

DECADE IN REVIEW—TECHNOLOGY

Technological advances transforming rheumatology

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Technological advances over the past decade have revolutionized many areas of rheumatology, ranging from diagnosis, prognosis and therapeutic development to the mechanistic understanding of rheumatic diseases. This overview highlights key technological innovations and discusses the major impact that these developments are having on research and clinical practice.

The past decade has been an exciting time of technological breakthroughs driving tremendous progress in rheumatology. Many of these innovations are high-throughput approaches that enable robust proteomic, genomic and epigenetic analyses ranging from the organism level to the single-cell level.¹ Here, we describe the key innovations (examples of which are described in Box 1 and illustrated in [Supplementary Figure 1 online](#)) and discuss how they have shaped our understanding of rheumatic diseases as well as our ability to diagnose and treat these disorders.

Historically, many major advances in the research and clinical practice of rheumatology were fuelled by technological innovations. For instance, the advent of MRI introduced a noninvasive method for visualizing bone and soft tissues in three dimensions that enables improved diagnosis. The development of flow cytometry greatly enhanced our ability to distinguish between and characterize distinct cell populations in tissue samples. Molecular cloning coupled with expression profiling using DNA microarrays has been pivotal in identifying key molecules and pathways in the pathogenesis of rheumatic diseases, and thus in uncovering novel therapeutic targets. Likewise, the past 10 years have brought us a new raft of technological advances—both incremental and disruptive—that are enabling us to interrogate and manage rheumatic diseases with increasing sophistication.

Proteomics is one notable area in which great progress has been made over the past decade, to far-reaching effect. Innovations

in proteomics, including advances in mass spectrometry and the emergence of protein-array technologies, have revolutionized our ability to identify proteins and post-translational modifications associated with disease. Indeed, mass spectrometry analyses of proteins in cartilage, synovial membrane, bone, synovial fluid, plasma and serum, as well as other tissues and bodily fluids, have uncovered molecules associated with pathological changes in osteoarthritis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other rheumatic diseases. Furthermore, array-based multiplex profiling of autoantibodies and cytokines has deepened our understanding of pre-disease and early disease states by enabling the characterization of autoimmunity prior to the onset of clinically apparent symptoms.² Several of the proteomic profiles gleaned with these technologies have potential for use as actionable biomarkers in predictive medicine. Most rheumatic diseases are heterogeneous and only certain subsets

of patients respond to any given therapy. Thus, proteomic profiles and other biomarkers associated with specific disease states or with drug responsiveness could identify individuals at high risk of developing the disease, who can then be enrolled in primary prevention trials or treated with preventative therapies. Proteomic profiles and other biomarkers could also serve as pharmacodynamic biomarkers to rapidly assess patients' responses to therapy. These proteomic technologies are ushering in a new era in biomarker discovery and have the potential to revolutionize the diagnosis and treatment of rheumatic diseases.

Large-scale sequencing is another technological *tour de force* that is transforming rheumatology. The advent of high-throughput DNA sequencing has made possible sequencing of the genome to identify both common and rare genetic variants associated with rheumatic diseases. This method can also be applied to sequencing the expressed genome, which includes thousands of gene transcripts that reflect activation and repression of pathways involved in rheumatic diseases. Such large-scale DNA sequencing can now digitally define the functional antibody and T-cell receptor (TCR) repertoires in autoimmune rheumatic diseases.^{1,3,4} In addition, deep sequencing of transcriptomes via RNA-seq measures the levels of transcripts and their isoforms, and can now even be done with single-cell resolution.⁵ Furthermore, epigenetic technologies, such as ATAC-seq (assay for transposase-accessible chromatin using sequencing),⁶ can probe disease-associated changes in DNA methylation and histone modification. The scale and

Box 1 | Advanced technologies in rheumatology*

- CyTOF mass cytometry measures the binding of multiple antibodies (each tagged with a distinct heavy-metal isotope) to cells⁴
- Single-cell antibody heavy and light chain sequencing enables bioinformatic generation of phylogenetic trees, which reveal clonal antibody families and guide the selection of antibodies for expression and characterization³
- Single-cell TCR sequencing coupled with amplification of functional genes characteristic of T-cell subsets provides insight into the specificity and function of TCRs⁴
- ATAC-seq analyses the epigenome of cells derived from an individual⁶
- iPOP combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from an individual to reveal medical risks and dynamic molecular changes in health and disease¹⁰

*See also [Supplementary Figure 1 online](#). Abbreviations: ATAC-seq, transposase-accessible chromatin using sequencing; CyTOF, cytometry by time-of-flight; iPOP, integrative personal omics profile; TCR, T-cell receptor.

efficiency of sequencing that can now be achieved with these approaches is facilitating unprecedented progress in both basic and translational research of rheumatic diseases, and will most likely transform clinical care in the future. However, a major challenge that these technologies bring is the need to store, retrieve and analyse the terabytes and petabytes of data that are being generated.

The past 10 years have also seen the development of mass cytometry (known as cytometry by time-of-flight [CyTOF]) and considerable advances in flow cytometry, enhancing our ability to analyse cellular markers and signalling pathways in rheumatic diseases.⁷ Mass cytometry uses heavy metals instead of fluorophores to label cells, thereby enabling measurement of >40 parameters per cell without spillover between fluorescence spectra. Meanwhile, flow cytometry has been improved by the introduction of new staining reagents, laser-excitable fluorescent compounds, coupling methods and dyes that can be used to monitor cell replication and physiological changes inside cells. As a result of these advances, CyTOF and polychromatic flow cytometry have enabled researchers to delve deeper than ever into the complexity of disease-relevant cell types and molecules, monitor their dynamics, and unravel their normal function as well as their contribution to rheumatic diseases.

Imaging techniques such as MRI and ultrasonography, although not new, have only recently begun to be incorporated into clinical trials and routine practice in rheumatology.⁸ MRI and ultrasonography are much better than conventional radiography at assessing soft-tissue abnormalities and detecting bone erosions,⁸ and are increasingly being used as noninvasive tools for detecting subclinical inflammation and progression of joint damage in arthritides. The growing use of these techniques in clinical practice and research is transforming diagnostic imaging. By enabling serial assessment of synovitis, interval imaging via MRI or ultrasonography yields dynamic biomarkers that are useful for monitoring the progression of disease or its response to therapy.

Last but not least, advances in stem-cell technologies are offering new opportunities in tissue engineering and regenerative rheumatology. Recent work on the small molecule kartogenin has shown that it is possible to direct the differentiation of mesenchymal stem cells into chondrocytes and thereby repair damaged cartilage.⁹ Moreover, induced pluripotent stem cells (iPSCs), first described in 2006, have emerged as a promising cell source for both drug screening and cell-replacement therapy.⁹ Patient-specific iPSCs are well-suited to autologous stem cell transplantation, because they elicit only minimal immune reactions and have the potential to be used to regenerate tissues, such as cartilage. Meanwhile, disease modelling using patient-specific iPSCs continues to expand our knowledge of pathophysiology and treatment.

In conclusion, technological innovations in the past decade have opened up new horizons in our efforts to understand and treat rheumatic diseases. Moving forward, it is anticipated that high-throughput approaches, especially those allowing for single-cell resolution, will move to the mainstream of rheumatology research and form the basis for next-generation diagnostics. The impact of high-throughput sequencing and other data-rich technologies will be maximized with the development of more powerful databases, analytical methods and analysis pipelines that can handle the vast amount of data being generated. Development of new biomarkers will bring forth an era of predictive medicine, in which individuals in pre-disease states can be identified so that primary prevention can be instituted and in which therapies can be selected for use in the patient populations most likely to benefit. Given the heterogeneity of most rheumatic diseases, the diverse molecular pathways mediating their pathogenesis and the multifaceted roles that these pathways have in normal and pathological states, advances in treatment are likely to require approaches that integrate genomic, transcriptomic, proteomic, metabolomic and autoantibody profiles, such as the recently described integrative personal omics profile, or iPOP.¹⁰

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Competing interests

W.H.R. declares that he is a member of the Board of Directors, consultant for, and owner of equity in Atreca, Inc. R.M. declares no competing interests.

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