In silico analyses of immune system protein interactome network, single-cell RNA sequencing of human tissues, and artificial neural networks reveal potential therapeutic targets for drug repurposing against COVID-19

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ABSTRACT

There is pressing urgency to better understand the immunological underpinnings of the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus clade 2 (SARS-CoV-2) in order to identify potential therapeutic targets and drugs that allow treating patients effectively. To fill in this gap, we performed in silico analyses of immune system protein interactome network, single-cell RNA sequencing of human tissues, and artificial neural networks to reveal potential therapeutic targets for drug repurposing against COVID-19. As results, the high-confidence protein interactome network was conformed by 1,588 nodes between immune system proteins and human proteins physically associated with SARS-CoV-2. Subsequently, we screened all these nodes in ACE2 and TMPRSS2 co-expressing cells according to the Alexandria Project, finding 75 potential therapeutic targets significantly overexpressed (Z score > 2) in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes of patients with several immunopathologies. Then, we performed fully connected deep neural networks to find the best multitask classification model to predict the activity of 10,672 drugs for 25 of the 75 aforementioned proteins. On one hand, we obtained 45 approved drugs, 16 compounds under investigation, and 35 experimental compounds with the highest area under the receiver operating characteristic (AUROCs) for 15 immune system proteins. On the other hand, we obtained 4 approved drugs, 9 compounds under investigation, and 16 experimental compounds with the highest multi-target affinities for 9 immune system proteins. In conclusion, computational structure-based drug discovery focused on immune system proteins is imperative to select potential drugs that, after being effectively analyzed in cell lines and clinical trials, these can be considered for treatment of complex symptoms of COVID-19 patients, and for co-therapies with drugs directly targeting SARS-CoV-2. Scripts can be downloaded at https://github.com/muntisa/immuno-drug-repurposing-COVID-19.
INTRODUCTION

The first zoonotic transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was located in China in December 2019\(^1\), and it is the causative agent of the coronavirus disease 2019 (COVID-19)\(^2\). The World Health Organization (WHO) declared the outbreak of COVID-19 as a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020\(^3\). Classified in the Coronaviridae family and Betacoronavirus genus, SARS-CoV-2 is the seventh CoV known to infect humans, along with 229E, NL63, OC43, HKU1, SARS-CoV and Middle East respiratory syndrome (MERS)\(^4\). Coronaviruses cause mild to severe respiratory diseases and have high mutation rates that result in high genetic diversity, plasticity, and adaptability to invade a wide range of hosts\(^5\).

The first genome of SARS-CoV-2 named Wuhan-Hu-1 (NCBI reference sequence NC_045512) was isolated and sequenced in China in January 2020\(^6\),\(^7\). SARS-CoV-2 is a single-stranded positive-sense RNA virus of about 30 kb in length\(^7\),\(^8\). The genomic structure is comprised of a 5‘ terminal cap structure, 14 open reading frames (ORFs) encoding 29 proteins, and a 3‘ poly A tail\(^9\). ORF1a and ORF1ab are the largest genes and codify 16 non-structural proteins (nsp1 to nsp16). According to Gordon et al.\(^10\), nsps are involved in antiviral response (nsp1), viral replication (the nsp3-nsp4-nsp6 complex), the protease 3C\(^{pro}\) (nsp5)\(^11\), the RNA polymerase (the nsp7-nsp8 complex), the single-strand RNA binding (nsp9), the methyltransferase activity (nsp10 and nsp16), the RNA-dependent RNA polymerase (nsp12)\(^12\), the helicase/triphosphatase (nsp13), the 3‘-5‘ exonuclease (nsp14), the uridine-specific endoribonuclease (nsp15), and the RNA-cap methyltransferase (nsp16)\(^13\). Lastly, the 3‘ terminus contains genes that codify the spike (S) glycoprotein, the envelope (E) protein, the membrane (M) glycoprotein, the nucleocapsid (N) protein, and several accessory proteins (3a, 3b, p6, 7a, 7b, 8, 9b, 9c and 10) (Figure 1A)\(^9\),\(^14\).

COVID-19 is caused when SARS-CoV-2 exploits the host cell machinery for its own replication and spread\(^15\). SARS-CoV-2 entry into human cells is mediated by the S glycoprotein that forms homotrimers protruding from the viral surface\(^16\). S1 and S2 are two functional subunits of the S glycoprotein. Six receptor-binding domain (RBD) amino acids (L455, F486, Q493, S494, N501 and Y505) of the S1 subunit directly bind to the peptide domain of angiotensin-covering enzyme 2 (ACE2) human receptor protein\(^17\),\(^19\). S1 glycoprotein is cleaved by the cathepsin L (CTSL) protease\(^21\), and the transmembrane serine protease (TMPRSS2) in a functional polybasic (furin) cleavage site at the S1-S2 boundary flanked for O-linked glycans\(^15\),\(^22\). S2 subunit mediates subsequent fusion between the human and viral membranes\(^23\),\(^24\).

ACE2 is a type I membrane protein widely expressed in nasal goblet secretory cells, lung type II pneumocytes, ileal absorptive enterocytes, among other host cells\(^8\),\(^25\),\(^26\), and participates in the maturation of angiotensin, a peptide hormone that controls blood pressure and vasoconstriction\(^27\). After virus entry, many severe ill COVID-19 patients developed clinical manifestations such as cough, mild fever, dyspnea, lung edema, severe hypoxemia, acute respiratory distress syndrome (ARDS)\(^28\), acute lung injury\(^29\), interstitial pneumonia, increased concentrations of fibrinogen and D-dimer plasma levels\(^30\),\(^31\), elevated levels of pro-inflammatory chemokines and cytokines such as interleukin (IL) 6\(^32\),\(^33\), low levels of type I and III interferons (IFNs)\(^32\), high levels of lactate dehydrogenase, hyperferritinemia, idiopathic thrombocytopenic purpura caused...
by spleen atrophy, formation of hyaline membrane, hilar lymph node necrosis, lymphopenia, intravascular coagulopathy, pulmonary thromboembolism, cerebrovascular events, severe metabolic acidosis, kidney and hepatic dysfunctions, secondary infections, septic shock and multi-organ failure.

Additionally, SARS-CoV-2 interacts with the immune system triggering dysfunctional immune responses to COVID-19 progression. Given that an excessive inflammatory response to the novel coronavirus is thought to be a major cause of disease severity and death, a better understanding of the immunological underpinnings is required to identify potential therapeutic targets. To fill in this gap, we performed in silico analyses of immune system protein-protein interactome (PPI) network, single-cell RNA sequencing (scRNA-seq) of human tissues, and artificial neural networks to reveal potential therapeutic targets for drug repurposing against COVID-19.

METHODS

Protein sets. We analyzed a total of 3,885 proteins related to the immune system. All proteins were extracted from the gene ontology (GO) terms: 0002376 immune system process, 0045087 innate immune response, and 0002250 adaptive immune response using David Bioinformatics Resource (https://david.ncifcrf.gov/) and the International ImMunoGeneTics information system (http://www.imgt.org), the InnateDB database (https://www.innatedb.com/), and a study of Patel et al., focused on essential proteins for cancer immunotherapy. On the other hand, Gordon et al., identified 332 human proteins physically associated with 26 of the 29 SARS-CoV-2 proteins using affinity-purification mass spectrometry. Lastly, we performed a PPI network between immune system proteins and human proteins physically associated to the SARS-CoV-2 proteins.

Protein-protein interactome network. The PPI network with zero node addition and a highest confidence cutoff of 0.9 was created using the human proteome of the Cytoscape StringApp, which takes into account experimental and in silico interactions. The degree centrality of a node represents the number of edges the node has in a network, and the betweenness centrality measures the number of times a node lies on the shortest path between other nodes. Human proteins physically associated with the SARS-CoV-2 proteins, and adaptive and innate immune system proteins were differentiated by colors in the PPI network.

Enrichment map analysis. The enrichment map analysis gives curated signatures of protein sets generated from omics-scale experiments. Proteins involved in our immune system network were analyzed by using g:GOSt (https://biit.cs.ut.ee/gprofiler/gost) to obtain significant annotations (false discovery rate - FDR < 0.001) related to the Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways, Reactome signaling pathways, and WikiPathways. Consequently, g:GOSt annotations were analyzed with the EnrichmentMap Pipeline Collection software to generate a biological process interactome network, which was visualized through the Cytoscape software.
**Single-cell RNA-sequencing data.** Ziegler et al. analyzed human scRNA-seq data to uncover potential targets of SARS-CoV-2 amongst tissue-resident cell subsets. They discovered ACE2 and TMPRSS2 co-expressing cells in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes. Consequently, we screened the 1,588 nodes previously obtained from the PPI network and revealed all genes whose RNAs were significantly overexpressed (Z score > 2) in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes according to the Alexandria Project (https://singlecell.broadinstitute.org/single_cell?scpbr=the-alexandria-project). Lastly, it is important to clarify that the scRNA-seq analyses were done in cells non-exposed to the novel coronavirus.

**Drug repurposing.** DeepChem package and Python Jupyter Notebooks were used to predict if drugs (DrugBank compounds) could be active for multiple protein targets (https://github.com/deepchem/deepchem). DrugBank (https://www.drugbank.ca/) contains comprehensive information about drugs, their mechanism of action, and their targets. The calculations used the GPU of Google Colab and the correspondent scripts could be found at GitHub repository: https://github.com/muntisa/immuno-drug-repurposing-COVID-19. The fully connected deep neuronal networks (FCNNs) have been used to find the best multitask classification model using 1,024 molecular circular fingerprints (CFPs) as input descriptors for 15,377 ChEMBL compounds and activity (1/0) for 25 target proteins as outputs/tasks. ChEMBL (https://www.ebi.ac.uk/chembl) is an open large-scale bioactivity database. The best model resulted from a grid search for the best parameters have been used to predict the activity of 10,672 drugs for 25 protein targets.

In the first step, CFPs of 1,024 values have been calculated for both ChEMBL dataset and DrugBank prediction set. The dataset was splitted into 80%-10%-10% training-validation-test subsets using RandomStratifiedSplitter. The training and validation subset were used to find the best hyperparameters for the FCNN with 1,000 neurons. The test set was used to verify the performance of the best model for each task/protein target (see Supplementary Table 8). The area under the receiver operating characteristic (AUROC) test was between 0.935 and 1.000 (mean = 0.989; standard deviation (SD) = 0.019).

The best model has 1,000 neurons in a hidden layer (dropout of 0.5) and it was used to predict the activity of 10,672 drugs from DataBank for 25 immune system targets: DDX3X, EGFR, C3, LDLR, CD74, CTSD, CD63, CTSN1, HSPA5, B4GALT1, CD44, ITGA2, MDK, CTSS, NFKBIA, ITGAM, MAPK3, CTNNB1, STAT3, TNFSF10, F2RL1, ATP6AP1, HIF1A, NEU1, and EPAS1 (see Supplementary Table 9). Lastly, the best predicted drug-target associations were filtered according to its first ATC level (https://www.whocc.no/atc_ddd_index/), the approval status by the US Food & Drug Administration (FDA) (https://www.accessdata.fda.gov/scripts/cder/def/) or the European Medicines Agency (EMA), the pharmacological indication, and the IUPHAR/BPS Guide to Pharmacology (https://www.guidetopharmacology.org/).

**RESULTS**

**SARS-CoV-2 structure and physical interactions with human proteins.** Figure 1B shows the PPI network of 332 human proteins and its interaction with the SARS-CoV-2
proteins according to Gordon et al.,\textsuperscript{10} (Supplementary Table 1). After filtering protein interactions with zero node addition and a highest confidence cutoff of 0.9, human proteins with the highest degree centrality were RAB8A (18), PRKAR2B (18), AKAP9 (16), PRKACA (14), CNTRL (13), CEP135 (13), RAB1A (12), CEP250 (12), PCNT (12) and CDS5RAP2 (12) (Supplementary Table 2). In other words, they are the most relevant proteins in the network and therefore contribute significantly to many signaling proteins related to the immune system. Finally, the most significant Reactome annotations (FDR < 0.001) where the 332 human proteins got involved in were metabolism of proteins (1.1 x 10\textsuperscript{5}), mitochondrial protein import (3.4 x 10\textsuperscript{6}), mitotic cell cycle (1.0 x 10\textsuperscript{5}), M phase (2.2 x 10\textsuperscript{5}), centrosome maturation (8.4 x 10\textsuperscript{5}), recruitment of mitotic centrosome proteins and complexes (8.4 x 10\textsuperscript{5}), nuclear pore complex disassembly (3.7 x 10\textsuperscript{5}), and host interactions of human immunodeficiency virus (HIV) factors (6.2 x 10\textsuperscript{4})\textsuperscript{70,71} (Figure 1C and Supplementary Table 3).

Protein-protein interactome network related to the immune system. Supplementary Figure 1 shows the extended version of the high-confidence PPI network of the immune system (n = 1,588 proteins) including 256 human proteins physically associated with SARS-CoV-2. Proteins with the highest degree centrality were UBA52 (399), GNB1 (218), APP (190), FPR2 (177), NCBP1 (175), NCBP2 (175), KNG1 (174), PIK3CA (166), PIK3R1 (162), and MAPK1 (159); and proteins with the highest eigenvector centrality were GNB1 (0.121), APP (0.118), KNG1 (0.117), FPR2 (0.116), GNB3 (0.116), GNG5 (0.116), GNB2 (0.116), AGT (0.114), SAA1 (0.112), and ANXA1 (0.111) (Supplementary Table 4). On the other hand, Figure 2 shows a smallest version of the immune system PPI network. Human proteins physically associated with SARS-CoV-2 and with the highest degree centrality were GNB1, RPL36, PABPC1, GNG5, UPF1, SRP54, SRP19, SRP72, EIF4H, and EXOSC8.

Enrichment map analysis. Immune system proteins of the PPI network (n = 1,588) were analyzed by using g:GOSt to obtain significant annotations (FDR < 0.001) related to KEGG signaling pathways, Reactome signaling pathways, and WikiPathways\textsuperscript{60–62}. The most significant KEGG signaling pathways were chemokine signaling pathway (5.1 x 10\textsuperscript{-20}), tumor necrosis factor (TNF) signaling pathway (4.9 x 10\textsuperscript{-20}), NF-kappa B signaling pathway (1.6 x 10\textsuperscript{-16}), IL-17 signaling pathway (1.7 x 10\textsuperscript{-11}), toll-like receptor (TLR) signaling pathway (2.7 x 10\textsuperscript{-07}), and T cell receptor signaling pathway (2.3 x 10\textsuperscript{-04}). The most significant Reactome pathways were immune system (2.1 x 10\textsuperscript{-50}), innate immune system (3.1 x 10\textsuperscript{-35}), cytokine signaling (5.1 x 10\textsuperscript{-31}), signaling by ILS (7.9 x 10\textsuperscript{-28}), infectious disease (1.5 x 10\textsuperscript{-24}), neutrophil degranulation (2.2 x 10\textsuperscript{-15}), viral mRNA translation (2.2 x 10\textsuperscript{-10}), and chemokine receptors bind chemokines (3.8 x 10\textsuperscript{-10}). Finally, the most significant WikiPathways were chemokine signaling pathway (6.9 x 10\textsuperscript{-15}), gastrin signaling pathway (6.2 x 10\textsuperscript{-08}), TNF related weak inducer of apoptosis (TWEAK) signaling pathway (6.2 x 10\textsuperscript{-08}), regulation of TLR signaling pathway (6.2 x 10\textsuperscript{-08}), T cell antigen receptor (TCR) signaling pathway (5.4 x 10\textsuperscript{-07}), and IL-1 signaling pathway (8.2 x 10\textsuperscript{-04}) (Supplementary Table 5).

Additionally, g:GOSt annotations were analyzed with the EnrichmentMap Pipeline Collection software\textsuperscript{59,63} to generate a GO biological processes interactome network of 470 nodes (Figure 3). The degree centrality of the most relevant biological processes associated with clinical features of COVID-19 were immune system process (433), immune response (381), leukocyte activation (189), cell death (164), cytokine production (163), apoptotic process (139), lymphocyte activation (129), cellular
response to cytokine stimulus (113), adaptive immune response (93), T cell activation (91), inflammatory response (84), innate immune response (71), immunoglobulin production (51), positive regulation of B cell mediated immunity (51), IL-1-mediated signaling pathway (44), TNF production (31), production of IFN-γ (24), antigen receptor-mediated signaling (24), response to virus (18), neutrophil activation (17), granulocyte activation (17), macrophage differentiation (17), hypoxia (14), dendritic cell differentiation (13), protein ubiquitination (11), blood coagulation (9), and reactive oxygen species (9) (Supplementary Table 6).

Single-cell RNA sequencing data analysis. Ziegler et al. discovered ACE2 and TMPRSS2 co-expressing cells in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes through scRNA-seq database analyses. Subsequently, we analyzed the RNA expression of 1,588 nodes previously obtained from the high-confidence PPi network using different single-cell databases from the Alexandria Project.

Chronic rhinosinusitis samples (18,036 cells) developed by allergic inflammation, and nasal scraping samples (18,704 cells) conform the nasal passage tissues which are made up of basal cells of olfactory epithelium, ciliated cells, endothelial cells, fibroblast, glandular epithelial cells, goblet cells, mast cells, myeloid cells, plasma cells, and T cells. Figure 4A and 4B show a heat map and a dot plot of genes whose RNAs were significantly overexpressed in nasal goblet secretory cells. The overexpressed genes, its Z score, and the percentage of nasal goblet secretory cells expressing were: ATP1B1 (2.28; 62%), CD55 (2.54; 61%), ELF3 (2.04; 76%), EPAS1 (2.11; 66%), and TNFSF10 (2.85; 51%). Figure 4C shows box plots comparing the mean log normalized expression of nasal passage cells where goblet cells had the highest mean (1.57). Lastly, Figure 4D details the t-distributed stochastic neighbor embedding (t-SNE) cell type where goblet cells showed the highest mean log normalized expression in relation to other nasal passage cells.

Epithelial cells of lung tissue (18,915 cells) are made up of ciliated cells; lymphatic cells; fibroblasts 1 and 2; macrophages 1, 2 and 3; mast cells; monocytes 1 and 2; neutrophil cells; proliferating cells; T cells; type I pneumocytes, and type II pneumocytes. Figure 5A and 5B show a heat map and a dot plot of genes whose RNAs were significantly overexpressed in lung type I pneumocytes. The overexpressed genes, its Z score, and the percentage of type II pneumocytes expressing were: C3 (3.61; 67%), CD44 (3.61; 58%), EPAS1 (3.61; 53%), HIF1A (3.61; 55%), HLA-DPB1 (3.61; 59%), ITGB6 (3.61; 55%), NPC2 (3.61; 76%), RPS23 (3.61; 51%), CTSH (3.39; 84%), RPS13 (3.19; 56%), HLA-DPA1 (3.04; 56%), CXCL2 (3; 63%), STAT3 (2.97; 55%), HSPA5 (2.95; 62%), LDLR (2.81; 72%), CTNNB1 (2.77; 54%), RPS20 (2.76; 60%), RPL3 (2.67; 70%), SLPI (2.67; 90%), NFKBIA (2.53; 84%), HLA-DRB1 (2.49; 69%), RPS12 (2.46; 74%), SDC4 (2.45; 69%), S100A10 (2.42; 63%), SQSTM1 (2.4; 54%), RPL23 (2.37; 61%), RPL4 (2.37; 66%), RPS24 (2.37; 63%), CSDE1 (2.36; 58%), EGR1 (2.32; 62%), HNRNPU (2.32; 55%), CD74 (2.23; 87%), CD63 (2.19; 72%), RPLP0 (2.19; 58%), EEF2 (2.18; 75%), ETS2 (2.18; 52%), DDX3X (2.17; 61%), HLA-DRA (2.17; 69%), RPL18 (2.16; 74%), PIGR (2.14; 77%), RPL8 (2.14; 83%), RPS3 (2.14; 69%), RPS4X (2.12; 72%), RPS6 (2.07; 86%), LRRFIP1 (2.05; 55%), and RPL19 (2.05; 68%). Figure 5C shows box plots comparing the mean log normalized expression of lung cells where type II pneumocytes had the highest mean (1.78). Finally, Figure 5D details the t-
SNE cell type where type II pneumocytes showed the highest mean log normalized expression in relation to other lung cells.

Samples from adult human duodenum and ileum (15,347 cells) are made up of cycling stem cells, enteroendocrine cells, goblet cells, quiescent stem cells, TA G1S cells, TA G2M cells, early enterocyte 1 cells, early enterocyte 2 cells, and absorptive enterocyte cells. Figure 6A and 6B show a heat map and a dot plot of genes whose RNAs were significantly overexpressed in ileal absorptive enterocytes. The overexpressed genes, its Z score, and the percentage of ileal absorptive enterocytes expressing were: ATP11B (2.67; 51%), ATP6AP1 (2.67; 52%), B4GALT1 (2.67; 55%), CD55 (2.20; 65%), CEACAM1 (2.67; 58%), CEACAM6 (2.19; 73%), CTS (2.20; 83%), CTSS (2.23; 74%), CXCL16 (2.67; 51%), EGFR (2.09; 57%), EPAS1 (2.67; 53%), F2RL1 (2.16; 61%), GNA11 (2.13; 65%), GRN (2.67; 67%), HIST1H2AC (2.67; 54%), HLA-DRB1 (2.67; 55%), ITGA2 (2.67; 53%), ITGA3 (2.67; 52%), MAPK3 (2.10; 67%), MDK (2.67; 65%), NEU1 (2.67; 53%), NPC2 (2.02; 67%), OPTN (2.67; 69%), PJA2 (2.67; 52%), PLOD2 (2.01; 86%), TAB2 (2.67; 51%), VAMP3 (2.01; 53%), VAMP8 (2.67; 73%), and VNN1 (2.02; 86%). Figure 6C shows box plots comparing the mean log normalized expression of intestine cells where ileal absorptive enterocytes had the highest mean (0.86). Lastly, Figure 6D details the t-SNE cell type where ileal absorptive enterocytes showed the highest mean log normalized expression in relation to other intestine cells.

**Drug repurposing.** The current work proposes an innovative virtual high-throughput screening to predict the activity of 10,672 compounds for 25 targets. After applying the best classification model, we ranked drugs per target and multi-targets taking into account several criteria: first ATC levels associated with COVID-19 symptoms, pharmacological indications, and the best AUROC values. Consequently, on one hand, we obtained 45 approved drugs, 16 compounds under investigation, and 35 experimental compounds with the highest affinities for 15 immune system proteins (Supplementary Table 10). On the other hand, we obtained 4 approved drugs, 9 compounds under investigation, and 16 experimental compounds with the highest multi-target affinities for 9 immune system proteins (Supplementary Table 11).

Figures 7A to 7C show the best-predicted experimental compounds, compounds under investigation, and approved drugs per immune system protein target. Regarding approved drugs, the C3 protein had the highest affinity with lanreotide (AUROC = 0.811); CTS with lopinavir (1), atazanavir (0.999), darunavir (0.999), amprenavir (0.997), saquinavir (0.997), fosamprenavir (0.996), and aliskiren (0.993); B4GALT1 with citicoline (0.939); CTSS with paritaprevir (0.993), zofenopril (0.989), and enzalutamide (0.983); MAPK3 with nelfinavir (0.980); STAT3 with digitoxin (1), and pibrentasvir (1); F2RL1 with etelcalcetide (0.869), and tesamorelin (0.837); HIF1A with topotecan (0.995), and clobetasol propionate (0.992); NEU1 with zanamivir (0.999), and peramivir (0.918); lastly, EGFR with torasemide (1), cabergoline (1), triamterene (1), allopurinol (1), quinine (1), erlotinib (1), methotrexate (1), imatinib (1), pemetrexed (1), nedocromil (1), oxaprozin (1), lapatinib (1), sunitinib (1), vandetanib (1), midostaurin (1), bosutinib (1), axitinib (1), rilpivirine (1), ruxolitinib (1), afatinib (1), ibrutinib (1), duvelisib (1), fostamatinib (1), and gilteritinib (1). Figure 7D shows a network of the best-predicted drugs for immune system multi-targets. Regarding approved drugs, beclomethasone dipropionate had the highest affinity with HIF1A (0.804), and STAT3 (0.978); rosoxacin with STAT3 (0.812), and EGFR (0.885);
halofantrine with EGFR (0.946), and CTSD (0.849); lastly, paritaprevir with CTSD (0.993), CTSS (0.993), and STAT3 (0.877).

DISCUSSION

Since the finding of patient zero in Wuhan, China, a wide spectrum of clinical manifestations has been discovered as we have understood the COVID-19 disease. The most common initial symptoms are cough, fever, anorexia, and dyspnea. The most common clinical features in severe COVID-19 patients are dyspnea, severe hypoxemia, lung edema, respiratory failure, ARDS, lymphopenia, cardiac arrhythmias, rhabdomyolysis, hyperferritinemia, intravascular coagulopathy, and pulmonary thromboembolism. Also, it has been observed that 15% of patients required supplemental oxygen and 5% of patients required mechanical ventilation. In addition, the smaller percentage of patients who required mechanical ventilation suffered comorbidities that lead to sepsis and septic shock. Nowadays, it is known that SARS-CoV-2 is capable of reaching other organs depending on the host. Different studies worldwide refer that clinical presentation vary between individuals, presenting manifestations not only respiratory tract infection, but also blood, skin, kidney, liver, ocular symptoms, neurologic signs, among others. Therefore, it is necessary to continuously review the reports on clinical manifestations in order to get to know the behavior of this disease as well as to think over the physiopathological mechanisms that allows us to better understand the related complications.

The effective immune response of the host, including the innate and adaptive ones, against SARS-CoV-2 seems to be essential to control and solve the infection. However, the clinical seriousness of COVID-19 could be associated to the excessive production of pro-inflammatory cytokines, known as ‘cytokine storm’. This clinical paradigm is still to be figured out, and that is why the effective treatment is still uncertain. It is indispensable to understand the immunological responses that are triggered off since the beginning of the infection with SARS-CoV-2, so as to make progress in search of effective therapeutic strategies.

Innate immune response executes the first line of antiviral defense and is essential to obtain immunity against viruses. Pattern recognition receptors (PRRs), codified by germline DNA, are responsible for recognizing widely common molecular patterns shared by pathogens of a certain group. Single-stranded and double-stranded viral RNAs produced during the replication phase of SARS-CoV-2 are recognized by endosomal TLRs (TLR7 and TLR8 or TLR3, respectively) and cytosolic RIG-I like receptors (RLRs), mainly RIG-I and MDA-5. After PRR engagement, downstream signaling pathways trigger the activation and nuclear translocation of key transcription factors, such as NF-κB, AP-1 and interferon regulatory factors (IRFs), and the ensuing expression of pro-inflammatory and anti-viral cytokines. Among the most relevant cytokines we can find interleukins (IL-1, IL-6 and IL-18), pro-inflammatory TNF-α and TNF-β, and type I and III IFNs. Consequently, cytokines induce antiviral processes potentiating the innate and adaptive immune responses, limiting CoVs replication capacity and inducing the elimination of the virus cell reservoirs. However, CoVs have developed mechanisms of immune evasion where viral factors inhibit viral recognition by PRR sensing, and cytokine expression and secretion. Individuals with severe COVID-19 have demonstrated remarkably impaired type I IFN values as
compared to mild patients\textsuperscript{79}, and the interferon-induced overexpression of ACE2 may be involved\textsuperscript{8}.

Mucosal immune responses against viruses are orchestrated by myeloid cells such as macrophages, conventional DCs, plasmacytoid DCs, and monocyte-derived DCs\textsuperscript{80}. Accumulating evidence suggests that deregulation of myeloid cell-mediated responses potentially triggers lymphopenia, cytokine release syndrome, acute respiratory distress syndrome\textsuperscript{44}, and pathogenic inflammation with high level secretion of IL-6, IL-2, IL-7, IFN-γ, IFN-I, and type III IFNs\textsuperscript{81} in COVID-19 patients with severe clinical manifestations.

Innate lymphoid cells (ILCs) are lymphoid-like immune cells that lack the expression of rearranged antigen receptors. The non-cytotoxic group I, II and III ILCs and the cytotoxic natural killer (NK) cells form the ILC family\textsuperscript{82}. Several clinical data have reported that NK cells decrease in peripheral blood of severe patients\textsuperscript{83,84}. An \textit{in vitro} study has identified that the CXCL9-11 chemokines are overexpressed in lung cells infected with SARS-CoV-2, suggesting that the CXCR3 signaling pathway drives NK cells from peripheral blood to lungs in COVID-19 patients\textsuperscript{85}. In addition, NK cells have the quality to induce lysis of infected cells causing severe hypoxemia and contributing to the cytokine storm resulting in ARDS.

T cells are involved in fundamental processes in viral infections. CD8 T cells eliminate infected cells and CD4 T cells help B cells for antibody production. Nevertheless, immunopathology is generated when T cells are dysregulated. Several reports have shown that moderate to severe COVID-19 patients with lymphopenia drastically reduce CD8 T cell and CD4 T cells in peripheral blood\textsuperscript{86,87}. T cells reduction in the blood is also a contribution of mechanisms such as inflammatory cytokine milieu, which is why lymphopenia has a correlation with TNF-α, IL-6 and IL-10\textsuperscript{88,89}. Conversely, clinical reports have shown that convalescent patients have low pro-inflammatory cytokine levels paired with restored bulk T cell frequencies\textsuperscript{88}.

The humoral immune response plays a main role in the clearance of cytopathic viruses and its memory response prevents reinfection. According to Huang \textit{et al}. and Wu \textit{et al}., IgM, IgA, and neutralizing IgG antibodies can be detected in 12, 14 and 10-14 days, respectively, after symptom onset on average, suggesting that SARS-CoV-2 causes a robust B cell response in the majority of COVID-19 patients\textsuperscript{90,91}. Indeed, antibodies binding the RBD of the S glycoprotein can have neutralizing properties, blocking virus interactions with the human protein receptor ACE2\textsuperscript{92}, thereby inhibiting/preventing target cell infection. The B cell response to SARS-CoV-2 protects from the primary infection and extends immunity against reinfection due to memory B cells that can respond quickly by producing high affinity neutralizing antibodies. However, it is yet impossible to predict the duration of memory responses due to the timing of the COVID-19 pandemic.

There is currently a limited number of known risk factors that confer susceptibility to COVID-19. Several routine blood tests and immunological biomarkers have been suggested to classify patients with mild and severe symptoms. The routine blood test biomarkers currently suggested are lymphocyte count\textsuperscript{93}, neutrophil to lymphocyte ratio\textsuperscript{94}, C-reactive protein\textsuperscript{95}, lactate dehydrogenase\textsuperscript{96}, ferritin\textsuperscript{97}, D-dimer and coagulation parameters\textsuperscript{98}, serum amyloid protein\textsuperscript{99}, N terminal pro B type natriuretic peptide\textsuperscript{99},
platelet count\textsuperscript{100}, ultrasensitive troponin, and creatine kinase MB\textsuperscript{101}. On the other hand, immunological biomarkers associated with different COVID-19 outcomes are CD4+, CD8+ and NK cell count\textsuperscript{87}; PD-1 and Tim-3 expression on T cells\textsuperscript{88}; phenotypic changes in peripheral blood monocytes\textsuperscript{102}; expression levels of IP-10, MCP-3, IL-1RA\textsuperscript{103}, IL-6\textsuperscript{104}, IL-8, IL-10, IL-2R, IL-1β\textsuperscript{105}, IL-4\textsuperscript{106}, IL-18, granulocyte macrophage colony stimulating factor (GM-CSF)\textsuperscript{107}, IL-2, IFN-γ\textsuperscript{108}, and anti-SARS-CoV-2 antibodies\textsuperscript{106,109}.

In an effort to better understand the immunological underpinnings of COVID-19, we performed a PPI network analysis, a scRNA-seq data analysis, and artificial neural networks to reveal potential therapeutic targets for drug repurposing. Gordon et al. identified 332 human proteins physically associated with 26 of the 29 SARS-CoV-2 proteins, using affinity-purification mass spectrometry\textsuperscript{10}. Consequently, we performed a PPI network between immune system proteins and human proteins physically associated to SARS-CoV-2. The protein with the highest degree centrality was UBA52, followed by GNB1, APP, FPR2, NCBP1, NCBP2, KNG1, PIK3CA, PIK3R1, and MAPK1 (Supplementary Figure 1 and Supplementary Table 4). UBA52 encodes a fusion protein that regulates ubiquitination of ribosome, and UBA52-deficient cells display decreased cell cycle arrest and protein synthesis\textsuperscript{110}. On the other hand, human proteins physically associated with SARS-CoV-2 proteins and with the highest degree centrality in our network were GNB1, RPL36, PABPC1, GNG5, UPF1, SRP54, SRP19, SRP72, EIF4H, and EXOSC8 (Figure 2). GNB1 encodes a protein that acts as a modulator in transmembrane signaling systems, including the GTPase activity\textsuperscript{10}.

After an enrichment analysis of the 1,588 immune system proteins of the PPI network, the most significant KEGG signaling pathways were chemokine signaling pathway, TNF signaling pathway, NF-kappa B signaling pathway, IL-17 signaling pathway, TLR signaling pathway, and T cell receptor signaling pathway. The most significant Reactome pathways were immune system, innate immune system, cytokine signaling, signaling by ILs, neutrophil degranulation, viral mRNA translation, and chemokine receptors bind chemokines. Lastly, the most significant WikiPathways were chemokine signaling pathway, gastrin signaling pathway, TWEAK signaling pathway, regulation of TLRs signaling pathway, TCR signaling pathway, and IL-1 signaling pathway (Supplementary Table 5).

Additionally, we generated a network of the GO biological processes related to the aforementioned immune system PPI network using the EnrichmentMap Pipeline Collection software\textsuperscript{59,63}. The GO biological processes with the highest degree centrality were immune system process, immune response, leukocyte activation, cell death, cytokine production, apoptotic process, lymphocyte activation, cellular response to cytokine stimulus, adaptive immune response, T cell activation, inflammatory response, innate immune response, immunoglobulin production, positive regulation of B cell mediated immunity, IL-1-mediated signaling pathway, TNF production, IFN-I production, antigen receptor-mediated signaling, neutrophil activation, granulocyte activation, macrophage differentiation, hypoxia, dendritic cell differentiation, protein ubiquitination, blood coagulation, and reactive oxygen species (Figure 3 and Supplementary Table 6). Interestingly, all biological processes obtained are closely related to clinical and pathophysiological manifestations of COVID-19\textsuperscript{28,35,76,77,111}.

There is pressing urgency to better understand the immune system behavior after SARS-CoV-2 infection. In light of this global effort, we discovered putative therapeutic
targets of the immune system by screening 1,588 high-confidence nodes into human tissues using scRNA-seq data. Ziegler et al. discovered ACE2 and TMPRSS2 co-expressing cells in nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes. None of these cells was exposed to the novel coronavirus but the analysis of the Alexandria Project data represents a large effort to characterize this immunopathology.

Nasal passage cells were taken from chronic rhinosinusitis samples developed by allergic inflammation. The significantly overexpressed genes and potential therapeutic targets in nasal goblet secretory cells were ATP1B1, CD55, ELF3, EPAS1, and TNFSF10 (Figure 4). Additionally, the most significant GO molecular functions (FDR < 0.001) were MHC class II protein complex binding in ATP1B1; virus receptor activity in CD55; DNA-binding transcription factor activity in ELF3; DNA-binding and RNA polymerase II cis-regulatory region sequence-specific DNA binding in EPAS1; lastly, cytokine activity and TNF receptor binding in TNFSF10.

Regarding epithelial cells of lung tissue, the significantly overexpressed genes and potential therapeutic targets in lung type II pneumocytes were C3, CD44, EPAS1, HIF1A, HLA-DPB1, ITGB6, NPC2, RPS23, CTSH, RPS13, HLA-DPA1, CXCL2, STAT3, HSPA5, LDLR, CTNNB1, RPS20, RPL3, SLPI, NFKBIA, HLA-DBB1, RPS12, SDC4, S100A10, SQSTM1, RPL23, RPL4, RPS24, CSDE1, EGFR, HNRNPU, CD74, CD63, RPLP0, EEF2, ETS2, DDX3X, HLA-DRA, RPL18, PIGR, RPL8, RPS3, RPS4X, RPS6, LRRFIP1, and RPL19 (Figure 5). In addition, the most significant GO molecular functions (FDR < 0.001) were C5L2 anaphylatoxin chemotactic receptor binding in C3; hyaluronic acid binding in CD44; DNA-binding transcription activator activity in HIF1A; peptide antigen binding in HLA-DPB1; integrin binding in ITGB6; cholesterol binding in NPC2; RNA binding in RPS23, RPS20 and RPS12; HLA-A specific activating MHC class I receptor activity in CTSH; mRNA 5'-UTR binding in RPS13; MHC class II receptor activity and peptide antigen binding in HLA-DPA1, HLA-DBB1 and HLA-DRA; chemokine activity and CXCR chemokine receptor binding in CXCL2; CCR5 chemokine receptor binding in STAT3; ATP binding in HSPA5 and DDX3X; virus receptor activity in LDLR; androgen and estrogen receptors binding in CTNNB1; 5S rRNA binding in RPL3, DNA binding in SLPI, ETS2 and EGR1; NF-kappaB binding in NFKBIA, fibronectin binding and thrombospondin receptor activity in SDC4; calcium ion activity in S100A10; ubiquitin binding in SQSTM1; large ribosomal subunit rRNA binding in RPL23, RPL19 and RPLP0; RNA binding in RPL4, RPS24, CSDE1, RPL18, RPL8, RPS4X, RPS6 and EEF2; double-stranded RNA binding in HNRNPU; CD4 receptor binding and cytokine binding in CD74; neutrophil and platelet degranulation in CD63; polymeric immunoglobulin receptor activity in PIGR; class I DNA-(apurinic or apyrimidinic site) endonuclease activity in RPS3; lastly, cadherin binding in LRRFIP1.

Regarding adult human duodenum and ileum tissues, the significantly overexpressed genes and potential therapeutic targets in ileal absorptive enterocytes were ATP11B, ATP6AP1, B4GALT1, CD55, CEACAM1, CEACAM6, CTSK, CTSS, CXCL16, EGFR, EPAS1, F2RL1, GNA11, GRN, HIST1H2AC, HLA-DRB1, ITGA2, ITGA3, MAPK3, MK, NEU1, NPC2, OPTN, PJA2, PLKD2, TAB2, VAMP3, VAMP8, and VNN1 (Figure 6). Additionally, the most significant GO molecular functions (FDR < 0.001) were ATP binding in ATP11B and ATP6AP1; alpha-tubulin binding in B4GALT1; bile acid transmembrane transporter activity in CEACAM1; protein heterodimerization...
activity in *CEACAM6*; peptidase activity in *CTSD*; proteoglycan binding in *CTSS*; chemokine activity in *CXCL16*; epidermal growth factor in *EGFR*; G protein-coupled receptor binding in *F2RL1* and *GNA11*; cytokine activity in *GRN*; DNA binding in *HIST1H2AC*; virus receptor activity in *ITGA2*; protease binding in *ITGA3*; MAP kinase activity in *MAPK3*; heparin binding in *MDK*; alpha-sialidase activity in *NEU1*; cholesterol binding in *NPC2*; polyubiquitin modification-dependent protein binding in *OPTN*; ubiquitin protein ligase activity in *PJA2*; iron ion binding in *PLOD2*; metal ion binding in *TAB2*; syntaxin-1 binding in *VAMP3*; chloride channel inhibitor activity in *VAMP8*; and, pantetheine hydrolase activity in *VNN1*.

Lastly, the complete list of functions of the 75 potential therapeutic targets is detailed in Supplementary Table 7.

There is currently an urgent need for effective COVID-19 drugs. High-throughput screening for drug discovery has been important in finding antiviral drugs focused on the spike protein and the main protease (Mpro) of SARS-CoV-2. However, computational structure-based drug discovery focused on immune system proteins is imperative to select potential drugs that, after being effectively analyzed in cell lines (i.e., African green monkey cells) and clinical trials, these can be considered for treatment of complex symptoms of COVID-19 patients. Drug repurposing offers a potentially rapid mechanism to deployment, since the safety profiles are known.

Consequently, we performed fully connected deep neuronal networks to predict drugs with the highest affinities per target and multi-targets. We identified 45 approved drugs, 16 compounds under investigation, and 35 experimental compounds with the highest AUROCs for 15 immune system proteins (Supplementary Table 10). Regarding approved drugs, cictoline (B4GALT1) provides neuroprotection; lanreotide (C3) has been approved for treatment of neuroendocrine tumors and acromegaly; amprenavir, atazanavir, saquinavir, darunavir, fosamprenavir and lopinavir had the highest affinities with CTSD and are employed for treatment of HIV-1 infection; nelfinavir (MAP3K) inhibits the HIV viral proteinase enzyme; rilpivirine (EGFR) is indicated for treatment of HIV-1 infection; aliskiren (CTSD) is a renin inhibitor for arterial hypertension; enzalutamide (CTSS) is an androgen receptor inhibitor that acts as an antineoplastic in prostate cancer; paritaprevir (CTSS) has been approved for treatment of chronic hepatitis C virus infection; zofenopril is an ACE inhibitor and is employed as both a cardioprotective and anti-hypertensive agent; tesamorelin (F2RL1) has been approved for treatment of HIV-infected patients as it is an growth hormone-releasing factor with lipolytic effect; etelcalcetide (F2RL1) is indicated for secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis; clobetasol propionate (HIF1A) is one of the most potent corticosteroids and is employed to treat psoriasis as well as inflammatory manifestations of corticosteroid-responsive dermatoses; topotecan (HIF1A) is an antineoplastic and immunomodulating agent; zanamivir and peramivir (NEU1) are indicated for treatment of influenza A and B; digitoxin (STAT3) is employed for treatment of congestive cardiac insufficiency, arrhythmias, and heart failure; pibrentasvir (STAT3) is indicated for treatment of patients with chronic hepatitis C virus; erlotinib, methotrexate, imatinib, pemetrexed, lapatinib, sunitinib, vandetanib, midostaurin, bosutinib, axitinib, ruxolitinib, afatinib, ibrutinib, and gilterinib had the highest affinities with EGFR and act as antineoplastic and immunomodulating agents; torasemide and triamterene (EGFR) act on cardiovascular system; allopurinol, quinine, and oxaproxin (EGFR) act on musculoskeletal system; cabergoline (EGFR) acts on nervous system; nedocromil (EGFR) acts on respiratory system; fostamatinib (EGFR) is indicated for treatment of chronic immune system; fostamatinib (EGFR) is indicated for treatment of chronic immune
thrombocytopenia; and duvelisib (EGFR) can produce a broad adaptive and innate immune cell inhibitory activity. Additionally, we identified 4 approved drugs, 9 compounds under investigation, and 16 experimental compounds with the highest multi-target affinities for 9 immune system proteins (Supplementary Table 11). Beclomethasone dipropionate (HIF1A and STAT3) is a highly potent glucocorticoid in the airway; rosoxacin (STAT3 and EGFR) is indicated for treatment of bacterial infection of respiratory tract; halofantrine (EGFR and CTSD) is employed for treatment of severe malaria; and, paritaprevir (CTSD, CTSS, and STAT3) is indicated for treatment of hepatitis C virus infection. After these analyses, a broad spectrum of possibilities for co-therapies are expanded; for instance, with drugs directly targeting SARS-CoV-2, including remdesivir.\(^\text{117}\)

The current COVID-19 pandemic offers a unique opportunity to strengthen mechanisms that promote the use of drug repurposing processes—considering the drug safety profile and the possibility of originate different adverse reactions in patients with distinct concomitant diseases—; inclusively, in the ongoing or future clinical trials, having the potential to reduce the time and costs for finding potential solutions to the current pandemic. Additionally, contributing to future analysis for high threat pathogens and rare diseases. This idea is welcomed by some other authors who conveyed on the potential of drug repurposing for common national and global health benefits.\(^\text{118}\) Between the several advantages of this process, the one which leads efforts to the use of the current information -on human pharmacology and toxicology- of safe and affordable generic drugs, is worth to remark. As also stated by Guy \textit{et al.}\(^\text{119}\), along with this statement, there is the urge to motivate the transparency and compliance of the highest ethical principles for the conduction of studies, including as a key potential for drug repurposing, the visualization and sharing of negative results. Mainly, promoting and assuring that well-designed randomized clinical trials are timely implemented, especially during health emergencies and crises. In this sense, drug repurposing will be fulfilling its main objective: proposing potential, prompt, cost-effective, and safe solutions for the public and global health problems, with a human-centered approach.

The COVID-19 pandemic has evidenced that there is a strong urge to strengthen health systems with a major emphasis on health prevention and the major need, especially of low and middle income countries, to publicly invest on research and development. Consequently, the benefits of innovation and the results of research should be always available and affordable to anyone in need, to comply with the goal of public health.\(^\text{120}\) This is of particular importance during the current pandemic situation and on its aftermath.

From a global health perspective, initiatives directed to the improvement of rapid data sharing are critical during health emergency. This rapid sharing includes undoubtedly a transboundary collaboration founded on the principles of reliability and accuracy of the data.\(^\text{121}\) Meaningfully, for preventing potential new or existing pathogens to become high threats to human health and global security, non-commercial basic research on microorganisms should be assured. Additionally, introducing and promoting genomic epidemiology and strengthening global laboratory alliances would contribute to the national and global rapid detection and containment of outbreaks, as also promoted by the WHO. Accordingly, every country is sovereign and should guarantee the protection and regulation of the use of its biological resources, specifically working towards the Fair and Equitable Sharing of Benefits. Nevertheless, international conventions on the topic and national legislations should include fast track options for research on
pathogens. Relevantly, the links between human, environmental, and animal health - the One Health approach - are widely recognized to be effective towards the prevention and reduction of the emergence and re-emergence of potential pandemic agents. This, not only pursuing to diminish the impact of epidemics or pandemics in the health systems, but also to underpin and reinforce economic, development, and social benefits.
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AUTHOR CONTRIBUTIONS

A.L.-C. conceived the subject, the conceptualization of the study, and wrote the manuscript. P.G.-R, N.C.K and C.B.-O. edited the manuscript and gave valuable scientific input. C.R.M. and E.T. performed the artificial neural networks. A.L.C., S.G., E.O.-P., D.C.-R., A.M.G.J., K.S.-R., A.G.-M., G.P.-M., J.M.G.-C., A.K.Z., S.M., Y.P.-C., A.C.-A., L.P.S.A., C.P.-C., J.B., N.V., L.A.Q., and C.P.-Y.-M. gave valuable scientific input and did data curation. A.L.-C. and C.P.-Y.-M. did founding acquisition. Lastly, all authors reviewed and approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

All data generated during this study are included in this published article (and its Supplementary Information files).
FIGURE LEGENDS

Figure 1. Physical interactions between human and SARS-CoV-2 proteins. A) Proteomic and genomic structure of SARS-CoV-2. B) Human proteins physically associated with SARS-CoV-2 proteins. All interactions were identified by colors. C) Most significant Reactome signaling pathways of the 332 human proteins associated with SARS-CoV-2.

Figure 2. Small version of the immune system protein-protein interactome network made up of proteins with the highest degrees of centrality.

Figure 3. Enrichment map of the gene ontology: biological processes from the immune system protein-protein interactome network.

Figure 4. Single-cell RNA-sequencing data analysis of the high-confidence immune system nodes in nasal passage cells. A) Heat map of significant overexpressed genes (Z score > 2) in nasal goblet secretory cells. B) Dot plot of significant overexpressed genes in nasal goblet secretory cells and percentage of cells expressing. C) Box plots of nasal passage cell types according to their mean log normalized expression. D) t-distributed stochastic neighbor embedding cell type and mean log normalized expression focused on nasal goblet secretory cells.

Figure 5. Single-cell RNA-sequencing data analysis of the high-confidence immune system nodes in lung cells. A) Heat map of significant overexpressed genes (Z score > 2) in lung type II pneumocytes. B) Dot plot of significant overexpressed genes in lung type II pneumocytes and percentage of cells expressing. C) Box plots of lung cell types according to their mean log normalized expression. D) t-distributed stochastic neighbor embedding cell type and mean log normalized expression focused on lung type II pneumocytes.

Figure 6. Single-cell RNA-sequencing data analysis of the high-confidence immune system nodes in intestine cells. A) Heat map of significant overexpressed genes (Z score > 2) in ileal absorptive enterocytes. B) Dot plot of significant overexpressed genes in ileal absorptive enterocytes and percentage of cells expressing. C) Box plots of intestine cell types according to their mean log normalized expression. D) t-distributed stochastic neighbor embedding cell type and mean log normalized expression focused on ileal absorptive enterocytes.

Figure 7. Drug repurposing analyses applying artificial neural networks. A) Best-predicted experimental compounds per immune system protein target. B) Best-predicted compounds under investigation per immune system protein target. C) Best-predicted approved drugs per immune system protein target. D) Best-predicted multi-target experimental compounds, compounds under investigation, and approved drugs. AUROC: Area under the receiver operating characteristic.