Challenge 26: DARTpaths Surgery Q&As

Q. How many chemicals do you expect to be tested for the model to have validity?

A. The ultimate aim is to create a tool that is representative of as many chemicals as possible that have been tested in more traditional preclinical species and alternative models. The focus is on developing a robust tool that contains enough detailed information to enable Sponsors to make considered judgements on the DART potential of a chemical. This should inform mechanistic understanding of a chemicals effect on DART, i.e. which biological target (e.g. receptor, enzyme) is involved, which species has an orthologue of that target, which compounds have been tested against this target in this model, etc.

Q. How wide does the chemical space tested in the model have to be?

A. The chemical space needs to be able to represent UVCB substances of the type generated by Shell (petrochemicals and petroleum products, chemical substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (see these sources for example chemical substances in this space https://www.concawe.eu/wp-content/uploads/2017/01/rpt_15-9.pdf and http://loa-reach.com/substance-information-and-obtaining-letters-of-access.html)). The chemical description of complex mixtures is not simple, see http://onlinelibrary.wiley.com/doi/10.1002/etc.3100/abstract for one approach to this problem. The chemical space also needs to cover chemicals such as agrochemical active substances that Syngenta invent see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4493826/. The list in appendix 1 of the Challenge brief describes the protein targets or biological pathways that may participate in a molecular initiating event (MIE) if perturbed. This list is not exhaustive and will increase over time. Any solution must include chemicals which affect many of these targets/pathways and be able to grow as more pathways/target protein data emerges. General, consumer and cosmetic chemicals should not be focus areas during Phase 1.

Q. What expectations are there on assessing complex substance with unknown compositions and if a UVCB has unknown or variable composition, how can the relationship between compounds and effects be determined?

A. Obviously where compositions are unknown the DART effects cannot be linked to a particular chemical. However, for the UVCB substances of interest we have information of specific toxicity markers (chemicals) in the mixture as well as ranges on carbon range and physico-chemical properties that are used to group these individual UVCB substances. For details and general problem setting see https://www.concawe.eu/wp-content/uploads/2017/01/rpt_15-9.pdf, http://loa-reach.com/substance-information-and-obtaining-letters-of-access.html and http://onlinelibrary.wiley.com/doi/10.1002/etc.3100/abstract. For a tool, a chemical search function on, for example CAS numbers, EC numbers, description, carbon range, boiling point range, marker chemicals in the complex substances may be considered.

Q. Are all species described in the Challenge brief (human, mouse, rat, rabbit, zebrafish, fruitfly, nemotode and slime mould) required in the final model? How many would be needed during Phase1 model development?

A. During Phase 1 the minimum species required would be human, rat and those used during the PREDART CRACK IT Challenge (*C. elegans*, *D. discoidium* and zebrafish). It would be expected that the final tool delivered at the end of Phase 2 would include all species described in the Challenge brief.

Q. Should the focus be on pathways related to the MIE and phenotype or the chemical?

A. There are several ways of approaching this problem. For example, the focus could be on defining what MIEs are activated by which chemicals and what phenotype this induces, or what genes are activated by which phenotypes. The Sponsor's main interests lie in understanding the

biology that underlies chemically-induced phenotype across species, but it is the responsibility of the applicant to propose an appropriate approach. The types of phenotypes produced and MIE/pathways involved by chemicals relevant to petrochemical and agribusiness companies would be an appropriate area to focus on. The ultimate aim is to capture the MIEs that underlie all known developmental toxicity phenotypes.

Q. By the end of Phase 1, does the software developed have to be a fully integrated graphical user interface, or can it be simpler to be further developed during phase 2?

A. The software at the end of Phase 1 can be simple, but it must be capable of clearly demonstrating functionality and usability by the end-user. The applicant/contractors must also demonstrate that the software developed/to be developed can be widely used across different systems within companies, institutions, etc. This can be a well-argued theoretical case by the end of Phase 1.

Q. Is the Syngenta use case focused on decreasing the burden of regulatory *in vivo* testing?

A. Yes. The focus is on improving internal decision making by de-risking the prioritisation of chemicals required for regulatory testing. It is not within the scope of this Challenge to develop a tool acceptable to regulators. However by engaging the regulators in the development and application of these models it will help to make eventual acceptance more straightforward.

Q. Is the use case within Shell around new product development?

A. No. The focus is on using a new tool to generate hypotheses and more detailed mechanistic understanding on chemicals within Shell's portfolios and their effects on DART to make better decisions on compound progression, selection of chemicals for testing and rationale selection of alternative species to test in with reduced need for conventional *in vivo* testing.

Q. How do you represent chemicals and chemical space?

A. The solution to this challenge has to be able to represent two different types of chemical space: single substance structure descriptors (options should include input of SMILES (simplified molecular-input line-entry system) or Inchi (International Chemical Identifier) identifiers, possibly also to draw a structure in a box) for the agrochemical active substances and petrochemicals and an appropriate descriptor set for the UVCB mixtures based on physicochemical and other properties.

Q. Are there plans to link up this Challenge with the pharmaceutical and/or cosmetics and personal care products industries?

A. There is no formal plan to collaborate specifically within this Challenge. However, these industries face similar issues as the agrochemical and petrochemical industry so there may be scope in the future to build on the product developed through this award. Consequently solutions that bring additional collaborators that build these links are welcome.

Q. When will the CRACK IT PREDART data become available?

A. At the moment it remains unpublished, solution providers should expect it early during Phase 2. The data types it covers are phenotypes (see e.g. http://www.sciencedirect.com/science/article/pii/S0887233317301510), RNA-seq data, and compound concentration in whole organisms (being *Caenorhabditis elegans* (nematode), *Danio rerio* embryo (zebrafish) and *Dictyostelium discoideum* (slime mold)) on ~40 different chemicals.