sbv IMPROVER
SYSTEMS BIOLOGY VERIFICATION

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Harness The Power of the Crowd to Address Computational and Biological Challenges

Dr Stéphanie Boué, Manager Scientific Transparency & Verification, Philip Morris International R&D

Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000 Neuchatel, Switzerland (Part of Philip Morris International group of companies)

ICBBS Tokyo 2017 – May 2017

Smoking is one of the causes of serious diseases such as cardiovascular diseases, lung cancer and chronic obstructive pulmonary disease.

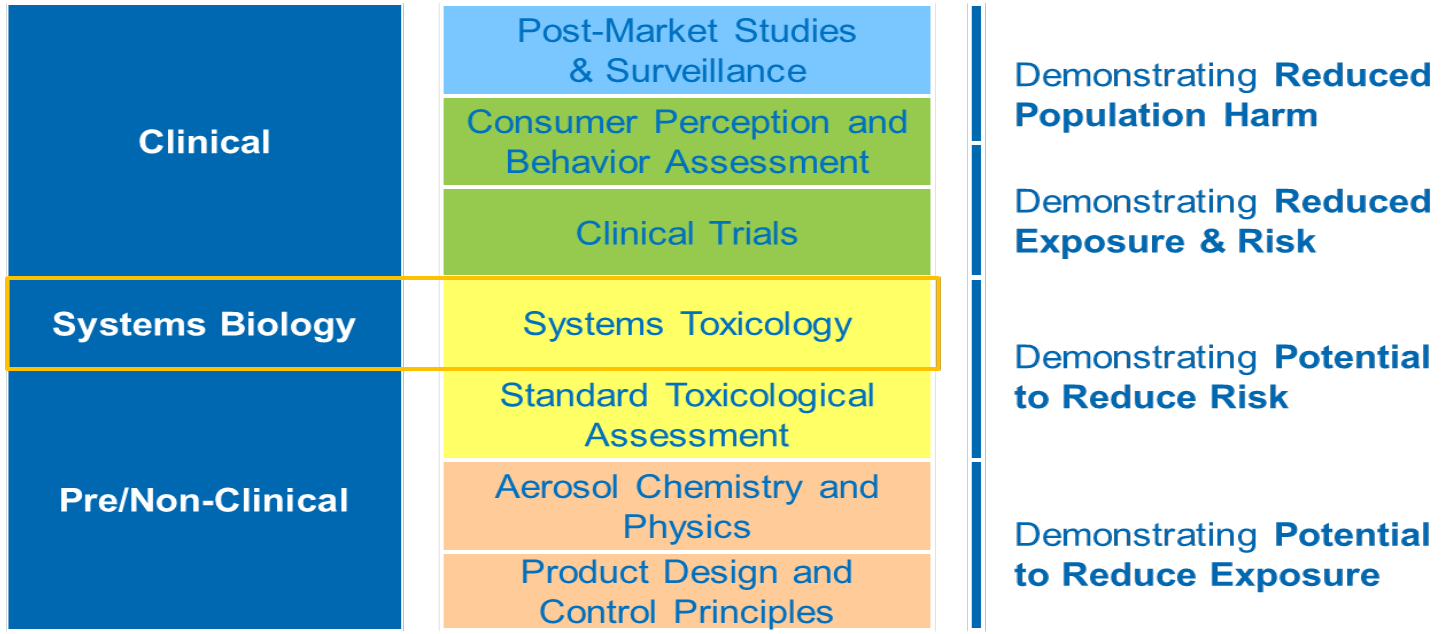
Philip Morris International is therefore developing novel products that may have the potential to reduce smoking-related disease risk compared to smoking cigarettes.

Scientific determination of the reduced risk potential of these products includes comparison of the biological impact with that of a reference cigarette (3R4F) on a mechanism-by-mechanism basis.

We want to share this data and encourage other stakeholders in inhalation toxicology to also share their data on the same platform.

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Scientific assessment strategy & Systems toxicology



Program: Systems Toxicology

- Demonstrate and quantify the Risk Reduction Potential of RRPs* in *vitro* and *in vivo*.
- Develop methods for the quantitative mechanism-based comparison of the biological impact of RRPs aerosol as compared to cigarette smoke.
- Further grow our mechanistic understanding of cigarette-smoke induced diseases.
- Independently verify our findings using community-based approaches.

** 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.*

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Systems toxicology assessment: Use disease mechanism understanding for product assessment

Exposure

Test items

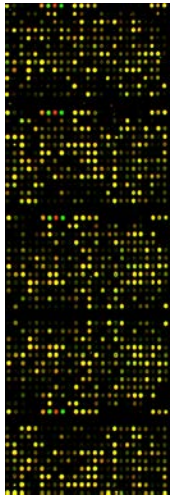
3R4F

Sham

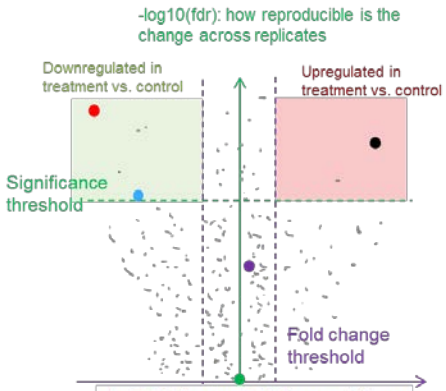
pRRP

Test system

Multi-Omics Data



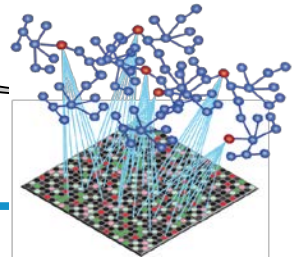
Systems Response Profile



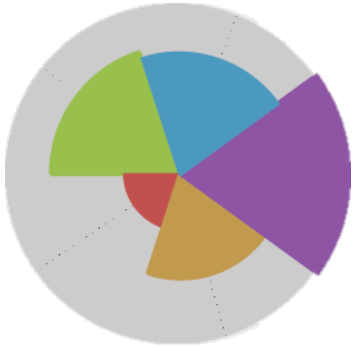
1 per condition vs. control

Biological Network models

- Inflammation (IPN)
- Cell Proliferation (CPR)
- Cell Stress (CST)
- Cell Fate (CFA)
- Tissue repair and angiogenesis (TRA)

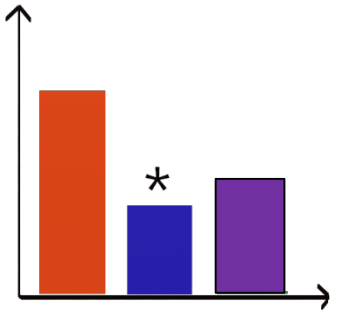


Network Perturbation Amplitudes



1 per condition vs. control

Biological impact factor (BIF)



comparing conditions

Σ

Hoeng J *et al*. A network-based approach to quantifying the impact of biologically active substances. **Drug Discovery Today,** 2012, 17:413-418 (PMID: 22155224)

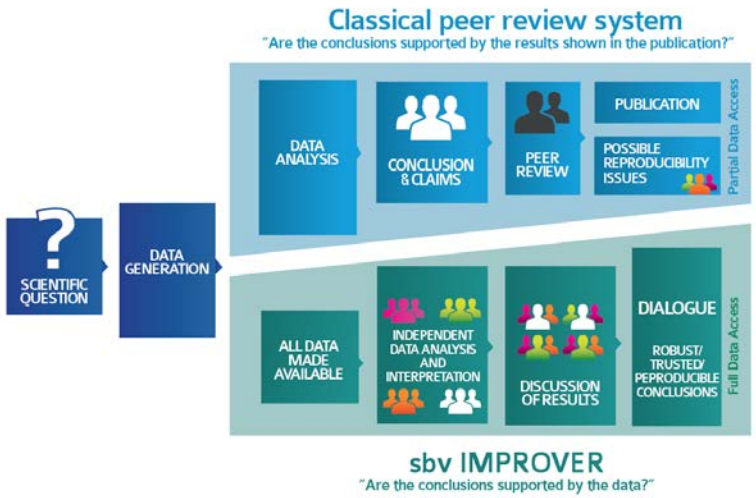
IMPROVER: Industrial Methodology for Process Verification in Research

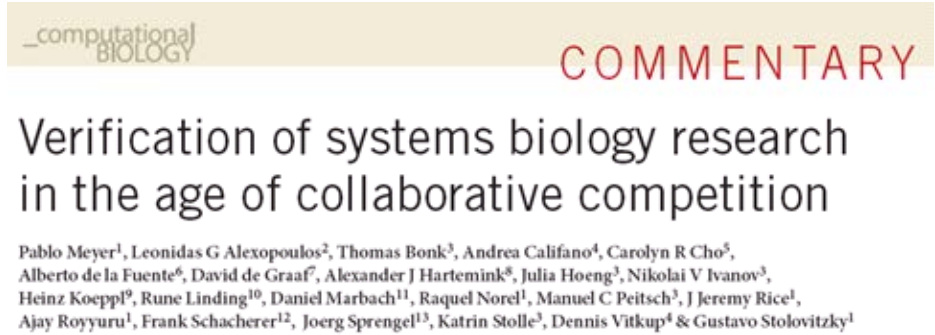
Project initiated 6 years ago and funded by Philip Morris International

Aims to provide a measure of quality control in R&D by identifying the building blocks that need verification in a complex industrial research pipeline

Aims to verify methods & data in systems biology / toxicology using double blind performance assessment

Complements the classical peer review system




_computational BIOLOGY

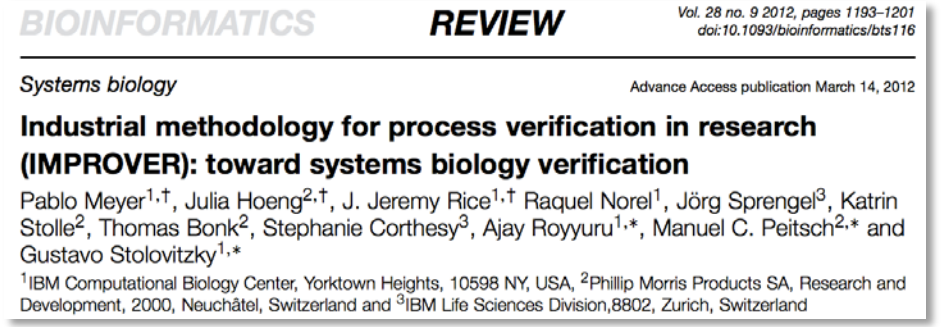
COMMENTARY

Verification of systems biology research in the age of collaborative competition

Pablo Meyer[1], Leonidas G Alexopoulos[2], Thomas Bonk[3], Andrea Califano[4], Carolyn R Cho[5], Alberto de la Fuente[6], David de Graaf[7], Alexander J Hartemink[8], Julia Hoeng[3], Nikolai V Ivanov[3], Heinz Koeppl[9], Rune Linding[10], Daniel Marbach[11], Raquel Norel[1], Manuel C Peitsch[3], J Jeremy Rice[1], Ajay Royyuru[1], Frank Schacherer[12], Joerg Sprengel[13], Katrin Stolle[3], Dennis Vitkup[4] & Gustavo Stolovitzky[1]

Collaborative competitions in which communities of researchers compete to solve challenges may facilitate more rigorous scrutiny of scientific results.

Nature Biotechnology 2011 Sep 8;29(9):811-5


BIOINFORMATICS REVIEW
Vol. 28 no. 9 2012, pages 1193–1201
doi:10.1093/bioinformatics/bts116
Systems biology
Advance Access publication March 14, 2012

Industrial methodology for process verification in research (IMPROVER): toward systems biology verification

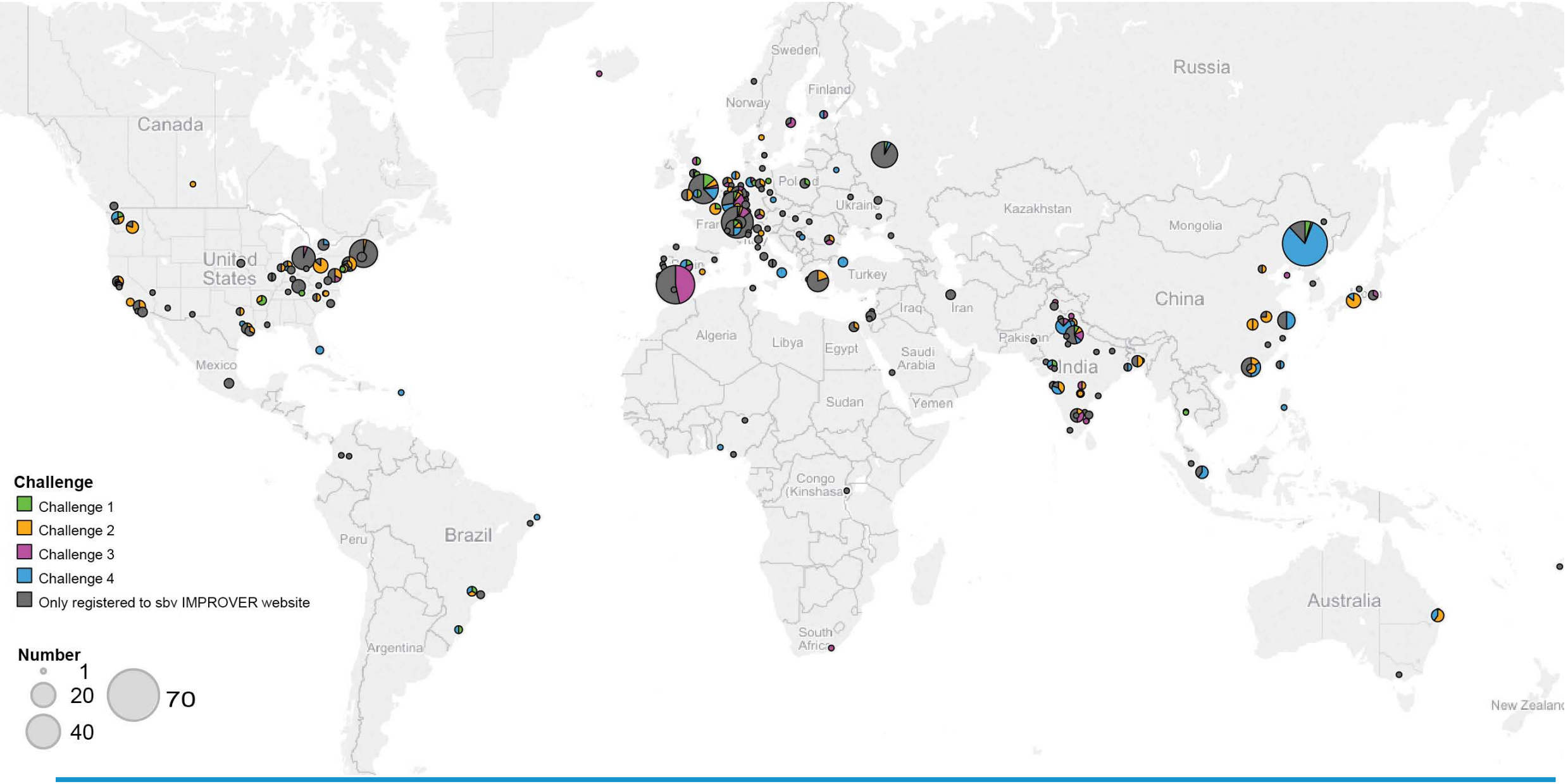
Pablo Meyer[1,†], Julia Hoeng[2,†], J. Jeremy Rice[1,†] Raquel Norel[1], Jörg Sprengel[3], Katrin Stolle[2], Thomas Bonk[2], Stephanie Corthesy[3], Ajay Royyuru[1,*], Manuel C. Peitsch[2,*] and Gustavo Stolovitzky[1,*]

[1]IBM Computational Biology Center, Yorktown Heights, 10598 NY, USA, [2]Phillip Morris Products SA, Research and Development, 2000, Neuchâtel, Switzerland and [3]IBM Life Sciences Division,8802, Zurich, Switzerland

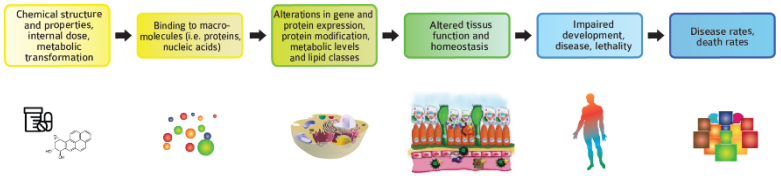
Bioinformatics 2012 28(9):1193-1201

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Worldwide participation in sbv IMPROVER (as of 2016)

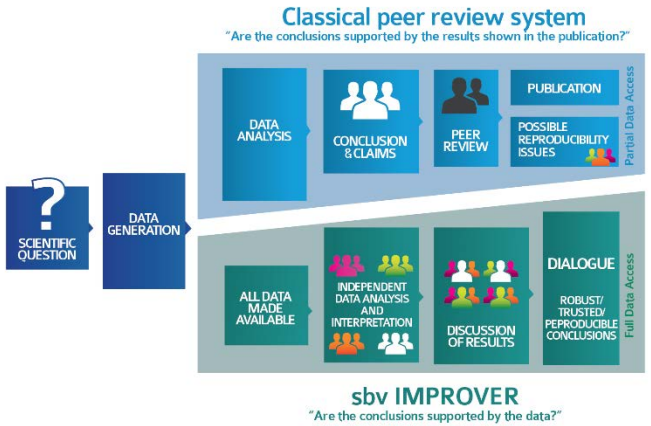


sbv IMPROVER leverages the crowd to complement classical peer review



Systems Toxicology data

Systems Toxicology methods



sbv IMPROVER
SYSTEMS BIOLOGY VERIFICATION

METHODS

DATA, RESULTS
CONCLUSIONS

COMPUTATIONAL CHALLENGES

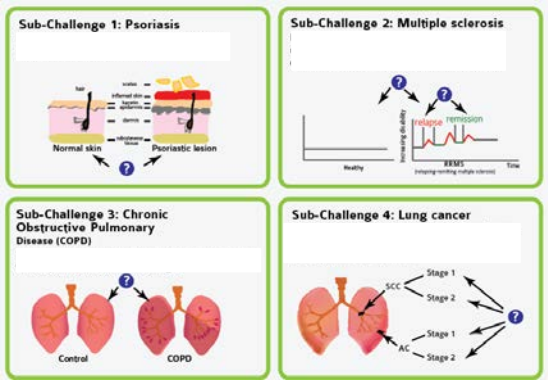
VERIFICATION PROJECT

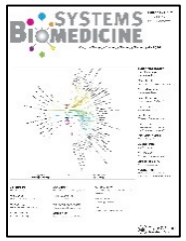
PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

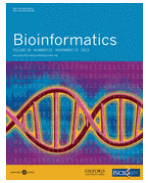
Past sbv IMPROVER computational challenges

Diagnostic signature challenge (2012):

- Verify computational approaches that classify clinical samples based on transcriptomics data in 4 disease areas

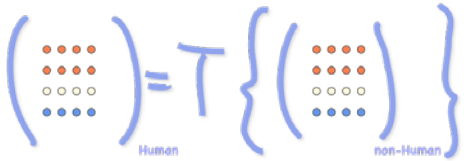


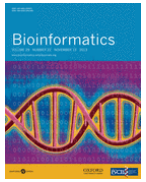




Species translation challenge (2013):

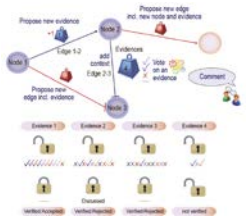
- Identify a function which maps measurements derived from systematic perturbations in one species to another
- Understand the system boundaries of the translatability concept
- Quantify the translatability between species





Network verification challenge (2014-2015)

- Engage the scientific community in the review of biological network models that are suitable for drug discovery, toxicological and mechanistic research in respiratory disease

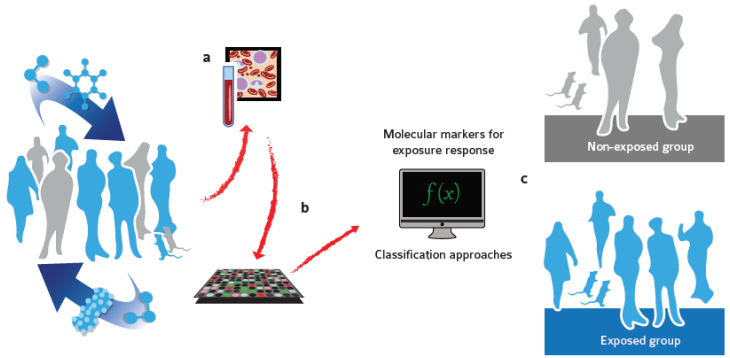


Pacific Symposium on Biocomputing 2015

F1000Research Open for Science

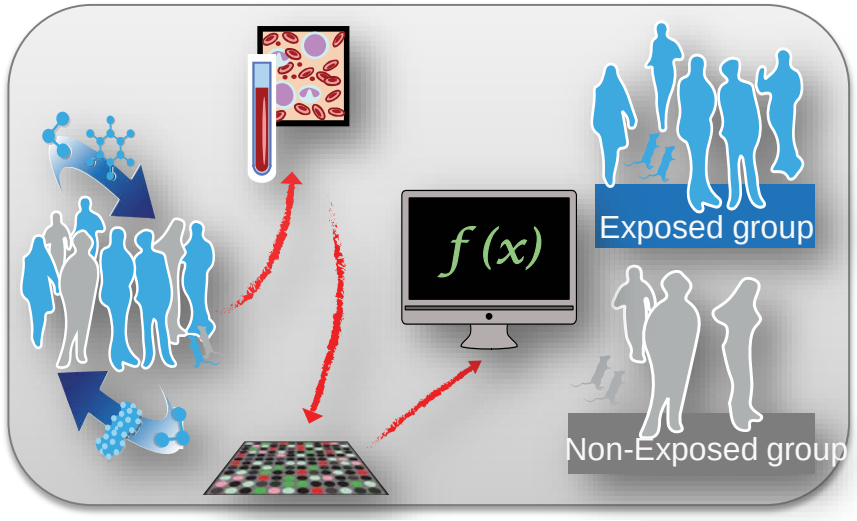
Systems Toxicology Computational challenge (2015-2016)

- Verify that a robust predictive signature can be extracted from gene expression data that differentiates smokers, former smokers, and never smoker subjects

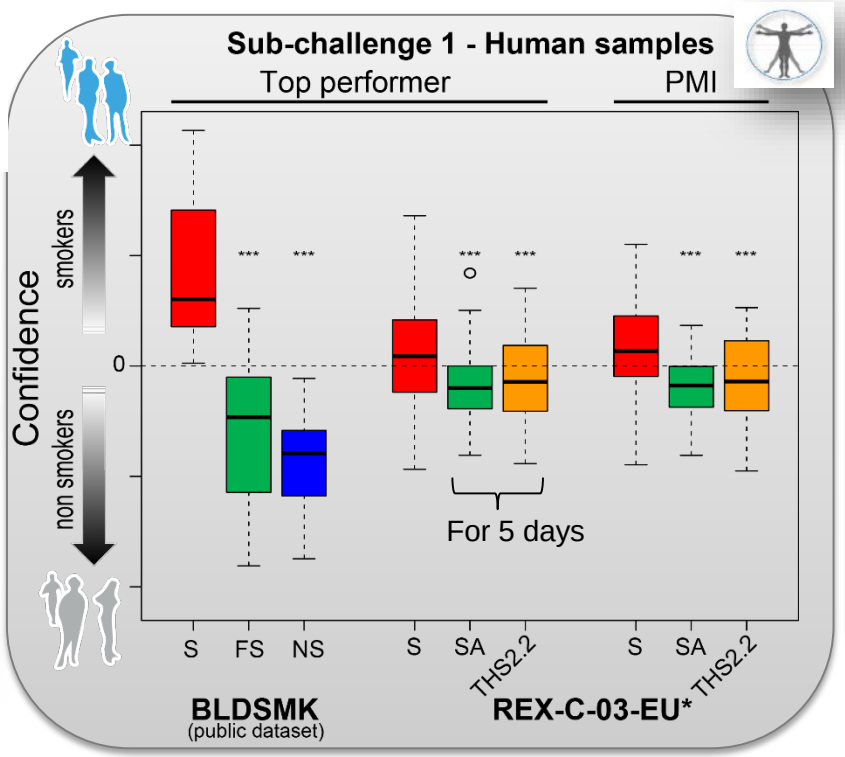


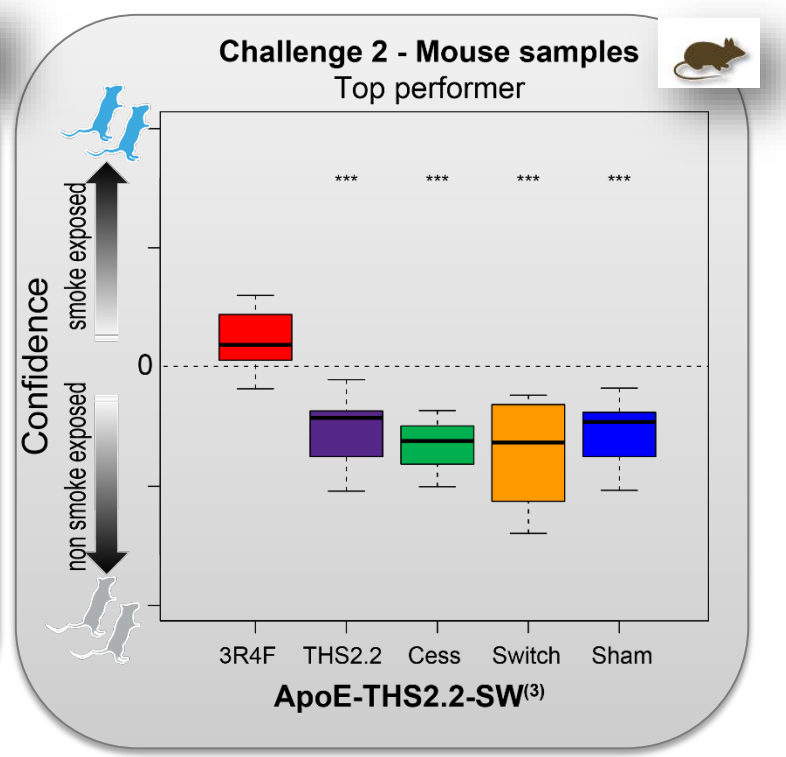
Whole blood exposure marker: Crowdsourcing validation of PMI's gene expression signature

sbv IMPROVER Systems Toxicology Computational Challenge[1]



- 135 registered participants
- 61 international teams
- 23 valid submissions





Gene Signature[2]

LRRN3, SASH1, PALLD, RGL1, TNFRSF17, CDKN1C, IGJ, RRM2, ID3, SERPING1, FUCA1

*In black genes common to the crowdsourcing signature***

S / 3R4F: Smoker / 3R4F exposed
FS / Cess: Former Smoker / Cessation
NS / Sham: Never Smoker / exposed to fresh air

SA: Smoking Abstinence
THS2.2: THS2.2

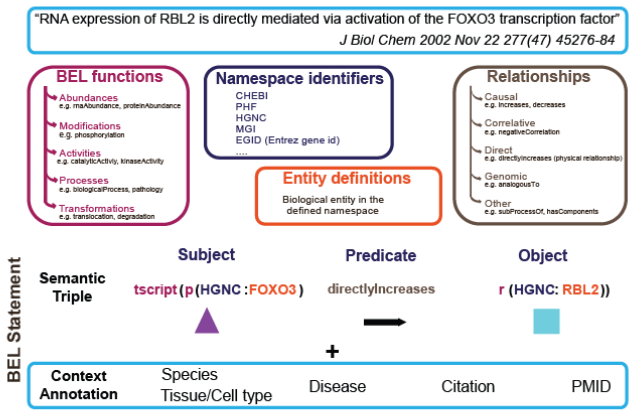
Switch: Switch to THS2.2

[1] *Poussin et al. Chemical research in toxicology. 2017*
[2] *Martin et al. Human & Experimental Toxicology. 2015*
[3] *Phillips et al. Toxicol Sci. 2016*

** similar results were obtained for REX-C-04-JP (not shown)*
*** selected by at least 2 teams*
**** significantly different from CC smoke exposed group*

Leveraging biological knowledge from scientists for network models refinement

A. The Biological Expression Language



B. The Bionet platform for crowd verification

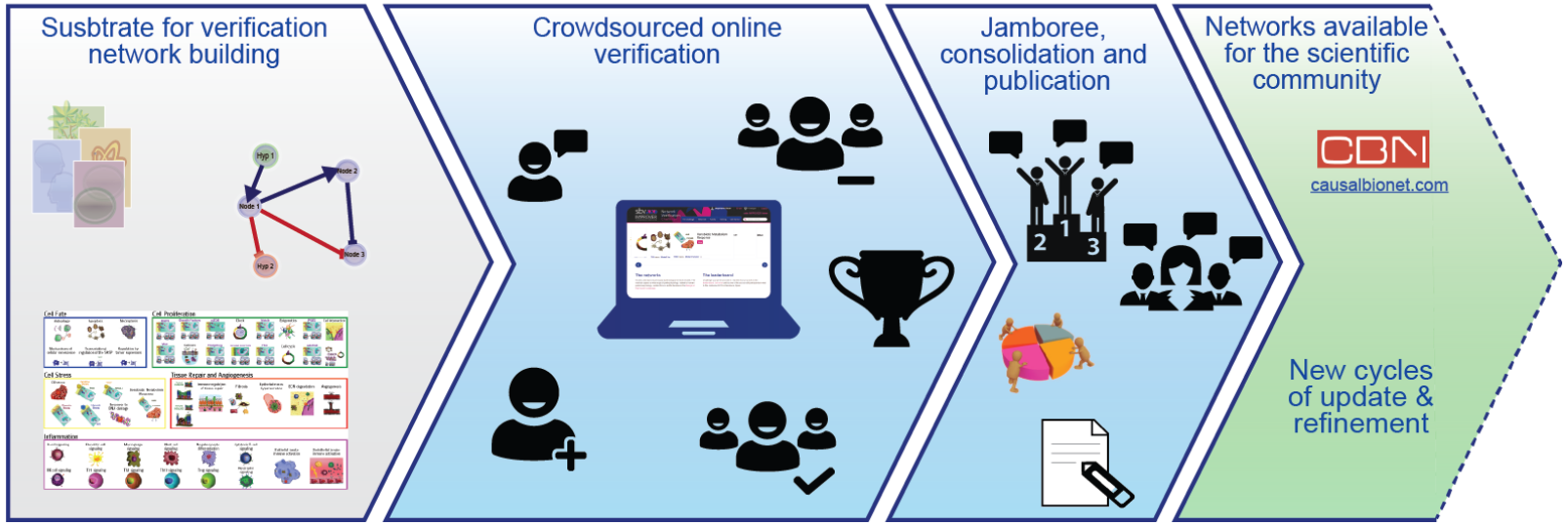
1 online platform

- ▶ Challenge explanation
- ▶ Network visualization
- ▶ Evidence visualization
- ▶ Comment and vote on evidence
- ▶ Create new edge / new supporting evidence
- ▶ Leaderboard / badges
- ▶ Activity feed

New networks, including xenobiotic metabolism response in liver, will be proposed for a new network verification challenge in the next months.

Participate at:
bionet.sbvimprover.com

C. The network verification challenge (NVC)

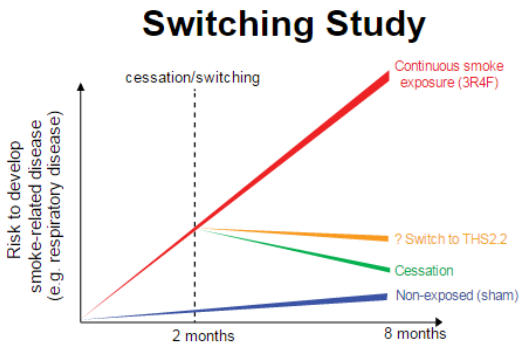


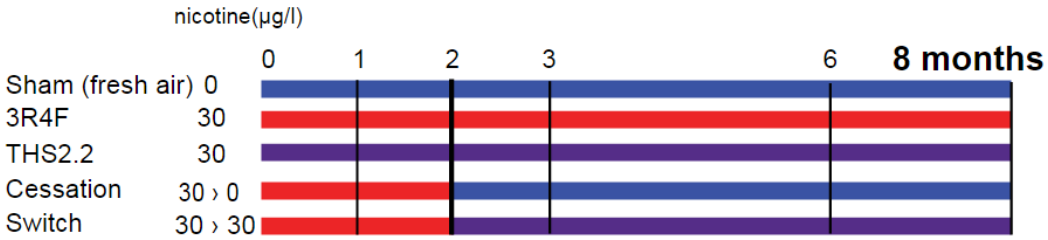
PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

From: Crowdsourcing and curation: perspectives from biology and natural language processing
Database (Oxford). 2016;2016. doi:10.1093/database/baw115

Mouse cardiovascular & respiratory model – 8 month inhalation study

Apoe$^{-/-}$





Cardiovascular, respiratory, and liver -related measurements covering apical and systems toxicology endpoints

Assessment of acute THS2.2 aerosol exposure in human nasal epithelial cultures

5 Repetitions - Parallel exposure

3R4F (0.25)
3R4F (0.15)
Air Control

THS2.2 (0.44)
THS2.2 (0.27)
THS2.2 (0.15)
Air Control

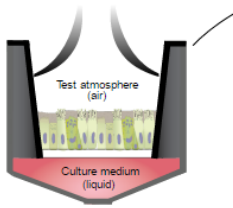
CYP1A1/1B1 activity
Secretion of mediators
Ciliary beating frequency
mRNA and miRNA profiles
AK-based cytotoxicity
Histology / Immunostaining

1 Repetition - THS2.2 Dose Range

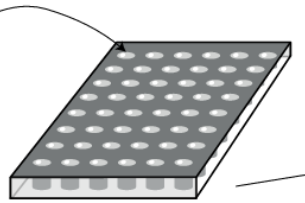
THS2.2 (1.79)
THS2.2 (1.02)
THS2.2 (0.77)
THS2.2 (0.55)
THS2.2 (0.37)
THS2.2 (0.22)
THS2.2 (0.14)
Air Control

AK-based cytotoxicity
Histology

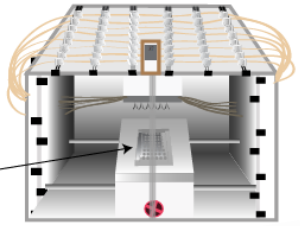
3D organotypic nasal tissue

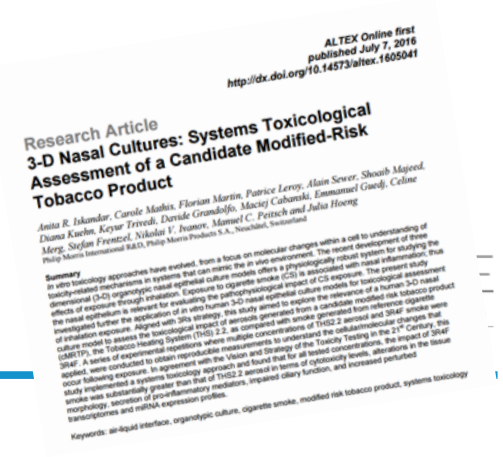


24-well Plate



Vitrocell® Exposure System

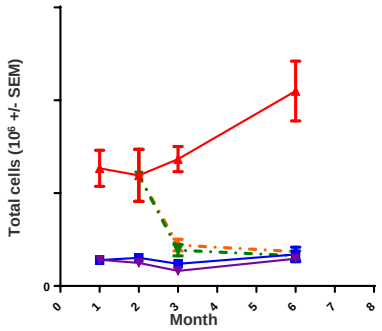




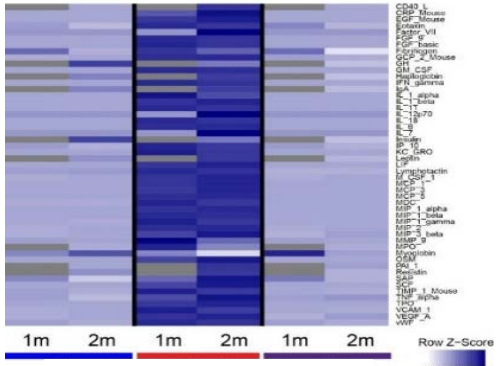
Use case - systems toxicology approach to investigate cardiovascular and pulmonary disease

Lung Inflammation

Total lung cells

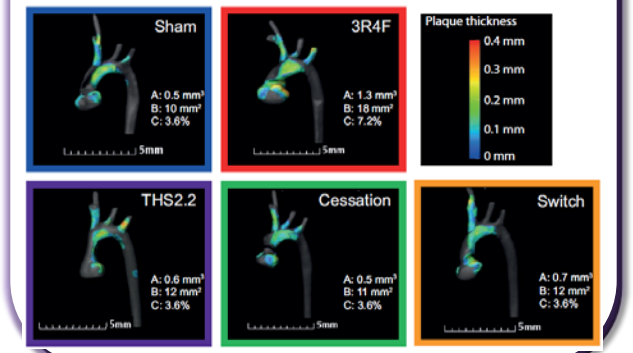


Mediators in bronchoalveolar lavage fluid

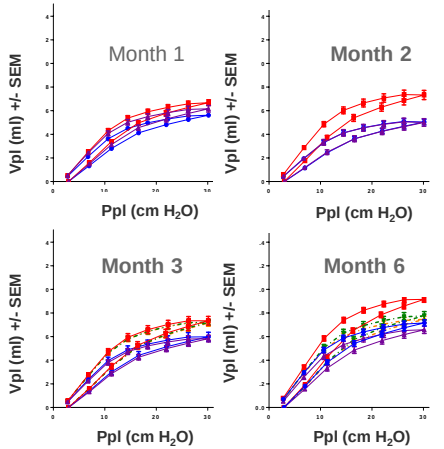


Cardiovascular

Micro CT



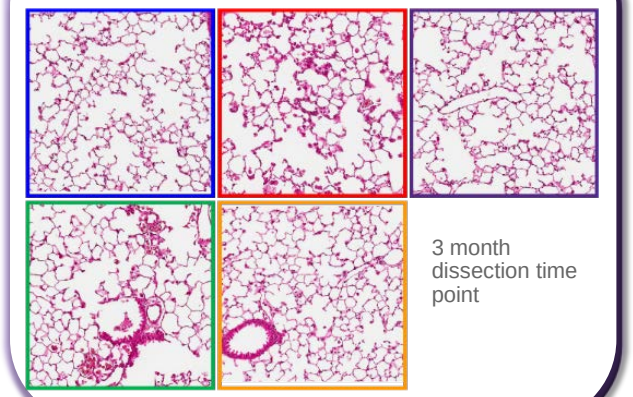
Lung function



Concomitant evaluation of CVD and COPD-related end points in Apoe$^{-/-}$ mice with platform 1 (THS2.2)

Sham 3R4F THS 2.2 Cessation Switch

Lung histopathology



3 month dissection time point

Phillips B, Veljkovic E, Boue S, Schlage WK, Vuillaume G, Martin F, et al. An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes. Toxicological sciences : an official journal of the Society of Toxicology. 2016 Feb;149(2):411-32.

"In conclusion, in this mouse model cessation or switching to THS2.2 retarded the progression of CS-induced atherosclerotic and emphysematous changes, while THS2.2 aerosol alone had minimal adverse effects"

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Datasets (accessed through the systox.sbvimprover.com platform):

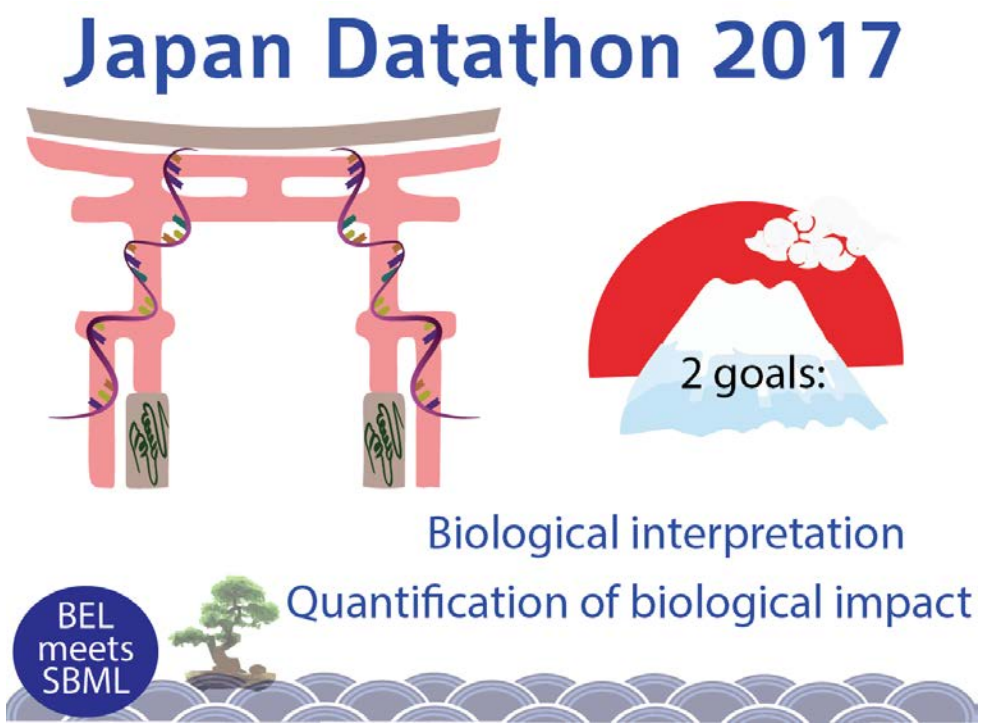
- Transcriptomics & proteomics datasets from the *in vivo* study (Apoe$^{-/-}$ 8 month inhalation)
- Transcriptomics dataset from the *in vitro* study (acute THS2.2 aerosol exposure of organotypic nasal epithelial cultures)

Questions:

- **What are the pathways/biological processes perturbed by exposure to cigarette smoke or to THS2.2 aerosol, a heat-not-burn product? After smoking cessation? After switching to THS2.2 aerosol?**

  ➔ Participants are expected to submit a write up with their biological interpretation
- **How would you quantify relative perturbations in the respective groups?**

  ➔ Innovative proposals will be conversed during the round table discussion
- Bonus track: Biological network models are at the center of systems biology. The Biological Expression Language (BEL) is a language for representing scientific findings in the life sciences in a computable form. SBML is a data format for encoding models of biological processes. What are the proposals/interfaces one might consider to convert between BEL statements and SBML models?



PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

sbv IMPROVER SYSTEMS BIOLOGY VERIFICATION POWERED BY GARUDA

Biological interpretation of omics data & Quantification of biological impact

June-August — September

Register and get access to data

Webinar

Team up (if you wish) & analyze/interpret the data

Upload your summary results

Confirm your attendance

October: Symposium — Later on

Teams share their results

Keynote presentations

Publish conclusions

Why participate?

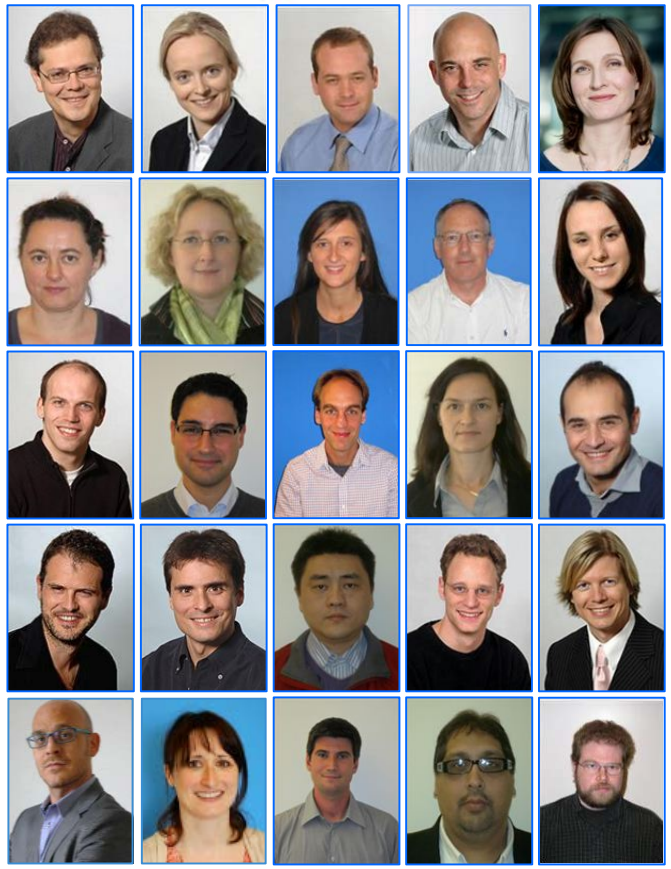
- Build the interface between communities
- Enhance your visibility and gain recognition
- Learn how to best make sense of big data
- Network and engage with peers to advance the field
- Present your work at the symposium

Stay tuned, Register, and Participate

We are looking forward to learning from each other!

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL



Thank you!

SBX

SciPinion

orangebus.

Douglas Connect
Working communities

ADVANTAGE
Integral

ADS

The sbv IMPROVER project, the websites and the Symposia are part of a collaborative project designed to enable scientists to learn about and contribute to the development of a new crowd sourcing method for verification of scientific data and results. The project is led and funded by Philip Morris International.

For more information on the focus of Philip Morris International's research, please visit www.pmiscience.com.

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL