ASMS Evening Workshop Proposal Report

Membrane Proteins, Nanodiscs, and Beyond: MS Analysis in Academia and Industry

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Membrane proteins make up over 50% of possible "druggable" targets, making them very attractive targets for academic and industrial research. Membrane proteins are inherently insoluble in aqueous solvents and require the presence of lipid or detergent to remain soluble, which makes their analysis by many biophysical techniques such as native mass spectrometry (MS) and x-ray crystallography very challenging. However, over the past 10 to 15 years, researches have begun to overcome such hurdles and are now producing native intact mass spectra for membrane protein complexes of ion channels, membrane bounds receptor molecules, transporters, and fully assembled lipoprotein nanodiscs.

Most of this pioneering work has been focused on native MS in the academic environment. Native MS analysis of membrane proteins within the pharmaceutical industry is still in its infancy compared to established structural biology techniques such as x-ray diffraction and cryo-EM.

The workshop was a panel discussion format where general and detailed topics were discussed. The panel was a mix of academic and industrial scientists with the following discussion topics:

1. Julian Whitelegge (UCLA, USA): MS determination of membrane proteins using denaturing SEC-MS and LCMS conditions
2. Jennifer Lippens (Amgen, USA): MS determination of membrane proteins using denaturing LCMS conditions and its application in pharma
3. Arthur Laganowsky (Texas A&M, USA): Membrane protein purification and detergent screening for optimal native-MS analysis
4. Idlir Liko (OMass, UK): Native-MS instrumentation optimization and analysis of membrane proteins
5. Wendy Sandoval (Genentech, USA): an industrial perspective on membrane protein MS

In total, Michael and I counted 110 attendees. The allocated room was the correct size. The room felt busy and well attended. It certainly did not feel empty.

Immediately prior to the panel discussion Michael and I introduced the concept of the workshop with a few introductory slides. We also stressed that audience please leave their questions until after the panel discussion; this would aid interaction and leave plenty of time for discussion. We receive positive feedback from many attendees that this was the correct thing to do.

The panelists were asked to present 2-3 slide for approximately 5-7 minute, which all panelist did successfully. This left approximately 45 minutes for panel and audience discussion and interaction. There was a large and very successful 45min discussion session immediately following the panel presentations. The audience was very interactive. Michael and I didn't feel that we had to drive the audience interaction/discussions. As expected the main discussion points were about membrane protein native-MS sample preparation and how to optimize the MS instrument for optimal spectral data quality. Also within this workshop, MS experiments for characterizing intact membrane proteins under denaturing and native conditions were heavily

discussed, focusing on current protocols used within both academia and industry for native MS analysis of membrane protein solubilized in “MS-friendly” detergents.

As facilitators, Michael and I also tried to emphasize how can the current membrane protein sample prep. be transitioned in to a more routine/industrialized and less subjective area. The presence of both Jennifer Lippens (Amgen) and Wendy Sandoval (Genentech) was highly useful to give a much needed industrial perspective on the subject of native-MS analysis of membrane proteins. Importantly, how these techniques can be used to support the structural biology and drug discovery efforts within the pharmaceutical industry were discussed by both Wendy and Idlir.