AsthmaMap: An interactive knowledge repository for mechanisms of asthma

Alexander Mazein, PhD,[a,b,c] Olga Ivanova, MSc,[a,d,e] Irina Balaur, PhD,[a] Marek Ostaszewski, PhD,[c] Valeriya Berzhitskaya, PhD,[f] Tatiana Serebriyskaya, PhD,[f] Thomas Ligon, PhD,[g] Jan Hasenauer, PhD,[h,i] Bertrand De Meulder, PhD,[a] Rupert W. Overall, PhD,[j,k] Ludovic Roy, MSc,[a] Richard G. Knowles, PhD,[l] Craig E. Wheelock, PhD,[m] Sven-Erik Dahlen, MD, PhD,[n] Kian Fan Chung, MD,[o] Ian M. Adcock, PhD,[o] Graham Roberts, DM,[p,q] Ratko Djukanovic, MD,[r,s] Johann Pellet, MSc,[a] Piotr Gawron, PhD,[c] Rudi Balling, PhD,[c] Anke H. Maitland-van der Zee, PharmD, PhD,[e] Reinhard Schneider, PhD,[c] Peter J. Sterk, MD,[e] and Charles Auffray, PhD,[a] the U-BIOPRED Study Group, the eTRIKS Consortium *Lyon, France; Moscow, Russia; Belvaux, Luxembourg; Amsterdam, The Netherlands; Munich, Germany; Stevenage, London, and Southampton, United Kingdom; and Stockholm and Solna, Sweden*

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We present the AsthmaMap, a machine- and human-readable representation of mechanisms underlying asthma. This is an open project driven by a community of experts in systems biomedicine, including lung diseases and computational systems biology specialists. The goal of this work is the integration of the existing knowledge from molecular biology, cell biology, and medicine on asthma into a molecular and cellular interaction map of the disease to make possible advanced data interpretation, hypothesis generation, and validation for many related projects. This map offers an updatable conceptual model of disease mechanisms that can be transformed into executable dynamic models for computational hypothesis testing and predictions.

Since the AsthmaMap project was first announced in a brief editorial,[1] it has evolved into a browsable online resource accessible via https://asthma-map.org in which map modules are composed into a single hierarchically organized system. The map is thus immediately accessible to researchers for data visualization and hypothesis generation. We describe the structure of the resource and offer video tutorials on the exploration of the underlying network and its application to data mapping.

THE RATIONALE OF THE PROJECT

To design prevention and treatment strategies for complex diseases such as asthma, it is necessary to understand its mechanisms and causes. Results from in-depth studies of asthma-related research are scattered across thousands of publications and new findings are constantly reported. To promote effective research, a dedicated resource is required where asthma mechanisms are assembled into a single repository, accessible in both human- and machine-readable formats, verified by domain experts, and used for advanced data interpretation and hypothesis generation beyond the current functional analysis approaches.

Recent advances in systems biology have enabled the creation of representations of mechanisms for multiple diseases[2] including recently published examples for rheumatoid arthritis,[3] atherosclerosis,[4] and regulated cell death in cancer.[5] These maps are used

From [a]the European Institute for Systems Biology and Medicine, Université de Lyon, Lyon; [b]the Institute of Cell Biophysics, Russian Academy of Sciences, Pushchino, Moscow; [c]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belvaux, Luxembourg; [d]Vrije Universiteit Amsterdam, Amsterdam; [e]Respiratory Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam; [f]Moscow Institute of Physics and Technology, Dolgoprudny, Moscow; [g]the Faculty of Physics and Center for NanoScience (CeNS), Ludwig-Maximilians-Universität, Munich; [h]the Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg; [i]the Faculty of Mathematics and Natural Sciences, University of Bonn, Endenicher, Bonn; [j]the Center for Regenerative Therapies Dresden (CRTD), Technische Universität Dresden, Dresden; [k]the German Center for Neurodegenerative Diseases (DZNE) Dresden, Dresden; [l]Knowles Consulting, Stevenage Bioscience Catalyst, Stevenage; [m]the Division of Physiological Chemistry 2, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm; [n]the Unit for Experimental Asthma and Allergy Research, Institute of Environmental Medicine (IMM), Karolinska Institutet, Solna; [o]the National Heart & Lung Institute, Imperial College London, London; [p]Clinical and Experimental Sciences and Human Development and Health, Faculty of Medicine, University of Southampton, Southampton; [q]the NIHR Southampton Biomedical Research Centre, [r]the Clinical and Experimental Sciences, University of Southampton Faculty of Medicine, University of Southampton, Southampton; and [s]the NIHR Southampton Respiratory Biomedical Research Unit, Southampton University Hospital, Southampton.

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Corresponding author: Alexander Mazein, PhD, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, 6 Avenue du Swing, L-4367 Belvaux, Luxembourg. E-mail: alexander.mazein@uni.lu.

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for modeling, hypothesis generation, and validation in a relevant clinical context as reviewed in the Disease Maps community article[2] and described in a recent publication about the Atlas of Cancer Signalling Network applied in preclinical studies.[6] Such resources are referred to as "disease maps" and are defined as conceptual models of the corresponding diseases, collections of interconnected signaling, and metabolic and gene regulatory processes[2,7] (https://disease-maps.org). The disease maps are literature-based resources, with their backbone established over well-defined hallmarks of a given disease.

A collective effort, initiated within the European Union–funded U-BIOPRED project (https://www.europeanlung.org/en/projects-and-research/projects/u-biopred) and further developed within the eTRIKS project (https://www.etriks.org), has led to the creation of the AsthmaMap resource, a map for a computational description of the mechanisms relevant to asthma development, progression, and treatment. The data for the map construction come from the published biomedical literature and from high-quality pathway databases. The search was focused on mechanisms that exist in the cell types included and have been shown to be part of asthma pathogenesis. The building of the resource is supported by experts in the field of asthma from the Amsterdam University Medical Centers, the University of Amsterdam, the National Heart & Lung Institute of Imperial College London, the Karolinska Institute Stockholm, and the University of Southampton (http://asthma-map.org/team).

RESOURCE ARCHITECTURE

The AsthmaMap consists of 3 interconnected layers of granularity: *Cellular Interactions*—an overview diagram of the involved cell types and corresponding pathways represented by cytokines and receptors; *Molecular Relations*—a collection of diagrams split according to cell types that can be seen as a single virtual map with an intermediate level of detail; and *Biochemical Mechanisms*—the most detailed layer where information is shown at the level of molecular processes. Each interaction at a lower level is reflected at a higher level. This enables semantic zooming; that is, the layers of the AsthmaMap represent the same systems, but with more or fewer details shown, depending on the zoom level.

The Cellular Interactions layer (https://asthma-map.org/ci) is a summary of the complexity of underlying mechanisms in connection to the cell types and tissues involved. It facilitates discussions with domain experts, and the creation and curation of the AsthmaMap conceptual shape: modules, cell types, receptors, cytokines and other mediators, and connected causes and effects.

The Molecular Relations layer (https://asthma-map.org/mr) is represented by diagrams for 16 cell types, including the following: dendritic, airway epithelial, macrophage, neutrophil, eosinophil, eosinophil precursor, mast cells, airway smooth muscle, fibroblast, B cells, T_H0, T_H2, ILC precursor, ILC2, goblet cells, and regulatory T cells. The planned development includes adding T_H1, T_H17, and ILC3 cell types. This layer was assembled using information from the AsthmaMap Cellular Interactions layer and the MetaCore pathway database (https://portal.genego.com). Information on selected relevant interactions was reduced and converted to the standard Activity Flow format,[1] and compatibility of the resulting modules was ensured for further processing and merging. The representation of the Molecular Relations layer is well suited for building qualitative Boolean models.

The Biochemical Mechanisms layer (https://asthma-map.org/bm) provides detailed definitions for biochemical reactions, essentially encoding the stoichiometric matrix of the network. This is the most detailed and most challenging layer of the AsthmaMap architecture: it requires manual curation and integration of the available information. The Biochemical Mechanisms layer is currently represented by 3 diagrams: mast cell, eosinophil, and eicosanoid modules. It is available in the Process Description format,[1] and the focus is on the molecular processes that describe the involved reactants, products, and modifiers, such as enzymes or inhibitors. This layer is suited for quantitative mechanistic models, and a mechanistic model of the mast cell in asthma is under development (https://asthma-map.org/model).

ONLINE EXPLORATION AND DATA VISUALIZATION

The MINERVA platform[8,9] is a tool for web-based visualization and exploration of maps and allows quick and easy access to the AsthmaMap content (Fig 1). Zooming and navigation are similar to the navigation of Google Maps thanks to the Google Maps API used by the MINERVA platform.[8] Annotation of the elements is visible in the left panel both for entities (identifiers for metabolites, proteins, genes, phenotypes) and for interactions (references to evidence sources). The content of the maps in MINERVA is searchable, and elements found are highlighted by markers of different colors.

To make this resource friendlier for clinical researchers, biologists, and data analysts, we offer the following brief video tutorials (https://asthma-map.org/tutorials):

1. A demonstration of browsing starting from the Cellular Interactions layer as a top-level view and an entry point to the AsthmaMap.
2. An explanation of how community curation is possible by adding comments directly to the map and thus providing feedback to the map developers.
3. Searching for drug targets in the AsthmaMap via built-in querying of DrugBank (https://www.drugbank.ca) and CHEMBL (https://www.ebi.ac.uk/chembl).
4. Brief instructions on the upload for visualization and exploration of custom experimental data. The eicosanoid map and a multiomics data set were used for this tutorial.[9]

OUTLOOK

The effort is designed as an open project. The commenting functionality in MINERVA (https://asthma-map.org/tutorials) can be used as an entry point for domain experts. Systems biologists and curators are invited to contribute and advance this collection into a reference resource in the area of asthma research.

We consider the map to be a "work in progress" and see it as an evolving resource. The overall framework is designed in a scalable manner to make it easy to maintain and expand the map. For example, cell types such as T_H1, T_H9, T_H17, natural killer T, ILC17, ILC22, and LTi shown in the Cellular Interactions layer need to be reflected in the Molecular Relations layer, and the corresponding mechanisms need to be added to the Biochemical Mechanisms layer.

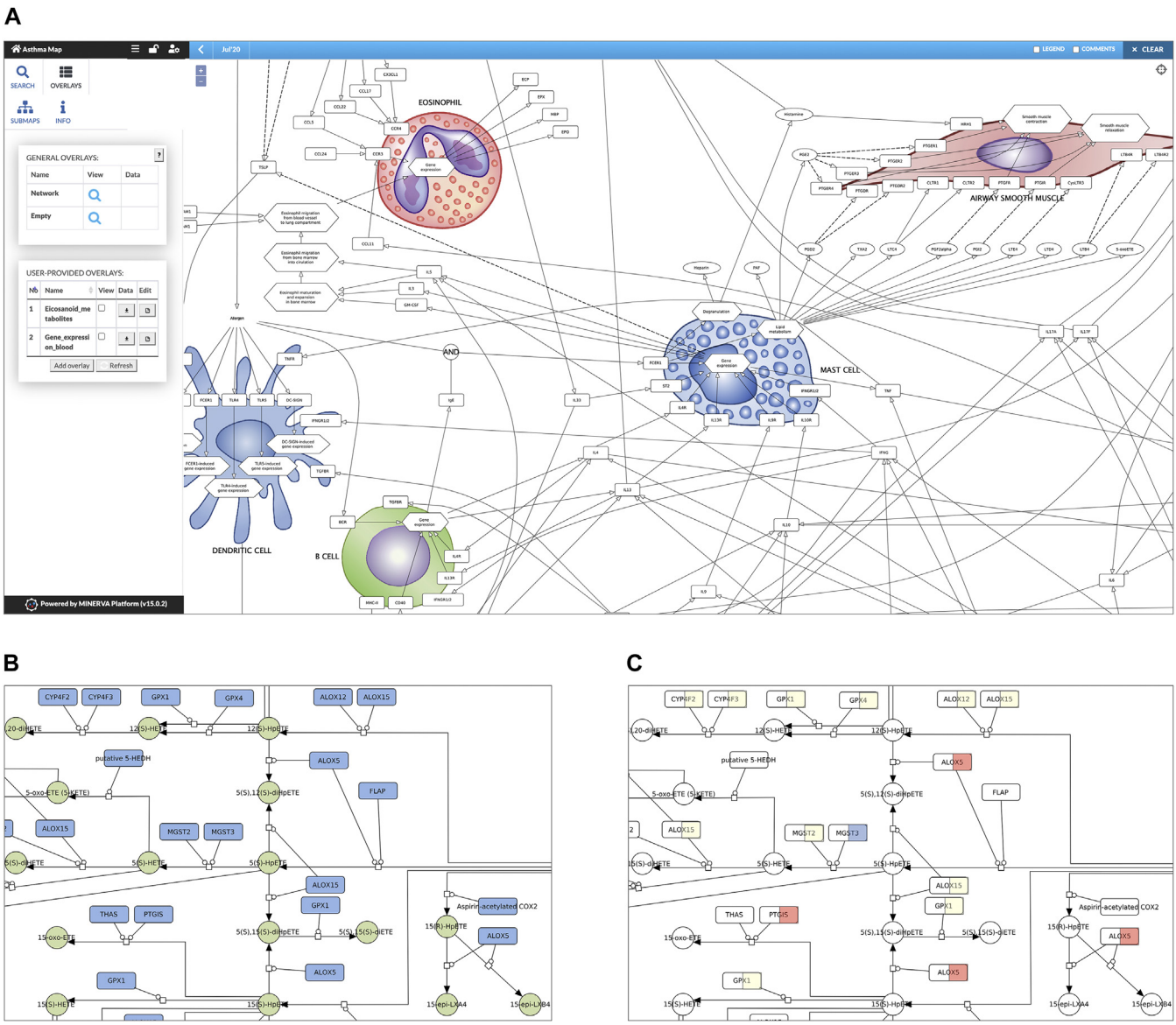

FIG 1. The AsthmaMap resource in MINERVA. **A,** The entry view of the AsthmaMap available for exploration in the MINERVA platform at https://asthma.uni.lu. **B,** The default view of a fragment of the eicosanoid production pathway. **C,** The same fragment of the eicosanoid production pathway with multiomics data mapped. More details and information on the data sets are provided at https://asthma-map.org/tutorials.

The development of the AsthmaMap in the future will be coordinated with similar projects in the field of allergic diseases, other respiratory diseases, and immune-system–related diseases,[2] including the coronavirus disease 2019 infection for which a large-scale community is fast-tracking the development of a dedicated disease map.[10] This collaboration will lead to the distribution of shared tasks and optimization of the work for all participants. It is also important for research focused on comorbidities and identification of mechanisms common to several diseases. Ultimately, it is possible that there will be collaborations on topics that at first sight might seem to be less likely related to asthma, for example, diseases that might share inflammatory profiles with asthma such as rheumatoid arthritis or inflammatory bowel disease. Furthermore, in systems medicine, there is a tendency of moving away from organ-specific diseases toward thinking about the whole-organism level and new disease ontologies.

The AsthmaMap is designed to be useful for biomedical scientists working in asthma as well as clinical scientists working on defining endotypes of asthma toward personalized medicine. It is intended as a reference resource for making sense of otherwise complex omics data sets by integrating and analyzing the previous knowledge and newly generated data. We believe this approach will become of clinical value by contributing to the design of clinical decision support systems and its use for allergy- and inflammation-related research in systems medicine and systems pharmacology. It is expected that on the basis of a detailed description of relevant molecular and physiological processes it

will be possible to move from ambiguous and imprecise descriptions of asthma phenotypes to evidence-supported descriptions of asthma endotypes via identification and validation of underlying mechanisms specific to various asthma subtypes. Eventually, the AsthmaMap aims to meet the demand for comprehensive phenotyping of single patients by capturing the biological networks that are operational at the individual level. This will serve to deliver more precise and personalized treatments for this prevalent class of chronic diseases.

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AVAILABILITY

The AsthmaMap is accessible through https://asthma-map.org.

METACORE LICENSE

The MetaCore license was purchased by the CNRS-EISBM team within the eTRIKS project for developing the Molecular Relations layer of the AsthmaMap.

The AsthmaMap project progresses in alliance with the efforts of the Disease Maps Community (https://disease-maps.org).

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