Disruptive innovation in rheumatology: new networks of global public-private partnerships are needed to take advantage of scientific progress

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Disruptive innovation in rheumatology: new networks of global public–private partnerships are needed to take advantage of scientific progress

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Patterns of innovation can be sustained (continuous) or rapid, sometimes even 'disruptive'. A major difference is that in order to support disruptive innovation the support networks and its infrastructure often need to be changed dynamically to accommodate a rapidly evolving landscape to establish the disruptive approach. For example, introducing electric cars disrupts the support network for gasoline cars (network of gas and service stations), and at the same time requires an entirely new system of charging stations. Such disruptions occur in science, and a wonderful example was the creation of monoclonal antibody technologies. The discovery of the principle for production of monoclonal antibodies by César Milstein and Georg Köhler fueled a rapid adoption of new antibody-based technologies in all areas of medicine. This transformation was strongly supported by the open workshops that catalogued antibodies from many laboratories into distinct 'clusters of differentiation', thereby providing a new 'support network' for the global use of well validated and standardised monoclonal antibodies. This new support network helped the pharmaceutical industry transition from a major focus on small chemical molecules (screened for effects in vitro) to a new targeted approach, first with recombinant proteins, later with monoclonal antibodies with the introduction of anti-tumour necrosis factor (TNF) antibodies as an example.

During the last two decades, in both the USA and Europe, the need to develop public–private partnership support networks has been recognised as a means to accelerate innovation and enable translation of the rapidly expanding cellular and molecular understanding of disease pathogenesis into the development of new therapeutic agents. In Europe, the Innovative Medicine Initiative (IMI) was formed to enhance public–private partnerships, and in the USA the Accelerating Medicines Partnership (AMP).[1] Identifying, validating and testing new targets based on enhanced understanding are at the core of both AMP and IMI. To facilitate continuous innovation, multi-institutional collaborations have started on projects such as the European Union funded project on tolerance in rheumatoid arthritis (RA; Rheuma Tolerance for Cure (RTCure)) and the National Institutes of Health (NIH)/Foundation for the NIH (representing industry and other partners) funded project designated the 'AMP for RA and systemic lupus erythematosus (SLE)'.

To bring these groups together, a meeting designated the 11th International Forum on Rheumatoid Arthritis was held from 25–27 September 2019 in Washington DC. The primary intention was to facilitate interactions among academic as well as industry-based scientists and clinicians from Europe, the USA and also East Asia.

This collaborative meeting was supported by NIH and its director Dr. Francis Collins, as well as by the pharmaceutical industry stakeholders in AMP and the IMI-RTCure project.

The RTCure programme is focused on the understanding of the longitudinal course of the disease, whereas the AMP is focused on better understanding of the contribution of various cell types to the local processes in the inflamed joints. Thus, several of the RTCure presentations focused on the understanding of the natural history of RA, where a prolonged RA-related autoantibody-positive period is present prior to the development of arthritis[2 3]. Subjects who are in this period of time are operationally defined through the presence of symptoms such as arthralgia as well as predictive biomarkers[4–7] and one study reported that development of arthritis was delayed after treatment with rituximab.[8] With great enthusiasm, the ongoing prevention trials in the USA and Europe were reported.[8] In the USA, the Stop-RA trial and in the UK the Arthritis prevention in the pre-clinical phase of RA (APPRIPRA) trial randomise people with anti-citrullinated peptide antibodies (ACPA) antibodies to an intervention (Hydroxychloroquine—USA, Abatacept—UK) or placebo for 1 year to test the hypothesis that fewer RA will develop in the intervention arm. In the Netherlands, patients with clinical suspect arthralgia and a positive MRI are randomised to either one dose of prednisone and 1 year methotrexate (MTX) versus placebo (Treat-Earlier study) and in Sweden a study (EudraCT-nr 2019-002673-62) with bifosfonates in one arm and placebo in the other is performed with the same hypothesis.

The focus of AMP is to take an unbiased approach focused on single-cell analysis to define the cell and molecular basis of synovitis.[9] Therefore, tissues and cells from patients with RA with synovitis are

Box 1 The newly identified cell types: on our way to a new periodic table for celltypes

1. *Expanded cell populations* in rheumatoid arthritis as compared with osteoarthritis synovium
a. THY1(CD90) +HLA-DRA^{hi} sublining fibroblasts (interleukin 6 (IL-6) production)
b. IL1B+proinflammatory monocytes
c. ITGAX+TBX21+autoimmune-associated B cells
d. PDCD1 +peripheral helper T (T_{PH}) cells
e. Follicular helper T (T_{FH}) cells
2.*New cell subsets* with functional implications
a. CD8 +T cell subsets by differential GZMK+, GZMB+ and GNLY +expression
b. Fibroblasts separated into multiple populations, including FAPα+THY1+sublining immune effector fibroblasts (mediate synovial inflammation) and synovial lining FAPα+THY1− destructive fibroblasts (mediate bone loss)

captured using ultrasound-guided biopsies. Using quantitative histological and bulk mRNA analyses as well as single-cell technologies, new insights were presented on the diversity of stromal cells (synovial fibroblasts and macrophages) as well as leucocyte populations including T cell subpopulations. Other data emphasised the capacity of synovial fibroblasts to interact with other non-lymphoid cells of the joint, such as endothelial cells. This creates a situation where chronicity of synovial inflammation may become partly independent of adaptive immunity, allowing the development of therapies that target these mechanisms.

Presentations from the Asian investigators highlighted the opportunity to exploit for discovery genetic differences in as drivers in disease phenotypes in Asian populations.

Important updates on each of these topics were presented, summaries of which are beyond the scope of this article. We would like to emphasise two simultaneously occurring disruptive elements that will need public–private collaborative ventures.

FINDINGS DERIVED FROM SINGLE-CELL STUDIES

Single-cell technologies define subpopulations that were previously thought to be homogeneous cell populations [9–11] and box 1. This realisation creates the opportunity to identify new targets, a finding that is relevant for the pharmaceutical industry as opportunities for drug development. At the same time, replication on tissues from different centres is required. This necessitates a new support network to make fast and reliable progress. The delivery of the Human Cell Atlas (an international consortium similar to the Human Genome Project) aims to enumerate all the individual cell types in each organ of the human body; AMP is providing an atlas of pathological synovial cells and cell states. This paves the road for a cellular basis to drive a new taxonomy of disease. AMP seems to provide the new periodic table of cell types, where the challenge will be what the fundamental rules for cells to work together are, almost like the rules that determine how elements of the periodic table can make molecules like H_2O.

Progress in studies focused on prevention

With at least four large prevention studies in Europe/USA and with the current exploration of regulatory pathways for preventive studies prior to the onset of arthritis by pharma and academic groups, the road to preventive interventions in RA is paved. This approach has the potential to be disruptive in the same way that assessments of cardiovascular risk and their management have changed the treatment landscape and patient expectations in cardiovascular diseases. This necessitates a new worldwide support network that includes the development and a global harmonisation of RA preclinical/at-risk classification criteria, as well as the establishment of multiple cohorts of individuals at risk for RA in which trials can be performed. A similar challenge remains for efforts aimed at treatments that induce tolerance for people with early RA, as exemplified from ongoing[12] studies in RTCure. These studies, in an identical fashion as occurred in prevention approaches for cardiovascular disease,[13] need support networks with well-standardised immune-surveillance assays and well-defined clinical endpoints, with supporting laboratory-based assays to determine the cellular basis for tolerance in RA. A joint effort in this area from RTCure and other international groups contributing cohorts and the development of adaptive immunity cell-based assays, using novel single-cell technologies and bioinformatics from the AMP consortium, will form the basis for the establishment of this highly needed support network.

It is important that the RTCure pharma-academia efforts are coordinated with USA based, as well as Asian and other international groups. To accomplish that task, criteria must be developed that are formally evaluated and internationally approved by the relevant professional and regulatory organisations. An additional point for harmonisation, as well as agreement by regulatory bodies, is outcome criteria for prevention and early intervention trials. New intervention studies will benefit from harmonisation between the currently ongoing trials which may benefit from already existing organisations such as Outcome Measures in Rheumatology (OMERACT) that are focused on validating outcome measures.

Taking on big challenges in addition to making incremental gains

Finally, a strongly stated theme with regard to future studies is to take on ‘big’ problems, that will require collaborative work between different groups and scientific communities, and as emphasised in this viewpoint, new support structures for work towards the goals of prevention and cure of RA.

Although the exact definition of such big issues is subjective, especially if one envisions international efforts beyond the highly successful collaborations focused on the genetics of RA,[14] one attractive possibility is to focus on the cellular, humoral and genetic bases for the transformation from systemic autoimmunity to autoimmune-associated joint inflammation and joint destruction. Tackling this problem will involve efforts to define initial cellular and humoral targets in the joints, including bone, cartilage and tendons. Also required is a better understanding of the relative roles in the synovium of local cellular versus humoral factors and the relative roles of leucocytes and stromal cells, respectively. Accomplishing this goal will require following at-risk populations, including temporal sampling and imaging of the synovium through to the development of classifiable disease, and then working to reverse synovitis and develop curative approaches.

Next steps

To shape a support network that is needed for the disruptive changes, we propose the establishment of a working group inclusive of academics, regional rheumatology societies, industry representatives, patients and funding agencies to design and implement an International RA Collaborative Network. From

that working group, suggestions for the design of such a network, the priorities for funding and implementation of precompetitive studies, as well as development of a data portal contributed to by all groups, could emerge in an organic manner. Also participation of regulatory agencies will be needed to enable clinical studies on prevention to result in approved and reimbursed prevention in clinical practice. Future closer transatlantic and global collaborations will capitalise on the legacy of the existing initiatives, for example, a collaborative IMI-AMP project as a follow-up project of current IMI and AMP initiatives. In fact, many industry partners participate in both consortia, and thus the legal framework for such collaborative efforts can follow the current structures which allow for very effective 1 to 1 collaborations on a deep data level, while the overall programme can be constructed to generate shared global data

The primary goals of the International RA Collaborative Network would be to build on existing public–private partnerships such as RTCure and AMP and shape a new support network for preventive and curative studies, and foster collaborations between individuals and communities prepared to develop and use these networks.

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