The Future of Rheumatology

By Reza Mirza, MD, FRCPC

Rheumatology is among the most rapidly advancing specialties. Though oncology rivals us, we reserve the pleasure of routinely attaining remission. As we approach the 75th year since the discovery of cortisone, the *Journal of the Canadian Rheumatology Association (CRAJ)* asked me to opine: What do the next 75 years hold?

Rheumatologists will secure the holy grail of personalized therapy. We have the means to modulate specific cellular, protein, or nuclear targets at will. The shot-gun, "inhibit-everything" approach employed glucocorticoids may work short-term but is not tenable in the long run. The burning question is what to target and in whom.

We know clinical phenotypes are insufficient to predict biochemical response. Small Japanese trials give us a taste of how to predict, using lymphocyte flow cytometry patterns.[1] We must continue to stratify our patients into more meaningful groups, as doctors have always done. We have the resolution: long-read sequencing, -omics, mass cytometry. We simply need to offer this data with high quality longitudinal treatment-response data to the altar of machine intelligence.

We are already experts at measuring and extrapolating phenotypes associated with the B-cell receptor, particularly in its soluble antibody form (we are ever grateful, Marv). We must proceed beyond the anti-cellular antibodies that define modern day rheumatology.

Our characterization of the innate arm is scanty, and we have less than half the lymphocyte story. Like Alice in Wonderland, we are blind to the wizard behind the curtain, the T-lymphocyte and its receptor. Unlike B-cells, T-cells can survey intracellular processes, can induce apoptosis where they stand, and their repertoire is estimated to be an order of magnitude more diverse.

The first hurdle we must overcome — to achieve the phenotyping required for personalized therapy — is characterization of the innate arm's molecular signaling patterns and the T-cell receptor. "Reactive lymphadenopathy" will go the way of the dodo. Instead, embrace this type of lab report: "Activated, proliferating cytotoxic T-lymphocytes present. Sequencing of these T-cells reveal a T-cell receptor with specificity for an unknown target." It will be so, until our knowledge is more refined.

Once we have completed our measuring, we can begin predicting. Virtual simulations of biology ("in silico") will continue marching endlessly forward towards the asymptotic perfect prediction. Many philosophers will give up on the age-old conundrum of whether free will exists. (Sadly, it does not exist beyond our own perception.) The unknown, activated T-cells in your pathology sample will be submitted to the clinical bioinformatist to have its receptor topology predicted by AlphaFold, bellowing in the server for his next puzzle.[2] In silico evaluation will determine the T-cell receptor's target-based affinity matching against all known and unknown proteins. Mind you, technically this isn't futuristic. All these tools exist; the future simply holds application and refinement (Do reach out if interested).

In 75 years, we will have the capacity to measure the vast data contained in blood using multi-sensory physicochemical properties, far beyond the two-dimensions of mass-spectrometry (mass and quantity). Imagine "The Array" ("The Matrix" was taken) where each constituent is evaluated by its response to a distribution of non-destructive wavelengths, allowing for unique fingerprinting. This vast expanse of data would eclipse our working memory by thousands of orders of magnitude. The machine would interpret and draw us a cartoon of the immune system with helpful red and bold lines at upregulated pathways leading us to the most proximal source of inflammation.

There will be no serotype-phenotype discordance, and diagnostic labels will be redefined using serotype-first approaches. Lines between specialties will blur when your rheumatoid patient has a profound signal for peripheral ulcerative keratitis or interstitial lung disease.

We will become well-read in genotypes, and their non-coding grammar. Gene editing will continue to boom-and-bust. Its current boom-cycle will bust once off-target effects are measured. The careful will advocate for reversible, non-curative treatments that consistently work and, crucially, do not spill over into gametes and forever perpetuate. There will be a push for ex-vivo genetic editing of cells, à la CAR-T cells.

The world will be starkly different in 75 years. Our power to dispel disease will grow dramatically, paralleling the existential threat we pose to ourselves. We have yet to shed our beast.

References:
1. Miyagawa I, Nakayamada S, Nakano K, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. *Rheumatology.* 2019; 58(2):336-344. doi:10.1093/rheumatology/key069.
2. Jumper J, Evans R, Pritzel A, et al. Highly accurate protein structure prediction with AlphaFold. *Nature.* 2021; 596(7873):583-589. doi:10.1038/s41586-021-03819-2.

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