Laboratory of Nanostructures for Diagnosing and Treatment of Allergic Diseases

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***RIRAAF**, Red de Investigación de Reacciones Adversas a Alérgenos y Fármacos, (Instituto de Salud Carlos III) (until end 2016)*
ARADyAL, Asthma, Adverse and Allergic reactions (RETICs, Instituto de Salud Carlos III) (starts in 2017)
ENDA, European Network on Drug Allergy

Keywords

Allergens, allergy, gold nanoclusters (Au-NC), dendrimers, dendritic cells (DC), DC-sign, dendrons, drugs, epitopes, exosomes, IgE, in vitro tests, immunotherapy, immunochemistry, material chemistry, microarrays, organic chemistry, proteomics, synthetic antigens, T-cells, toll like receptors (TLR)

Research Lines

- ✓ **Adverse reactions to drugs**:
  - Immunological mechanisms in IgE mediated reactions
  -Design of in vitro tests for diagnosing IgE mediated reactions in drug allergy
  - Immunological mechanisms in T cell mediated reactions
- ✓ **Adverse reactions to allergens:**
  -Analysis of underlying cellular mechanisms at effector phase
  -Induction of tolerant responses
- ✓ **Nanoengineered biological vesicles with anti-inflammatory and immunosuppressive activities.**

Scientific Activity

We are a multidisciplinary team integrated by clinicians and basic researchers that develop our research activities in hospital centers and research institutes with a translational character for improving the diagnostic and treatments of patients with allergic reactions and therefore the patient´s quality of life. Our studies are focused to better understand immune regulation of adverse reactions to drugs and allergens in order to accurately treat these allergic disorders. Our research in Bionand is related to the design, synthesis and characterization of molecular nanostructures for the study of their interaction with components of the immune system (immunoglobulin E (IgE), T-cells, dendritic cells (DC),…), as well as the study of properties on molecules and nanosystems (chemical structure, tridimensional conformation, size,…) in the context of immune molecular recognition. The experiments proposed in our current projects require a deep understanding of aspects of organic chemistry, material chemistry, proteomics, biosensing, animal model studies, as well as skills to foster collaboration and mutual understanding between clinicians and basic researchers from distinct disciplines. Our research deals with nanotechnology, organic chemistry and biomedicine with eventual application on treatment and diagnosis of allergic diseases.

Research lines:

✓ **Adverse reactions to drugs**

Hypersensitivity reactions to drugs (HDRs) usually appear during their clinical use and constitute a serious health problem, as they are an important cause of patient morbidity and mortality. During HDRs there is a drug covalent binding to endogenous proteins, forming adducts that render the immunogenic drug and thereby induce an allergic immune response producing IgE antibodies or T cells that specifically recognize the adduct. This phenomenon is complex and it is still not well known whether in allergic subjects there is a preferential/non preferential binding of drugs to endogenous proteins and/or these adducts are processed in different ways by the immune system. In the formed-adduct, both the chemical structure provided by the drug and the carrier protein contribute to the generation of the antigenic determinant. One disadvantage of the classical carriers is that on their surface the haptens are randomly distributed and therefore the use of nanoconjugated dendrimers may help to solve this problem. The group has developed PolyAMinoAMide (PAMAM) dendrimers decorated on the periphery with penicilloyl moieties (penicillin-derivate), which mimics the recognition of natural hapten-protein conjugates. In fact, IgE to penicillins can be determined by immunoassay using penicilloyl-dendrimer conjugates coupled to cellulose or other solid surfaces. These approaches can be used to design consistent prototypes using dendrimers, which will allow having complete control and knowledge about the structure of the conjugate, and the possibility to modify the number of haptens, the size of the carrier and even adding different hapten models in a carrier dendrimer.

Our goal is to get a better understanding about the HDRs in order to design new diagnostic and therapeutic approaches, including microarrays, to help in the clinical management of drug allergic patients. In this research area the studies are focused at the humoral level (immediate adverse reactions) and at the cellular level (non-immediate adverse reactions).

A brief schematic explanation of aims related to every sub-research line are described following:

- Immunological mechanisms in IgE mediated reactions: (i) new drug antigenic determinants identification, characterization and synthesis; (ii) identification of target carrier proteins modified by drugs; (iii) Analysis of the effector and tolerant immunological response by applying a cellular model including dendritic cells and lymphocytes.

- Design of in vitro tests for diagnosing IgE mediated reactions in drug allergy: (i) hapten-protein adducts and hapten-dendrimer nanoadducts design; (ii) adducts IgE response specificity studies by using immunoassays and cell activation techniques; (iii) development of new materials, including nanostructures and different solid phases for detecting IgE response to drugs.

- Immunological mechanisms in T cell mediated reactions: (i) studies of drug interaction with cells involved in first stage allergic reaction; (ii) cell contribution of effector phase and tolerance maintenance in non-immediate reactions to drugs; (iii) Identification of biomarkers for early diagnosis.

✓ **Adverse reactions to allergens**

Food allergy is defined as an immunologically adverse reaction to foods and can range from acute and life-threatening to chronic. The prevalence of food allergy appears to be on increase, affecting 3-4% of adults and 4-8% of children. There is not treatment of food allergy beyond strict allergen avoidance, which has a negative impact on quality of life of the patients and furthermore resulting in growth failure in children. Since many food allergens cross-react each other, elimination diet is ineffective or not feasible for many patients.

There is a major need for the development of new therapeutic approaches to treat food allergic disorders. Specific immunotherapy for food allergy has been difficult since serious life-threatening side effects may occur, especially with subcutaneous allergen immunotherapy. However, in recent years, treatment of food allergic patients with oral allergen immunotherapy as well as with sublingual immunotherapy has successfully resulted in desensitization and in some cases tolerance to the food allergen. sIT treatments have been performed using crude protein extracts containing whole allergen molecules with the risk of inducing an allergic reaction. Strategies aimed at reducing the allergenicity include chemical modification or the use of T cell peptides which do not crosslink with specific IgE. Synthetic peptides seem to be a promising approach to induce immune tolerance; however, it might be necessary to use adjuvants in order to enhance the immune response induced by these peptides. Advanced strategies include the use of toll-like receptor (TLR) ligands or DC-SIGN, which trigger DC maturation, as major targets for the development of vaccine adjuvants. Dendrimer bifunctionalization with T cell epitopes and DC receptor agonists provide a great opportunity to integrate all the elements necessary to interact with target immune cells. These nanostructures will be more effective interacting with the immune system, thereby skewing the allergic response towards Th1 as well as reducing the time of the treatment. These studies will be applied in experimental models of food allergy in order to evaluate the induction of immune tolerance. The long-term goal will be to use these nanostructures to treat food allergic patients.

A brief schematic explanation of aims related to every sub-research line are described following:

- Analysis of cellular underlying mechanisms at effector phase: (i) phenotypic and functional features of effector cells (T, B and NK lymphocytes and DC) that participate in the allergic response; (ii) role of Treg cells in the maintenance of tolerance response.

- Induction of tolerant responses: (i) underlying mechanisms in specific immunotherapy with allergens; (ii) development of dendritic structures with the ability of including allergen epitopes and immunoregulator molecules as novel approaches for the development of vaccines.

✓ **Nanoengineered biological vesicles with anti-inflammatory and immunosuppressive activities**

Conventional anti-inflammatory and immunosuppressive therapies based on natural or synthetic drugs for the treatment of auto and non-autoimmune diseases or organ transplantation experience severe limitations such as a poor efficacy and harsh adverse effects. The emergence of nanotechnology with the use of nanoparticles as drug delivery systems have received a high interest to treat diseases allowing to reduce toxicity, enhance the sustain release, and improve the selectivity to the site of action. Exosomes represent a novel class of biological vesicles, which are seen as excellent candidates to carry drugs or biomolecules due to their biocompatibility, small size (i.e high diffusion), ability to modify their phenotype, and to present molecule on their surface. We aim to design engineered exosomes exhibiting anti-inflammatory and immunosuppressive activities by i) improving the transfection of therapeutic agents into those biological vesicles by using allergen functionalized nanoparticles, and ii) enhancing the intrinsic immunosuppressive activity of exosomes.

Collaborations

❖ **University Grenoble-Alpes** (France), Dr. Xavier Le Guevel. Exosomes and gold nanoclusters for immunotherapy.

❖ **Royal Institute of Technology** (Sweden), associate Professor Michael Malkoch. Design of dendrimers and complex macromolecules for drug allergy studies.

❖ **IMDEA-Nanoscience and University Complutense of Madrid** (Spain), Professor Nazario Martín. Immunological studies of fullerens.

❖ **Instituto de Investigaciones Químicas** (CSIC, Spain), Dr. Javier Rojo. Nanostructures including glycodendrimers for immunotherapy.

❖**Centro de Investigaciones Biológicas** (CSIC, Spain), Dr. Dolores Perez-Sala. Proteomic studies in drug allergy.

❖ **ALK-ABELLO Laboratories** (Spain). Evaluation of immunological mechanisms involved in the efficacy of sublingual immunotherapy with LTP (Pru p3) in allergic patients, mono or polysensibilized, to LTP from food.

❖ **Paul-Ehrlich Institute** (Langen, Germany), Dr. Stephan Scheurer. Immunological evaluation of compounds for specific immunotherapy.

❖ **Institute of Translational Medicine, University of Liverpool** (England), Professor Munir Pirmohamed. Pharmacogenetic studies.

❖ **Institute of Translational Medicine, University of Liverpool** (England), Dr. Dean Naisbitt. Study of selective reations to betalactams and obtention of clones from T lymphocytes specific to amoxicillin and clavulanic acid, from peripheral blood samples and positive skin tests for analyzing the immunological recognition of different structures.

❖ **University of Nancy**, Prof.Guéant (Univ. de Nancy, France). Pharmacogenomic studies.

Research Projects in the last 5 years

- Development of antibiotic conjugates with nanostructures or proteins and their application to the in vitro diagnosis of antibiotic allergy, CP15/00103, Miguel Servet Grant, Instituto de Salud Carlos III (2016-2018). PI: Maria Isabel Montañez Vega. Grants cofunded by European Regional Development Fund (ERDF) and European Social Fund (ESF).

- Desarrollo de un microarray con aductos fármaco- proteína / nanoestructura para el diagnóstico de alergia a antibióticos, PI-0179-2014, Fundación Progreso y Salud (2015-2017). PI: Maria Isabel Montañez Vega

- Development of nanostructural materials with potential applications in drug allergy diagnosis: towards immunoassays and cellular tests (basophil activation tests), IEF Marie-Curie Grant (Mª Isabel Montañez Vega)), European Commission (2012-2014).

- Exosomas diseñados como nanopartículas teranóstica para la vacunación, Fundación Salud 2000 (Merck-Serono) (2015-2017). PI: Xavier Le Guevel. Grants cofunded by European Regional Development Fund (ERDF) and European Social Fund (ESF).

- Effect of the physicochemical properties of nanoparticles to the biodistribution and to the immunoresponse of dendritic cells. Applications of nanoparticles for immunotherapy of allergic disease, CP12/00310, Miguel Servet Grant, Instituto de Salud Carlos III (2013-2015). PI: Xavier Le Guevel. Grants cofunded by European Regional Development Fund (ERDF).

- Desarrollo de nanoestructuras para el diseño de vesículas biológicas con actividades antiinflamatoria e inmunosupresora, PI15/00898, Instituto de Salud Carlos III (2016-2018). PI: Adriana Ariza. Grants cofunded by European Regional Development Fund (ERDF).

- Desarrollo de materiales nanoestructurados dendriméricos con aplicaciones potenciales en el diagnóstico de alergias a fármacos: inmunoensayos y test de activación celular, PI-0699/2011, Fundación Progreso y Salud (2012-2016). PI: Adriana Ariza .

- Exosomas diseñados con nanopartículas teranósticas para el tratamiento de alergia, PI-0209-2014, Fundación Progreso y Salud (2015-2017). PI: Francisca Gómez

- Estudio de biomarcadores y factores de riesgo relacionados con el desarrollo de una respuesta alérgica diferencial frente a amoxicilina o clavulánico, PI15/01206, Instituto de Salud Carlos III (2016-2018). PI: Mª José Torres. Grants cofunded by European Regional Development Fund (ERDF).

- Identificación y caracterización inmunológica de conjugados de betalactámicos con proteínas y nanoestructuras para su aplicación al diagnóstico in vitro de reacciones alérgicas IgE, PI12/02529, Instituto Salud Carlos III (2013-2015). PI: Mª José Torres

- Respuesta IgE a antibióticos betalactámicos: análisis de la contribución de diferentes estructuras químicas al reconocimiento por los anticuerpos e identificación de proteínas candidatas, Fundación Salud 2000 (Merck-Serono) (2011-2014). PI: Mª José Torres

- Diseño de nanoestructuras sintéticas hapteno-portador para la detección de anticuerpos IgE en reacciones de hipersensibilidad a betalactámicos, PI-0545-2010, Consejería de Salud (2011-2013). PI: Mª José Torres

- Desarrollo de prototipos experimentales de conjugados hapteno-carrier para aplicación diagnóstica en las reacciones de hipersensibilidad a fármacos, CTS 06603, Consejería de Economía, Innovación, Ciencia y Empleo (2011-2014). IP: Mª José Torres. Grants cofunded by European Regional Development Fund (ERDF).

- Red de Investigación de Reacciones Adversas a Alergenos y Fármacos (RIRAAF), RETIC RD12/0013/0001, Instituto de Salud Carlos III (2013-2016). Current coordinator: Mª José Torres. Grants cofunded by European Regional Development Fund (ERDF)

▪Asma, Reacciones Adversas y Alérgicas, RETIC RD16/0006/0001 (2017-2021). Coordinator: Mª José Torres. Grants cofunded by European Regional Development Fund (ERDF).

▪ Estudio del papel del sistema inmune innato e identificación de biomarcadores en respuestas anafilácticas y de tolerancia inducida a alérgenos alimentarios de origen vegetal, PI15/00559, Instituto Salud Carlos III (2016-2018). PI: Cristobalina Mayorga Mayorga. Grants cofunded by European Regional Development Fund (ERDF).

▪ Estudios de la modulación de la respuesta inmunológica y desarrollo de modelos de tolerancia a alérgenos de origen vegetal utilizando nanoestructuras polifuncionales, PI12/02481, Instituto Salud Carlos III (2013-2015). PI: Cristobalina Mayorga Mayorga

▪ Estudio de los mecanismos inmunológicos implicados en la inmunoterapia específica con alérgenos. Papel de las células T reguladoras y efectoras específicas, PI-0542-2010, Consejería de Salud, Junta de Andalucía (2011-2013). PI: Cristobalina Mayorga Mayorga.

▪ Caracterización de la alergenicidad de proteínas de origen vegetal (panalergenos). Estudios de la modulación de la respuesta inmunológica y desarrollo de modelos de tolerancia utilizando nanoestructuras polifuncionales, CTS-7433, Consejería de Economía, Innovación, Ciencia y Empleo (2012-2016). PI: Cristobalina Mayorga Mayorga. Grants cofunded by European Regional Development Fund (ERDF).

▪ Diseño de epítopos hipoalergénicos del Pru p 3 acoplados a nanoestructuras dendriméricas para su utilización en inmunoterapia en alergia alimentaria, PI0347-2012, Consejería de Igualdad, Salud y Políticas Sociales (2013-2015). IP: Ana Aranda

Publications in the last 5 years

▪ A Yahia-Ammar, D Sierra, F Mérola, N Hildebrandt and X Le Guével. Self-Assembled Gold Nanoclusters for Bright Fluorescence Imaging and Enhanced Drug Delivery. ACS Nano, 2016, 10, 2591-2599. DOI: 10.1021/acsnano.5b07596

▪ C Mayorga, E Perez-Inestrosa, N Molina and MI Montañez. Development of nanostructures in the diagnosis of drug hypersensitivity reactions. Current Opinion in Allergy and Clinical Immunology, 2016, 16, 300-307. DOI: 10.1097/aci.0000000000000282

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▪ TD Fernández, A Ariza, F Palomares, MI Montañez, M Salas, A Martín-Serrano, R Fernández, A Ruiz, M Blanca, C Mayorga and MJ Torres. Hypersensitivity to fluoroquinolones: The expression of basophil activation markers depends on the clinical entity and the culprit fluoroquinolone. Medicine, 2016, 95, e3679. DOI: 10.1097/md.0000000000003679

▪ MJ Torres, MI Montañez, A Ariza, M Salas, TD Fernandez, N Barbero, C Mayorga and M Blanca. The role of IgE recognition in allergic reactions to amoxicillin and clavulanic acid. Clinical and Experimental Allergy, 2016, 46, 264-274. DOI: 10.1111/cea.12689

▪ C Mayorga, G Celik, P Rouzaire, P Whitaker, P Bonadonna, JR Cernadas, A Vultaggio, K Brockow, JC Caubet, J Makowska, A Nakonechna, A Romano, MI Montanez, JJ Laguna, G Zanoni, JL Gueant, H Oude Elberink, J Fernandez, S Viel, P Demoly, MJ Torres o behalf of In vitro tests for Drug Allergy Task Force of EAACI Drug Interest Group. In vitro tests for Drug Hypersensitivity Reactions. An ENDA/EAACI Drug Allergy Interest Group Position Paper. Allergy, 2016, 71, 1103-1134. DOI: 10.1111/all.12886

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▪ L Martín-Pedraza, M González, F Gómez, N Blanca-López, M Garrido-Arandia, R Rodríguez, MJ Torres, M Blanca, M Villalba and C Mayorga. Two nonspecific lipid transfer proteins (nsLTPs) from tomato seeds are associated to severe symptoms of tomato-allergic patients. Molecular Nutrition & Food Research, 2016, 60, 1172-1182. DOI: 10.1002/mnfr.201500782

▪ E. MI Montañez, F Najera, C Mayorga, AJ Ruiz-Sanchez, Y Vida, D Collado, M Blanca, MJ Torres and E Perez-Inestrosa. Recognition of multiepitope dendrimeric antigens by human immunoglobulin Nanomedicine: Nanotechnology, Biology and Medicine, 2015, 11, 579-588. DOI: 10.1016/j.nano.2015.01.006

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Patents

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