

## **Antigenic mapping of hCG – what are we measuring?**

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Immunoassay measurements of human chorionic gonadotropin (hCG) contribute significantly to the clinical management of pregnancy, pregnancy-related disorders and trophoblastic tumors. As for other complex analytes, differences in hCG results obtained using different methods may affect clinical interpretation with potentially adverse consequences for patient care. Factors contributing to these method-related differences include analyte heterogeneity, lack of standards or inappropriate standards, and lack of agreement about the clinically most relevant specificities of monoclonal antibodies (mAbs) used in diagnostic immunoassays. Ambiguous nomenclature may also cause confusion about what methods are measuring. Data from external quality assessment (EQA) and proficiency testing schemes consequently demonstrate significant method-related differences in results.

The recent hCG Antibody Epitope Mapping Workshop held under the auspices of the International Society of Oncodevelopmental Biology and Medicine (ISOBM) characterized epitopes and specificities of hCG mAbs for different clinical applications from 7 diagnostic companies and published recommendations on the most appropriate hCG mAb combinations for different diagnostic purposes. For routine applications assays measuring a broad spectrum of hCG/hCGb variants preferably at equimolar levels seem to be most suitable. This can be achieved by combining mAbs directed against epitopes located around the cystine knot (epitope  $\beta_1$ ) with mAbs against epitopes at the top of loops 1 and 3 on hCG $\beta$  ( $\beta_2$ ,  $\beta_4$ ). The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a Working Group (WG) on improvement of Standardisation of hCG (established by U.-H. Stenman; chaired by C. Sturgeon), giving it the broad remit of exploring how best to improve comparability of results for a complex analyte, taking hCG as a prototype. Clear user-friendly nomenclature for hCG-related isoforms was therefore developed and its universal adoption is currently being promoted. This nomenclature enables unambiguous description of the isoforms individual hCG methods recognize. The IFCC WG then prepared highly purified preparations of six important hCG isoforms, subsequently recognized by the WHO as International Reference Reagents (IRR). The first such reagents to be calibrated in molar rather than arbitrary units, these will enable improved characterization of immunoassays for hCG by manufacturers, thereby providing a valuable means of establishing what methods are measuring. Studies are also in progress to assess the suitability of the 1<sup>st</sup> hCG IRR 99/688 as a replacement for the present 4<sup>th</sup> International Standard for hCG, IS 75/589.