29 PLASMACYTOID DENDRITIC CELLS AS A TREATMENT TARGET

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In the 1970s, Hooks *et al*. at the National Institutes of Health noted the presence of interferon in the blood of approximately 70% of patients with active systemic lupus erythematosus (SLE). They concluded that interferon may play a role in the pathogenesis of SLE.[1] Additional evidence linking interferon and SLE emerged in the form of isolated case reports.[2] With the introduction of the interferon gene signature in the early 2000s, interferon science evolved to even greater heights.[3 4] The burning clinical question was whether the interferon pathway could be inhibited and whether this would impact lupus disease activity. With the success of the anifrolumab development programme, additional strategies to subdue interferon pathway activation were explored.[5–7] The plasmacytoid dendritic cell (pDC), a mass producer of type I and III interferons, was a very compelling target. Abundant in the skin as well as other organs in patients with SLE, development programs evolved with litifilimab and daxdilimab. The former monoclonal antibody binds blood cell dendritic antigen 2 (BDCA2), a protein selectively expressed on pDCs.[8] BDCA2 ligation results in the suppression of type I and III interferon production as well as other proinflammatory cytokines and chemokines. Building upon the successes of the phase 2 programme,[9 10] litifilimab is currently in phase III studies of both SLE and cutaneous lupus. Daxdilimab, a cytolytic antibody that targets Immunoglobulin-like transcript 7 (ILT7), is also in development for the treatment of SLE.[11] Strategies to dampen SLE disease activity are incredibly eclectic, and the interferon pathway is no exception. Regardless of which approach rises to the top, the future is bright for our patients with SLE.

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Learning Objectives

- Discuss the role of interferons in the pathogenesis of SLE
- Describe strategies to inhibit interferons with a particular emphasis on plasmacytoid dendritic cells
- Analyze litifilimab and daxdilimab SLE clinical trial data

30 CAR-T: FROM OUR CANCER EXPERIENCE TO OTHER OPTIONS

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Cellular immunotherapy (particularly chimeric antigen receptor (CAR) T-cell therapy) has become a consolidated therapeutic reality in hematologic neoplastic diseases, but it is mainly seen as having a promising future. Considered advanced therapy medicinal products, their development has so far originated from proposals made by academic centers and later gaining market authorization by large pharmaceutical companies, which are defining the distribution and implementation of these products in patients from whom the T cells are obtained and subsequently incorporated with the chimeric antigen receptor. This unidirectional model of academic development and industrial implementation has clear advantages but also evident drawbacks.

At the Hospital Clíic of Barcelona, we have developed a second-generation CAR-T (with 4-1BB as a co-stimulatory motif) targeting CD19 (ARI0001 or varnimcabtagene autoleucel), which is fully publicly funded and has received authorization for use under the hospital exemption regulation. It is the first academic and European CAR-T approved worldwide for acute lymphoblastic leukemia B and is currently undergoing evaluation under the Priority Medicines (PRIME) designation by the European Medicines Agency (EMA), trying to obtain centralized marketing authorization. Alongside ARI0001, we are also close to obtaining 'hospital exemption' for ARI0002h (cesnicabtagene autoleucel), an anti-BCMA CAR-T for multiple myeloma. Obviously, all these academic products meet the same quality requirements as commercial products and must also demonstrate effectiveness within the ranges of commercial products in clinical trials for approval. Possibly, with these Barcelona products, we are paving the way to enable academic production to provide treatment options in cases where pharmaceutical companies are not interested in developing these products (such as rare diseases like pediatric tumors or even autoimmune diseases to low frequent autoantigens). Beyond cancer, other immune-mediated diseases (such as autoimmune disorders and systemic lupus erythematosus) are probably the next challenges for CAR-T immunotherapies.

31 OTHER TARGETS: EXPECTATIONS FROM RESEARCH ON PATHOGENIC MECHANISMS

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Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral