in autoimmunity will require access to patients to obtain clinical research materials and studies (the ‘raw material’), as discussed above, and adequate financial support for the necessary human capital and infrastructure. According to Sung *et al.*³⁹, conducting human clinical research in the United States alone requires the participation of more than 20 million patients annually, assuming a 5% rate of trial

completion. Improvement in the partnerships between patients and the professionals involved in clinical and translational research must be sought to facilitate the access of patients to study participation and the acquisition of patient-related materials, as patients are required for every step of the process. Recruitment of study subjects must be improved and streamlined, facilitating the integration of clinicians into the research chain, simplifying the process of obtaining the approval of human study institutional review boards and patient consent and increasing the involvement of the insurance companies in the funding of translational research to increase financial support for the patient care costs during translational research study in autoimmunity, as is being done for oncology in many parts of the United States (<http://www.cancer.gov/clinicaltrials/education/laws>). The latter effort will help to increase the trial completion rate as well as provide the obvious financial benefits that will increase the translational medicine ‘buying power’ of the current commitments. This process will benefit from the involvement of the disease-specific foundations and their better integration together and with academia.

With respect to financial capital, there is an urgent need to increase the support for biomedical research in general and for translational research and medicine in particular. The current limitations in this area are alarming. Approximately \$100 billion per year is invested in biomedical research in the United States— one third of which is provided by the NIH and the rest being provided by pharmaceutical and biotechnology sectors—and only a proportion of this money is applied directly to the area of autoimmunity research. For example, the US National Institutes of Allergy and Infectious Disease is able to commit approximately \$185 million per year to autoimmunity, not including the one-time funding by the American Recovery and Reinvestment Act, as a result of other commitments. But this and the overall NIH funding have remained flat in 1998 dollars since 2002. The inability to apply sustained scientific-inflation-indexed increases to biomedical research funding is extremely detrimental to long-term research planning and programs, especially given that it takes nearly a generation to move from early discovery stages to clinical approval⁴⁰. Mechanisms need to be established to create a sustainable source of funding independent of political factors. Joseph Loscalzo and David Korn have argued that stable funding for biomedical research will require a guaranteed growth rate of 8–9% to allow this sector to appropriately proceed^{41,42}. Investment in biomedical research could also be considered a necessary infrastructure that requires the creation of a financial trust. Interestingly, the nonprofit organization Research America! estimated that 60% of Americans would be willing to withhold \$1 per week in taxes for the funding of health-related research, which would come to approximately \$5 billion per year for a biomedical research trust⁴³. Healthcare consumption in the United States is approximately \$2.5 trillion per year, which represents 17% of Gross Domestic Product (ref. 44). Compared to an investment in research of only \$0.1 trillion per year, or less than 2-3% of total health expenditures, this is arguably an inadequate number considering that technology-oriented private entities typically commit larger sums to research and development relative to revenues⁴⁵.

Concluding remarks

An open question is whether society will be able to afford the cost of innovation and the price of success linked to translational research⁴⁶. An optimistic view is that, if successful,

the application of therapeutics in a more rational and targeted manner will result in direct and indirect savings that will offset the increased costs associated with the anticipated expansion of therapeutic offerings. It is interesting to consider that currently approved therapeutics consistently have a rate of effectiveness that is no more than 50% when examined at the population level in a broad group of diseases⁴⁷. This percent may even be lower in the case of biologic therapies, which often do not achieve an induction of remission in greater than 20–30% of patients in some autoimmune diseases and with some therapeutic agents⁴⁸. By coupling a biologic marker with a therapeutic agent through translational medicine, the promise and fruits of translational research should be within reach.

ACKNOWLEDGMENTS

The authors thank T. Rath, C. Pola and L. Paradiso for assistance in assembling data related to recent approvals of therapeutic agents in autoimmunity and assembling the manuscript. R.S.B. was supported by US National Institutes of Health grants DK44319, DK53056, DK51362, DK88199 and the Harvard Digestive Diseases Center (grant DK34854). F.O.N. is supported by a Senior Investigator award of the National Institutes of Health Research, Wellcome Trust Programme grant GR078173MA, Medical Research Council UK Programme grant G0601387 and the UK Department of Health via the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's & St. Thomas' National Health Service Foundation Trust in partnership with King's College London.

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Box 1**Therapeutic progress in autoimmune diseases**

There are currently 25 approved biologic agents for autoimmunity, not including intravenous immunoglobulins (IV IgGs), which are often used in the treatment of autoimmunity⁵⁵. IV IgGs are the purified and pooled IgG molecules obtained from up to 30,000 donors that, when administered to patients with primary immune deficiency or a wide variety of autoimmune conditions, show marked salutatory effects through a number of different mechanisms, including blocking of the neonatal Fc receptor for IgG and engagement of inhibitory Fc- γ receptors, such as Fc- γ RIIb^{56,57}. An examination of recent progress in this area has been enlightening. From 2006 and 2011 (refs. 49–53), 13 new agents for the treatment of autoimmune disorders were approved by the FDA. Notably, four of these approved drugs are new formulations of IV or subcutaneous IgG, and only 9 of the 13 drugs are agents against specific therapeutic targets. Only four out of these nine agents target immune molecules for which a therapeutic has not been previously developed: interleukin-6 (IL-6) receptor⁵⁸, the p40 subunit of IL-12 and IL-23 (ref. 59), BLyS (B lymphocyte stimulating factor)⁶⁰ and sphingosine 1 receptor (S1PR)⁶¹ (Fig. 1). These observations underscore the need to better understand the pathogenesis of autoimmune diseases and the organizational challenges in converting an understanding of autoimmune mechanisms of disease into approved therapeutic modalities. For example, IL-6 and the IL-6 receptor were identified in 1986 (ref. 62) and 1988 (ref. 63), respectively, however, an approved biologic agent targeting these molecules did not appear until 2010, a transitional period of 24 years.

Box 2**Common challenges to translational research**

The implementation of translating scientific understanding into biologic agents is not identical to the process of manufacturing, despite embodying similar principles in many of its aspects, as reflected in the use of a value-added chain or a map for the process. Translational medicine is an organic, reiterative process that requires continuous interactive feedback between varied disciplines to ensure its success and ability to innovate. There is, however, a tendency to rigidly cling to a value-added definition that might only perpetuate the ‘silo’ architecture of the organizational components needed for translation, discouraging the necessary redesign into an effective process for therapeutic development. Translational medicine is therefore the result of many poorly integrated activities distributed throughout the academic, governmental and private sectors. The challenges associated with bringing forward translational medicine within a coherent framework have been extensively discussed, including the need for new, efficient organizational models that promote innovation and team-oriented science, such as in an ‘adhocracy’ as proposed by Henry Mintzberg^{39,54,64–68}. However, it is clear that for translational research and medicine to operate more effectively, functional interactions should exist between the community, academia, government and both the financing and operational components of industry³⁴. Such crosstalk would not only leverage existing structures but may also establish a forward-thinking and logically integrated framework involving all stakeholders, and, most importantly, patients. The majority of these challenges apply to any research field; however, several issues that derive from the need to further understand the biologic basis of autoimmune diseases are unique for the translation linked to these disorders.

Box 3**Integrating the complexity of factors involved in autoimmune disease**

Existing common scientific platforms can be leveraged for the large-scale analysis of the human immune system, genetic (and epigenetic) structure of the host and composition of the human commensal microbiome. In immunology the BD Lyoplate or automated high-dimensional flow cytometry data analysis^{69,70} and in genetics the immunochip and whole-genome (exome) sequencing⁷¹ can be coupled with increasingly available procedures and algorithms to define the human microbiome, including next-generation sequencing coupled with analytic tools (for example, quantitative insights into microbial ecology)⁵ and standardization of the clinical phenotypic databases that allow for proper data analysis. National and international ongoing efforts can facilitate an available infrastructure; some of these efforts include the Federation of Clinical Immunology Society Centers of Excellence, the NIH Center for Human Immunology, Autoimmunity and Inflammation and other regional consortia that are emerging around specific diseases. But this is only a start, and the study of the genetics, cancer and neurology communities—examination of complex human genetics⁴, clinical cancer therapy development and its personalization⁷² and the Alzheimer's disease Neuroimaging Initiative, respectively—will probably produce examples of the generation and sharing of data that will guide clinical studies and unveil the basis for better means of autoimmune disease diagnosis and prognostication.

Box 4**Focused studies allowing more successful drug trials**

Can a case be made for pursuing the area of exploratory investigator-initiated drug studies (so called ‘phase 0’ clinical studies) in autoimmunity to promote the success of human clinical studies⁷³? Retrospective subset analyses of clinical studies deemed to be failures may increasingly support an affirmative answer to this question. For example, although the treatment of ulcerative colitis with myeloid-cell-produced β interferon was originally considered a clinical failure, a closer analysis showed that individuals with a decrease in IL-13 production within the colon correlated with clinical benefit^{74,75}. These informative examples highlight the need to ascertain a more detailed understanding of disease and its surrogate mechanistic markers. Because the source of these biologic signals may reside within the affected tissues, as in ulcerative colitis, this may pose a challenge for diseases in which the clinically relevant tissue is not accessible. Translational success in autoimmune diseases may therefore depend on an increasing personalization of disease mechanisms, as has been shown in cancer treatment with the approval of therapies such as vemurafenib (zelboraf) for melanomas associated with specific mutations in *BRAF* or crizotinib (xalkori) for non-small-cell lung cancer linked to anaplastic lymphoma kinase (ALK)-associated chromosomal translocation, as well as their companion diagnostics when applied to autoimmune diseases^{76,77}.

Figure 1.

Yearly therapeutic approval of drugs and biologics by the FDA between 2006 and 2011. New molecular entities and biological license applications approved by the FDA's Center for Drug Evaluation and Research (CDER) and biological products approved by the Center for Biologics Evaluation and Research (CBER) are shown relative to the approval of drugs related to autoimmunity (approved by CBER or CDER) for each year. The approval numbers were retrieved from the FDA's drug approval databases (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu>; <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/default.htm>) and references 49–53. New molecular entities are shown in light blue, biological license applications are shown in dark blue, approved biological products are shown in gray, and approved drugs and biologics related to autoimmunity are shown in light purple. IV, intravenous; SQ, subcutaneous; PID, primary immune deficiency; RA, rheumatoid arthritis; MS, multiple sclerosis.

Figure 2. Operational challenges for translational research and medicine. Adapted from references 7, 12, 39 and 54 and the Harvard Catalyst website. Translational research is defined based on the operational hurdles that must be overcome (top). These layers include: T0, the fundamental studies and applied research that define cellular mechanisms, their relationship to disease and, consequently, the identification of therapeutic targets and methods of treatment (new molecular entities); T1, first phase 1 studies in humans that aim to define proof of mechanism and proof of concept; T2, phase 2 and 3 clinical trials that are necessary for the approval of a therapeutic agent for clinical use; T3, phase 4 clinical trials that are associated with optimizing the therapeutic use of an agent in clinical practice; and T4, the outcome or comparative effectiveness research that serves to determine the ultimate utility and cost effectiveness of an agent relative to others currently in use. Critical path research (red), as defined by the FDA, or the valley of death, as defined by the pharmaceutical industry, comprises research related to the T0, T1 and T2 stages. Each of these activities possesses many overlapping sets of challenges, as listed in the gray box.

Figure 3.

Tissue banks in autoimmunity-related translational research. It is crucial to classify autoimmune diseases based on molecular pathways to improve the ability to predict disease course (through surrogate markers) and better link therapeutic agents to specific subsets of molecularly defined patients. This classification will require more human experimentation as well as mechanisms to support this process through development of standardized methods of tissue acquisition, archiving, sequential high-throughput molecular analyses and ongoing phenotypic data acquisition (preferentially through linkage to an electronic medical record (EMR)) to allow for the bioinformatic testing of relevant hypotheses, as summarized in the schematic diagram.

Figure 4. An organizational model for translational research and medicine in autoimmunity: the Biomedical Research Centre (BRC) at Guy’s and St. Thomas’ Hospital and King’s College London. The BRC, as part of the Experimental Medicine Hub at Guy’s Hospital, is a ‘one-stop shop’ for translational research. It stretches over nearly 10,000 m² of dedicated clinical research space. The top floor contains key administrative functions that bring together hospital research and developmental functions, university functions, a joint clinical trials office, meeting space and a desk area for the faculty of translational medicine. A dedicated purpose-built clinical research facility containing a good manufacturing practice (GMP) facility, an immune monitoring facility, a procedure room and a tissue processing laboratory is located one floor below along with a commercial phase 1 clinical trials unit. Other floors are occupied by a GMP pharmacy, a stem cell laboratory and a genomics core. GSTFT R&D, Guy’s and St Thomas’ NHS Foundation Trust research and development; JCTO, joint clinical trials office; NIHR,, National Institute for Health research; CLRN, comprehensive local research network; PCRN, primary care research network; RDS, research design services; ES, embryonic stem.