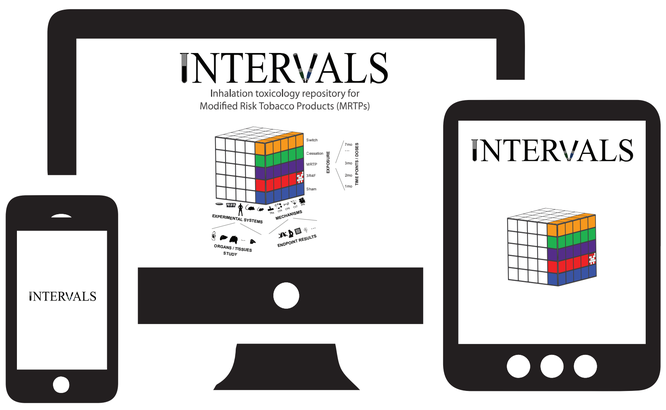
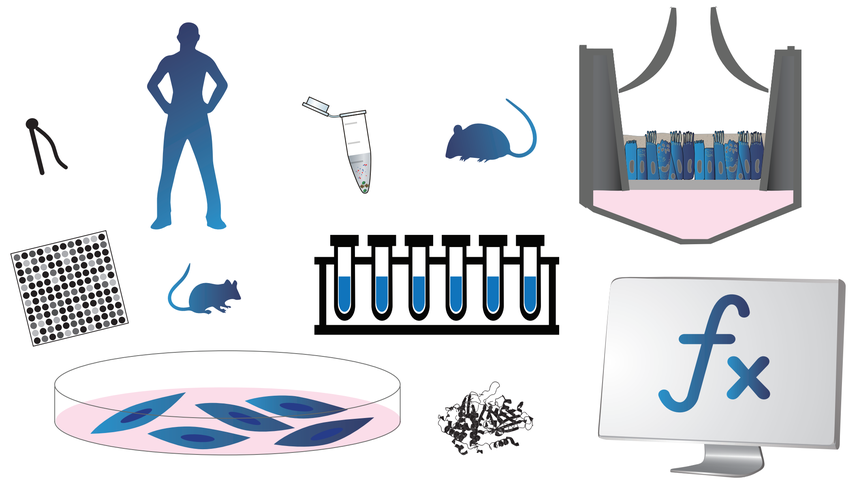
Sharing and verifying systems toxicology data via the INTERVALS and sbv IMPROVER platforms

The sbv IMPROVER team and Systems Toxicology Department
Biomedical Research, PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000
Neuchâtel, Switzerland (Part of Philip Morris International group of companies)

Introduction and Objectives

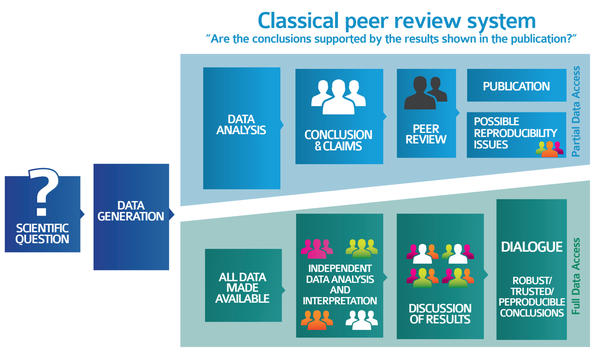


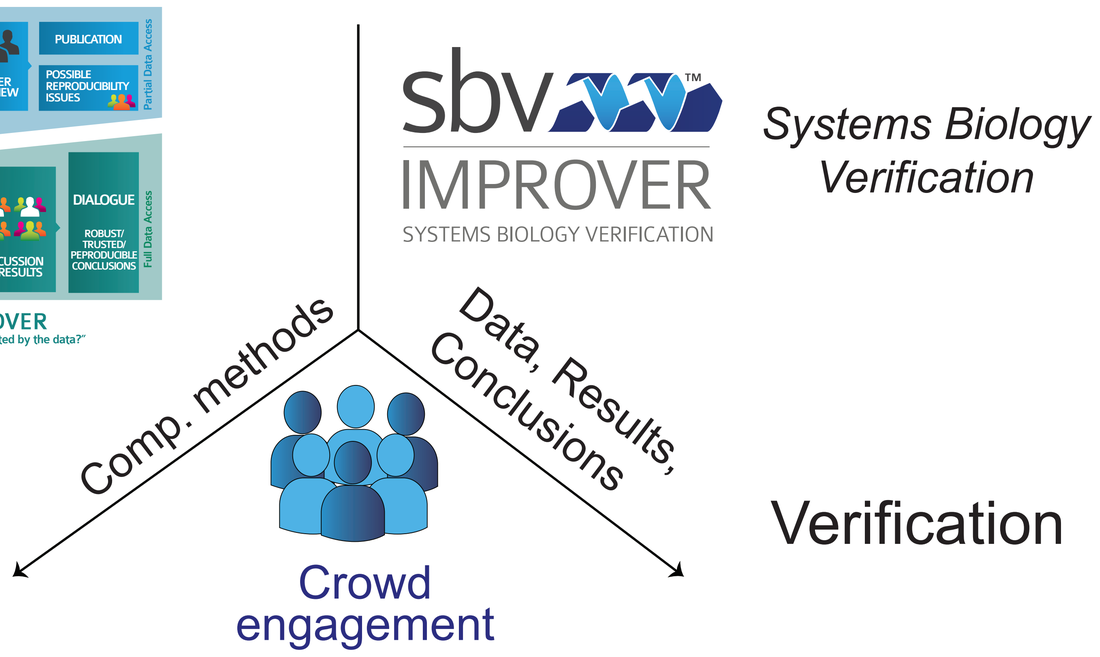
https://systox.sbvimprover.com



Data + Computational methods

Decompose into verifiable building blocks





Abstract

Large international programs increasingly generate large and complex toxicology-relevant data sets. Moreover, industrial R&D endeavors may generate even larger amounts of data but are not as proactive in the area of data sharing. Therefore, sharing these industry-owned datasets represents a great opportunity to push forward frontiers of knowledge for the scientific community as a whole.

A proof of concept database and website ('INTERVALS') has been developed to share results from *in vivo* inhalation studies as well as *in vitro* studies conducted by Philip Morris International R&D that assess potential Modified Risk Tobacco Products (MRTP). Data modeling took into account the latest standards in terms of data sharing and reproducible research. Given the successful development of the initial infrastructure, the goal is to grow this initiative to establish a public repository for 21st century pre-clinical systems toxicology MRTP assessment data.

In addition, with a goal to maintain scrutiny in data analysis and interpretation, we have developed and applied the sbv IMPROVER methodology to verify the output of research processes in industry. Whereas computational methods are benchmarked using computational challenges, a verification program engaging panels of independent experts confirms the excellence of the scientific methods used and the integrity of the results shared.

Transparency in Science

Several studies have shown that much peer-reviewed scientific literature is not reproducible for a variety of reasons [1,2].

Contributing factors include inadequate documentation of methods and datasets and insufficient sharing of data and methods with the community, which are essential for an experiment's replication or analysis.

It is crucial that the science is right, i.e. to ensure that:
- experiments are repeated
- reagents are validated
- analyses and statistical tests are appropriate
- all results, including negative and positive controls are shown
- if appropriate, the study is blinded

A consistent, science-based framework should be used for identification of innovative alternative products that could significantly reduce disease and death caused by cigarette smoking [3,4]. Moreover, processes and/or platforms such as INTERVALS that encourage transparent sharing of data in a way that allows easy review and understanding should facilitate objective evaluation of the evidence [5].

1. Begley, C. G. et al. Reproducibility in science: improving the standard for basic and preclinical research. Circulation research 116, 116-126 (2015)
2. Iorns, E. et al. New forms of checks and balances are needed to improve research integrity. F1000Research 3, 119 (2014)
3. Kozlowski, L. T. et al. Obsolete tobacco control themes can be hazardous to public health: the need for updating views on absolute product risks and harm reduction. BMC public health 16, 432 (2016)
4. Morven Dialogues. Core Principles Concerning the Implementation of Effective and Workable Tobacco, Nicotine, and Alternative Products Policies for Reducing Disease and Death from Tobacco Use. (2015)
5. Combes RD, Balls M. A critical assessment of the scientific basis, and implementation, of regulations for the safety assessment and marketing of innovative tobacco-related products. Alternatives to laboratory animals : ATLA. 2015 Sep;43(4):251-90.

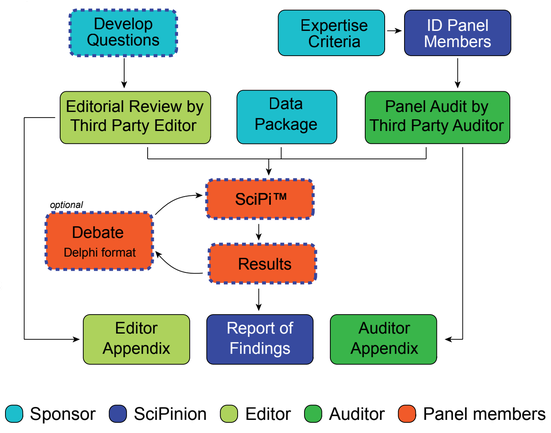
Novel Tobacco Products and Alternative Products Supporting Harm Reduction

Smoking causes serious diseases, including cardiovascular disease, lung cancer and chronic obstructive pulmonary disease. In addition to existing strategies of reducing smoking-related harm (i.e., preventing initiation and promoting smoking cessation), a growing number of health authorities and experts now believe that giving smokers access to less harmful alternatives can be a major benefit to public health. This tobacco harm reduction approach depends on developing products that meet two conditions. Firstly they need to present less risk of harm than continued cigarette smoking and second they should be satisfying so that smokers switch to them [6]. Philip Morris International (PMI) is developing a portfolio of potentially reduced risk products (RRPs*) to address a wide range of adult smoker preferences [7].

6. Smith, M. R. et al. Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. Regulatory toxicology and pharmacology : RTP , 201
7. Learn more at http://pmiscience.com

Independent Verification

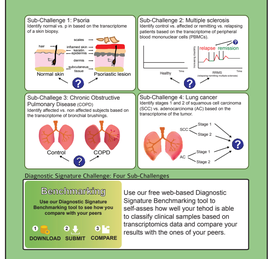
To complement the peer review of publications reporting individual studies, a deeper review was conducted to obtain an independent assessment of several nonclinical and clinical studies, including *in vivo* inhalation studies, *in vitro* assays, and clinical PK studies designed to evaluate the relative effects of P1 in comparison with a reference cigarette.
We engaged SciPinion LLC (https://scipinion.com/) to identify and recruit key opinion leaders in 5 separate panels in an objective and nonbiased manner. At no stage was PMI aware of the identity of the individuals who participated in the review. The reviewers had access to all publications and raw data from the studies via a web portal designed for external review. The reviewers were asked multiple questions regarding study design, methods, quality of data, and interpretation of results to judge the validity of the conclusions regarding the relative effects of THS 2.2. **Overall results were very positive, being supportive or very supportive of the study methods and results.**



sbv IMPROVER Challenges

Diagnostic Signature Challenge

The goal of this Challenge was to assess and verify computational approaches that classify clinical samples based on transcriptomics data.
The high quality of predictions confirmed strongly the approach values.



Use our free web-based Diagnostic Signature Benchmarking tool to self-asses how well your tehod is able to classify clinical samples based on transcriptomics data and compare your results with the ones of your peers.

Symposium 2012, Boston (USA)

Tarca AL, et al. Strengths and limitations of microarray-based phenotype prediction: lessons learned from the IMPROVER Diagnostic Signature Challenge. Bioinformatics. 2013 Nov 15;29(22):2892-9

Special issue in Systems Biomedicine.

Species Translation Challenge

Changes in phosphorylation status and gene set activation induced by cellular response to 52 different perturbations in human cells can be predicted to a certain extent given responses generated in rat cells.

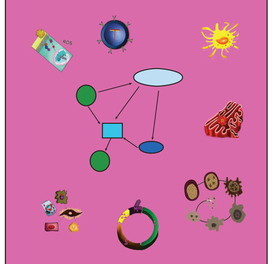
Symposium 2013, Athens (GR)

Poussin C, et al. The species translation challenge--A systems biology perspective on human and rat bronchial epithelial cells. Scientific Data. 2014;1:140009.
Rhrissorrakrai K, al. Understanding the limits of animal models as predictors of human biology: lessons learned from the sbv IMPROVER Species Translation Challenge. Bioinformatics. 2015 Feb 15;31(4):471-83.

Special issue in Bioinformatics

Diagnostic Signature Challenge

The NVC Challenge aimed at verifying the biological network models to ensure their relevance to lung biology and COPD.

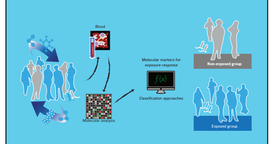


Symposium 2014, Montreux (CH)
Symposium 2015, Barcelona (ES)

sbv IMPROVER team. Reputation-based collaborative network biology. Pacific Symposium on Biocomputing Pacific Symposium on Biocomputing. 2015:270-81.
sbv IMPROVER team and challenge best performers. Enhancement of COPD biological networks using a web-based collaboration interface. F1000Research. 2015;4:32.
sbv IMPROVER team and challenge best performers. Community-Reviewed Biological Network Models for Toxicology and Drug Discovery Applications. Gene regulation and systems biology. 2016;10:51.

Systems Toxicology Challenge

The SysTox Challenge aimed at verifying that robust and sparse human-specific and species-independent gene signatures of exposure response can be extracted in whole blood gene expression data from human and rodent to predict exposed and non-exposed group labels.

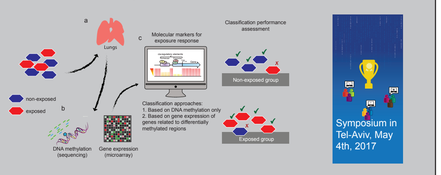


Special session at ISMB2016 and Symposium 2016, Orlando (USA)

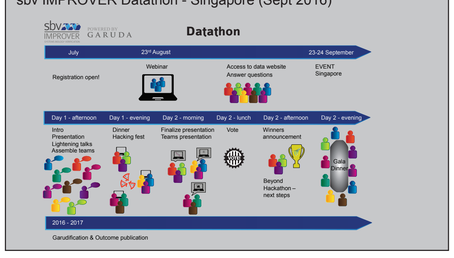
Poussin C, Belcastro V, Boué S, Martin F, Sewer A, Titz B, et al. The systems toxicology challenge: Marker of exposure response identification in blood. Toxicology letters. 2016;259:S174.

Datathons and Mini-computational Challenges

sbv IMPROVER Epigenomics Challenge - Israel (Feb-May 2017)



sbv IMPROVER Datathon - Singapore (Sept 2016)



Competing Financial Interest

The research described in this poster was sponsored by Philip Morris International

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

* Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment and commercialization. Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.