transduction which primarily targets liver cells. Unexpectedly, despite successful restoration of plasma FD, AP complement activity was not recovered in the treated mice. Further investigation showed that plasma FB was mostly missing in the AAV8/mature FD-treated FD KO mice. Similar FB depletion also occurred in wild-type but not C3 KO mice after AAV8/mature FD treatment.

Conversely, depletion of FB was not observed in mice treated with AAV8/pro-FD gene transduction or in mice with ectopic expression of mature FD in bone marrow/blood cells via retrovirus-mediated gene transduction.

When Hepa1-6 cells were induced to express C3, FB and mature FD, intact FB was lost from the culture supernatant. Vemircopan was able to prevent FB depletion, unlike FD monoclonal antibody.

Finally, the depletion of FB by AAV8/mature FD effectively prevented the development of disease in murine models of atypical hemolytic uremic syndrome and C3 glomerulopathy.

Conclusion: Our data suggest that the regulation of FD by MASP3 and the segregated biosynthesis of FD, FB and C3 have physiological significance. The ectopic expression of mature FD in the liver causes C3-dependent FB depletion, a phenomenon that could be exploited for the treatment of complement-mediated AP diseases.

I have no potential conflict of interest to disclose.

I did not use generative AI and AI-assisted technologies in the writing process.

WCN26-8197

BUDESONIDE MODULATES B- AND T-CELL IMMUNITY IN PEYER'S PATCHES: IMPLICATIONS FOR IGA NEPHROPATHY

(Article No. 105070)

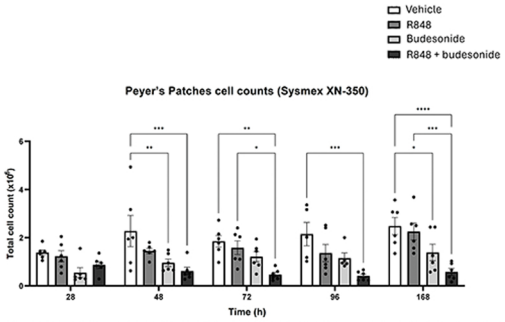
Roza Ghotbi[*1], Jens Kristensen[2], Krassimir Mitchev[2], Johan Häggblad[2]

[1]Medical Affairs, Calliditas Therapeutics AB, Stockholm, Sweden; [2]Clinical Development, Calliditas Therapeutics AB, Stockholm, Sweden

Introduction: IgA nephropathy (IgAN) is a chronic, immune-mediated kidney disorder characterized by gut-derived renal deposition of galactose-deficient IgA1 antibodies in the glomeruli of the kidney. Peyer's patches (PPs) in the distal ileum serve as key sites for B-cell priming, IgA class switching, and mucosal immunity. Budesonide, the active substance of nefecon (an FDA-approved targeted-release budesonide formulation), has demonstrated B-cell suppressive effects, yet its tissue-specific immunomodulatory role in PPs remains incompletely defined. The objective of this study was to investigate the immunological impact of orally administered budesonide on B- and T-cell subsets in murine PPs following in vivo stimulation with R848, a TLR7/8 agonist that activates mucosal immunity.

Methods: Female Balb/c mice were randomized into four treatment groups: vehicle (10% dimethyl sulfoxide in phosphate-buffered saline), R848 alone, budesonide alone, and R848 + budesonide. Budesonide (3 mg/kg) was administered orally at 6 and 24 hours post-intraperitoneal R848 injection. Mice were sacrificed at 28, 48, 72, 96, and 168 hours post-treatment. PPs were harvested for flow cytometric analysis of B- and T-cell subsets, activation markers (CD69, CD25, CD86), proliferation (Ki67), cytokine production (interferon [IFN]-γ, interleukin [IL]-10), and apoptosis (cleaved caspase-3). Ex vivo stimulation with R848 (500 ng/mL) was performed for 72 hours to assess cell viability and phenotype.

Results: The R848 + budesonide group showed reduced total PP cell counts (Figure) and increased apoptosis (cleaved caspase-3+ cells). Significant reductions were observed in CD19+ B cells, IgA+ and IgG+, IgD− subsets, germinal center B cells (GL7+, CD95+), and plasma blasts (CD138+), with transient increases in IgA+ plasma cells at 48 and 72 hours. T-cell analysis revealed decreased CD3+ counts and elevated proportions of activated (CD69+, CD25+), costimulatory (CD86+), proliferating (Ki67+), and regulatory (FOXP3+) T cells. IL-10+ and IFN-γ+ Tregs were reduced, indicating a shift in regulatory balance. Early B-cell activation (CD69+, CD25−) increased, while Ki67+ B-cell proliferation declined over time. Ex vivo stimulation showed poor viability (2–20%) but mirrored in vivo trends.



Cell counts obtained from PPs. Mice received R848 or vehicle 1 intraperitoneally, followed by budesonide or vehicle 2 orally. Cells were isolated from ileal PPs and total cell counts obtained for each animal. Statistics were calculated using two-way ANOVA with Tukey's multiple comparison test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. ANOVA, analysis of variance; PP, Peyer's patch.

Conclusion: Budesonide, particularly following stimulation by R848, exerts robust immunomodulatory effects in PPs by suppressing B-cell populations involved in IgA production and altering T-cell activation. To our knowledge, this is the first time a study has shown apoptotic cells within the PPs after oral treatment with budesonide. These findings support the localized action of nefecon for the treatment of IgAN. Further studies using transcriptomic profiling and disease models are warranted to elucidate budesonide's immunological mechanisms in PPs.

I have potential conflict of interest to disclose.

Funding/commercial Support: Calliditas Therapeutics

I did not use generative AI and AI-assisted technologies in the writing process.

WCN26-8271

SOCIAL VULNERABILITY AND LUPUS NEPHRITIS CLUSTERING IN BARRANQUILLA, COLOMBIA: INTEGRATING CLINICAL REGISTRY DATA WITH A POPULATION VULNERABILITY INDEX

(Article No. 105071)

Maria-Paula Aroca[*1], Gustavo Aroca-Martinez[2], Santos Depine[3], Kanery Camargo- Rodriguez[4], Nicoll Fontalvo-Avila[4], Valentina Pérez-Jiménez[5], Esteban Vasquez[4], Andres Cadena[6], Joanny Sarmiento[6], Karen Manjarres[6], Valmore Bermúdez[7]

[1]CIDEACC, Centro de Investigación Clínica de la Costa, Barranquilla, Colombia; [2]Nephrology, Centro de Investigación Clinica de la Costa Universidad Simon Bolivar, Barranquilla, Colombia; [3]Nephrology, Asociación Latinoamericana de Nefrología e Hipertención, Buenos Aires, Argentina; [4]CIDEACC, Centro de investigacion Clinica de la Costa, Barranquilla, Colombia; [5]Nephrology, Centro de investigacion Clinica de la Costa, Barranquilla, Colombia; [6]Nephrology, Clinica de la Costa, Barranquilla, Colombia; [7]Nephrology, Asociación Latino Américana de Nefrología e Hipertencion, Maracaibo, Venezuela

Introduction: Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE), with its incidence and progression potentially influenced by structural socioeconomic inequalities. The Population Renal Health paradigm (Burgos-Calderón, Depine, and Aroca-Martínez, 2021) shifts from individual risk assessment to population and territorial vulnerability analysis by integrating social determinants of health (SDOH). To operationalize this approach, the Population Vulnerability Index (PVI) was developed as a quantitative geospatial tool that measures SDOH across the Colombian Caribbean region, enabling systematic comparison of territorial vulnerability. In parallel, the RENELUP registry collects and georeferences LN cases throughout Colombia. This study cross-references RENELUP data from the city of Barranquilla with PVI scores to examine how SDOH influence disease distribution patterns in this urban setting.

Methods: To analyze the spatial distribution of LN cases registered in RENELUP in Barranquilla, Colombia, and their relationship with social vulnerability levels defined by the PVI. A density-based clustering algorithm (DBSCAN, 500m radius) was applied for spatial cluster analysis of LN cases registered in RENELUP in Barranquilla to identify high-concentration hotspots. The PVI was created by integrating 60 variables

across nine vulnerability dimensions (economic, cultural, housing, health access, educational, environmental, technological, political, and geographic) using data from official sources such as the national census, quality of life surveys, health ministry records, water quality monitoring systems, victimization risk indices, and meteorological APIs. Social vulnerability distribution was evaluated in city blocks within neighborhoods with the highest case concentrations, categorized by PVI scores as follows: high vulnerability (PVI $>$ 0.7), moderate vulnerability (PVI 0.3-0.7), and low vulnerability (PVI $<$ 0.3).

Results: Spatial analysis identified significant clustering patterns of LN cases in specific urban areas. The 12 neighborhoods with the highest concentration of RENELUP-registered cases exhibited a predominant distribution of high social vulnerability, as indicated by the PVI. In neighborhoods with high LN case concentrations, the vast majority of blocks showed high vulnerability: Las Malvinas (98.3% high vulnerability), Evaristo Sourdis (96.3%), and La Chinita (87.0%). The Kernel density analysis revealed hotspots coinciding with areas of elevated PVI scores, suggesting potential spatial correlation between disease concentration and social vulnerability.

Figure 1. Population Vulnerability Index (PVI) Calculation Methodology

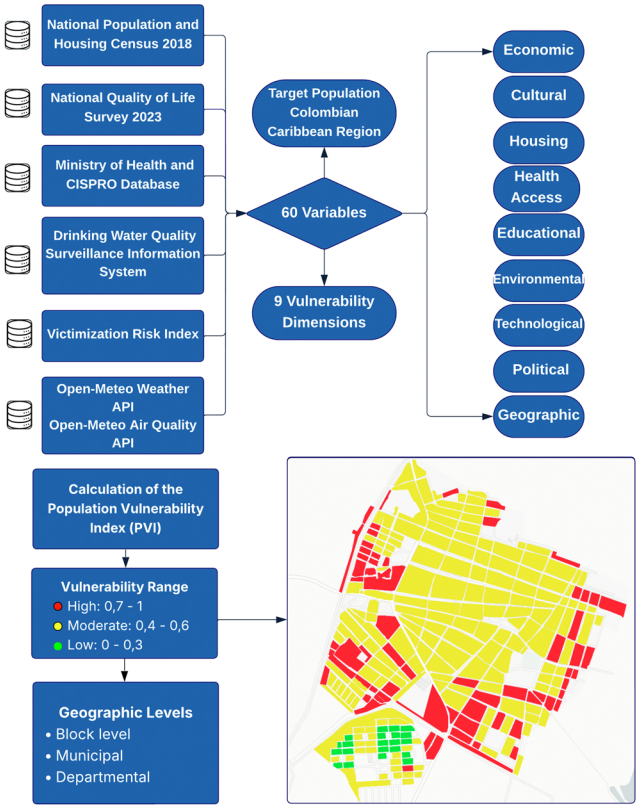


Figure 2. Identification of Lupus Nephritis Hotspots in Barranquilla Using DBSCAN Clustering (500m radius) and Kernel Density Analysis

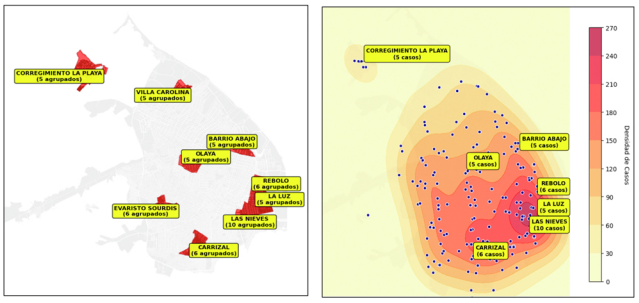
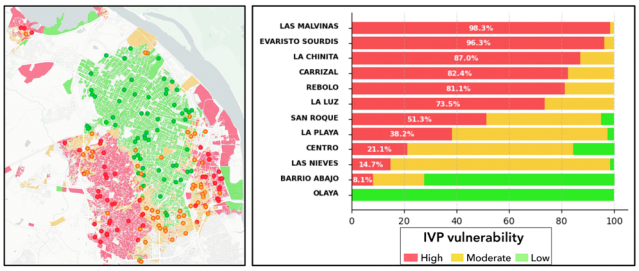


Figure 3. Spatial Relationship Between LN Cases and PVI: (A) PVI block Distribution with Georeferenced LN Cases and (B) PVI Distribution in Top 12 Neighborhoods with Highest LN Concentration



Conclusion: This descriptive spatial analysis revealed a pattern of LN case clustering in neighborhoods with high social vulnerability, as indicated by the PVI. While these preliminary findings suggest that SDOH may influence disease distribution, further statistical analyses are needed to establish significant associations. Nevertheless, the integration of RENELUP clinical data with PVI scores demonstrates the potential of this approach for identifying at-risk populations. Future studies should employ inferential spatial statistics to quantify the relationship between social vulnerability and LN incidence, ultimately guiding evidence-based resource allocation in areas of greater need.

I have no potential conflict of interest to disclose.

I did not use generative AI and AI-assisted technologies in the writing process.

WCN26-9056

DISTINCT TRANSCRIPTOMIC RESPONSES REVEAL A REGULATORY ROLE OF PIEZO1 IN PODOCYTE ADAPTATION TO MECHANICAL STRESS

(Article No. 105072)

Miki Nagase*[1], Kaori Mikami[1], Takashi Nagase[2]
[1]Department of Anatomy, Kyorin University School of Medicine, Tokyo, Japan; [2]Geriatric Health Services Facility, Kunitachi Aoyagien Tachikawa, Tokyo, Japan

Introduction: Hemodynamic factors such as glomerular hypertension and hyperfiltration are major contributors to glomerular injury. However, the molecular mechanisms by which glomerular cells sense and respond to mechanical forces remain poorly understood. Piezo1, a mechanosensitive ion channel, regulates diverse physiological and pathological processes, including hypertension and hypertensive nephropathy. Here, we investigated the role of Piezo1 in podocytes under basal and pressure-loaded conditions using genetically modified mice and cultured podocytes.

Methods: Podocyte-specific Piezo1 knockout mice (pPiezo1 KO) and littermate controls (pPiezo1 WT) were generated by crossing Nphs1Cre/+ mice with Piezo1flox/flox mice. Hypertensive nephropathy was induced by short-term salt-loaded angiotensin II infusion (AII/HS, 2 weeks) and long-term salt-loaded aldosterone infusion with uninephrectomy (UNx/Ald/HS, 6 weeks). RNA-sequencing was performed on glomeruli from pPiezo1 WT and KO mice, as well as cultured podocytes treated with or without the Piezo1 activator Yoda1.

Results: Under basal conditions, pPiezo1 WT and KO mice showed no differences in blood pressure, albuminuria, renal histology, or podocyte ultrastructure. Following AII/HS, both groups developed comparable hypertension; however, pPiezo1 KO mice exhibited significantly greater albuminuria, podocyte injury, and glomerulosclerosis. Similar findings were observed in the chronic UNx/Ald/HS model. Transcriptome analysis of glomeruli revealed altered expression of several genes, including *Rhpn1* and *Fgfbp1*. In cultured podocytes, Yoda1 stimulation induced distinct transcriptional changes, including *Pai1*, *Sgk1*, and *Mcp1*. Podocyte injury in AII/HS-treated pPiezo1 KO