

Gut feelings

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Propositions

1. Adverse drug reactions (ADRs) are one of the main reasons for the interruption of cancer treatment or alterations in dose regimens in pharmacotherapy. Therefore, it is important to generate new *in vitro* data that can be applied in the modelling of drug responses and induced toxicity, and to improve the translatability of such data to the human clinical setting. (*This thesis*)
2. As 3D cultures of organoids provide a deeper insight into human biological processes, cell-cell interactions, and drugs' efficacy and/or toxicity, they constitute a better alternative to standard 2D *in vitro* cell models. (*Chapters 2, 4, 5 and 6*)
3. A co-culture model that combines colon organoids and macrophages is a promising tool to investigate inflammation-associated drug toxicity and disease modelling. (*Chapter 6*)
4. The identified marker gene and the overlap in affected biological processes between cancer patients and colon organoids are a starting point for the investigation of translatable biomarkers and ultimately will contribute to the advancement of future clinical practice. (*Chapter 3*)
5. Whole genome transcriptomic analysis is an important tool for human risk assessment as it provides a more comprehensive understanding of molecular mechanisms underlying drug toxicity, by linking gene responses to cellular phenotypes.
6. Advanced *in vitro* experimental designs integrated with multi-omics analysis provide a more complete insight into drug responses and induced-toxicity mechanisms as well as a better understanding of the onset and progression of diseases.
7. Colon and small intestine show distinct drug-induced responses and gene expression changes, which, from a clinical perspective, can contribute to the improvement of precision medicine.
8. "The more we know, the more we realize there is to know," – *Jennifer Doudna*
9. "I have not failed. I have successfully discovered 10 000 things that won't work." – *Thomas Edison*
10. "Anything that can go wrong will go wrong" (Murphy's law). Despite the challenges, the PhD journey was also an amazing one.
11. "Tenho em mim todos os sonhos do mundo." (I have in me all the dreams of the world) – *Fernando Pessoa*