Establishing an Academic–Industrial Stratified Medicine Consortium: Psoriasis Stratification to Optimize Relevant Therapy

Probably the most important change in dermatological care over the next quarter century will be the introduction of stratified medicine into routine clinical practice (Bell, 2014). This is a common goal of physicians, industry, and patients. Stratified medicine is not a new concept and is synonymous with the term personalized or precision medicine. It is best understood as a process that moves prescribing from its current "trial-and-error" basis to one that is targeted not only to the causes of disease but also to the needs of the individual patient, thereby fulfilling the premise of the right drug for the right patient. The ability to prosecute a stratified approach to prescribing has been led by the field of oncology in which most new therapies are released alongside a companion diagnostic. For instance, in the targeted management of breast cancer, trastuzumab is preferentially prescribed to those patients whose cancer expresses the human EGF receptor-2 (Slamon and Pegram, 2001).

The stratified medicine approach is beginning to percolate into the management of immune-mediated inflammatory disease. For instance, the anti-IL-13 biologic lebrikizumab is known to be far more effective for the treatment of asthma patients with high, as opposed to low, serum levels of periostin (Corren et al., 2011). In the management of inflammatory skin disease, the stratified approach is nascent but its successful prosecution will require close partnership among clinicians, scientists, patients, and industry. The development of the UK Medical Research Council (MRC)–funded stratified medicine consortium in psoriasis—Psoriasis Stratification to Optimize Relevant Therapy (PSORT)—is an excellent example of such partnership working, which is so vital to the concept of translational research whereby discovery and proof-of-principle testing can lead to improved patient care and commercialization. In December 2011, the British prime minister, David Cameron, announced a research initiative on stratification of disease to be implemented by the MRC. An application was made to this call for psoriasis to be recognized as an exemplar disease for stratification with an initial focus on biologic therapies. This Editorial provides the background and objectives to the PSORT consortium that commenced in September 2014.

The genesis of the consortium goes back 30 years, to the early 1980s, when the initial challenges to the dogma of psoriasis as primarily a disorder of epidermal keratinocytes were made and the concept of the central pathomechanistic role of T cells was introduced (Valdimarsson et al., 1986). This new paradigm was cemented by the observation that cyclosporine (a rudimentary T-cell-targeted approach) was an effective therapy for psoriasis—a consequence of an academic–industry collaboration with Sandoz, then the manufacturers of the drug (Griffiths et al., 1986). Further evidence of academic–industry collaboration arose from a number of sources, including Gottlieb, who reported that a lymphocyte-selective toxin, DAB_{389} IL-2, targeted to IL-2R-expressing cells (*i.e.*, T cells as opposed to keratinocytes) was an effective therapy for psoriasis (Gottlieb et al., 1995). The biologic era for psoriasis dawned with the approval of alefacept (Ellis and Krueger, 2001), followed by efalizumab and cytokine-targeted therapies, primarily tumor necrosis factor (TNF)-α and then IL-12/IL-23 (ustekinumab). The approval of the first of the anti-IL-7 biologics, secukinumab, for the treatment of moderate to severe psoriasis in the United States and European Union

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Box 1. The British Association Of Dermatologists Biologic Interventions Register (BADBIR)

- Founded in 2007; funded until at least 2017
- Unique, long-term, Web-based pharmacovigilance register for psoriasis patients on biologic or conventional systemic therapies
- Viewed as international gold standard psoriasis registry
- 152 Dermatology Centres in the United Kingdom and Ireland recruiting to BADBIR
- 11,048 patients recruited: 7,102 on biologics and 3,946 on conventional systemic therapies
- High-quality phenotypic and quantitative disease severity data
- High-quality follow-up data on response to therapy and persistence of response
- More than 30% have serial serum samples and/or RNA and DNA banked

Source: http://www.badbir.org

occurred in early 2015 (Sanford and McKeage, 2015). A notable feature of this journey has been the close working relationship between clinicians, scientists, and industry—a necessary tripartite partnership in translational research.

Although biologic therapies have been transformational in the management of severe psoriasis, the known variability in both the short-term response and the persistence of that response to the drug is problematic. Such problems are tractable by a stratified approach. Psoriasis is a model disease for stratification because (i) unlike in other immune-mediated inflammatory diseases, such as rheumatoid arthritis, biologics are licensed for use as monotherapy; (ii) response to therapy is relatively easy to quantify and; (iii) the diseased tissue (skin) is accessible for sequential sampling by biopsy—a minimally invasive and patient-accepted technique. The MRC's guidance specified that the consortium should embrace open collaboration rather than competition, with sharing of expertise across institutes and sectors with industry engaged as equal partners from the outset. The consortium is to be a dynamic platform and the programmatic support is milestone-driven.

In October 2012, key UK academics and clinicians with expertise in treating psoriasis and potential industry partners united by a strong research interest in the disease came together in a one-day scoping workshop in London, funded by the MRC and chaired by Sir John Bell. This invaluable meeting enabled active engagement among potential investigators, industry, and the Psoriasis Association of Great Britain and Ireland. Industry partners embraced the opportunities inherent in the stratified medicine approach to managing psoriasis and were generous in offers of support ranging from in-house expertise to data sets to finance. This formed the basis for the PSORT consortium application to the MRC in 2013. Using biologic therapies as the target for stratification, the main objective of PSORT is to use clinical, pharmacological, genetic, and immune biomarkers to predict and reproducibly stratify the response of psoriasis to biologic therapies. This could result in biologics being used at minimal effective doses and form the basis for an algorithm or stratifier scalable for clinical use with the potential for significant health-care savings.

The success of the PSORT application is founded on four pillars: (i) the main academic applicants have collaborated successfully for many years (in some cases, more than 20) on different aspects of psoriasis research and clinical management (Smith *et al.*, 2009; Strange *et al.*, 2010); (ii) the bioresource available to the consortium in the form of the British Association of Dermatologists Biologic Interventions Register (http://www.badbir.org (see Box 1); Burden *et al.*, 2012) to test the clinical utility of biomarkers; (iii) the track record of the investigators' collaboration with industry for many years; (iv) the involvement of expertise beyond basic science and dermatology, including bioinformatics, systems medicine, biostatistics, health economics, pharmacology, and research management; and (v) the involvement from the outset of patients in the planning and design of the studies that form the Work Strands of the consortium.

The work of PSORT is structured around a dynamic integrative platform of two related elements of research, or Work Strands: (i) Clinical and Pharmacology Studies; and (ii) Immune Biomarkers in Skin and Blood. The Work Strands move the research questions through the traditional discovery, refinement, and validation phases (Figure 1). An objective of the PSORT program is to identify and characterize psoriasis endotypes (endophenotypes). This terminology was first introduced into the asthma field to define subtypes of disease, both functionally and pathologically, by a molecular mechanism or by a treatment response (Anderson, 2008).

PSORT's work will focus on adalimumab (anti-TNF), ustekinumab (anti-IL-12/23), and secukinumab (anti-IL-17A) in the first instance, but the dynamic aspect of the program allows inclusion of new biologics and small molecules as they become available for psoriasis. Work Strand 1 involves discovering disease endotypes associated with treatment outcome; assessing the influence of blood drug levels and antidrug antibodies on outcome; and assessment of adherence. Work Strand 2 concerns the discovery and

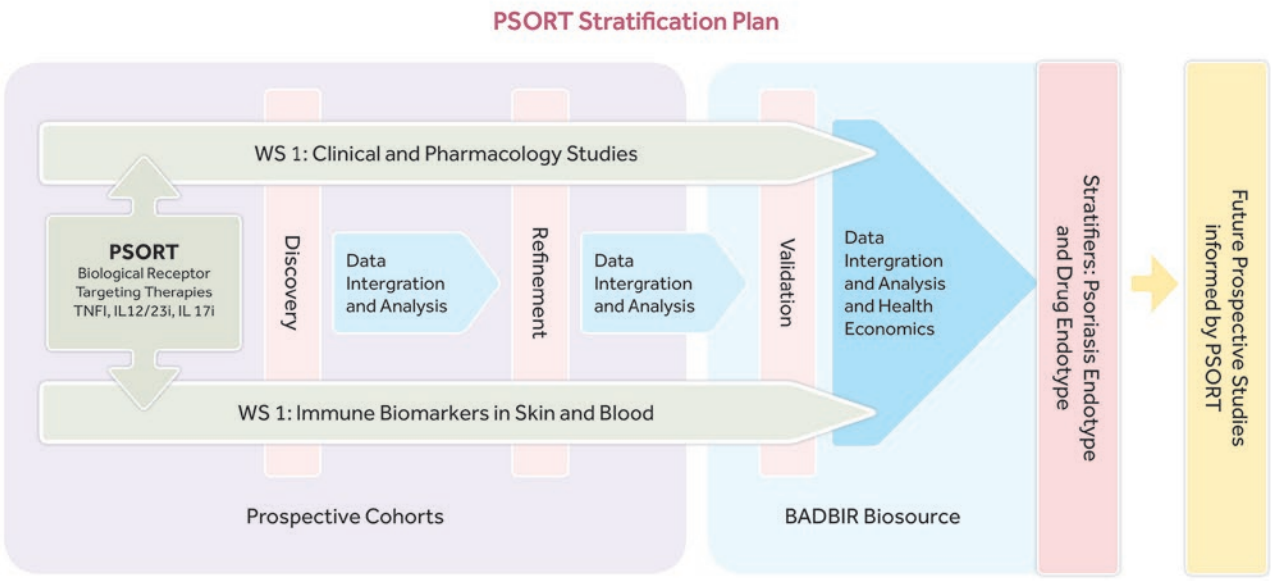

Figure 1. Psoriasis Stratification to Optimize Relevant Therapy (PSORT) stratification plan. The dynamic platform consists of two integrated Work Strands (WS): Clinical and Pharmacology Studies and Immune Biomarkers in Skin and Blood. Three biologics—adalimumab (TNFi), secukinumab (IL17i), and ustekinumab (IL12/23i)—will be assessed via serial serum samples for drug levels, antidrug antibodies, and serial sampling of skin and blood for mRNA and immune biomarkers in an initial discovery phase. Refinement of identified signatures will be validated in the British Association of Dermatologists Biologic Interventions Register bioresource. Data are collected via a TranSMART data warehouse. The PSORT stratifier for psoriasis and drug response endotypes will be subject to clinical trial in the UK National Health Service to assess utility and feasibility and potential for health-care savings.

validation of molecular and immune signatures (comprising disease and drug endotypes), in skin and blood, that stratify responses and assessment of key biomarkers for investigation of mechanisms of response.

The results of these investigations are stored in a tranSMART data warehouse (http://www.transmartfoundation.org), allowing seamless integration of PSORT multiomic data and clinical phenotypes with a highly curated selection of preexisting public data. TranSMART offers the PSORT consortium and partners a unified, secure, and importantly sustainable research environment to apply a range of systems biological and machine learning methods for biomarker discovery. As the PSORT project scales in its data generation and integration, hosting of the PSORT–tranSMART will be transferred to the MRC-eMEDLAB, providing direct, secure access to substantial high-performance computing facilities. There is both the ability and the desire to add data from other resources (e.g., the European Molecular Biology Laboratory and ENCODE) as and when they become available, which will, in turn, help to ensure the durability of the consortium.

The consortium is composed of 18 partners, all of whom have signed a legally binding consortium agreement, a living document that determines, among other operational issues, the detail of intellectual property (both background and foreground) and commercialization of discoveries. There are currently 10 industry partners (7 pharmaceutical and 3 diagnostic companies; Table 1), but it is likely that this will change over the 4 years of the consortium as partners may, under the terms of the agreement, either leave or join PSORT. Examples of industry engagement in PSORT ranges from in-house expertise on development of the tranSMART data warehouse (Janssen), RNA Seq analysis (GSK-Stiefel), and embedding of PSORT Work Strand 2 objectives of sequential sampling for skin and blood transcriptomics in a subset of subjects in a UK commercial phase III trial of secukinumab in psoriasis patients deemed to have failed TNF-inhibitor biologics (Novartis). The diagnostic companies will engage more fully if and when a scalable stratifier for predicting response to biologics or a biologic is identified. Perhaps the crux of the MRC and the UK government's strategic investment in this area is that industry wishes to be involved in PSORT and stratification of psoriasis is important to them. Such interest can be articulated thus: (i) taxonomic classification of psoriasis, based on mechanisms, will identify cohorts of patients suited to proof-of-principle testing of new molecules; (ii) stratification tools will facilitate accurate targeting of new molecules to patient/drug endotype; (iii) establishment of minimal effective dosing will inform best practice; (iv) PSORT will inform other IMIDs because psoriasis is the lead disease for new molecules (e.g., anti-IL-17 and anti-IL-12/23); and (v) value will be added through cross-referencing of data in other MRC-funded stratified medicine programs (e.g., rheumatoid arthritis–MATURA consortium) using tranSMART.

The PSORT consortium's collaborators include those who curate databases, psoriasis patient cohorts, and registries in Europe and the United States. The management of the consortium places partnership with industry at its heart in that the steering committee is cochaired by the director

Table 1. Psoriasis Stratification to Optimize Relevant Therapy (PSORT) partners.

The University of Manchester
King's College London
University of Newcastle
Queen Mary University of London
University of Liverpool
Greater Glasgow Health Board
Centre for Addiction and Mental Health
Guy's and St Thomas' NHS Foundation Trust
AbbVie
Becton Dickinson and Company
Celgene Limited
Janssen Research and Development LLC
MedImmune Limited
Novartis Pharmaceuticals UK Limited
Pfizer
The Psoriasis Association of Great Britain and Ireland
Qiagen Manchester Limited
Sanquin Blood Supply Foundation
Stiefel Laboratories
GlaxoSmithKline

(clinical academic) and the chair of the industry partner subgroup; both Work Strands have industry coleads and a separate intellectual property and commercialization subgroup is represented on the steering committee by its chair, as is the patients subgroup. The durability and future-proofing of the consortium beyond its initial 4 years of funding are dependent on additional industry and academic partners. For further information, please refer to the consortium's website, http://www.psort.org.uk.

One may ask what the drive is for industry to collaborate so readily with PSORT. Industry participation in PSORT is driven strongly by the opportunity to be able to select the right patients to test new therapies definitively based on large, well-phenotyped patient cohorts and associated molecular tests. Ultimately, this will reduce the cost of development by eliminating failures early and accelerate clinical development of the best new entities. Industry also appreciates that obtaining regulatory and cost/benefit approval for expensive, potent biologic therapies in dermatology does, and will, require it to acquire a considerable body of positive evidence of efficacy, safety, health, economic, and patient outcome data. PSORT promises to create the leading "public sector/clinically led" stratified medicine development platform that will provide the optimal environment for it to create this body of data as efficiently as possible.

Stratified medicine is the great ambition of clinical translational research and will, in our opinion, change the landscape of dermatological practice in the next decade. To realize this requires big team science working in open collaboration with the commercial sector and with patient groups. That the MRC has selected psoriasis as 1 of only 12 diseases across the whole of medicine worthy of programmatic investment is a unique and exciting opportunity for those of us involved in psoriasis research and treatment. If successful, PSORT will benefit patients, health-care practitioners, and industry and will act as a platform for innovation, commercialization, and international research collaboration.

CONFLICT OF INTEREST

ADB receives paid consultancy, lectures, and/or research for Amgen, Abbvie, Celgene, Lilly, Novartis, Pfizer, Napp, Boehringer Ingelheim, and Janssen. JNWNB has received honoraria for advisory boards and lectures at sponsored symposia together with grants for research in the past 5 years from Abbvie, Amgen, Celgene, Janssen, Lilly, Novartis, and Pfizer. CEMG is in receipt of research grants and/or has received honoraria from AbbVie, Actelion, BMS, GSK, Janssen, Leo Pharma, MSD, Pfizer, Novartis, Sandoz, Eli Lilly, and UCB Pharma. FON is a consultant for Amgen, Lilly, Novartis, Pfizer, Janssen, Celgene, Sanofi, and GSK. NJR has been a consultant for Stiefel, a GSK company, Genentech, and Amgen and received sponsorship or grant funding from Novartis, Leo Pharma, Celgene, AstraZeneca, Stiefel, a GSK company, and BMS. RBW has received research funding from Abbvie, Novartis, Pfizer, and Leo (and GSK through pre-PSORT) and served as a consultant/speaker and or received honoraria from Amgen, Abbvie, Celgene, Pfizer, Novartis, Janssen, and Leo.

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PSORT

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