DOI: 10.1111/cea.13211

EDITORIAL

WILEY

AsthmaMap: An expert-driven computational representation of disease mechanisms

Data interpretation is currently a bottleneck in disease-related research. The plethora of data being produced can overwhelm our current ability to interpret and utilize them in a manner that will have a clinical impact. Advances in the detailed representation of disease mechanisms provide new solutions for bringing together prior knowledge and newly generated 'omics data for applications in personalized medicine. Computational resources for cancer, Parkinson's disease, Alzheimer's disease and influenza[1-4] have been built and are defined as disease maps. These are conceptual models of disease mechanisms that include relevant signalling, metabolic and gene regulatory processes with evidence of their relationships to pathophysiological causes and outcomes.[5] These maps are designed to be used as tools for new discoveries and for building an interface between experimental laboratory research and medicine. It is important to point out that the disease map approach is not offered as a replacement of the existing generic pathway-based solutions for functional analysis. In fact, at the stage of 'omics data interpretation, generic functional analysis naturally complements disease maps and enables exploration of unknown mechanisms. What makes the disease maps approach innovative is that a disease map is a single interconnected system of modules, and an effort is made to create missing pieces to systematically describe disease hallmarks.

The AsthmaMap (http://asthma-map.org) is a project focused on developing a pathway-based representation of asthma mechanisms using literature search, accessible databases, input from experts in the respiratory field and a collection of tools for creating and managing the content. One of the main achievements of this project has been the active collaboration between domain experts, clinicians and biologists who have actively contributed to defining the way the resource has been developed. This level of engagement is essential for making it a trusted source of information for researchers in the field of asthma.

The AsthmaMap consists of three interconnected layers of granularity: Cellular Interactions, Activity Flow and Process Description (Figure 1). The multiscale architecture allows managing the complexity using a modular approach and hierarchically organized content, and also enables integrating heterogeneous information from other resources even if they use different standards for storing information. *The Cellular Interaction layer* (http://asthma-map.org/ci/) is designed by computational biology and asthma domain experts and used to determine the content of the detailed layers. This is the environment for communication between asthma experts and computational biologists, for defining the asthma hallmarks and determining which modules need to be included in the representation of asthma mechanisms. *The Activity Flow layer* (http://asthma-map.org/af) currently consists of cell-specific maps with 2650 nodes and 4716 edges in total and includes 831 unique entities. It is semi-automatically assembled based on *the Cellular Interaction layer*. In this way, the resource becomes highly flexible, less dependent on manual work, and it can be easily updated when new information becomes available. *The Process Description layer* includes a collection of modules that correspond to *the Activity Flow layer* and are made available for browsing via Google Map API in the MINERVA platform (http://asthma-map.org/pd/).

In order to properly describe a disease, it is important to include the dynamic nature of the disease, which requires the development of dynamic computational models. This approach is challenging; however, as by constructing a model and introducing assumptions, it is much harder to update the model and keep it evolving. In the AsthmaMap, we have adopted a strategy to overcome this: (a) we keep the static core map based on published research and therefore traceable and updatable; (b) as the map is stored in the standard SBGN format compatible with SBML, it is possible to convert it into a computational model and different types of models can be developed from the static conceptual model including logical, mechanistic and multiscale models.[5,6]

The reconstruction of disease mechanisms still depends significantly on a particular skill set and experience of the contributors. There is a need for protocols and guidelines regarding controllable step-by-step progress and available options depending on the project objectives. Identified difficulties of assembling a disease map for asthma include complexity management, automatic layout algorithms to reduce manual work, interfaces for communication with clinicians and biologists, defining reusable modules and consistency in the quality of the curation. To address this, advances in approaches are continuously being made within the Disease Maps Project and other friendly collaborating efforts (http://disease-maps.org/relatedefforts).

Future developments of the AsthmaMap will include the following aspects.

- *Potential recovery mechanisms*. The current state of the art in disease maps is looking mainly into the pathways directly affected by a disease, "broken" mechanisms or mechanisms that are triggered by a disease. Within the AsthmaMap project, we also aim to introduce mechanisms that could lead to re-establishing the nonasthmatic healthy state and the effects of drug interventions.
- *Progressing in alliance with other projects*. Within the Disease Maps Project, we plan to initiate disease maps for allergic rhinitis,

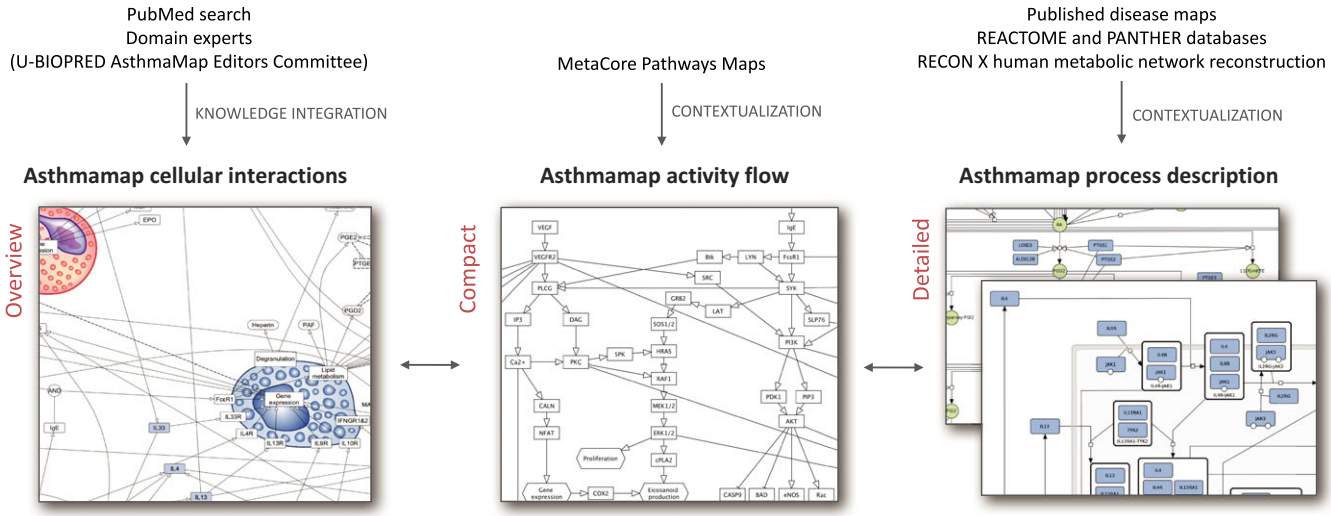

FIGURE 1 Interconnected Layers of Granularity in the Description of Asthma Mechanisms

atopic dermatitis and chronic obstructive pulmonary disease. Creating overlapping clusters of disease maps in allergies, autoimmune diseases and lung diseases will enable faster progression, identify shared mechanisms and study comorbidities while avoiding duplicated efforts.

- *Building use cases*. Carefully collecting and building new pipelines for practical use of disease maps: predictive computational models, examples of hypotheses produced and followed by validation experiments, making new discoveries part of clinical decision support systems. For example, for better targeting and repurposing of existing drugs and finding new leads for drug development.

Disease maps are used for modelling, advanced hypothesis generation and their subsequent validation in relevant clinical contexts in cancer.[7-9] Despite these successful examples, this area is still largely underexplored. Bringing basic research to patients presents significant challenges that have not yet been fully assessed and requires a contribution of experts at all steps including professionals in clinical decision support systems (CDSS), patient decision support systems (PDSS) and the corresponding regulations.

We are currently at the stage of data analysis and interpretation with the AsthmaMap in which the aim was to identify molecular signatures and the pathway profiles that describe different phenotypes of asthma. We invite collaboration on a larger scale to bring our understanding of the mechanistic details closer to CDSS and PDSS. This anticipates a framework that will involve (a) statisticians for data analysis; (b) clinicians and biologists to make sense of data in the context of the AsthmaMap and complementary approaches such as generic pathway analysis solutions; (c) mathematical modellers for refining hypotheses in silico; (d) respiratory researchers for hypothesis validation; and (e) experts in CDSS and PDSS to make the final link. In particular, we would like to engage more centres to generate and then validate hypotheses that are being produced in this effort. A feasibility study is needed for the final step of employing disease maps towards advancing CDSS and PDSSs in allergies.

The development of new technological solutions opens up promising possibilities for an efficient construction of disease maps and their applications. The AsthmaMap enables 'omics data visualization and interpretation in the asthma-specific context. With the resulting improved understanding of this complex disease, this approach in the long term is expected to lead to its redefinition based on underlying mechanisms (definition of endotypes of asthma) and to targeted therapeutics of treatable mechanisms, which are necessary for the delivery of personalized or precision medicine of asthma.

ACKNOWLEDGEMENTS

Funded in part by the Innovative Medicines Initiative (U-BIOPRED no115010, eTRIKS no 115446). We are grateful to all the contributors listed at http://asthma-map.org/team/. The AsthmaMap effort is part of the Disease Maps Project (http://disease-maps.org/).

ORCID

Alexander Mazein http://orcid.org/0000-0001-7137-4171

Alexander Mazein[1]
Richard G Knowles[2]
Ian Adcock[3]
Kian Fan Chung[3]
Craig E Wheelock[4]
Anke H Maitland-van der Zee[5]
Peter J Sterk[5]
Charles Auffray[1]
AsthmaMap Project Team

[1]*European Institute for Systems Biology and Medicine, CIRI UMR5308, CNRS-ENS-UCBL-INSERM, Université de Lyon, Lyon, France*
[2]*Knowles Consulting, Stevenage Bioscience Catalyst, Stevenage, UK*
[3]*Airway Disease, National Heart & Lung Institute, Imperial College London, London, UK*
[4]*Division of Physiological Chemistry 2, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden*
[5]*Respiratory Medicine, Academic Medical Center, Amsterdam, The Netherlands*

Correspondence:
Alexander Mazein, European Institute for Systems Biology and Medicine, CIRI UMR5308, CNRS-ENS-UCBL-INSERM, Université de Lyon, Lyon, France (amazein@eisbm.org)

REFERENCES

1. Kuperstein I, Bonnet E, Nguyen HA, et al. Atlas of cancer signalling network: a systems biology resource for integrative analysis of cancer data with Google Maps. *Oncogenesis*. 2015;4:e160.
2. Fujita KA, Ostaszewski M, Matsuoka Y, et al. Integrating pathways of Parkinson's disease in a molecular interaction map. *Mol Neurobiol*. 2014;49:88-102.
3. Mizuno S, Iijima R, Ogishima S, et al. AlzPathway: a comprehensive map of signaling pathways of Alzheimer's disease. *BMC Syst Biol*. 2012;6:52.
4. Matsuoka Y, Matsumae H, Katoh M, et al. A comprehensive map of the influenza A virus replication cycle. *BMC Syst Biol*. 2013;7:97.
5. Mazein A, Ostaszewski M, Kuperstein I, et al. Systems medicine disease maps: community-driven comprehensive representation of disease mechanisms. *NPJ Syst Biol Appl*. 2018;4(1):21.
6. Ostaszewski M, Gebel S, Kuperstein I, et al. Community-driven roadmap for integrated disease maps. *Brief Bioinform*. 2018;4:1-12.
7. Chanrion M, Kuperstein I, Barrière C, et al. Concomitant Notch activation and p53 deletion trigger epithelial-to-mesenchymal transition and metastasis in mouse gut. *Nat Commun*. 2014;5:5005.
8. Jdey W, Thierry S, Russo C, et al. Drug-driven synthetic lethality: bypassing tumor cell genetics with a combination of AsiDNA and PARP inhibitors. *Clin Cancer Res*. 2016;23:1001-1011.
9. Kuperstein I, Grieco L, Cohen DPA, Thieffry D, Zinovyev A, Barillot E. The shortest path is not the one you know: application of biological network resources in precision oncology research. *Mutagenesis*. 2015;30:191-204.