NEW HORIZONS
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Allergome: Bioinformatic tools to manage the increasing knowledge of allergens

Summary

Information technology, molecular biology and nanotechnology are related entities, that fully express their powerfulness once applied to biomedical fields. Almost two decades of research have given us an increasing knowledge of allergen structures. Genomics studies by means of nanotechnology have suggested the possible use of proteomics in both research and clinical applications. Bioinformatics applied to allergological research simplifies the approach to the increasing wealth of knowledge that can be produced by the former two methodologies. Both basic research and clinical work in allergology should be redesigned in the light of the combined use of information technology, allergenic molecules and microarrays.

The web server Allergome (www.allergome.org) represents a free, independent and open resource whose goal is to provide an exhaustive repository of data related to all the IgE-binding compounds. The main purpose of Allergome is to compile a list of allergenic sources and molecules by using the widest possible selection and sources. A further development of the Allergome platform is the Real Time Monitoring of IgE sensitization module (ReTiME) that allows uploading of raw data from both *in vivo* and *in vitro* testing, thus representing the first attempt to have IT applied to allergy data mining. More recently, a new module (RefArray), a tool for literature mining, has been released.

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Introduction

Allergic diseases are related to the exposure to a number of sensitizing organisms in the environment. Allergen-carrying organisms should be classified and data should be available for evaluation and study. The increasing knowledge of allergenic molecules has given further stimulation for the identification, characterization, and comprehensive classification of allergen sources. Molecular biology, nanotechnology and information technology (IT) are the main fields where allergy research and clinical practice should be directed. Bio-immunochemical techniques and molecular biology are allowing the identification of an increasing number of allergenic structures [1-4]. Nanotechnologies are used in the development of proteomic microarrays, initially employing allergenic extracts [5-10], but more recently native and recombinant purified allergens [11-16]. In a similar way IT is enabling us to create online databases that can be easily reached by worldwide users. In the last two decades several research groups and institutions have started to accumulate information and data from available sources in order to create databases of the scientific knowledge of allergens.

A number of allergen databases are now accessible [17]. Their features sometimes make them very similar, but sometimes the basic idea behind their creation leads to unique resources. Characteristics and features are available directly on the web or described in scientific journals [18-22].

In this article we report the current status of one of these bioinformatics resources dedicated to allergy data collection and analysis: the Allergome platform (www.allergome.org). Four main aspects of the Allergome platform will be discussed: a) classification of allergenic organisms; b) classification of allergen molecules; c) literature on allergens (text mining); and d) raw data on allergen reactivity (data mining).

Allergenic organisms

Several hundreds of organisms inducing IgE-mediated diseases otherwise known as allergenic sources have been described so far. Organism grouping on the basis of their taxonomical classification has been the first attempt in order to reduce the number of extracts to deal with. Some simplification has been achieved on the basis of families and

orders. Nevertheless, there are still quite long lists of allergenic extracts available from many diagnostics and immunotherapy companies, reflecting in part the lack of a rationale for a simplification of allergenic source lists, but also environmental-based selection criteria rather than immunologic ones. Furthermore, the identification of new allergenic sources is still an ongoing process. New organisms potentially causing global [23] or limited/occasional exposure/sensitization [24-26] have recently been described.

Comprehensive lists or databases of all the known allergenic sources are not available to date, and the information is spread in thousands of published papers and very often in meeting proceedings. Most of this information is not available, although it should constitute the basis of allergenic source knowledge. In addition to supplying information on allergens as molecules, the main goal of the Allergome database is to define a list of organisms inducing allergies on the basis of published literature. The still expanding knowledge of allergenic sources is a continuous challenge facing anyone attempting to build up a comprehensive list of allergen molecule [27;28]. Thus, a reliable database of allergenic organisms should be established and the molecular perspective should enable us to define whether we are dealing with either a novel allergenic source [29] or with a newly discovered source containing a formerly known allergenic structure [30]. For instance, this classification process related to molecular allergenic reactivity should lead to the redefinition of several well-known allergenic organisms (e.g. grass species) as part of a unique cluster of immune reactivity, having IgE co-recognized structures [4;31].

As of March 2006, the Allergome database contains 1,057 descriptions of allergenic organisms. More than half of them (577) still require allergen molecule identification. This applies not only to rare organisms inducing allergy, but even to common allergenic sources such as grass pollen. (62 species have been identified as allergenic, 21 are still lacking allergen molecule characterization.)

The continuous discovery of new allergenic sources and new ways of exposure related to the emergence of allergy as a problem in developing countries and the globalization in terms of the mobility of people and goods, represents a new challenge in our efforts to establish the most up-to-date list of allergenic sources. Furthermore, exposure to allergens within occupational settings should be monitored. Rare allergic sensitization should not be disregarded as non-relevant, and "orphan" allergens should be studied to build up the most comprehensive allergenic organism resource ever.

Allergen molecules

Allergen molecule databases available via the Internet and their most relevant features have been reviewed and a comparative evaluation of these resources has recently been reported [17].

The official list of allergens of the IUIS/WHO subcommittee for allergen nomenclature is based on criteria first defined in 1986, and revised in 1995 [2;32]. The activities of the IUIS subcommittee and their web product are crucial, as they avoid arbitrary assignment of the same allergen name by different authors, and should allow the unequivocal identification of allergens as well as other structures related to the immune system (i.e. CD markers). The main limitation of many allergen databases derives from the incomplete listing of described allergens. As for allergen organisms, a great effort should be made to release the most complete list of allergenic molecules based on dynamic criteria, regardless of their prevalence in the general population. The same dynamic criteria could be used for the definition of clusters of allergens. In fact, many classified allergens share structure and IgE reactivity. It would be useful to identify genuine and unique allergen structures representative of allergen groups. The dynamic nature of IT could help in this regard. It could enable a reliable allergenicity grading of both novel and established allergens. As the wealth of data on allergen molecules is rapidly expanding, new tools should be developed to achieve this goal.

As of March 2006, the Allergome database contains 1,198 allergenic molecules and 371 isoforms. About half of them are found in the IUIS list of allergen nomenclature. Classification in the Allergome database is an ongoing process based on publications from the past forty years, and on current papers. Figure 1 clearly depicts the time trend in allergen identification.

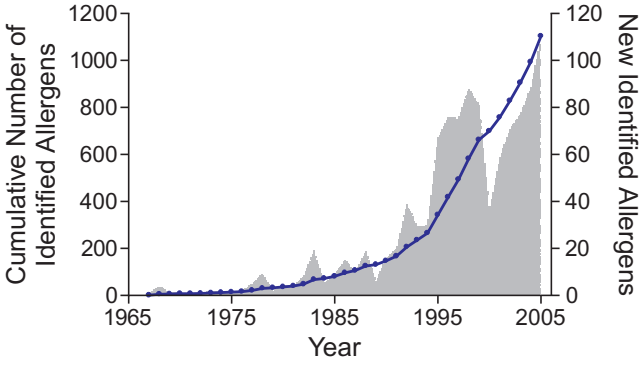

Figure 1. Time trend of identification of new allergens during the last forty years. The black line shows the cumulative number of allergens (left Y axis). The grey area is the year by year number of identified allergens (right Y axis). Data are extracted from the Allergome database (www.allergome.org).

Literature mining

The cause and the effect of our knowledge in biomedicine is the publication of an increasing number of original papers in scientific journals. Extraction, integration, management of information discovery and synthesis of these sometimes highly heterogeneous data represent a crucial need [33]. A specific research field is now dedicated to developing informatics tools for literature mining [34]. Through literature mining major themes and topics can be easily summarized, large result sets quickly evaluated, and trends and associations in references promptly revealed. The same time trend of biomedical publications is recorded in the allergy field as well. Figure 2 reports the distribution of studies dealing with any aspect of allergenic molecule characterization published in the last 40 years. The overall number of publications in this field is now around 7,100, and just in the first two months of 2006 about 200 new papers have already been published on aspects of the allergen topic. Due to the increase in the number of identified allergens and their future use in clinical research, the number of published papers is expected to critically increase in the near future. No specific tools, either literature databases or literature miners specific for the allergy field, are available at the moment. Only two web sites, InformAll and Allergome, reports citations for each allergen. This way to present citations

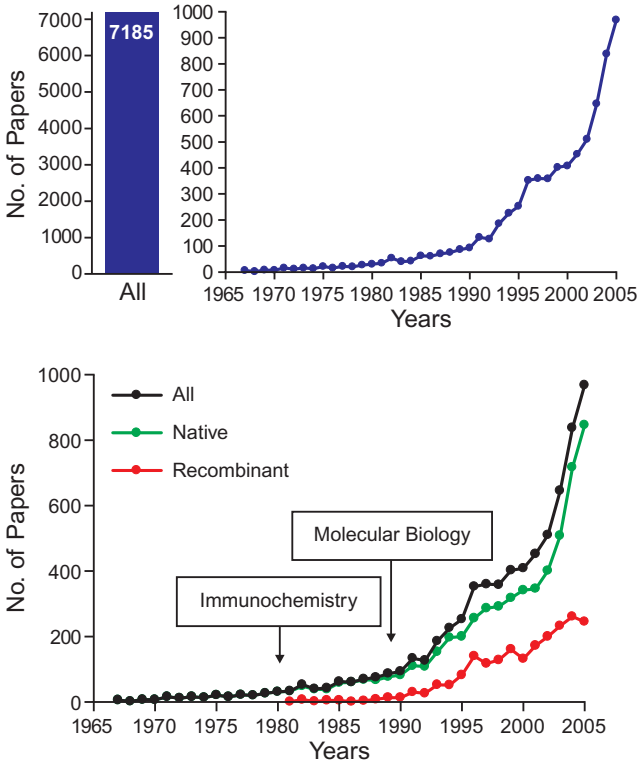

Figure 2. Published papers in international scientific journals dealing with at least one basic or clinical aspect of an allergen. Curves for papers dealing with native or recombinant allergens are shown. Data are extracted from the Allergome database (www.allergome.org).

is not or is only partially dynamic and does not offer a cross-sectional view of literature data. The rapidly expanding field of allergen knowledge is prompting us to develop new computational methods for managing, analyzing and visualizing literature data [34;35]. Recently, the RefArray module has been released within the Allergome platform. A search engine enables the user to select a number of allergens. Each search results in the definition of an array of reference citations which concern the retrieved molecule and the various aspects of research. This information is arranged in a web-based array. A list of fully described citations may be retrieved and easily imported in some of the more popular reference managers. This process makes it possible to reach defined info and data on specific allergens.

Data mining

General medical information can be managed through Internet resources, in order to obtain an electronic medical or health record for each patient. A comprehensive overview of the patient's clinical history can thus be retrieved by any authorized person. This IT approach to medical data managing results in a simple and quick way for patient/physician interaction, in optimization of health care costs for patients and healthcare providers, and in a reduction of errors [36]. It is now evident that the storing of this mass of information is creating a mine of real time clinical data.

Allergies are the most common diseases worldwide and allergen-based diagnostic and epidemiological data are available from several studies.

In an attempt to supply at least published information on allergenic molecules, a static prevalence table is available in each Allergome monograph. The use of IT in allergy data mining should be evaluated in the near future. A project to develop a web-based platform linked to the Allergome platform called Real Time Monitoring of IgE sensitization (ReTiME) has been released. The ReTiME platform allows uploading of raw diagnostic data from both *in vivo* and *in vitro* testing by any contributor worldwide. This should represent the first attempt to have IT applied to allergy data mining. Interfacing laboratory instruments with the Allergome-ReTiME platform will be a great research resource for anyone dealing with daily routine work.

Current and future strategies of the Allergome project

Data to feed the Allergome database have been collected starting from year 1999 and the original software was designed and developed between 2000 and 2002. Version 1 of the Allergome software was released in 003 and at the moment it is the sole dynamic database for allergen molecules. Data, stored in archives, are retrieved using the latest updated information [20]. The aim of the Allergome database is to collect in a single web-based resource basic and clinical information, and data about any allergenic organism and its molecular structures capable to induce an IgE-mediated disease. Each allergen description in the dynamic monograph includes data to identify the allergen by its updated nomenclature, the source, and the biochemical and immunochemical features by means of a number of given or linked information. Each monograph is comprehensively referenced. Allergome developers are attempting to give a friendly interface to the web site to allow users to easily access information. A powerful internal search engine allows navigating within the web site without launching a new search each time. No computational tools have been developed within the Allergome web site. A collaborative study has been established with researchers working in a Swiss immunology department who developed an original algorithm attempting to define the allergenic nature of molecules on the basis of motif recognition [37]. The motif discovery is now run every month by using an updated list of sequences from the Allergome database. The obtained motifs are then displayed in allergen monographs, and can be both searched and used for internal searches [38]. In an attempt to improve visualization of information in the database an algorithm to generate a graph giving a representation of both sequence homology and IgE co-recognition has been developed [39]. This tool, the O-ring, can be activated within each allergen monograph and dynamically scans the sequence homology and the IgE co-recognition sections to visualize allergen reciprocal relationships (Figure 3).

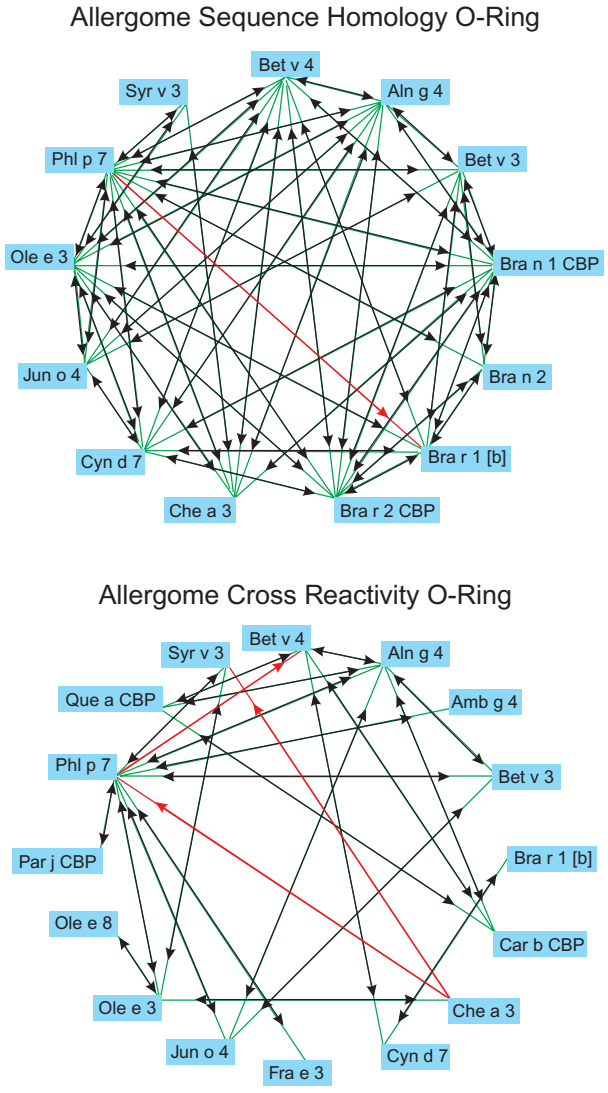

Figure 3. The Allergome O-ring. An attempt to dynamically display biochemical and immunochemical relationships among allergens. The figures show pollen calcium-binding protein relationship in either sequence homology (top) or IgE co-recognition (bottom).

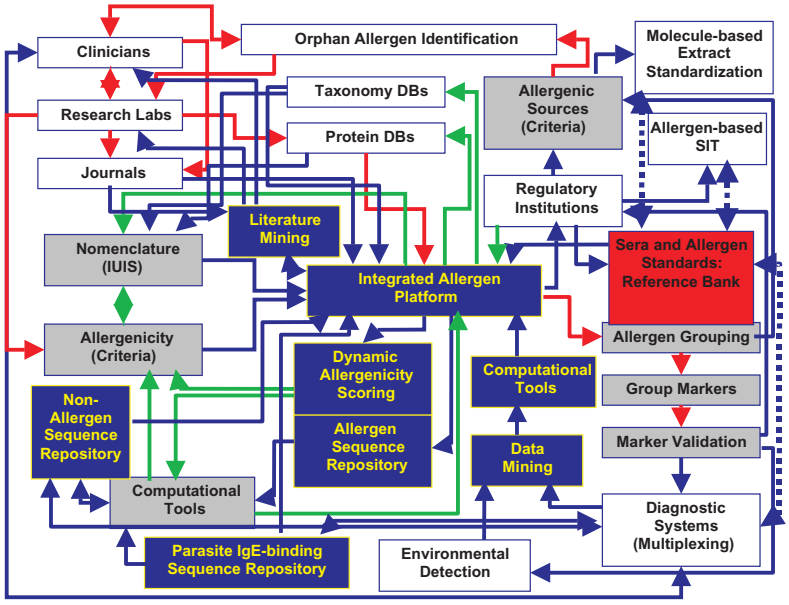

Figure 4. Networking allergy resources from bench to bed, linking regulatory needs and practical issues.

Conclusions

It's now time to start using these three new tools, molecular biology, nanotechnology and IT, as a great opportunity to adapt and transform the information that is now available. Genomic analysis of allergenic sources is producing a mass of data in terms of new allergenic structures to be classified [40-42]. An effort should be made to quickly integrate all these data, but at the same time having a list of unique non-redundant allergens, with isoforms and variants listed as part of their unique representative molecule [43].

Microarray-based proteomics experiments measuring IgE by means of purified native or recombinant molecules will add value in this direction. Combined information on a set of highly reliable allergen sequences should be available.

As in many other biomedical fields people involved in the allergy field should consider starting to apply specific and integrated new tools to allergy research and clinical practice. An integrated view of a potential network of contributors is presented in figure 4.

Notes and acknowledgments

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