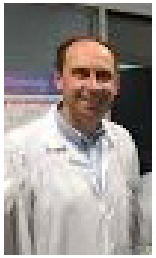
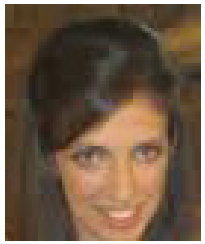
3.3.7 Drug Hypersensitivity and Innate Immune Response





Publications: 7 | **Q1:** 5

COMPOSITION

Teresa Bellón Heredia.
Investigadora Senior (Contrato Miguel Servet -I2). Jefe de laboratorio. FIBHULP

- **María del Rosario Cabañas Moreno.** *Facultativo Especialista de Área en Alergología. Hospital Universitario La Paz*
- **Sofía Caiqin Linares Reyes.** *Investigadora Predoctoral. FIBHULP*
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STRATEGIC OBJETIVES

- Cutaneous adverse drug reactions are unpredictable and represent a plethora of skin diseases with various degrees of severity. The spectrum ranges from mild to potentially fatal multisystem maladies. Those of most concern are usually referred to as severe cutaneous adverse reactions (SCARs), and include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug induced hypersensitivity syndrome or hypersensitivity síndrome (DIHS/HSS), Stevens-Johnson's syndrome (SJS), and toxic epidermal necrolysis (TEN). Among them, SJS and TEN are the most severe clinical entities and are nowadays considered as variants of the same disease characterized by keratinocyte necrosis and epidermal detachment with the formation of subepidermal bullae. From the immunopatohogenic point of view, SCARs are T-cell mediated type IV hypersensitivity reactions. However, T cells can orchestrate different types of immune responses and this functional heterogeneity has led to a further sub-classification into type IVa-IVd hypersensitivity that considers the distinct cytokine production pattern by T cell subpopulations, and emphasizes the participation of different effector cells causing inflammation and tissue damage. Current knowledge supports the active participation of cytotoxic lymphocytes in different clinical entities.
- Our project aims to a better understanding of the immune mechanisms underlying the etiopathogenesis of these diseases. The study is performed in the framework of the consortium PIELenRed (Plataforma interdisciplinar para el estudio de reacciones cutáneas graves en red) integrated by researchers belonging to different hospitals in Madrid. A Biobank of biological samples has been created linked to the epidemiological registry
- Reactivation of latent herpesvirus has been described during the development of some of the previously mentioned clinical entities. In order to improve our understanding of the behavior of the immune system during viral replication, a collaboration was established with the Kidney Transplant Unit (Nephrology Service, HULP). Kidney transplant recipients were followed immediately before and after transplant in order to identify patients with active CMV replication. Samples from the patients have been stored in the Biobank for immunological studies.
- Desensitization procedures have allowed the treatment of patients with drug allergies with their first line medications or when there are no alternatives available. A new project has been initiated to understand mechanism of tolerance in patients undergoing drug desensitization procedures
- General objectives for the next 5 years
- The main objectives are:
  - I) Biobanking of samples of severe cutaneous adverse reactions to medications (DRESS, AGEP and SJS/TEN) associated to the registry PIELenRed, and integrated in the international registry RegiSCAR.
  - II) To investigate in vitro test for drug causality assessement.
  - III) To explore the involvement of the innate immune response (in particular natural cytotoxic activity) during the development of SCARs.
  - IV) Identification of biomarkers of susceptibility.
  - V) Analysis mechanisms leading to tolerance in patients undergoing drug desensitization

RESEARCH LINES

- Biobanking of biological samples from patients with severe cutaneous adverse reactions to medications (DRESS, AGEP and SJS/TEN).
- Development and evaluation of in vtro tests for drug causality assessment.
- Identification of biomarkers of susceptibility.
- Involvement of NK receptors in the etiopathogenesis of Stevens-Johnson syndrome /Toxic epidermal necrolysis (SJS/TEN).
- Differential analysis of the cytokine pattern involved in different SCARs (AGEP, DRESS and SJS/TEN).
- Identification of biomarkers of tolerance to drug desensitization procedures

RESEARCH ACTIVITY

Publications

- **Entrala A, Loli-Ausejo D, Pérez T, Losantos , Cabañas R, Caballero T.** Real-life Experience of Subcutaneous Plasma Derived C1-Inhibitor as Long-term Prophylaxis in HAE-C1INH. J Invest Allerg Clin. 2024; 34(4): 261-3. Editorial Material. IF: 4.8; Q1
- **Fernández-Concha I, Pose K, de las Vecillas L, Lluch-Bernal M, Tomás-Pérez M, Soto T, de la Guía AL, Cabañas R.** Successful Desensitization to Lenalidomide in Leukocytoclastic Vasculitis. J Invest Allerg Clin. 2024; 34(5): 352-3. Editorial Material. IF: 4.8; Q1
- **Lluncor-Salazar M, Phillips-Anglés E, Pedrosa M, Lamacchia D, Hernanz A, Prior N, Cabañas R, Caballero T.** Determinants of Disease Activity in Adults With Hereditary Angioedema due to C1-Esterase Inhibitor Deficiency. J Invest Allerg Clin. 2024; 34(6): 406-9. Editorial Material. IF: 4.8; Q1
- **Mir-Ihara P, Vecillas LD, Heredia R, Fiandor A, González-Muñoz M, Zamarrón E, Prados C, Cabañas R.** Protocol for Successful Desensitization to Ivacaftor and Elexacaftor/Tezacaftor/Ivacaftor in a Delayed Hypersensitivity Reaction Confirmed by the Lymphocyte Transformation Test. J Invest Allerg Clin. 2024; 34(3): 211-3. Article. IF: 4.8; Q1
- **Nitola-Mendoza L, Sánchez-Cardenas M, Rodríguez-Chitiva N, Mora Gutiérrez JM, Rodríguez-Pena R, Romero-González G, Bleda Perez M, Cuenca Casbas P, Calsina-Berna A, Alvaro-Pardo M, Granados Casas V, Garrido Ballart P, Beroiz Groh P, Bover J, Miralles Basseda R, Leiva-Santos JP, Alonso-Babarro A, Julia-Torras J.** Nomenclature in Palliative and Kidney Supportive Care: Not Just at the End-of-Life. Nefrologia. 2024; 44(4): 475-45-. Review. Not Indexed
- **Pose K, Narváez-Fernández E, de la Guía AL, De Las Vecillas L, Domínguez-Ortega J, Lluch-Bernal M, Fiando A, Cabañas R.** A Tailored 7-to 10-Day Lenalidomide Desensitization Protocol. J Invest Allerg Clin. 2024; 34(1): 49-50. Editorial Material. IF: 4.8; Q1
- **Souza RD, Bellón T, Benito EF, Cudós ES.** Flow Cytometric Analysis of Skin Blister Fluid Cells: A Promising Tool in the Differential Diagnosis of Acute Cutaneous Graft-versus-host Disease and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Actas Dermosifiliogr. 2024; 115(10): 1042-4. Editorial Material. IF: 2.8; Q2

Research projects

- **Bellón Heredia T.** Contrato Miguel Servet Categoria B (CES06/016). ISCIII. 2007-2025. Managment centre: FIBHULP

- **Bellón Heredia T.** Creación de un centro de referencia para el estudio de los mecanismos implicados en las reacciones de hipersensibilidad a las membranas de hemodiálisis basadas en polysulfona (PI-3009). Nipro Euope NV. 2017-Ongoing. Managment centre: FIBHULP
- **Bellón Heredia T.** ELISpot como método diagnóstico para identificación del fármaco causal en pacientes con reacciones graves de hipersensibilidad cutánea a medicamentos: comparación con TTL. FIBHULP. 2023-2025. Managment centre: FIBHULP
- **de las Vecillas Sánchez L.** Estudio de la inmunomodulación celular inducida en las desensibilizaciones a quimioterápicos tras reacciones inmediatas y tardías. Sociedad Española de Alergología e Inmunología Clínica. 2022-2024. Managment centre: Fundación SEAIC

Patents and trademarks

- **Selgas Gutiérrez R, Bellón Heredia T, Rodríguez Sanz AI, Álvarez Builla J, Vaquero López JJ, Sánchez Alonso P, Alajarín Fernández R, inventors; FIBHULP, Universidad de Alcalá, assignees.** Use of compounds derived from salts of pyridazine[1′,6′:1,2]pyrido[3,4-b]indolinium as anti-inflammatory agents. P201331143, PCT/ES2014/070603; 2013 July 25.
- **Selgas Gutiérrez R, Bellón Heredia T, Rodríguez Sanz AI, Álvarez Builla J, Vaquero López JJ, Sánchez Alonso P, Alajarín Fernández R, inventors; FIBHULP, Universidad de Alcalá, assignees.** Use of compounds derived from salts of piridazine[3,2-b]benzimidazolium as anti-inflammatory agents. P201430411, PCT/ES2014/070603; 2013 July 25.