The Spanish multidisciplinary research network for allergic diseases

MJ Torres[1-4], Agundez J[5], Barber D[6], Bartra J[7,8], Davila I[9], Escribese MM[10], Fernandez-Rivas M[11], Ferrer M[12], Perez-Inestrosa E[3,13], Villalba M[14], Mayorga C[1-3]

[1]Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA, Málaga
[2]Allergy Clinical Unit, Hospital Regional Universitario de Málaga, Málaga
[3]Centro Andaluz de Nanomedicina y Biotecnología-BIONAND, Málaga
[4]Medicine Department, Universidad de Málaga-UMA, Málaga
[5]University Institute of Molecular Pathology Biomarkers, UEx, Cáceres; ARADyAL Instituto de Salud Carlos III, Spain
[6]School of Medicine, Institute for Applied Molecular Medicine, Universidad CEU San Pablo, Madrid
[7]Allergy Section, Pneumology Department, Institut Clínic Respiratori (ICR), Hospital Clínic de Barcelona, Barcelona
[8]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona
[9]Allergy Service, University Hospital of Salamanca, Salamanca, Spain. Department of Biomedical and Diagnostics Sciences, Faculty of Medicine, University of Salamanca, Salamanca, Spain. Institute for Biomedical Research of Salamanca (IBSAL), Salamanca
[10]School of Medicine, Department of Basic Medical Sciences, Universidad CEU San Pablo, Madrid
[11]Allergy Dept. Hospital Clínico San Carlos, Universidad Complutense, IdISSC, ARADyAL, Madrid
[12]Department of Allergy and Clinical Immunology, Clínica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona
[13]Departamento de Química Orgánica, Universidad de Málaga-IBIMA, Málaga
[14]Biochemistry and Molecular Biology Department, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Madrid

Corresponding
Maria J Torres
AllergyService, pabellón 6, primera planta.
Málaga Regional University Hospital
Plaza del Hospital Civil s/n, 29009 Malaga, Spain.
E-mail: mjtorresj@uma.es

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Summary

Thematic networks of cooperative health research (RETICS) are organisational structures promoted by the Instituto de Salud Carlos III of the Spanish Ministry of Science with the objective of carrying out cooperative research projects addressing challenges of general interest for the society in the health field. The RETICS of Asthma, Adverse Drug Reactions and Allergy (ARADyAL) was funded in 2016 for a 5 years programme (2017-2021). ARADyAL integrates basic and clinical research in the areas of allergy, immunology, genetics, nanomedicine, pharmacology, and chemistry, with special interest in the research of new biomarkers, and the design and evaluation of new intervention strategies for allergic patients with severe phenotypes.

The consortium is composed by 28 groups across Spain, which includes 171 clinical and basic researchers: 17 clinical groups that cover more than 10.000.000 patients of all ages and from urban and rural areas; and 11 basic groups that develop their activities mostly at university and research institutes. ARADyAL has proposed a research program organised in three different areas focused on Precision Medicine: **Program 1**. Mechanisms and prediction of adverse drug reactions and allergic diseases; **Program 2**. Towards a precise diagnosis of allergic diseases; and **Program 3**. Predicting interventions in allergic diseases. There is also one transversal program dedicated to training. The network has a Direction Committee and an External Advisory Scientific Committee, which advise the global network coordinator who has recognised expertise in the field. ARADyAL is a unique meeting-point for clinicians and basic scientists that are already working on allergy.

Keywords: Allergy, Research, Networks, Biomarkers, Mechanism, Diagnosis, Treatment

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Resumen

Las Redes Temáticas de Investigación Cooperativa en Salud (**RETICS**) son unas estructuras organizativas promovidas por el Instituto de Salud Carlos III del Ministerio de e Sanidad, Consumo y Bienestar Social con el objetivo de llevar a cabo proyectos de investigación colaborativos que aborden desafíos de interés general para la sociedad en el campo de la salud. La RETICS de Asma, Reacciones Adversas a Fármacos y Alérgicas (ARADyAL) comenzó en 2016 y fue financiada por un periodo de 5 años (2017-2021). ARADyAL integra la investigación básica y clínica en diferentes áreas de conocimiento, alergia, inmunología, genética, nanomedicina, farmacología y química, con especial interés en la investigación de nuevos biomarcadores, y el diseño y evaluación de nuevas estrategias de intervención para pacientes alérgicos con fenotipos graves.

El consorcio está compuesto por 28 grupos de toda España, que incluyen 171 investigadores clínicos y básicos: 17 grupos clínicos que cubren a más de 10.000.000 de pacientes de todas las edades y de áreas tanto urbanas como rurales; 11 grupos básicos que desarrollan sus actividades principalmente en universidades e institutos de investigación. ARADyAL propone un programa de investigación organizado en tres áreas diferentes centradas en la medicina de precisión: **Programa 1**. Mecanismos y predicción de reacciones adversas a medicamentos y enfermedades alérgicas; **Programa 2**. Hacia un diagnóstico preciso de enfermedades alérgicas; y **Programa 3**. Predicción de intervenciones en enfermedades alérgicas. Además, hay un programa transversal dedicado a la formación. La red cuenta con un Comité de Dirección y un Comité Científico Asesor Externo, que asesoran a la coordinadora de la red la cual tiene experiencia reconocida en el campo. ARADyAL es un punto de encuentro único para médicos y científicos básicos que ya están trabajando en alergias.

Palabras clave: Alergia, Investigación, Redes, Biomarcadores, Mecanismo, Diagnóstico, Tratamiento.

Introduction

Thematic networks of cooperative health research (RETICS) are organisational structures promoted by the Instituto de Salud Carlos III (ISCIII) of the Spanish Ministry of Science. The objective of a RETICS is to carry-out cooperative research projects addressing challenges of general interest for the society in the health field. RETICS respond to the health priorities of the Spanish Government plan for scientific and technical research and innovation, with the aim to shorten the interval between the production of new knowledge and its transfer and real applicability in the clinical-practice.

In this manuscript,we present the RETICS of Asthma, Adverse Drug Reactions and Allergy (ARADyAL) funded by the ISCIII in 2016 for a 5 years programme (2017-2021). ARADyAL integrates basic and clinical research in the areas of allergy, immunology, genetics, nanomedicine, pharmacology, and chemistry, with special interest in research of new biomarkers and the design and evaluation of new intervention strategies for allergic patients with severe phenotypes.

1.- why do we need a spanish research network in allergic diseases?

Patterns, prevalence, and socioeconomic impact of allergic diseases

The worldwide-growing burden of allergic diseases has been defined as the “allergy epidemic”. Allergic rhinitis (AR), asthma, atopic dermatitis (AD), drug hypersensitivity reactions (DHR),and food allergy (FA) are the most frequent allergic diseases.

Asthma is one of the most common major non-communicable diseases, affecting almost 300 million people worldwide [1]. Incidence and prevalence differ between children and adults, and by sex across the lifespan. There is a large geographical variation in prevalence, severity, and mortality. Asthma prevalence is higher among high-income countries, but it is increasing in low- and mid-income countries [2, 3].

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Asthma has a substantial impact on health-related quality of life (HRQL), especially in those with a severe phenotype. Asthma is a leading cause of years lived with disability (YLD) and of burden of disease measured by disability-adjusted life years (DALYs).

Severe asthma and asthma mortality are more frequent in adults[1,2,4,5]. Asthmais responsible for a numerous doctor and emergency visits due to exacerbations and inadequate control, resulting in high associated health-care costs that increase with asthma severity (Table 1)[6].

AR is the most prevalent allergic disease, and one of the most common chronic diseases, being the most frequent reason for allergy consultations in Spain [7](Table 2).AR reduces HRQL, impairssleep-quality and cognitive function, causes irritability and fatigue, and,although not associated with severe morbidity and mortality,is associated with work and school absenteeism causing important direct and indirect costs, actually greater than those ofasthma [3, 8, 9] (Table 1).

AD is one of the most common inflammatory skin diseases, affecting more than 200 million people worldwide, mostly children. Itsprevalence is higher amongaffluent countries, where its incidence increases continuously.AD leads to debilitating pruritus, sleeplessness, and impairs HRQL. AD poses the highest global non-fatal burden of all skin diseases in terms of YLD and DALYs [1, 3, 4, 10, 11] andhas an important economic impact(Table 1)[10, 12, 13].

FA prevalence has been increasing in affluent countries, being considered the “second wave of the allergy epidemic”. The actual prevalence is difficult to establish due to the heterogeneity of the epidemiological studies and definitions (Table 1)[14]. There are age and geographical differences. In the Spanish *Alergologica* surveys, the frequency of food allergic patients has been increasingly diagnosed in outpatient clinicsfrom 1992 (3.6%) to 2015 (11.4%), being three times higher after two decades[15-18] (Table 2).Additionally, the most severe FA phenotypes are increasing, accounting for higher rates of anaphylaxis and hospital admissions, mostly in children and adolescents [19, 20].

FA management involves the avoidance of the culprit food(s), which requires continuous vigilance by patients and families. Living with a FA entails fear, uncertainty, anxiety, depression, social isolation, and has a very negative impact on HRQL. Children with FA have poorer HRQL than children with insulin-dependent diabetes[21].

Additionally, FA has a heavy economic burden in terms of direct medical, out-of-pocket, and opportunity costs[22].

The DHR prevalence is unknown. In a recent systematic review the pooled prevalence of adverse drug reactions was 7.9%, being higher in females, adults, and hospitalised patients [23]. This figure overestimates drug allergy,increasing the need of delabellingDHR. In fact, in a large study, drug allergy was only confirmed in 15.2% of suspected reactions[24], and in a recent meta-analysis, only 2.8% of patients with reported penicillin allergy had a confirmed diagnosis[25]. DHR may be severeandlife-threatening, being the main cause of anaphylaxis in hospitalised patients [19, 20]. As for FA, the frequency of patients diagnosed withDHR in outpatient clinics of Spain has been increasing from 1992 (12.6%) to 2015 (18.7%) in the *Alergologica* studies (Table 2)[16-18, 26].The impact of DHRs on HRQL and their cost is unknown but expected to be substantial. DHRs entail both direct and indirect costs. Additionally, their misdiagnosis has negative medical and economic impact in hospitalised patients [27].

Identifying aetiology and mechanisms for preventing, diagnosing, and treating allergic diseases

The recent advances in molecular and clinical research in respiratory, food, and hymenoptera allergy have contributed to the knowledge on structure and functions of allergens. This knowledge has resulted in a better characterisation and standardisation of allergen extracts for the development of diagnostic tools and therapies. In the field of DHR, diagnosis is more complex as the proper active drug or its metabolite can be involved. Several important questions

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related to allergens/drugs and allergic sensitisation remain unansweredand it would be necessary to advance in: (i) structures of homologous allergens to studycross-reactivity for all major allergen types, (ii) the effect of allergens/drugs on innate immune cells and signal transduction initiated by allergens/drugs in effectors cells, and (iii) definition of "susceptibility to allergic/drugs sensitisation" at the molecular level.

Alabour-intensive work has focused on understanding the aetiologyof allergic diseases and underlying mechanisms to develop effective prevention measures, advance in their diagnosis, and develop safe and more effective therapies. Also, it is necessary to develop new *in vitro* diagnostic tests or improve the existing ones. Such development or improvement could have a positive impact and make it easier to achieve a "true" diagnosis of allergy.

The rising tendencyin allergic diseases is associated with changes in lifestyle [28]. One of the sequelae of this change in lifestyle is the impact of the microbiome since changesinits composition and/or metabolism are thought to influence the immune system [29]. Onthe other hand, epidemiological studies have revealed an association between pollution and allergic respiratory diseases due to its impact on both the subject and the allergen [30, 31].

The genetic make-up of an individual is an important predisposing determinant for the development of allergic immune responses. Allergic patients differ in the entire environmental exposures through the whole life. This constitutes the exposome, which cansignificantly influence the epigenetic regulation of the immune system and tissue cells. Thereremaining questions concern which of the many components, in what combination, in which patients, and with what kind of genetic background behave as decisive elements leading to allergic disease. Future research should not only try to elucidate the structural basis of allergenicity but also focus with equal intensity on the many additional factors from the environment and the host. This might finally result in new concepts of diagnosis, therapy, and prevention. For this reason, there is a need to perform multidisciplinary studies including a high number of patients and this can only be doneestablishing networks.

2.- Aradyal programmes

ARADyALhasproposed a research program organised in three different areas focused on Precision Medicine(Figure1).

Program 1. Mechanisms and prediction of adverse drug reactions and allergic diseases

It is widely acceptedthat there is an inter-individual variability regardingsusceptibility, clinical course, and response to therapy. However, the mechanisms underlying such variability are far from being understood[32-40].

Therefore, the main objectives of this program are to study the molecular and cellular aspects that constitute the starting-point of allergic sensitisation and the immunological mechanisms underlying the risk, the progress to severe clinical presentations, and the clinical evolution and response to pharmacotherapy. The ultimate goals of this research areto identify biomarkers of susceptibility or clinical evolution, to translate these biomarkers to bedside, to use such biomarkers as a proof of mechanism and to develop models that can be of utility in the research of mechanisms that bring-out allergic diseases or adverse drug reactions[39, 41-45].

One of the focuses of this program is the search forfactors (genetic or metabolic) thatcan explain why drugs or allergens can trigger anallergic response only in some individuals. In addition, the events occurring downstream of the triggering mechanism also show large inter-individual variability in terms of clinical evolution and severity and in immunological mediators.The development of novel mass-spectrometry procedures has allowed the identification of reactive drug metabolites involved in DHR, including amoxicillin and non-steroidal anti-inflammatory drugs (NSAIDs)[32, 38, 46-51] thatmay elicit an immune response[51]. Asdrug metabolic profiles are often determined by variability in the genes coding for drug-metabolising enzymes, it is conceivable that an altered drug metabolism may predispose to DHR. Moreover, there is a special interest in studying the biological/biochemical function a proteins as well as

environmental substances, drugs or xenobiotics that alter or even trigger the responses and could be related to its allergenicity.

The development of the specific objectives (Figure 1) following a strategic integration of effort among traditionally segregated disciplines and within the whole ARADyAL consortium will hold great promise for personalised medicine.

Program 2. Towards a precise diagnosis of allergic diseases

There are many disease variants among allergic diseases, and patients with similar clinical characteristics (phenotypes) can differ enormously in disease evolution and treatment response. Endotypes take into accountnot only clinical symptoms but also variations in biological, immunological, and pharmacogenomic characteristics.

Current clinical diagnostic guidelines often ignore this important disease heterogeneity and causal pathways, leading to contradictory results. Therefore, it is absolutely necessary to further classify allergic diseases, including asthma, AR, FA, and DHR into endotypes and to develop affordable procedures that allow a better characterisation and stratification of allergic diseases, a precise diagnosis, and personalised treatmentsfor optimisingcare and reducing costs[52-54] (see specific objectives in Figure 1).The diagnosis of allergic reactions to food and inhalant allergens is a challenge as clearly “one size does not fit all”. This pushes us to search for the optimal way to perform a precise diagnosis. Considering FA, a wealth of evidence suggests that the same plant-food can cause sensitisation to a diverse range of allergens, with differences in severity, dosage thresholds, and geographical variations [55]. It is of prime importance to improve the molecular diagnosis in FA[56-59]. Particularly, we must take into account that the sensitisation and reaction elicitation may be induced via different routes and this may influence the appearance of severe food-allergic reactions.

DHRsneed to be correctly labelledafter performing an evaluation in an allergy unit following well-validated protocols [60]. However, achieving an accurate diagnosis is complex and time-

consuming, and tests must be tailored to specific drugs, clinical manifestations, and underlying mechanisms. Such tests often require performing drug provocation tests, with an inherent risk for patients. Altogether, this makes the management of DHR patients expensive for the health-care system.

It is important to consider that drugs are small molecules that behave as haptens and bind to a carrier protein, leading to the formation of adducts, which are responsible for immunological responses [51, 61-63]. The lack of knowledge of the candidate target proteins and the formed adducts is one of the main limitations for the development ofsimple and useful *in vitro* tests. Another important limitation is the low population size from which data on severe allergic reactions can be obtained.

To develop and validate new tests, access to large numbers of biological samples of well characterised patients is crucial. This can be overcome only with the involvement of expert clinicians using standardised protocols, and importantly, by creating an integrated network that allows different hospitals and laboratories to collaborate and exchange samples and data.

Program 3. Predicting interventions in allergic diseases

A great problem in allergic diseases is the difficulty for predicting and monitoring the effect ofinterventionson an individual-patient basis. Evidence is based on big, multicentre trials, in which subjective medication scores of actively treated patients are compared with placebo-treated ones, hamperingindividual-patient information[64, 65].Defining alternative objective biomarkers is difficult as these biomarkers are generally used as secondary outcomes with low predicting potential[66, 67].

Achieving individual prediction is pivotal for daily clinical-practice. In many cases, allergic disease coincides with different co-morbidities, and it is often difficult to assign the contribution of allergic sensitisation to the global clinical phenotype. There is an urgent need to advance in theunderstanding of underlying mechanisms, to design improved biomarker strategies that allow

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select, predict, and monitor the effect of therapeutic options as well as identify new therapeutic targets (see specific objectives in Figure 1).

The increase in therapeutic options, including symptomatic medications, allergen-specific immunotherapy,and biologics makes it necessary to create treatment guidelines in which each therapeutic option is consideredin the best way to maximise the benefit for the patient and the society.

New biological drugs offer new therapeutic options, but there is still a need to optimisetheiruse, to define anintervention period, and to integrate them in anaetiological approach of the allergic disease as a whole[68]. Immunotherapy is the unique intervention that offers the possibility of modifying the course of the allergic disease.

When such tolerance induction is successful, using the adequate product, prescribed on a clinically relevant sensitisation, for the adequate time, it has a clear benefit in about 70% of patients[69, 70].However, it is nearlyimpossible to predict whichpatients will benefit from the intervention.We need to design new monitoring tools with specific biomarkers that should becloser to clinical and sensitisation profilesandto incorporate them intoclinical-practice in order to maximise the position value of the aetiological intervention.

In an integrated therapeutic approach, new biological drugs, developed for severe allergic patients, could be temporary used to revert the disease and stabilise the patients, and to allow a future specific intervention. Likewise, a symptomatic intervention will help decrease symptoms and maintain such benefits along time[71]. Identifying candidate patients for allergy-prevention interventions, especially among children,is a priority for developing a new evidence-based intervention.

For validating these therapeutic algorithms, big prospective collaborative trials in the context of collaborative networks are needed. Real-life monitoring of the outcomes of the interventions must be provided. Common omics-based biomarkers to the different interventions are to be developed and validated. Understanding underlying causes of theallergy epidemic and

developing a prevention strategy, both primary (allergy prevention) and secondary (severity prevention), will be crucialto bring an end to theincreasing allergy epidemic.

3.- ARADyALOrganisation

Structure, members, common tools and platforms, standardised protocols and procedures, database, biobank, evaluation

ARADyAL is a translational network that combines innovative approaches in the field of immunology, genetics, nanomedicine,pharmacology, and chemistry with a special focus on the search for new biomarkers, and designing and evaluating interventionstrategies for patients with severe allergic phenotypes.

These goals can be only achieved with the integrated work of multidisciplinary researchers. The ARADyALconsortium is composed by 28 groupsacross Spain, whichincludes 171 clinical and basic researchers: 17clinical groups that cover more than10.000.000 patients of all ages and from urban and rural areas; and 11 basic groups thatdevelop their activities mostly at university and research institutes(Figure 2).

ARADyAL is organised into three different scientific programs (described above) plus one transversal program dedicated to training. The network has a Direction Committee and an External Advisory Scientific Committee which advise the global network coordinator.The ARADyAL coordinator has recognised expertise in the field and is also the principal investigator of a group. Each scientific program constitutes a distinct area of research with clear and integrated ARADyALobjectives (Figure1). Scientific program coordinators will be in charge of the different research activities grouped in work packages and guaranteeing the adequate functioning of the different groups, monitoring the progress of the projects in course, advising about collaborations, and of dissemination events related to each program.

This network represents a unique meeting-point for both clinicians and basic scientists that are already working on biomedical problems on asthma, allergy, and adverse drug reactions.

Clinicians with long experience in the evaluation of allergic reactions aim to solve the important questions that arise in clinical-practice and to provide well-phenotyped cases and controls from representative Spanish areas. Itis important to address patient diversity within Spain, ensuring an adequate sampling of patients included in epidemiological studies and combining both research and clinical profiles. This is crucial to cover a broad panel of pathologies and allergens with a strong geographical variation.

Basic scientists try to answerthe questions by evaluating the mechanisms, developing chemical structures and nanostructures, identifying and validating new biomarkers, and digging into the disease genetic basis.

For these purposes,the groups have produced consensus protocols and documents usingcommon platforms as a database and a biobank for the management of biological samples used in the different research lines. ARADyAL has developed a database in which the information of patients with allergic reactions to drugs and allergens from the different clinics and studies can be stored and be used in further projects. In addition to demographic data, an enormous amount of information has been generated atvarious clinical activities during the allergological work-up, as

well as protein analysis, genotyping in genetic studies aimed to determine the potential predisposition to develop these pathologies or the response to treatment. The integration of all this information for its best use is complex and represents a great challenge. For this reason, the necessary technological support has been designed and developed to create an integrated work environment allowing secure, integrated, and shared storage of data, computer services, and calculation capacity to develop the project.

The biological samples are very importantfor the different ARADyAL activities and are be managed in a Biobanksettled in agreement with the Biomedical Research Law 14/2007, and the Royal Decree of Biobanks RD1716/2011.

With the generated synergies, it will be possible to develop innovative approaches for diagnosis (endotypes, risk factors, and molecular diagnosis) and precise treatment for allergic diseases,with the final aim to increase the quality of life of allergic patients.

Teaching and researcher mobility

The teaching program is considered pivotal in ARADyAL. There is a teaching commission constituted by 10 members (5 clinical investigators and 5 basic researchers) that reports directly to the Direction Committee.

The teaching commission, with the agreement of the Direction Committee, has defined three main educational objectives: (i) to provide the pre-doctoral researcher (basic and clinical) with the necessary knowledge to improve their training and to facilitate the consecution of a Ph.D. degree;

(ii) to provide the post-doctoral researcher with an adapted program to improve their knowledge on the topics that are objectives of the network; and (iii) to promote the interaction and exchange of knowledge between clinical and basic researches. The main tools to achieve theseobjectives are the annual general meeting, in which the groups present their results and there is specific time for interaction, oriented to the exchange of experiences and information, and the constitution of alliances for investigation; the biannual summer school, focused on a specific topic; small workshop meetings; virtual meetings; and expert conferences.

Besides, ARADyALmembers offer specific university courses. Finally, the ARADyALwebsite is of utmost importance in sharing information and training. Currently, the main protocols of the different groups are at the disposal of the researchers, with the final objective of unifying the methodology. The organisation of online specific coursesis under development.

Concerning the mobility program, it is organised in a pre-doctoral mobility program, which offers 2-4 month stages in ARADyALcentres, and a post-doctoral mobility program, which

offers 4-8 months stages in ARADyALcentres, although stages in renowned national and international non-ARADyALcentres are also allowed. This program needs specific financial resources(Figure 3).

Communication

The communication policy of ARADyAL is to disseminate the research carried-out in this network to the whole research community, to the Spanish National Health System (NHS), health professionals, patient associations, pharmaceutical industry, and general public. One of the main tools we use is the website "aradyal.org". This website represents a tool for dissemination, but also for improving communication betweenthe ARADyAL consortium andstakeholders. It is also used to host an online repository containing information on research results, scientific

publications, patents, resources, platforms,and other outcomes arising from the activities. Additionally, the website contains general information on recent news, a calendar highlighting relevant events, a short video summarising the network main objectives and a sample of five podcasts elaborated by every research group on the network.

These podcasts are randomly selected from those presented on another subpage (http://aradyal.org/entrevistas/) where all podcasts are available. Further information include the aims of the network, the organisation, the different groups that compose ARADyAL(including a specific webpage for every group), the research programs, information related to resources like platforms and biobank; links to the teaching program, to the communication website, and a link to access available positions.

Besides,the website contains links to the intranet where ARADyAL members can access internal resources.

Furthermore, ARADyALhas the challenge to communicate recent advances to the general population. To achieve that, we have recently implemented a section for scientific divulgation on our webpage and start our path in the social networks, aiming to reach all the potential interested followers among the general population.

4.- Aradyal strategy

Projects and clinical trials. The patient as the centre of the research

From the ARADyALobjectives (Figure1), several projects emerged depicting the genetic associations of allergic diseases[72], understanding the allergic-diseaseburden [73-77], or profiling DHR pharmacokinetics and pharmacodynamics [45]. Other projects relate tothe discoveryof biomarkers that predict severe allergic diseases[78], or to theidentification ofthe most prevalent allergens in the Mediterranean area, to prevent severe allergic reactions. In the area of DHR, several projects approach this problem, one analysing drugs and drug metabolites as antigenic determinants, trying to characterise the drug-protein interaction that enables an IgE-mediated reaction[40, 79]. This project will allow the design of new diagnosis platforms for DHR.

The third group of projectsfocuses its efforts on therapeutic interventions likeintegrating *omic* tools applied to changes towards tolerance induced by immunotherapy[80], or studying molecular allergen modifications to induce immunomodulation. It also designs novel strategies for food allergy immunotherapy[81-83].

Other projects focus on detecting early intervention to prevent allergic inflammation or immune deviation[84-86]. This area is also working on theharmonisation of rapid drug sensitisation procedures andthe last objective is to improvethe use of current biological drugs.

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With the introduction of omalizumab monoclonal antibody directed against human IgE, a new immunological therapeutic intervention was introduced to the pharmacological portfolio. Recently, we have gained a progressive understanding of the value of this new drug.

It is important to gather all available data in order to issue guidelines and consensus documents that minimise the cost to the health-system, and to guarantee access to adequate therapeutic intervention for individuals suffering from allergy[87]. Moreover, other biological drugs (biologics) for asthmatreatmenthave been recently incorporated by the Spanish NHS and there is a needto position these drugs adequately to ensure the population's maximumtherapeutic benefit.

Improving and designing new interventions could be achieved by performing clinical trials. For that reason, different trials are under development by thegroups, one example is the developmentof new adjuvants for oral immunotherapy. Another example is a recently finished clinical trial ofthe use of omalizumab for cholinergic urticaria resistant to antihistamines, which has no treatment[88].

Translational medicine, from bench to bedside

The connection between the laboratory bench and the daily clinical-practice is contributing to improve the diagnosis and treatment of patients. One of the approaches revolutionising day-to-day with patients in any medical discipline is translational medicine.

Physicians and scientists must provide personalised diagnostic and therapeutic strategies through multidisciplinary and collaborative approaches that combine advances in the knowledge of molecular tools, techniques developed by researchers at laboratories, and the design of effective treatment protocols [89].

Based on our experience, the molecular information obtained in the basic groups of ARADyALallows optimising the prediction of patients' responses to therapy and must be shared among the members of the Network.Such data involve a complete panel of well-characterised

allergens, derivatives, and biomarkers, the development of diagnostic tests based on molecular mechanisms that improve their specificity and sensitivity such as DNA and protein microarrays, and powerful omics techniques such as genomics, metabolomics, proteomics, and pharmacogenomics.

On the other hand, the experience of clinical researchers is required to transfer this information to patients in an adequate way within the framework of clinical trials that includethe appropriate control groups, so that these investigations are validated in the clinical environment. This procedure has a clear purpose: improving the diagnosis, achieving the expression of biomarkers of the disease, analysing the differences between the health and disease, the risk of acquiring a disease, the severity of symptoms, the alteration of certain metabolic pathways and metabolites;discovering therapeutic targets for biological products, drugs, and gene therapy; and verifying the response to therapy. This constant feedback results in design of therapeutic strategies and provides an improvement in the effectiveness of therapeutic agents. Finally, it is evident that one of the aspects that are not completely satisfied with the multicentric trials carried-out to validate a given treatment or diagnostic tool is the ability to follow or, rather, to predict the evolution of a given patient. This is, of course, an essential medium- or long-term objective within ARADyAL in order to obtain more tangible benefits not only in terms of social welfare but also towards a particular patient from a biomedical point of view.

The fact that we have a very active group in charge of disseminating the results obtained within ARADyAL highlights our need to incorporate a third addressee in the proposed model, the information that is transmitted from the bench to the patientmust continue to flow until reachingsociety and, thus,until closingthe circle. With this, we intend to offer a new translational research model of a more circular and inclusive nature for the general population. This promises more appropriate, effective, and sustainable impacts on the target population.

Converting research into marketable products and services

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The progress of the activities of ARADyAL represents a unique opportunity to build the local resource capability of the different research groups. ARADyAL will be a route to create job opportunitiesin scientific, technological, enterprise, and clinical fieldsas a consequence of the capabilities and translation of scientific achievements. Besides, it will represent an opportunity to develop a culture for innovation on thetechnological, enterprise, and clinical levels.

The combination of both technology-push and market-pull will be the driving force to achieve an improvement in the clinical-care of patients.

One of the main objectives of ARADyAL is to increase the cooperation that allows the involvement of industry in R&D consortia to increase the success rate of market-oriented exploitation. We are aware that it is importantto achieve the success of the management capacity of the participants individually, but above all, the organisation of the consortium to manage the respective risks, and in the event that risk becomes a real challenge, to be able to findcooperatively the best solutions is crucial.

We are committed to anorganisational change at different levels. Market-oriented exploitation of innovative technologies is sometimes hampered by an organisational bottleneck and, therefore, the ability to circumvent such bottlenecks through organisational change is often underestimated. Indeed, it is a key element for market success.

The active dissemination of research results through conferences, trade fairs, workshops, publications, etc., sometimes offers the only possibility of obtaining feedbackon the economic potential and recommended routes of exploitation oriented towards the market. The analysis ofthetype of technological application that the pharmaceutical industry and, most importantly, clinical-practice claimis an important development parameter in our objectives.

Even the best prepared and executed market-oriented exploitation process fails if the demand is not justified or not strong enough. This lack of coordination can result in a mismatch between innovation and investment.

In order to successfully commercialise the result of the research, it is necessary to have a broad knowledge of the production processes and the challenges of integrating innovation into clinical-practice. Therefore, it is relevant to beable to convince those interested in the advantages and integration of our innovation. Formal and informal standards play a vital role. Some developed technologies may open new markets ormarket niches that, being the first and, for some time, the only supplier, create a quasi-standard product positioning.

To avoid a significant impact on the correction of methodologies and applications to clinical-practice in the field of allergy, avoiding a chain of subsequent steps, our innovation trajectory must be a continuous process of activities between basic, clinical, and sector business.

5.- Conclusions

In summary, the collaborative work developed by ARADyAL groups has allowed to develop different experimental models that are crucial for analysing the mechanisms involved in allergic diseases, such as mast cell activation, food allergy exacerbated by non-steroidal anti-inflammatory drugs, mice anaphylactic model, allergen-intestinal or respiratory mucosa interaction. There are important results that are applicable to diagnosis: (i) discovery of mechanisms associated with severe phenotypes and comorbidities; (ii) identification of new and clinically relevant allergens; (iii) identification of carrier proteins and structural details of the binding site that is important in DHRs; (iv) development of high-capacity dendrimeric nanostructures, nanoparticles, and platforms. In the case of treatment of allergic diseases, advances in interventional studies have been made: (i) design and validation of dendrimeric systems for immunotherapy; (ii) pharmacogenomic and drug metabolism analysis; (iii) design of

databases to collect the use and adverse effects of biological drugs in allergic diseases to optimise the rational use of drugs; (iv) Identification of candidate genes for pharmacogenomic studies of response to asthma treatment.

The translational network ARADyAL represents a unique platform to generate synergies for clinicians and basic scientists that are already working on biomedical problems on asthma, allergy, and adverse drug reactions. This will make it possible to understand the underlying mechanisms of allergic diseases, which isnecessary to develop innovative approaches for prevention, diagnosis, and treatment.

Conflict of interest

None of the authors have any conflict of interest, nor have they received any money for this study. Research is part of their daily activities. All authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis.

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Table 1. Key epidemiologicaland socioeconomic data of different allergic diseases

Allergic disease	Key epidemiologicaland socioeconomic data	Ref.
Asthma	Prevalence: 272.7 million people worldwide Incidence: 43.1 million people YLDs: 10,623 DALYs: 22.8 million, with a 3.3% increase from 2007 to 2017. Disease ranking for DALYs: 30th in females, 32nd in males. Mortality: all age deaths 0.5 million people, with a 0.7% reduction from 2007 to 2017; age standardised death rate 6.3 per 100,000, with a 23.9% reduction from 2007 to 2017; age standardised YLL 152.8 per 100,000 with a 25.8% reduction from 2007 to 2017. Costs of asthma in the European Union, USA and Canada: - Annual incremental healthcare cost in adults: 964€ for intermittent asthma, 11,703€ for severe persistent asthma. - Annual incremental of non-healthcare costs in adults: from 136€ to 3,461€.	[1, 4-6]
Allergic rhinitis	Prevalence: up to 40% of the population worldwide High prevalence in the developed nations of the Northern Hemisphere: 23%-30% in Europe, 12%-30% in USA. Great variability (2.9% to 54.1%) in the non-Western populations of the Southern Hemisphere. Cost: 24.8 billion USD in the USA.	[7-10]
Atopic dermatitis	Prevalence: 205.5 million people worldwide Incidence: 27.1 million people YLDs: 9003 DALYs: 9 million, with an 11.6% increase from 2007 to 2017. Germany: 2,200€ direct and 1,200€ indirect costs per patient and year USA: non-healthcare costs of 10,000 USD per patient and year.	[1, 4, 5, 10-13]
Food allergy	Prevalence in Europe, definitions: - Reported reactions to foods: 17.3% (95%CI 17.0%-17.6%) - Food sensitisation: by skin tests 2.7% (2.4%-3.0%), by serum specific IgE 10.1% (9.4%-10.8%). - Confirmed FA by oral challenge: 0.9% (0.8%-1.1%). - Higher in Central and Northern EU countries. Prevalence in Asia, definitions: - Food-specific IgE sensitisation: 7.0-16.8% in China (highest in Hong Kong), 8.0% in Russia (Tomsk), 19.1% in India. - Probable food allergy (immediate reaction to a food and positive skin test/serum IgE): 0.2-1.5% in China (highest in Hong Kong), 0.9% in Tomsk, 0.1% in India.	[14, 90]
Drug allergy	Self-reported drug allergy: pooled prevalence of 7.9% (95% CI 6.4%-9.6%). Prevalence of confirmed allergy to penicillin derivatives (adverse reaction+ skin test + oral challenge): - All ages: 2.8% (95%CI 1.8-3.9%) - Below 18 years: 1.9% (95%CI 1.3-2.6%) - Adults: 7.7% (95%CI 6.5-9.0%)	[23, 25]

YLDs: years lived with disability; DALYs: disability adjusted life years (composite measure of disease burden capturing premature mortality and prevalence and severity of ill health); YLL: years of life lost; FA: food allergy; CI: confidence interval.

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Table 2. *Alergologica* surveys. Frequency of different allergic diseases diagnosed in outpatient clinics in Spain in the *Alergologica* surveys of 1992 (N= 4005), 2005 (N= 4991) and 2015 (N=2914).

Alergologica	1992	2005	2015
Rhinoconjunctivitis (%)	51.9	55.5	52.5
Asthma (%)	35	28	21.2
Drug allergy (%)	12.6	14.7	18.7
Food allergy (%)	3.6	7.4	11.4
Urticaria/Angioedema (%)	9.7	11	11.5
Contact dermatitis (%)	2.4	4.2	4.3
Atopic dermatitis (%)	2.5	3.4	3.4
Hymenoptera venom allergy (%)	0.7	1.5	2.5

The frequency of allergic diseases diagnosed is not the prevalence of these diseases in the Spanish population.

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LEGENDS TO FIGURES

Figure 1. ARADyAL research programmes. The network has a coordinator and is structured in three research programmes and a transversal teaching and mobility programme. The database and biobank are pivotal for the network.

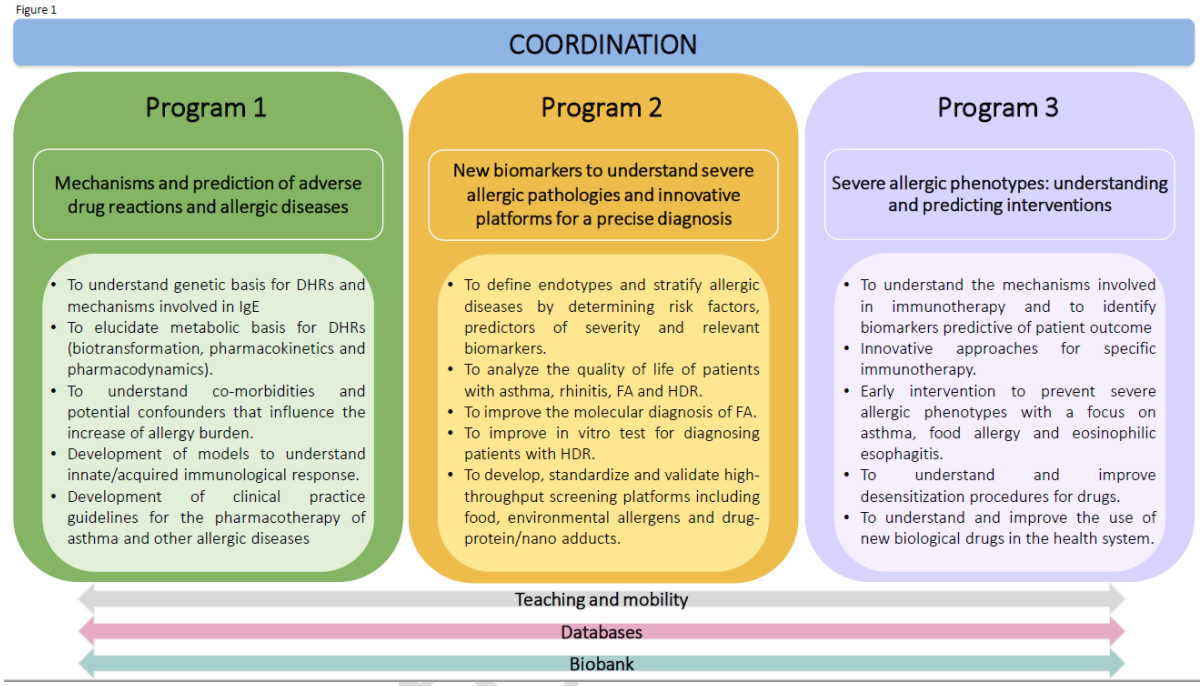

Figure 2. ARADyAL participants through Spain. There are three types of groups: Clinical research, basic research and clinical associates.

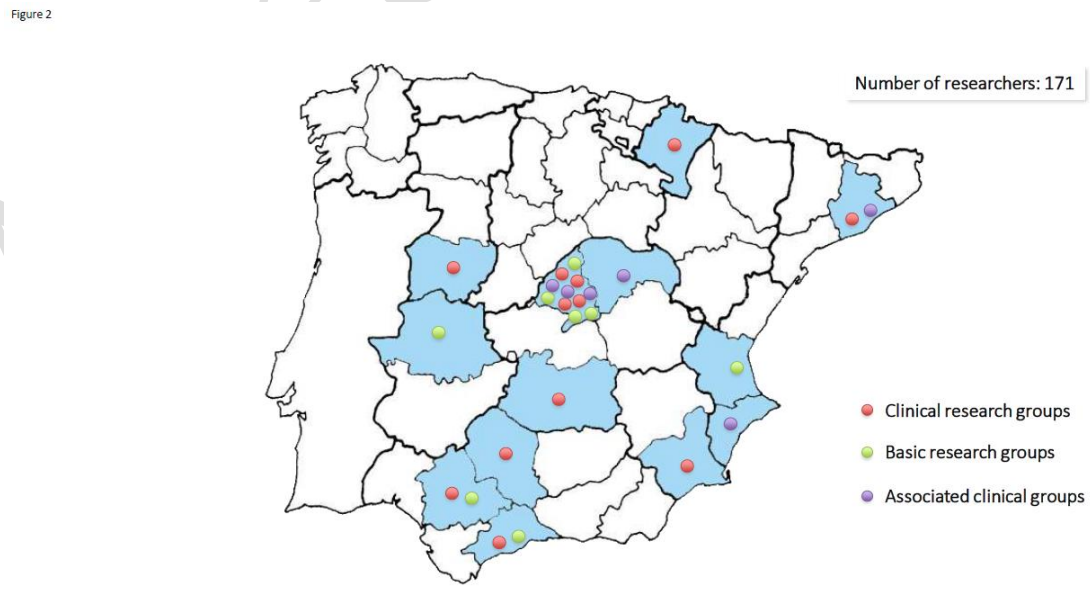

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Figure 3. ARADyAL training and mobility program. Main resources to train pre and post-doctoral researchers.

Figure 3