

**Disruptive Innovation in Rheumatology; New Networks of
 Global Public-Private Partnerships are Needed to Take
 Advantage of Scientific Progress**

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Viewpoint

Title: Disruptive Innovation in Rheumatology; New Networks of Global Public-Private Partnerships are Needed to Take Advantage of Scientific Progress

Subtitle: IFRA 2019: Emerging Opportunities for International Collaborations to Advance Rheumatoid Arthritis Treatment and Prevention

Invited Authors: V. M. Holers^{1*}, T. W. J. Huizinga^{*}, J. H. Anolik, C.D. Buckley, M. Benner, V. Bykerk, S. E. Connolly, K. D. Deane, J. Guo, M. Hodge, F.O. Nestle, C. Pitzalis, S. Raychaudhuri, S. C. Hoffman, K. Yamamoto, Z. Li, , L. Klareskog

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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” (CD), thereby providing a new “support network” for the global use of well validated and standardized 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-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 recognized 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 is 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 RA (Rheuma Tolerance for Cure, RTCure) and the NIH (National Institutes of Health)/FNIH (Foundation for the NIH, representing industry and other partners) funded project designated the “AMP for RA and SLE”.

To bring these groups together, a meeting designated the 11th International Forum on Rheumatoid Arthritis (IFRA) was held from September 25-27, 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 program 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 has indeed already been reported where development of arthritis was delayed after treatment with rituximab (8). With great enthusiasm the Such individuals are currently participating in ongoing prevention trials in the USA and Europe were reported [8,9]. In the USA, the Stop-RA trial and in the UK the APPRIPRA trial randomize people with 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 randomized to either one dose of prednisone and one year MTX versus placebo 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.

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The focus of AMP is to take an ~~disease deconstruction~~ unbiased approach focused on single cell analysis to define the cell and molecular basis of synovitis ~~in established arthritis~~ [9]. ~~Therefore~~ ~~that end, a focused work plan has been organized to capture~~ tissues and cells from RA patients with synovitis ~~using are captured using~~ ultra-sound guided biopsies. Using quantitative histologic and bulk mRNA analyses as well as single cell technologies, new insights were presented on the diversity of stromal cells (synovial fibroblasts (FLS) and macrophages) as well as leukocyte populations including T cell subpopulations. Other data emphasized 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 thus mandating~~ 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~~ ~~that additional studies~~ in Asian populations ~~provide new insights~~.

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Important updates on each of these topics were presented, summaries of which are beyond the scope of this article. We would like to emphasize 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 [10-12]. This realization 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 centers 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 H₂O.](#)

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 & 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 has changed the treatment landscape and patient expectations in cardiovascular diseases. This necessitates a new worldwide support network that includes the development and a global harmonization 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 [13] studies in RTCure. These studies, in an identical fashion as occurred in prevention approaches for cardiovascular disease [\[15\]](#), need support networks with well-standardized 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 organizations. An additional important point for harmonization and standardization, as well as agreement by regulatory bodies, are outcome criteria for prevention and early intervention trials. [New intervention studies will benefit from harmonization between the currently ongoing trials which may benefit from already existing organizations such as OMERACT that are focused on validating outcome measures such as OMERACT.](#)

Taking on big ~~challenges-problems~~ 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 emphasized 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 leukocytes 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

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RA Collaborative Network. From that working group, suggestions for the design of such a network, the priorities for funding and implementation of pre-competitive studies, as well as development of a federated data portal contributed to by all groups, could emerge in an organic manner. Future closer transatlantic and global collaborations will capitalize on the legacy of the existing initiatives [e.g. 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 so the legal framework for such collaborative efforts can follow the current structures which allow for both very effective 1 to 1 collaborations on a deep data level, while the overall picture program can be shared more constructed to generate shared as global goals 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 not only a new support network for preventive and curative studies, but also foster collaborations between individuals and communities prepared to develop and utilize these networks.

1. Dolgin, E., *Massive NIH-industry project opens portals to target validation*. Nat. Rev. Drug Discov., 2019. doi: 10.1038/d41573-019-00033-8.
2. Malmström, V., A.I. Catrina, and L. Klareskog, *The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting*. Nat. Rev. Immunol. 17: p. 60-75.
3. Holers, V.M., et al., *Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction*. Nature Rev. Rheum., 2018. 14: p. 542-557.
4. Gerlag, D.M., et al., *EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis*. Ann. Rheum. Dis., 2012. 71: p. 638-641.
5. Demoruelle, M.K., et al., *Anti-citrullinated protein antibodies are associated with neutrophil extracellular traps in the sputum in relatives of rheumatoid arthritis patients*. Arth. Rheum., 2017. 69: p. 1165-1175.
6. Rombouts, Y., et al., *Anti-citrullinated protein antibodies acquire a pro-inflammatory Fc glycosylation phenotype prior to the onset of rheumatoid arthritis*. Ann. Rheum. Dis., 2015. 74: p. 234-241.
7. Mankia, K., et al., *Prevalence of periodontal disease and periodontopathic bacteria in anti-cyclic citrullinated protein antibody-positive at-risk adults without arthritis*. JAMA Netw. Open, 2019. 5: p. e195394.
8. Gerlag, D.M., et al., *Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study*. Ann. Rheum. Dis., 2019. 78: p. 179-185.
9. Al-Laith M et al. Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol. Trials. 2019 Jul 15;20(1):429.
10. Zhang, F., et al., *Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry*. Nat Immunol., 2019. 20: p. 928-942.

11. Croft, A.P., et al., *Distinct fibroblast subsets drive inflammation and damage in arthritis*. Nature, 2019. 570: p. 246-251.
12. Mizoguchi, F., et al., *Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis*. Nat. Commun., 2018. 9: p. 789.
13. Benham, H., et al., *Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients*. Sci. Transl. Med., 2015. 7.
14. Okada, Y., et al., *Genetics of rheumatoid arthritis contributes to biology and drug discovery*. Nature, 2014. 506: p. 376-381.
15. [Jackson R., et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet, 2005, 9457, 434-441](#)

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Single cell technologies define subpopulations that were previously thought to be homogeneous cell populations [9-11]]. This realization 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 centers 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 H₂O.

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 & 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 has changed the treatment landscape and patient expectations in cardiovascular diseases. This necessitates a new worldwide support network that includes the development and a global harmonization 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 [14], need support networks with well-standardized 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 organizations. An additional important point for harmonization and standardization, as well as agreement by regulatory bodies, are outcome criteria for prevention and early intervention trials. New intervention studies will benefit from harmonization between the currently ongoing trials which may benefit from already existing organizations such as 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 emphasized 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 [13], 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 leukocytes 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 pre-competitive studies, as well as development of a data portal contributed to by all groups, could emerge in an organic manner. Future closer transatlantic and global collaborations will capitalize on the legacy of the existing initiatives e.g. 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 program 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 not only a new support network for preventive and curative studies, but also foster collaborations between individuals and communities prepared to develop and utilize these networks.

1. Dolgin, E., *Massive NIH-industry project opens portals to target validation*. Nat. Rev. Drug Discov., 2019. doi: **10.1038/d41573-019-00033-8**.
2. Malmström, V., A.I. Catrina, and L. Klareskog, *The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting*. Nat. Rev. Immunol. **17**: p. 60-75.
3. Holers, V.M., et al., *Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction*. Nature Rev. Rheum., 2018. **14**: p. 542-557.
4. Gerlag, D.M., et al., *EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis*. Ann. Rheum. Dis., 2012. **71**: p. 638-641.
5. Demoruelle, M.K., et al., *Anti-citrullinated protein antibodies are associated with neutrophil extracellular traps in the sputum in relatives of rheumatoid arthritis patients*. Arth. Rheum., 2017. **69**: p. 1165-1175.
6. Rombouts, Y., et al., *Anti-citrullinated protein antibodies acquire a pro-inflammatory Fc glycosylation phenotype prior to the onset of rheumatoid arthritis*. Ann. Rheum. Dis., 2015. **74**: p. 234-241.
7. Mankia, K., et al., *Prevalence of periodontal disease and periodontopathic bacteria in anti-cyclic citrullinated protein antibody-positive at-risk adults without arthritis*. JAMA Netw. Open, 2019. **5**: p. e195394.
8. Gerlag, D.M., et al., *Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study*. Ann. Rheum. Dis., 2019. **78**: p. 179-185.

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9. Zhang, F., et al., *Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry*. Nat Immunol., 2019. **20**: p. 928-942.
10. Croft, A.P., et al., *Distinct fibroblast subsets drive inflammation and damage in arthritis*. Nature, 2019. **570**: p. 246-251.
11. Mizoguchi, F., et al., *Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis*. Nat. Commun., 2018. **9**: p. 789.
12. Benham, H., et al., *Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients*. Sci. Transl. Med., 2015. **7**.
13. Al-Laith M et al. Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol. Trials. 2019 Jul 15;20(1):429.
14. Jackson R., et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet, 2005, 9457, 434-441
15. Okada, Y., et al., *Genetics of rheumatoid arthritis contributes to biology and drug discovery*. Nature, 2014. **506**: p. 376-381.