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Where are we at regarding species translation? A review of the sbv IMPROVER challenge

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Animal models serve an important purpose in fundamental research aimed at understanding the molecular networks underpinning biological and cellular mechanisms. In drug development and toxicological risk assessment, compound testing usually starts by *in vitro* experiments, followed by *in vivo* testing using rodents as a mammalian model. This practice assumes that such animal models respond to active substances through similar mechanisms. Yet in spite of many effective uses of animal models, numerous findings have also been unsuccessfully translated to humans, as evidenced by the failure of many clinical trials. These failures clearly stem from our lack of detailed understanding of inter-species differences that precludes naïve translation of knowledge derived from animal models directly to human, but also further distinction among available rodent models, including xenograft, genetic or syngeneic models. Such limitations are driving the development of increasingly more complex *in vitro* systems, ranging from 3D-organoid tissue cultures derived from primary cells to so-called human Organs-on-chips (Huh *et al.*, 2013) and Human-on-a-chip (Marx *et al.*, 2012). However, it is still early days, and replacing complex model organisms with a battery of *in vitro* systems that adequately recapitulates human biology is a journey that has just begun.

In this context, a pertinent question to ask is 'to what extent perturbations induced in rodent cells are conserved and hence predictable, in human cells?'

This important question was addressed in the form of a challenge titled 'Species Translation Challenge' in the framework of sbv IMPROVER (systems biology verification, Industrial Methodology for PROcess VErification in Research) (Meyer *et al.*, 2012), a collaborative initiative by IBM Research and Philip Morris International (PMI) R&D that uses crowd-sourcing approaches to address fundamental questions in systems biology. For 4 months, starting in May 2013, the Species Translation Challenge was articulated around four sub-challenges focusing on different aspects of translatability within and between species. The results of this challenge provide insights on (i) the accuracy of predictions in the context of the diversity and dimensionality of data types generated at various levels of the biological system; (ii) the importance of temporal information (more time points) to gain resolution in sequential molecular events, especially if the activation time window is shifted between species; (iii) heterogeneity of results from similar computational methods, which is probably due to different methodological choices made at distinct steps of the process (e.g. data preprocessing, feature selection, classification algorithm) that are problem dependent; (iv) a consensus network that describes the conservation and divergence of biological pathways and interactions in response to a subset of stimuli. A total of 28 teams, comprising 51 scientists from 14 countries across Europe, North America, Asia and Australia submitted predictions. The submissions of each team were evaluated by an independent panel of scientists and the results of the Species Translation Challenge were presented, and best performers were rewarded at the sbv IMPROVER Symposium last October 2013 in Athens, Greece. Three best-performing teams were recognized in the first sub-Challenge. Team AMG involved scientists from University of California Santa Barbara (USA), University of Groningen (Netherlands) and Rutgers University (USA). The other best performers in this sub-Challenge were Clemson University (USA) and Wayne State University (USA). Team AMG was also best performing in sub-Challenges 2 and 3. Five teams were recognized as joint best performers in sub-Challenge 4: one from Max Planck Institute for Dynamics of Complex Technical Systems (Germany), a Swiss team from University of Lausanne and Institute of Bioinformatics, one from Pacific Northwest National Laboratory (USA) and two separate teams from University of Pittsburgh (USA). Details of each team are published on the sbv IMPROVER website (http://www.sbvimprover.com).

This issue of *Bioinformatics* contains six articles dedicated to the overall results, and the detailed description of best-performing computational methods that arose from the Species Translation Challenge.

The current work constitutes a proof of principle that the molecular responses induced by active substances in an *in vitro* system are to some extent predictive of the responses observed in the same system of another species. A more detailed understanding of the range of applicability of the translation concept will impact the predictability of signaling responses, mode of action and efficacy of drugs in the field of systems pharmacology

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as well as increase the confidence in the estimation of human risk from rodent data in the context of toxicological risk assessment. Details about the experimental methods and publicly released data are available online (Poussin *et al*., 2014).

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