Searches for biomarkers using highly sensitive techniques might reveal more about pathogenesis of a disease than provide clinically useful molecular tests

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The era of modern medicine is often linked to the first clinical application of penicillin in 1943.[1] How far we have come in 80 years where we can now identify and measure concentrations of biomarkers in body fluids equivalent to a few crystals of sugar dissolved in an Olympic swimming pool. In their *JNNP* paper, Wieske *et al* describe how recently developed Olink technology directly identifies divergent changes in expressed proteins in the serum of patients with worsening or improving chronic inflammatory demyelinating polyradiculopathy (CIDP) and they propose these might be explored as biomarkers for disease activity[2] . They may have inadvertently stumbled on changes that might help the understanding of CIDP pathogenesis?

Biomarkers are currently the object of clinical academic interest. Highly sensitive analytical platforms such as Simoa and Ella analyse known molecules at sub pg/mL levels singly or in small multiplexes. Mass spectrometry offers more promiscuous molecular identification on cleaned samples. Olink, using Proximal Extension Assays ('protein PCR') advances ultra-sensitive platform technology to benchtop discovery in biofluid samples. Olink relies on 'primers' and therefore can only currently measure 1472 proteins from the human proteome of 17 000 proteins. It is remarkable that only 106 heterogenous but well-chosen CIDP patients could produce any significant changes at all.

CIDP is an uncommon inflammatory disease of the peripheral nerves, resulting in substantial disability (50% unable to walk at some stage in their disease course).[3] We still have little clear idea of the pathogenesis, and the split of humorally mediated autoimmune nodopathies from (possibly) T-cell mediated CIDP has highlighted this.[4] Wieske's study identified 48 proteins that changed with disease activity, of which five (IRAK4, SUGT1, DCTN1, NT5C3A and GLRX) altered consistently with worsening or improvement. None of these differentiate a group with clinically or immunologically active disease however, and distinguishing a CIDP patient with active from inactive disease would be impossible meaning these proteins are not really suitable as disease activity biomarkers.

The pathways of B-cell antigen response activation are probably key to many immune responses. We know that Guillain-Barré syndrome is almost certainly triggered by molecular mimicry responses to glycan motifs shared by *Campylobacter jejuni* and peripheral nerve gangliosides.[5] In this study, three of the five identified molecules with directional change (IRAK4, SUGT1 and GLRX) are involved in the complex B-cell signalling pathways often responding to basic glycan motifs, involving MYD88, Toll-like receptors, Brutons tyrosine kinase (BTK), NFκB and others. We have been hunting hard for proteins that might initiate CIDP which are relatively easy to find, but we must not forget older clues such as increased γδ T-cells suggesting that carbohydrate antigen stimulation might be relevant.[6] The current study aligns with this.

These findings might open opportunities for therapeutic suggestions; BTK inhibitors are being tried in multiple sclerosis and myasthenia gravis, but not yet in CIDP. Inhibiting this pathway that is activated in CIDP might be both therapeutic and enlightening?

We have come a long way in 80 years, stumbling on discoveries at many junctures. Perhaps this is another that will open doors to transformative care in this rare disease?

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