Developing metabolomics for a systems biology approach to understand Parkinson's disease

Willacey, C.C.W.

PROPOSITIONS

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1. Chemical derivatization with isotope-coded derivatization prior to RPLC-MS/MS analysis can improve stability of the analytical performance, retention of analytes, quantitative performance and throughput of the method. *(Chapter 2)*

2. The use of chemical derivatization can bring life back to outdated mass spectrometry systems that were deemed unsuitable due to lack of sensitivity. *(Chapter 3)*

3. The use of isotope-coded derivatization can reduce the cost of analysis by removing individual internal standards. This will hopefully make quantitative metabolites available to scientist with a limited budget *(Chapter 2, 3 and 5)*

4. Capturing and sharing the absolute quantitative neurochemical profile of the healthy mammalian brain will allow researchers to further improve our understanding of connectivity and vulnerabilities associated with neuronal function and diseases. *(Chapter 4)*

5. Systems biology has the ability to further our understanding of diseases by integrating a vast amount of data that the human mind would not be able to comprehend in a lifetime. *(Chapter 5)*

6. An obstacle with existing human GEMs is their insufficient use of standard identifiers for many metabolites and reactions *(Robinson JL et al. 2020, Science Signalling, Vol. 13, Issue 624)*. This is often overlooked by researchers, but we need to use identifiers to ensure that we are communicating information when we refer to the same metabolite or chemical, also in different research fields. Different preferences of naming in different fields can be overcome with a unique identifier, and that is even more important for complex molecules and working work with large scale data and multidisciplinary teams.

7. The beauty of the connectome is its precision and specificity, but it is hard to imagine useful network models that implement all of the details of cell-to-cell connectivity *(Bargmann CI & Marder E, 2013, Nature Methods, 10, pages 483–490)*. Such a precise and specific network can be improved by understanding the metabolic signature to underpin the connectivity.

8. Uncertainty about anatomical labels for subcortical structures hinders comparisons across studies because of potential spatial inaccuracies in co-registration to standard space, it is critical to maintain probabilistic atlas labels *(Pauli, WM et al., 2018, Scientific data, 5, 180063)*. This approach can be further improved by using metabolomics to create additional anatomical markers by highlighting the metabolic signature of each structure.

9. The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies *(Hamburg MA & Collins FS, 2010, New England Journal of Medicine, 363:301-304)*. The application of metabolomics to the diagnosis landscape can provide an additional tool in personalized medicine by including the exposome, which has been shown to influence health and treatment response, and several exposomic factors are in principle modifiable.

10. If this pandemic has taught us anything, it is that we are resilient and adaptive to change.

11. If you just focus on the smallest details, you never get the big picture right *(Leroy Hood).* This is like buying baby clothes. If you focus so much on buying the perfect outfit for the family photo, you soon realise that the baby has already grown out of it.

12. Simplicity is the ultimate sophistication. *(Leonardo da Vinci).* This is still true and should be used by scientists to support interdisciplinary research to ensure the message is transferred clearly.