Near-atomic level insights into the gap junctions resolved by CryoEM

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Gap junctions play a fundamental role in biology by establishing direct pathways for cells to rapidly and reversibly exchange chemical and electrical information. Despite their importance to physiology and established roles in a wide range of human disease, there has remained a lack of high-resolution structural information on this family of proteins that has limited our mechanistic understanding of how these channels operate. This dearth of understanding has been due to inherent difficulties associated with traditional methods requiring the crystallization of membrane proteins. Recent advances in the field of single particle CryoEM have provided an alternative and highly effective methodology for the determination of membrane protein structures. This enabling technology is now being complemented with tools developed to study membrane proteins in their near-native lipid environment (e.g., lipid nanodiscs). Our laboratory has harnessed these tools to characterize the structure of native connexin-46/50 gap junction channels, which we have resolved to 1.9 Å resolution by CryoEM – providing an unprecedented level of structural detail for this family of proteins. We will discuss the methodological advancements in membrane biochemistry and CryoEM image-processing that were critical to achieving this technological feat, as well as the critical biological insights into these channels and their remarkable interaction with the local lipid environment that we have gleaned at this near-atomic level resolution. Finally, we provide our perspective on how we believe continued developments in these technologies will be critical to deepening our understanding of membrane biology and to providing the detailed molecular blueprints required for successful structure-guided drug development.

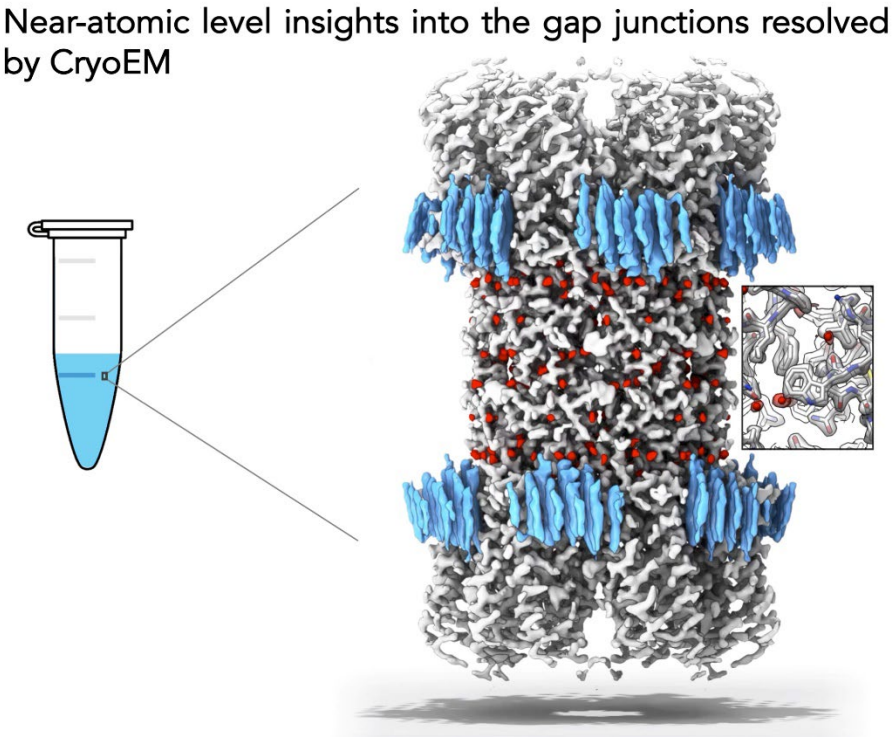

Figure 1