

ARADyAL: The Spanish Multidisciplinary Research Network for Allergic Diseases

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J Investig Allergol Clin Immunol 2021; Vol. 31(2): 108-119

doi: 10.18176/jiaci.0629

■ Abstract

Thematic cooperative health research networks (RETICS) are organizational 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 society as a whole in the field of health care. The RETICS of Asthma, Adverse Drug Reactions, and Allergy (ARADyAL) received funding in 2016 for a 5-year program (2017-2021). ARADyAL integrates basic and clinical research in the areas of allergy, immunology, genetics, nanomedicine, pharmacology, and chemistry, with special interest in research on new biomarkers and the design and evaluation of new interventions for allergic patients with severe phenotypes.

The consortium comprises 28 groups across Spain, including 171 clinical and basic researchers, 17 clinical groups that cover more than 10 000 000 patients of all ages from urban and rural areas and 11 basic groups active mostly at universities and research institutes. ARADyAL has proposed a research program organized into 3 different areas focusing on precision medicine, as follows: Program 1, Mechanisms and prediction of adverse drug reactions and allergic diseases; Program 2, Toward a precise diagnosis of allergic diseases; and Program 3, Predicting interventions in allergic diseases. There is also 1 common program dedicated to training. The network has a Steering Committee and an External Advisory Scientific Committee, which advise the global network coordinator, who has recognized expertise in the field. ARADyAL is a unique meeting point for clinicians and basic scientists who are already working in allergy.

Key words: Allergy. Research. Networks. Biomarkers. Mechanism. Diagnosis. Treatment.

■ 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. Red. Biomarcadores. Mecanismo. Diagnóstico. Tratamiento.

Introduction

Thematic networks of cooperative health research (RETICS) are organizational 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 society in the field of health care. RETICS respond to the health care priorities of the Spanish government plan for scientific and technical research and innovation, with the aim of shortening the interval between the production of new knowledge and its transfer to and applicability in clinical practice.

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

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 noncommunicable diseases, affecting almost 300 million people worldwide [1]. Incidence and prevalence differ between children and adults and by sex throughout life. There is a large geographical variation in prevalence, severity, and mortality. Asthma is more prevalent in high-income countries, although its prevalence is increasing in low- and middle-income countries [2,3].

Asthma has a substantial impact on health-related quality of life (HRQOL), especially in people with a severe phenotype. It is a leading cause of years lived with disability (YLD) and of burden of disease measured in disability-adjusted life years (DALYs). Severe and fatal asthma are more frequent in

adults [1,2,4,5]. Asthma is responsible for numerous visits to the doctor and the emergency room owing to exacerbations and inadequate control, resulting in high associated health care costs that increase with the severity of the disease (Table 1) [6].

AR is the most prevalent allergic disease. It is also one of the most common chronic diseases and the most frequent reason for allergy consultations in Spain [7] (Table 2). AR reduces HRQOL, impairs sleep quality and cognitive function, causes irritability and fatigue, and, although not associated with severe morbidity and mortality, leads to work and school absenteeism, generating important direct and indirect costs, which are actually greater than those of asthma [3,8,9] (Table 1).

AD is one of the most common inflammatory skin diseases, affecting more than 200 million people worldwide, mostly children. Its prevalence is higher among affluent countries, where its incidence continues to increase. AD leads to debilitating pruritus and sleeplessness and impairs HRQOL. It poses the highest global nonfatal burden of all skin diseases in terms of YLD and DALYs [1,3,4,10,11] and has a major economic impact (Table 1) [10,12,13].

The prevalence of FA has been increasing in affluent countries, with the disease now being considered the “second wave of the allergy epidemic”. The actual prevalence is difficult to establish owing to the heterogeneity of epidemiological studies and definitions (Table 1) [14]. In addition, there are age and geographical differences. In the Spanish Alergologica surveys, the frequency of FA increased 3-fold over 2 decades (from 3.6% in 1992 to 11.4% in 2015) [15-18] (Table 2). Additionally, the most severe FA phenotypes are increasingly frequent, accounting for higher rates of anaphylaxis and hospital admissions, mostly in children and adolescents [19,20].

Management of FA involves avoidance of the culprit food(s), which requires continuous vigilance by patients and families. Living with FA entails fear, uncertainty, anxiety, depression, and social isolation and has a very negative impact on HRQOL. Children with FA have poorer HRQOL than children with insulin-dependent diabetes [21]. FA also generates a heavy economic burden in terms of direct medical, out-of-pocket, and opportunity costs [22].

The prevalence of DHR is unknown. In a recent systematic review, the pooled prevalence of adverse drug reactions was 7.9%, that is, higher in females, adults, and hospitalized patients [23]. This figure overestimates drug allergy, thus increasing the need for delabeling of DHR. In fact, in a large

Table 1. Key Epidemiological and Socioeconomic Data for Allergic Diseases

Allergic Disease	Key Epidemiological and 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-standardized death rate 6.3 per 100 000, with a 23.9% reduction from 2007 to 2017; age-standardized YLLs 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 health care cost in adults: €964 for intermittent asthma, €11 703 for severe persistent asthma. - Annual incremental non-health care costs in adults: from €136 to €3461.	[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 the USA. Considerable variability (2.9% to 54.1%) in the non-Western populations of the Southern Hemisphere. Cost: US \$24.8 billion 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: €2200 in direct costs and €1200 in indirect costs per patient and year USA: non-health care costs of US \$10 000 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 sensitization: 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 sensitization: 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]

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

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 severe and life-threatening and is the main cause of anaphylaxis in hospitalized patients [19,20]. According to the *Alergologica* studies, the frequency of patients with FA diagnosed with DHR in outpatient clinics in Spain increased from 12.6% in 1992 to 18.7% in 2015 (Table 2) [16-18,26]. The impact of DHRs on HRQOL and their cost is unknown, although it is expected to be substantial. DHRs entail both direct and indirect costs. Additionally,

misdiagnosis has a negative medical and economic impact in hospitalized patients [27].

Identifying Etiology 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 our knowledge of the structure and functions of allergens. This knowledge has resulted in better characterization and standardization of allergen extracts for the development of

Table 2. Frequency of Allergic Diseases Diagnosed in Outpatient Clinics in Spain in the Alergologica Surveys of 1992 (N=4005), 2005 (N=4991), and 2015 (N=2914)^a

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

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

diagnostic tools and therapies. In the field of DHR, diagnosis is more complex, as the active drug or its metabolite can be involved. Several important questions related to allergens/drugs and allergic sensitization remain unanswered, and advances are necessary in the following areas: (1) structures of homologous allergens to study cross-reactivity for all major allergen types, (2) the effect of allergens/drugs on innate immune cells and signal transduction initiated by allergens/drugs in effectors cells, and (3) definition of “susceptibility to allergy/drug sensitization” at the molecular level.

Increasing our understanding of the etiology of allergic diseases and the underlying mechanisms requires considerable work if we are to develop effective prevention measures, advance in diagnosis, and develop safe and more effective therapies. Furthermore, it is necessary to design new in vitro diagnostic tests or improve the existing ones. Such a development or improvement could have a positive impact and make it easier to achieve a “true” diagnosis of allergy.

The increasing frequency of 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 changes in its composition and/or metabolism are thought to influence the immune system [29]. Moreover, epidemiological studies have revealed an association between pollution and allergic respiratory diseases owing to its impact both on the patient and on 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 terms of their environmental exposures throughout their lives, and the exposome can significantly influence the epigenetic regulation of the immune system and tissue cells. Questions remain with respect to how the many components, combinations, types of patient, and genetic background behave as decisive elements leading to allergic disease. Future research should try not only to elucidate the structural basis of allergenicity, but also to focus equally on the many additional factors associated with the environment and the host. Such an approach might lead

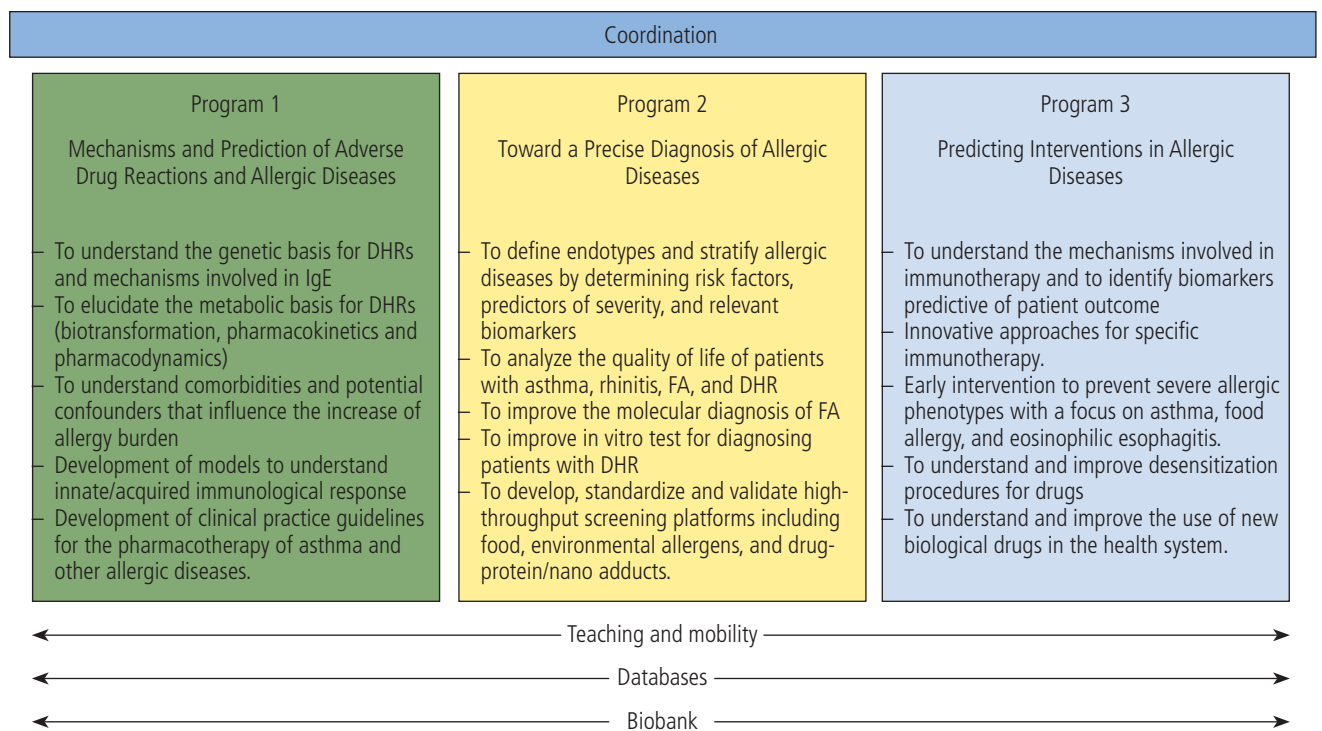


Figure 1. ARADyAL research programmes. The network has a coordinator and is structured into 3 research programs and a common teaching and mobility program. The database and biobank are pivotal for the network.

to new concepts of diagnosis, therapy, and prevention; hence the need for multidisciplinary studies including a high number of patients, which can only be achieved through networks.

ARADyAL Programs

ARADyAL has proposed a research program organized into 3 different areas focused on precision medicine (Figure 1).

Program 1. Mechanisms and Prediction of Adverse Drug Reactions and Allergic Diseases

It is widely accepted that there is interindividual variability in susceptibility, 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 sensitization and the immunological mechanisms underlying risk, progress to severe clinical presentations, clinical course, and response to pharmacotherapy. The ultimate goals of this research are to identify biomarkers of susceptibility and clinical course, to translate these biomarkers to the bedside, to use such biomarkers as proof of the underlying mechanism, and to develop models that can be of utility in research into mechanisms underlying allergic diseases or adverse drug reactions [39,41-45].

One of the focuses of this program is the search for factors (genetic or metabolic) that can explain why drugs or allergens can trigger an allergic response in specific individuals. In addition, the events occurring downstream of the triggering mechanism also show large interindividual variability in terms of clinical course and severity and immunological mediators. The development of novel mass-spectrometry procedures has enabled the identification of reactive drug metabolites involved in DHR, including amoxicillin and nonsteroidal anti-inflammatory drugs (NSAIDs) [32,38,46-51], which may elicit an immune response [51]. As drug metabolic profiles are often determined by variability in the genes coding for drug-metabolizing enzymes, it is conceivable that altered drug metabolism may predispose to DHR. Moreover, there is special interest in studying the biological/biochemical function of proteins, as well as of environmental substances, drugs, and xenobiotics that alter or even trigger the responses and could be related to allergenicity.

The development of the specific objectives (Figure 1) following strategic integration of efforts between traditionally segregated disciplines and within the ARADyAL consortium seems very promising for personalized medicine.

Program 2. Toward a Precise Diagnosis of Allergic Diseases

There are many variants in allergic diseases, and patients with similar clinical characteristics (phenotypes) can differ enormously in disease course and response to treatment. Endotypes take into account not 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 enable better characterization and stratification, precise diagnosis, and personalized treatments with the aim of optimizing care and reducing costs [52-54] (see specific objectives in Figure 1). The diagnosis of allergic reactions to food and inhalant allergens is challenging, since it is clear that “one size does not fit all”. Consequently, we must search for the optimal way to reach an accurate diagnosis. Considering FA, a wealth of evidence suggests that the same plant food can cause sensitization to a diverse range of allergens, with differences in severity and dosage thresholds and geographical variations [55]. It is of paramount importance to improve molecular diagnosis in FA [56-59]. In particular, we must take into account the possibility that sensitization and reaction are induced via different routes, thus affecting the onset of severe allergic reactions to food.

DHRs need to be correctly labelled after evaluation in an allergy unit following well-validated protocols [60]. However, reaching an accurate diagnosis is complex and time-consuming, and tests must be tailored to specific drugs, clinical manifestations, and underlying mechanisms. Such an approach often requires drug provocation tests, with their inherent risks for patients. Altogether, this makes management of DHR patients expensive for the health care system. It is important to remember 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 immune responses [51,61-63]. The lack of knowledge of the candidate target proteins and the formed adducts is one of the main limitations to the development of simple and useful in vitro tests. Another important limitation is the low population size from which data on severe allergic reactions can be obtained. In order to develop and validate new tests, access to large numbers of biological samples from well-characterized patients is crucial. This difficulty can be overcome only with the involvement of expert clinicians using standardized protocols and, importantly, by creating an integrated network that enables various hospitals and laboratories to collaborate and exchange samples and data.

Program 3. Predicting Interventions in Allergic Diseases

The difficulty in predicting and monitoring the effect of interventions on an individual-patient basis is a major problem in allergic diseases. Evidence is based on large-scale, multicenter trials, in which subjective medication scores of actively treated patients are compared with those of placebo-treated patients, thus preventing data from being reported on an individual basis [64,65]. Defining alternative objective biomarkers is difficult, as these are generally used as secondary outcomes with low predictive potential [66,67].

Achieving individual prediction is pivotal for daily clinical practice. In many cases, allergic disease coincides with various comorbidities, and it is often difficult to assign the contribution of allergic sensitization to the global clinical phenotype. There is an urgent need to advance in our understanding of underlying mechanisms, to identify new therapeutic targets, and to design

improved biomarker strategies that enable us to select, predict, and monitor the effect of therapeutic options (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 option is considered in such a way as to maximize the benefit for the patient and for society. New biological drugs offer new therapeutic options, although there is still a need to optimize their use, to define an intervention period, and to integrate them in an holistic approach to the etiology of the allergic disease [68]. Immunotherapy is the only intervention that offers the possibility of modifying the course of an allergic disease. When such tolerance is successfully induced using the appropriate product prescribed for a clinically relevant sensitization and for an adequate amount of time, it has a clear benefit in about 70% of patients [69,70]. However, it is nearly impossible to predict which patients will benefit from the intervention. We need to design new monitoring tools with specific biomarkers that should be closer to clinical and sensitization profiles and to incorporate them into clinical practice in order to maximize the position of the etiological intervention.

In an integrated therapeutic approach, new biological drugs developed for severely allergic patients could be used temporarily to revert the disease, stabilize the patient, and enable a specific intervention. Likewise, a symptomatic intervention will help decrease symptoms and maintain these benefits over time [71]. Identifying candidates for allergy prevention interventions, especially among children, is a priority area in the development of a new evidence-based intervention.

In order to validate these therapeutic algorithms, large-scale prospective collaborative trials in the context of collaborative networks are needed. Real-life monitoring of the outcomes of the interventions must be provided. omics-based biomarkers

that are common to the different interventions should be developed and validated. Understanding the underlying causes of the allergy epidemic and developing a prevention strategy—both primary (allergy prevention) and secondary (severity prevention)—will be crucial if we are to curb the increasing allergy epidemic.

Organization of ARADyAL

Structure, Members, Common Tools and Platforms, Standardized 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 the design and evaluation of interventions for patients with severe allergic phenotypes. These goals can only be achieved through an integrated work of multidisciplinary researchers. The ARADyAL consortium is composed of 171 clinical and basic groups in 28 groups across Spain: 17 clinical groups covering more than 10 000 000 patients of all ages and from urban and rural areas; and 11 basic groups, mostly at university and research institutes (Figure 2).

ARADyAL is organized into 3 scientific programs (described above) plus 1 common program dedicated to training. The network has a Steering Committee and an External Advisory Scientific Committee, which advise the global network coordinator. The ARADyAL coordinator has recognized 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 ARADyAL objectives (Figure 1). Scientific program coordinators are in charge of various research activities that are grouped into work packages and guarantee adequate functioning of the different groups, monitor the progress of ongoing projects, advise on collaborations, and disseminate events related to each program.

This network represents a unique meeting point for both clinicians and basic scientists who are already working on biomedical problems in 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. It is important to address patient diversity within Spain, ensuring an adequate sampling of patients included in epidemiological studies and combining both research and clinical profiles. Such an approach is crucial if we are to cover a broad panel of diseases and allergens that vary widely according to their geographic location. Basic scientists try to answer the questions by evaluating mechanisms, developing chemical structures and nanostructures, identifying and validating new biomarkers, and analyzing in depth the genetic basis of the disease.

For these purposes, the groups have produced consensus protocols and documents using common platforms as a database and a biobank for the management of biological samples used in the research lines. ARADyAL has developed a database in which information on patients with allergic

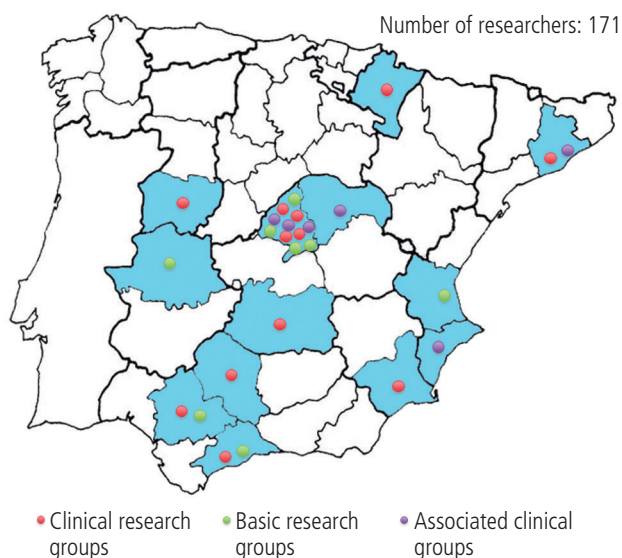


Figure 2. Distribution of ARADyAL participants throughout Spain. The 3 types of groups are clinical research, basic research, and clinical associates.

reactions to drugs and allergens from the various clinics and studies can be stored and used in future projects. In addition to demographic data, an enormous amount of information is generated at various clinical activities during the allergy work-up, as well as in protein analysis and genotyping in genetic studies aimed at determining the potential predisposition to develop these diseases or the response to treatment. Integrating this information for optimal use is complex and hugely challenging. Therefore, 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.

Biological samples play a key role in the activities of ARADyAL and are managed in a Biobank according to Biomedical Research Law 14/2007, and the Royal Decree on Biobanks RD1716/2011.

The synergies generated will make it possible to develop innovative approaches for diagnosis (endotypes, risk factors, and molecular diagnosis) and specific treatment for allergic diseases, with the aim of improving the quality of life of allergic patients.

Teaching and Researcher Mobility

The teaching program is a pivotal element of ARADyAL. The Teaching Committee comprises 10 members (5 clinical investigators and 5 basic researchers) who report directly to the Steering Committee. With the agreement of the Steering Committee, the Teaching Committee has defined 3 main educational objectives: (1) to provide predoctoral researchers (basic and clinical) with the necessary knowledge to improve their training and to facilitate the road toward a doctorate; (2) to provide postdoctoral researchers with an adapted program to improve their knowledge on the topics that are the objectives of the network; and (3) to promote interaction and exchange of knowledge between clinical and basic researchers. The main tools to achieve these objectives are the annual general meeting, at which the groups present their results and there is specific time for interaction. The meeting is oriented toward the exchange of experience and information and the constitution of alliances for investigation. A biannual summer school focusing on a specific topic is organized, as are small workshop meetings, virtual meetings, and expert conferences. Furthermore, ARADyAL members offer specific university courses. Finally, the ARADyAL website plays a key role in

the sharing of information and training. Currently, the main protocols of the different groups are at the disposal of the researchers, with the objective of harmonizing methodology. Specific online courses are now being organized.

The mobility program is organized as a predoctoral program offering 2- to 4-month training periods in ARADyAL centers and a postdoctoral mobility program offering 4- to 8-month training periods in ARADyAL centers, although periods in renowned national and international non-ARADyAL centers are also allowed. This program requires 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, the Spanish National Health System, health professionals, patient associations, the pharmaceutical industry, and the general public. One of the main tools we use is the website “aradyal.org”, which acts as a tool for dissemination and for improving communication between the ARADyAL consortium and stakeholders. In addition, the website is used to host an online repository containing information on research results, scientific publications, patents, resources, platforms, and other outcomes arising from the activities. The website contains general information on recent news, a calendar highlighting relevant events, a short video summarizing the network’s main objectives, and a sample of 5 podcasts prepared by each of the research groups in the network. These podcasts are randomly selected from those presented on another subpage (<http://aradyal.org/entrevistas/>), where all podcasts are available. Further information includes the aims of the network, the organization, the different groups that compose ARADyAL (including a specific webpage for each group), the research programs, information related to resources such as platforms and biobank, as well as links to the teaching program, to the communication website, and for access to available positions. The website contains links to the intranet, where ARADyAL members can access internal resources.

ARADyAL has the challenge to report recent advances to the general population. To achieve this goal, we recently implemented a section for publication of scientific information on our webpage and have started to become active on social networks, with the aim of reaching all potential interested followers among the general population.

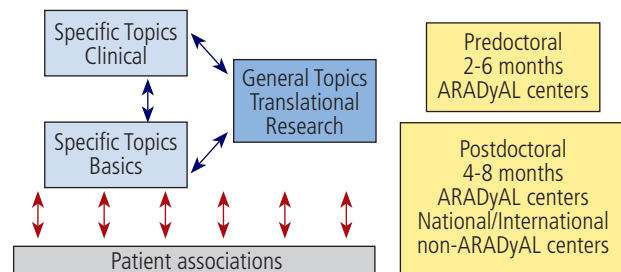


Figure 3. ARADyAL training and mobility program showing the main resources for training pre- and postdoctoral researchers.

ARADyAL Strategy

Projects and Clinical Trials: The Patient as the Center of Research

The objectives of ARADyAL (Figure 1) yielded several projects covering the association between genetics and allergic diseases [72], the burden of allergic disease [73-77], and the pharmacokinetics and pharmacodynamics profile of DHR [45]. Other projects involve the discovery of biomarkers [78] and the identification of the most prevalent allergens in the Mediterranean area, both of which are aimed at preventing severe allergic reactions. Various projects address DHR,

and one analyzes drugs and drug metabolites as antigenic determinants in an attempt to characterize the drug-protein interaction that enables an IgE-mediated reaction [40,79]. This project will pave the way for new diagnostic platforms for DHR.

The third group of projects focuses on therapeutic interventions such as integrating omic tools to assess changes in tolerance induced by immunotherapy [80] and assessment of molecular modifications to allergens with the aim of inducing immunomodulation. It also designs novel immunotherapy strategies for food allergy [81-83]. Other projects focus on detection of early interventions to prevent allergic inflammation and immune deviation [84-86], harmonization of rapid drug sensitization procedures, and improvement in the use of current biological drugs.

The monoclonal antibody omalizumab, which targets human IgE, is a new therapeutic intervention in the pharmacological portfolio. In recent years, we have gradually increased our understanding of the value of this drug. It is important to gather all available data in order to issue guidelines and consensus documents that minimize the cost to the health system and to guarantee that allergic individuals have access to adequate therapeutic interventions [87]. Other biologics for asthma treatment recently incorporated into the Spanish NHS should be adequately positioned to ensure maximum benefit for the population.

New interventions could be designed and improved in clinical trials. Consequently, ongoing developments include a trial aiming to develop new adjuvants for oral immunotherapy. Another example is a recently completed trial on the use of omalizumab in antihistamine-resistant cholinergic urticaria, for which no treatment is currently available [88].

Translational Medicine: From Bench to Bedside

Strengthening the connection between the laboratory bench and daily clinical practice is helping to improve diagnosis and treatment. Translational medicine is one of the approaches revolutionizing day-to-day interaction with patients in many medical disciplines. Physicians and scientists must provide personalized diagnostic and therapeutic strategies through multidisciplinary and collaborative approaches that combine advances in the knowledge of molecular tools, techniques developed by researchers in laboratories, and the design of effective treatment protocols [89].

Based on our experience, the molecular information obtained in the basic science groups of ARADyAL makes it possible to optimize prediction of response to therapy and must be shared among the members of the network. These data have the following applications: design of a complete panel of well-characterized 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. Furthermore, the experience of clinical researchers is required to transfer this information to patients appropriately within the framework of clinical trials that include suitable control groups, so that these investigations are validated in clinical practice. This process has several

clear purposes: improving diagnosis; achieving expression of biomarkers of the disease; analyzing the differences between health and disease, the risk of acquiring a disease, the severity of symptoms, and the alteration of certain metabolic pathways and metabolites; discovering therapeutic targets for biological products, drugs, and gene therapy; and verifying the response to therapy. Constant feedback results in the design of therapeutic strategies and improves the effectiveness of therapeutic agents. Finally, it is noteworthy that the ability of multicenter trials to validate a given treatment or diagnostic tool continues to be unsatisfactory, since this modality prevents us from predicting the progress of a given patient. Breaching this gap is a key medium- to long-term objective of ARADyAL, with the aim of ensuring more tangible benefits not only in terms of social welfare, but also in terms of tailored treatment based on biomedical findings.

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 partner in the proposed model; the information transmitted from the bench to the patient must continue to flow until it reaches society at large, thus closing the circle and providing the general public with a more circular and inclusive translational research model. Such an approach promises more appropriate, effective, and sustainable impacts on the target population.

Converting Research Into Marketable Products and Services

The progress of the activities of ARADyAL represents a unique opportunity to build the local resources of the research groups. ARADyAL will be a route to creating job opportunities in scientific, technological, commercial, and clinical fields as a consequence of the translation of scientific achievements to daily practice. ARADyAL will also provide an opportunity to develop a culture for innovation on the technological, entrepreneurial, and clinical levels. The combination of technology push and market pull will be the driving force behind improved clinical care.

One of the main objectives of ARADyAL is to strengthen the cooperation between industry and R&D consortia and thus increase the success rate of market-oriented projects. While it is important to ensure the management capacity of the participants individually, the organization of the consortium in order to prioritize management of risks. Furthermore, in the event that risk becomes a real challenge, the organization must be able to collaborate to find the optimal solution.

We are committed to organizational change at various levels. Market-oriented application of innovative technologies is sometimes hampered by organizational bottlenecks. Therefore, the ability to circumvent such bottlenecks through organizational change is often underestimated. Indeed, it is a key element for market success.

Active dissemination of research results through forums such as conferences, trade fairs, workshops, and publications is sometimes the only means of obtaining feedback on the economic potential and recommended market-oriented routes of development. Analysis of the type of technological application that the pharmaceutical industry provides and, more importantly, clinical practice demands is a key parameter in

our objectives. Even optimally prepared and applied market-oriented processes fail if the demand is not justified or strong enough. This lack of coordination can result in a mismatch between innovation and investment.

In order to successfully commercialize the results of research, it is necessary to have a broad knowledge of the production processes and the challenges of integrating innovation into clinical practice. Therefore, we must be able to convince those interested in the advantages and integration of our innovation. Formal and informal standards play a vital role. Some technologies may open new markets or market niches for the first time, thus enabling the supplier to position the product as a standard.

In order to ensure a significant impact of the appropriate application to clinical practice in the field of allergy and avoid a chain of subsequent steps, our innovation pathway must be based on a continuous process of activity between basic science, clinical practice, and the business sector.

Conclusions

In summary, the ARADyAL network has made it possible to develop experimental models that play a key role in analyzing the mechanisms involved in allergic diseases, such as mast cell activation, food allergy exacerbated by NSAIDs, a murine model of anaphylaxis, and the interaction between allergen and intestine or respiratory mucosa. The main results applicable to diagnosis are as follows: (1) discovery of mechanisms associated with severe phenotypes and comorbidities; (2) identification of new and clinically relevant allergens; (3) identification of carrier proteins and structural details of the binding site that are important in DHRs; and (4) development of high-capacity dendrimeric nanostructures, nanoparticles, and platforms. Advances in the treatment of allergic diseases have been made in interventional studies, as follows: (1) design and validation of dendrimeric systems for immunotherapy; (2) pharmacogenomic and drug metabolism analysis; (3) design of databases to record the administration and adverse effects of biological drugs in allergic diseases and thus optimize the rational use of drugs; (4) identification of candidate genes for pharmacogenomic studies of response to asthma treatment.

The translational network ARADyAL represents a unique platform for generating synergies between clinicians and basic scientists who are already working on biomedical problems in asthma, allergy, and adverse drug reactions. The contribution of ARADyAL will make it possible to understand the underlying mechanisms of allergic diseases and thus enable us to develop innovative approaches for prevention, diagnosis, and treatment.

Funding

Institute of Health “Carlos III” of the Ministry of Economy and Competitiveness, cofunded by the European Regional Development Fund (ERDF) and RETICS ARADyAL RD16/0006.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ *Manuscript received March 6, 2020; accepted for publication June 25, 2020.*

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