HCPs – What's in a name? MCP-1

The Vanderlaan et al. article published in 2018 is still one of the best summaries of biopharma's experience with Host Cell Proteins (HCPs). In the section on cytokines (starting on page 4), the article reviews the experience BMS had in 1997 with the CHO host cell protein *Monocyte chemoattractant protein*, also known as MCP-1. In the 2021 BEBPA HCP Conference, Karen Price (BMS) presented an updated review of BMS's Phase 2a psoriasis trial. BMS classified the adverse events into two categories: (1) those related to histamine release symptoms, and (2) those that were constitutional symptoms (e.g., fever). Using late 1990's technology, BMS was able to identify an impurity that had significant sequence homology to human MCP-1, and then fix the purification process. In some of today's CHO proteome databases, the protein name "MCP-1" is not found. This HCP is instead identified as "C-C motif chemokine 2." Whatever the name, it is a smaller glycosylated protein, and it has many Lys and Arg residues which generate short hydrophilic peptides when it is digested with trypsin. There aren't as many ideal tryptic peptides as one would find for larger HCPs, so MCP-1 can be more difficult to detect. We often detect MCP-1 in early process intermediates, and it is one of those "problematic HCPs" that needs to be monitored during process development. By using mass spectrometry, one can track the clearance of problematic HCPs like MCP-1 from one column to the next.

https://pubmed.ncbi.nlm.nih.gov/29693803/

IDENTIFICATION OF HAMSTER MCP1 HOST CELL PROTEIN IMPURITY AS THE POTENTIAL CULPRIT FOR CLINICAL ADVERSE EVENTS

- **Speaker:** Karen ***Price***, Bristol-Myers Squibb Company
- **Abstract:** Identification of Hamster MCP1 Host Cell Protein Impurity as the Potential Culprit for Clinical Adverse Events Karen D Price, MS, DABT, Scientific Director, Nonclinical Safety – Bristol -Myers Squibb Abatacept, a CTLA4Ig fusion protein, is a selective costimulatory inhibitor marketed for the treatment of rheumatoid arthritis. During early clinical development (circa 1997), the program was put on clinical hold due to a series of adverse events in a Phase 2a psoriasis trial. The clinical adverse events could generally be separated into two categories: those that were histamine-like characterized by lacrimation, flushing, rhinitis, edema face/tongue, throat tightness, blurred vision, urticaria, or an anaphylactoid reaction, and those that were constitutional symptoms including fever, chills, tremors, arthralgia, and myalgia. In response to these findings, an integrated comprehensive investigation as to the possible causative factor(s) (drug, excipient, impurity) was immediately initiated. As part of that investigation, the ability of abatacept drug product to induce basophil histamine release in vitro was assessed using blood from five subjects in the IM101-005 study. These data showed that an impurity present in abatacept drug product could induce in vitro histamine release in whole blood from one subject that experienced a histamine-like reaction. It further demonstrated that this impurity was not present in the new-process material, at least at a concentration that could induce histamine release in the blood of that particular subject. This histamine-releasing activity appeared to reside predominantly in peak 2 following C3 reverse-phase chromatography, and the impurity in peak 2 had significant sequence homology with monocyte chemoattractant protein-1 (MCP-1), a potent inducer of histamine release.
- (Day 2: Management of Individual HCP Impurities Session)