ELECTRONIC SUPPLEMENTARY MATERIAL 8

Key factors of the deranged antiviral response in elderly patients with COVID-19: a machine-learning analysis

Tamara Postigo[1], Alicia Ortega[1,2], Alejandro Álvaro-Meca[3,4], Daniel Vélez-Serrano[5], Nadia García-Mateo[1,2], Ana P. Tedim[1,2], Raquel Almansa[1,2,6], Jose María Eiros[7], David de Gonzalo-Calvo[2,8], Anna Moncusí-Moix[2,8], Clara Gort-Paniello[2,8], Manel Perez-Pons[2,8], Marta Molinero[2,8], Marta Dominguez-Gil[7], Amanda de la Fuente[1,2], Laura González-González[1,2], Tania Luis-García[1,2], Fátima Rodríguez-Jara[2,8], Noelia Jorge[1,2], Jessica González[8], Gerard Torres[2,8], Oliver Norberto Gutiérrez-Pérez[9], Maria José Villegas[9], Sonia Campo[9], Eva Ayllon[9], Tomás Ruiz Albi[10], Julio de Frutos Arribas[10,11], Ainhoa Arroyo Domingo[10], Jesica Abadia-Otero[12], Julia Gómez Barquero[12], Wysali Trapiello[13], Luis Javier Garcia Frade[9], Luis Inglada[12], Felix del Campo[10,11,14], Ferran Barbé[2,8,15], Antoni Torres[2,15,16], Raúl López-Izquierdo[17,†], Jesús F. Bermejo-Martin[1,2,18 ,†,*], CIBERES-UCI-COVID group.

† These senior authors contributed equally to this article.

Institutions:

[1]Group for Biomedical Research in Sepsis (BioSepsis). Instituto de Investigación Biomédica de Salamanca, (IBSAL), Gerencia Regional de Salud de Castilla y León, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain.

[2]Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Avenida de Monforte de Lemos, 3-5, 28029 Madrid, Spain.

[3]Department of Preventive Medicine and Public Health, Faculty of Health Science, Universidad Rey Juan Carlos, Madrid, Spain.

[4]Centro de Investigación Biomédica en Red en Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Avenida de Monforte de Lemos, 3-5, 28029, Madrid, Spain.

[5]Department of Statistics and Operations Research, Universidad Complutense de Madrid, Madrid, Spain.

[6]Department of Cellular Biology, Hystology and Pharmacology. University of Valladolid, Av. Ramón y Cajal, 7, 47005 Valladolid, Spain.

[7]Microbiology Service, Hospital Universitario Rio Hortega, Gerencia Regional de Salud de Castilla y León, Calle Dulzaina, 2, 47012 Valladolid, Spain.

[8]Translational Research in Respiratory Medicine, University Hospital Arnau de Vilanova and Santa Maria, IRB Lleida, Av. Alcalde Rovira Roure, 80, 25198 Lleida Spain.

[9]Hematology Service. Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Calle Dulzaina, 2, 47012 Valladolid, Spain.

[10]Pneumology Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Calle Dulzaina, 2, 47012 Valladolid, Spain.

[11]Deparment of Medicine, Dermatology and Toxicology, School of Medicine, University of Valladolid, Av. Ramón y Cajal, 7, 47005 Valladolid, Spain.

[12]Internal Medicine Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Calle Dulzaina, 2, 47012 Valladolid, Spain.

[13]Clinical Analysis Service. Hospital Clínico Universitario de Valladolid, Gerencia Regional de Salud de Castilla y León, Av. Ramón y Cajal, 3, 47003 Valladolid, Spain.

[14]Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III, Av. de Monforte de Lemos, 3-5, 28029 Madrid, Spain.

[15]Catalan Institution for Research and Advanced Studies, Passeig de Lluís Companys, 23, 08010 Barcelona, Spain.

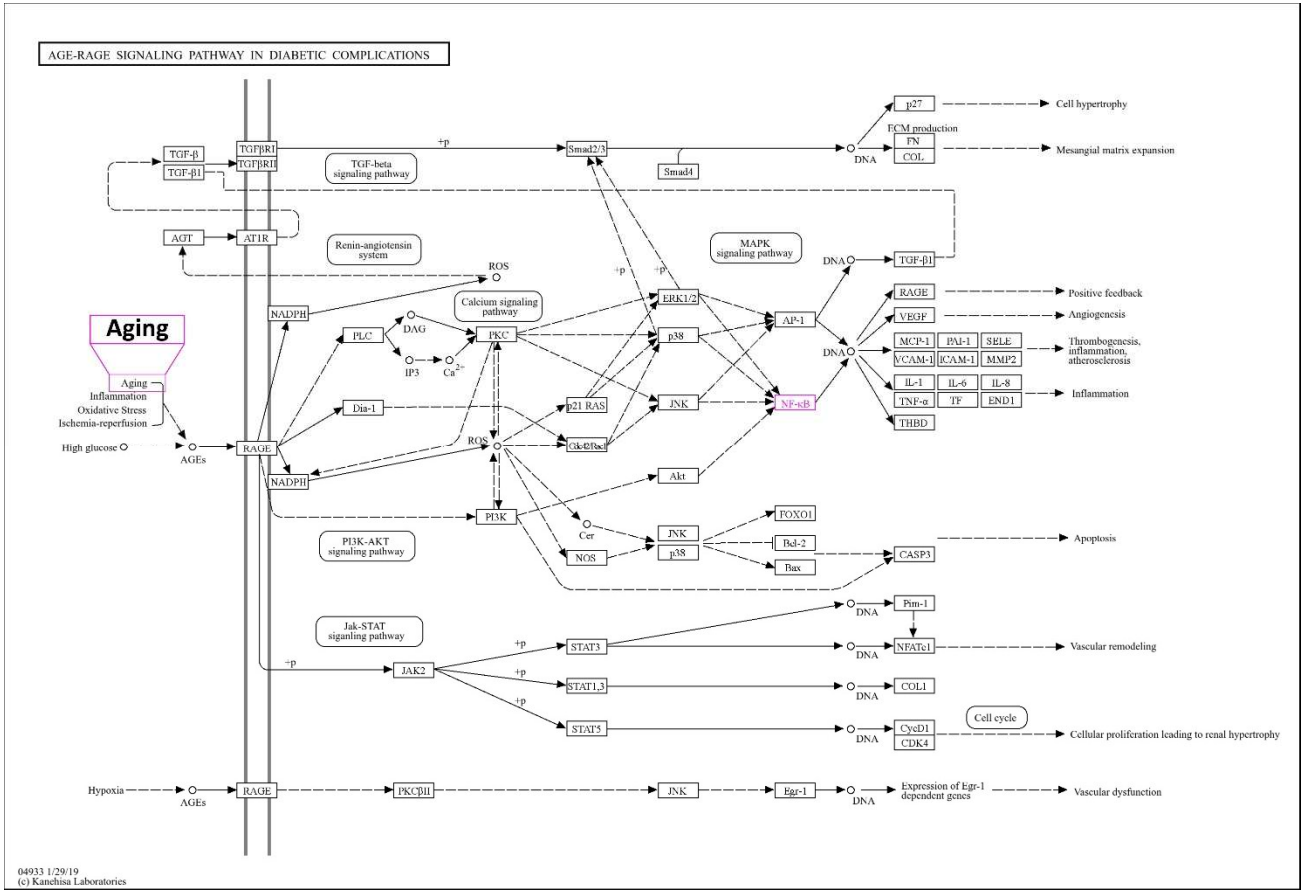
[16]Department of Pulmonology, Hospital Clinic de Barcelona, Universidad de Barcelona, Institut D investigacions August Pi I Sunyer (IDIBAPS), Carrer del Rosselló, 149, 08036 Barcelona, Spain.

[17]Emergency Department, Hospital Universitario Rio Hortega, Gerencia Regional de Salud de Castilla y León, Calle Dulzaina, 2, 47012 Valladolid, Spain.

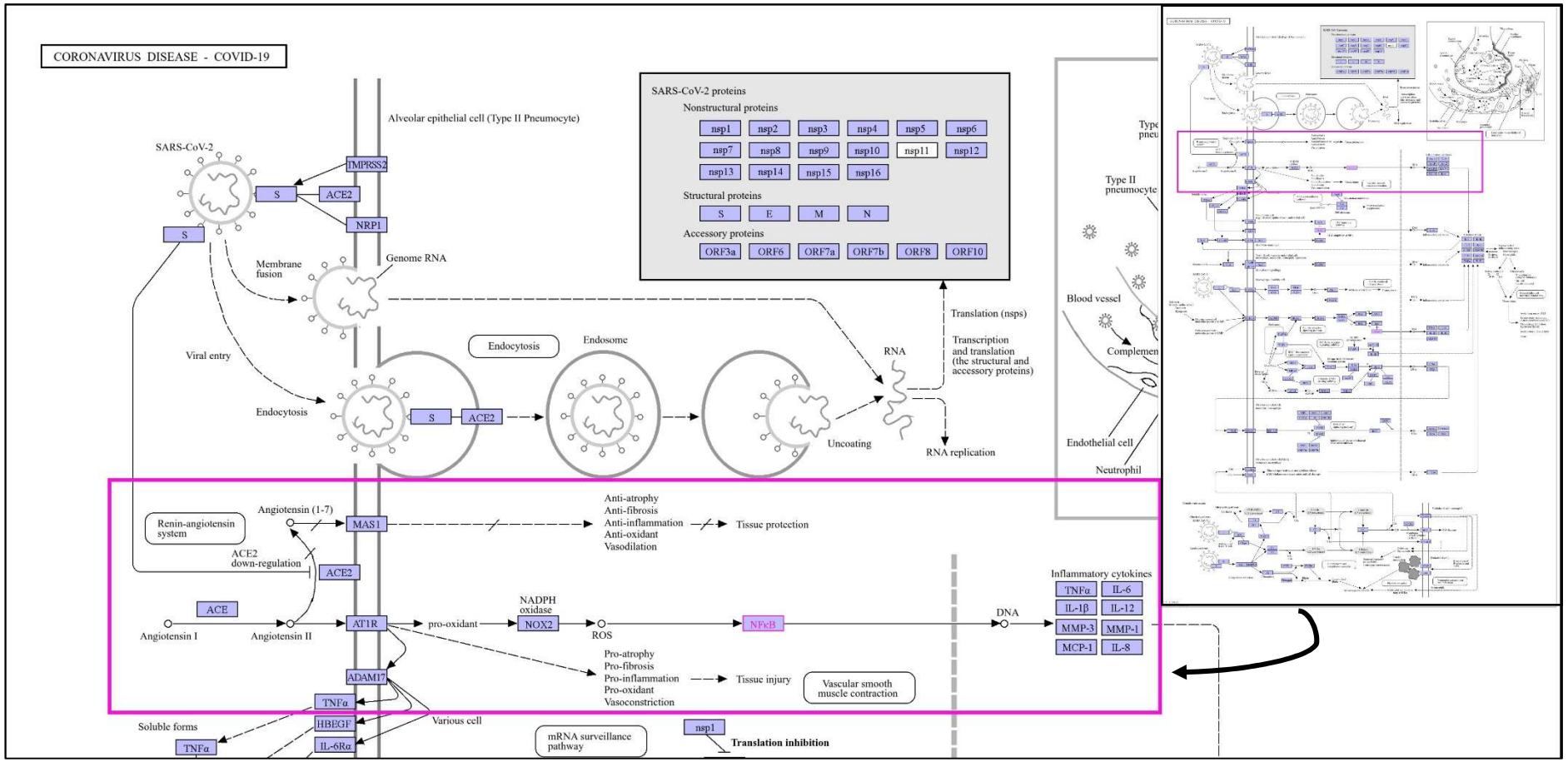
[18]Department of Medicine, Faculty of Medicine, University of Salamanca, Salamanca, Spain.

Corresponding Author: Dr. Jesús F Bermejo-Martin, Department of Medicine, Faculty of Medicine, University of Salamanca, C. Alfonso X El Sabio, s/n, 37007 Salamanca, Spain, jfbermejo@usal.es, +34 923 294 500 Ext. 1885.

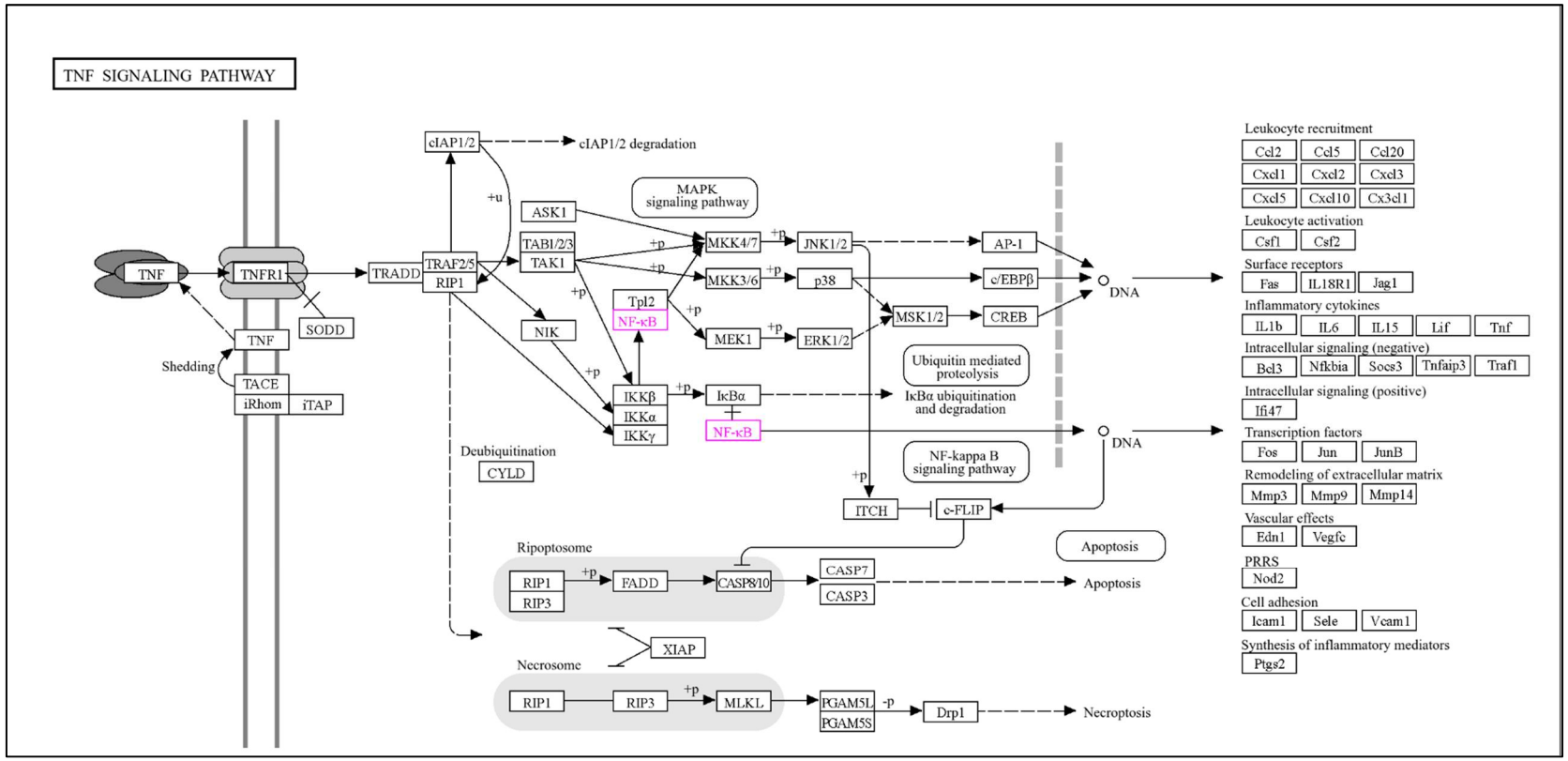
ELECTRONIC SUPPLEMENTARY MATERIAL 8



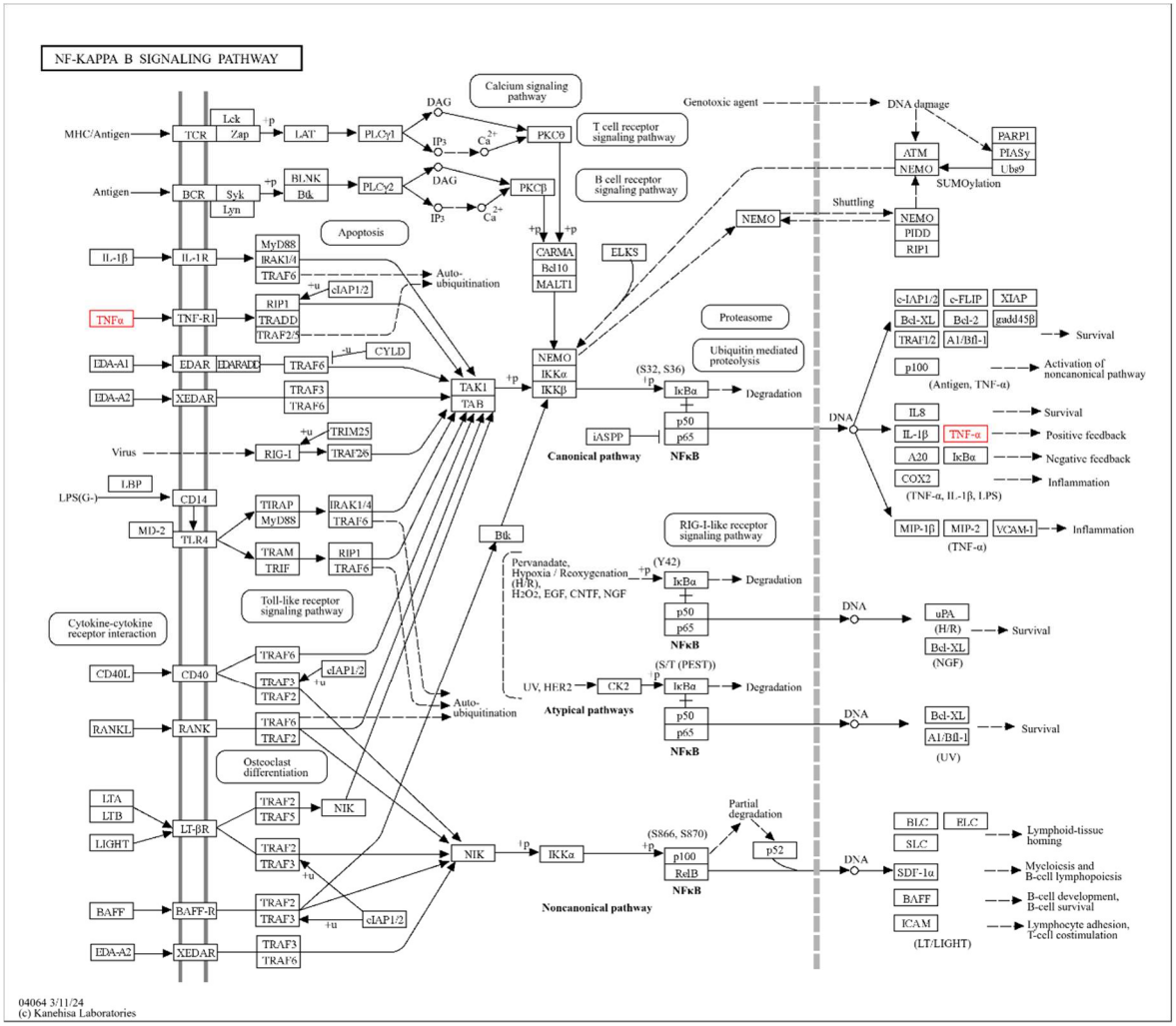
Supplementary Figure S11. 'AGE-RAGE signaling pathway in diabetic complications' reference pathway obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG). *Advanced glycation end products (AGEs): group of compounds produced primarily due to aging and under certain pathological conditions. The major receptor for AGEs is RAGE. AGE/RAGE signaling elicits activation of multiple intracellular signal pathways resulting in NF-kappaB activity. NF-kappa B promotes the expression of pro-inflammatory cytokines such as IL-6 and TNF-alpha and a variety of atherosclerosis-related genes, including tissue factor (TF; F3). **Biomarkers in this study included in this pathway: CCL2 (MCP-1), IL6, TNFα, and ET-1 (END1).**



Supplementary Figure S12. **'**Coronavirus disease - COVID-19' pathway obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG). Mechanism of infection of SARS-CoV-2 and signaling involved. SARS-CoV-2 infects cells through the angiotensin-converting enzyme 2 (ACE2) receptor. **Biomarkers in this study included in section of the pathway: TNFα, IL6, and CCL2 (MCP-1).**



Supplementary Figure S13. **'**TNF signaling reference pathway' obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG). TNFR1 signaling induces activation of many genes, primarily controlled by two distinct pathways, NF-kappa B pathway and the MAPK cascade, or apoptosis and necroptosis. **Biomarkers in this study included in this pathway: CXCL10, IL6, IL15, and ET-1 (Edn1).**



Supplementary Figure S14. ‘Nuclear factor-kappa B (NF-kappa B) signaling reference pathway’ obtained from Kyoto Encyclopedia of Genes and Genomes (KEGG).