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The Wednesday Report: Precision medicine, novel approaches

Precision medicine, taking an individualized, molecular approach to risk assessment and clinical care, is not a new concept.

Although first envisaged in the realm of oncology, Wednesday's plenary discusses the application of this approach for cardiometabolic disease. The development of metabolomics technologies, which combine genetic and functional information, is one driver, as discussed by **Karsten Suhre (Weill Cornell Medicine, Qatar)**. Since 2008, when the first study combining both genotyping and metabolic characterization was published,[1] this area has evolved with the aim of translating functional insights for many disease-related associations, including cardiovascular disease and type 2 diabetes, to risk assessment and clinical care. *'Every association tells a story'*…..Recent research has provided a basis for genotype-linked differences in the metabolic response to angiotensin converting enzyme inhibitor treatment, based on analysis of 517 metabolites in subjects from the KORA F4 study, and suggested that the combination of genotype-metabolomic approaches may offer insights into genotype-dependent side-effects of these treatments.[2] Indeed, in 2014, Shin et al[3] published an 'atlas' of 145 genetically influenced metabotype profiles, offering the possibility of future exploration of the effects of individual genetic variants across hundreds of metabolites at one time. Such findings have opened up the possibility of rational metabolic engineering as a tool for targeted intervention in human metabolism, as well as the use of 'omics' approaches in health monitoring. *'Ultimately, deep phenotyping information offers the key to understanding the genetics of human metabolism.'*

In an exciting overview, **Matthias H. Tschöp (Helmholtz Diabetes Center & Technische Universität München, Munich, Germany)** provided a rationale for metabolic precision medicine in the development of pharmacotherapy for obesity and related metabolic disorders. Previously, treatments for obesity have had mixed fortunes, with development littered with failures in development, and withdrawals due to side effects not fully acknowledged at the time of launch. A new paradigm for drug development in obesity treatments is clearly needed, and research focused on incorporation of metabolically-related peptide hormone receptors, including glucagon-like peptide-1 (GLP-1), within one peptide offers new hope. Evidence shows that the individual activities of each receptor harmonize resulting in better overall metabolic activity. Professor Tschöp presented data for the latest of these peptides, a monomeric peptide triagonist incorporating GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors within a single peptide. These have shown unprecedented activity in rodent models in reducing body weight and fat mass via reduction in blood glucose, cholesterol and insulin, and increased fibroblast growth factor 21 (FGF21).[4] Thus, synergistic glucagon action to increase energy expenditure, GLP-1 action to reduce caloric intake and improve glucose control, and GIP action to potentiate the incretin effect, suggesting benefit in obesity.

Furthermore, improved understanding of the role of the central nervous system in mediating body weight effects may offer new directions, such as the combination of GLP-1 with dexamethasone, shown in animal models to promote anorexigenic signals, without off-target effects on the thymus or changes in endogenous hypothalamic pituitary axis activity. GLP-1/T3 combination has been shown to improve lipid handling in the liver, reverse hypercholesterolemia and atherosclerosis in *LDLR* deficient mice, as well as improve thermogenic activity in white adipose tissue. *'The era of metabolic precision medicine*

offers new hope in obesity management – but also highlights the need for improved biomarkers and diagnostics.'

Erik Stroes (Academic Medical Center, Amsterdam, the Netherlands), highlighted novel approaches in targeted therapy for atherosclerosis, which aim to optimize the benefit/risk profile. These developments also underline the need for a therapeutic paradigm shift from a 'group' to individualized approach, focusing on atherosclerotic burden rather than risk. Advances in multimodal imaging have provided a foundation for application of novel therapies, helping to guide individualized therapy.

In terms of therapy, recent development of the human monoclonal antibodies to PCSK9 has shown the benefit of a targeted approach, especially in individuals at greatest unmet clinical need, notably familial hypercholesterolaemia, as well as statin intolerance. The question remains whether these treatments reduce cardiovascular events in high risk patients, with definitive answers awaited from ongoing outcomes studies. Of course, cost is a major limitation, which further underlines the need for rationalization of treatment to those patients at highest risk. Antisense targeting of apolipoprotein(a) [apo(a)] may offer treatments for elevated lipoprotein(a), a cardiovascular risk factor for which there are no specific therapies, as well as severe hypertriglyceridaemia. Once again, there are limitations, including side effect issues. Indeed, during EAS Congress, plans for a Phase III trial using an antisense approach in amyloid cardiomyopathy have been put on hold, pending safety issues, notably, thrombocytopenia, which also recently appeared unexpectedly in a separate apoCIII trial with volanesorsen.[5] These issues have not been seen with mipomersen or apo(a) antisense approaches, which use different antisense platforms. Finally, nanotechnology, has been investigated in the setting of atherosclerosis, although studies indicate the need for better selection of targets and local delivery agents; cost also remains an issue. *'Novel therapies will help to tailor treatment to the high risk individual, with antibody/antisense approaches offering the possibility of precise molecular targeting. Finally, nanomedicine offers the possibility of improving efficacy and minimizing the risk of side effects.'*

Lastly, **Daniel Gaudet (University of Montreal, Quebec, Canada)** highlighted the complex phenotype of chylomicronaemia, encompassing both familial chylomicronaemia syndrome and multifactorial chylomicronaemia, which due to significant unmet clinical needs is a focus for novel drug development. Emerging therapies, including gene-based therapies and antisense oligonucleotide treatments targeting apoCIII, have provided new approaches for management. Perhaps more importantly, development has also opened avenues for research into the mechanisms of postprandial metabolism, offering targets for future therapeutic potential.

References

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