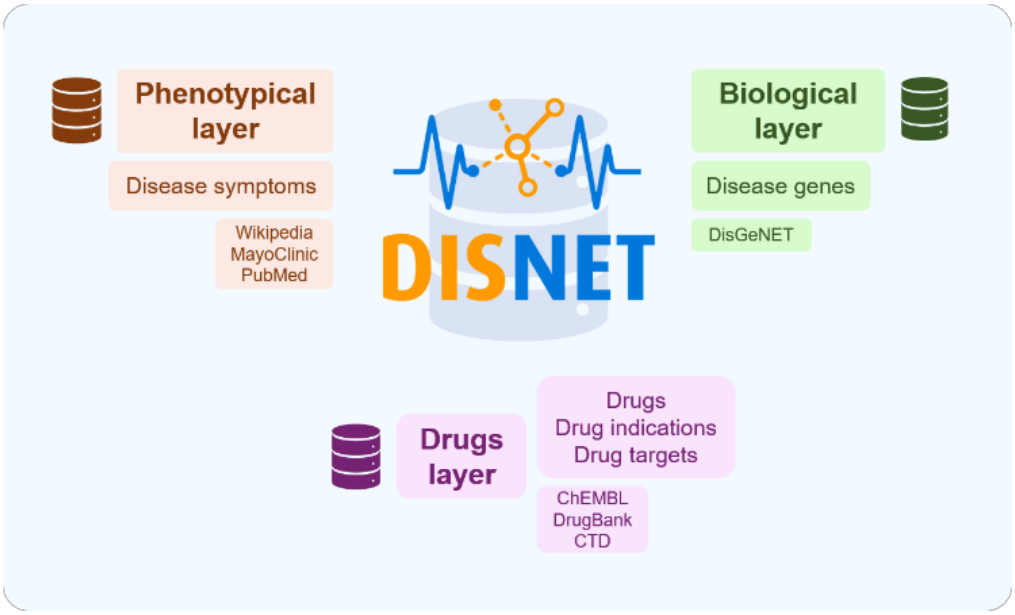
Supplementary material – Publication III

SM 1—Gathered data additional information



Supplementary Figure 1. Summary of the database for the DISNET project. Data integration in the three layers of DISNET: the phenotypical level in orange, the biological level in green, and the drug level in pink. For each layer, the studied entities and data sources are shown. CTD, The Comparative Toxicogenomics Database.

Supplementary Table 1. Summary of data typology for entities studied in the analysis.

	Entities	Description	DISNET layer	Count	Identifiers	Sources	Access date
All diseases	Diseases	Data representing diseases	Phenotypical	9,225	DISNET's own identifiers	Wikipedia Mayo Clinic PubMed	February 2018 – January 2021 (twice a month)
			Biological	24,314	UMLS CUIs	DisGeNET	May 2020
			Drugs	9,116	UMLS CUIs	CTD	May 2020
	Symptoms	Data representing symptoms and phenotypical effects	Phenotypical	2,248	UMLS CUIs	Wikipedia Mayo Clinic PubMed	February 2018 – January 2021 (twice a month)
			Drugs	851	UMLS CUIs	ChEMBL	May 2020
	Genes	Data representing genes	Biological	20,610	NCBI identifiers	DisGeNET	May 2020
	Proteins and targets	Data representing proteins and drug targets	Biological	18,521	UniProt Accession Numbers	UniProt	May 2020
			Drugs	1,594	ChEMBL identifiers	ChEMBL	May 2020
	Drugs	Data representing drugs of different molecular types	Drugs	3,944	ChEMBL identifiers	ChEMBL	May 2020
				2,540	DrugBank identifiers	DrugBank	May 2020
COVID-19	Symptoms	Data representing COVID-19 studied symptoms	Phenotypical	76	UMLS CUIs	Wikipedia	December 2020
						ECDC	December 2020
						Mayo Clinic	March – February 2021
	Genes	Data representing COVID-19 related genes, mentioned in scientific research literature	Biological	75	NCBI identifiers	DisGeNET COVID-19 data	November 2020

CTD, Comparative Toxicogenomics Database; CUI, Concept Unique Identifier; ECDC, European Centre for Disease Prevention and Control; NCBI, National Center for Biotechnology Information; UMLS, Unified Medical Language System.

Supplementary Table 2: Summary of data typology for relationships studied in the analysis.

Relationships	Description	DISNET layer	Count	Sources	Access date
Disease–symptom	Associations between diseases and their related symptoms	Phenotypical	211,362	Wikipedia Mayo Clinic PubMed	February 2018 – January 2021 (twice a month)
Disease–gene	Associations between diseases and their related genes	Biological	358,209	DisGeNET	May 2020
Gene–protein	Associations between genes and the proteins they encode	Biological	15,770	DisGeNET	May 2020
Drug–disease	Associations between diseases that are indications for drugs and drugs	Drugs	628,036	CTD	May 2020
Drug–target	Associations between targets to which drugs are directed and drugs	Drugs	7,727	ChEMBL	May 2020
				DrugBank	December 2020
Drug–symptom	Associations between symptoms considered to be indications for drugs and drugs	Drugs	10,475	ChEMBL	May 2020

CTD, Comparative Toxicogenomics Database.

Supplementary Table 3. Identifiers considered as COVID-19 in the DR pipeline.

Disease ID	ID terminology	Disease source	Disease name
C000657245	MeSH	DisGeNET	Coronavirus Disease 2019
C0206750	UMLS CUI	DisGeNET	Coronavirus infections
C1175743	UMLS CUI	DisGeNET	SARS coronavirus
DIS014279	DISNET	Mayo Clinic	Coronavirus
DIS014304	DISNET	Mayo Clinic	COVID-19
DIS014312	DISNET	Mayo Clinic	Coronavirus disease 2019 (COVID-19)
DIS014594	DISNET	Mayo Clinic	Corona virus, also known as Coronavirus disease 2019 (COVID-19)
DIS014599	DISNET	Mayo Clinic	COVID-19, also known as Coronavirus disease 2019 (COVID-19)
DIS014989	DISNET	Mayo Clinic	Novel coronavirus, also known as Coronavirus disease 2019 (COVID-19)
DIS015952	DISNET	Mayo Clinic	COVID-19-associated multisystem inflammatory syndrome in children, also known as Multisystem inflammatory syndrome in children (MIS-C)

Supplementary Table 4. Most-representative symptoms of COVID-19 present in Wikipedia, European Centre for Disease Prevention and Control (ECDC), and Mayo Clinic reports.

Symptom CUI	Symptom name
C0010200	Coughing
C0013404	Dyspnea
C0003126	Anosmia
C0011991	Diarrhea
C0015672	Fatigue
C0018681	Headache
C0031350	Pharyngitis
C0042963	Vomiting
C0231528	Myalgia
C0242429	Sore throat
C0683369	Clouded consciousness
C0231218	Malaise

Supplementary Table 5. Some of the genes related to COVID-19, extracted from DisGeNET-provided associations.

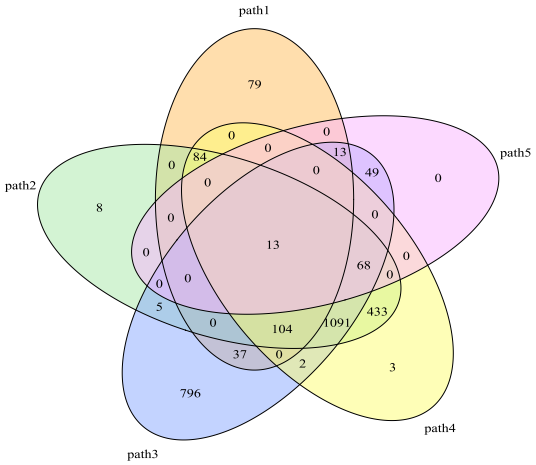
Gene ID	Gene symbol	Gene name
183	*AGT*	Angiotensinogen

1636	*ACE*	Angiotensin I converting enzyme
59272	*ACE2*	Angiotensin I converting enzyme 2
3569	*IL6*	Interleukin 6
43740568	*S*	Surface glycoprotein
43740570	*E*	Envelope protein
43740575	*N*	Nucleocapsid phosphoprotein
43740578	*ORF1ab*	ORF1a polyprotein;ORF1ab polyprotein

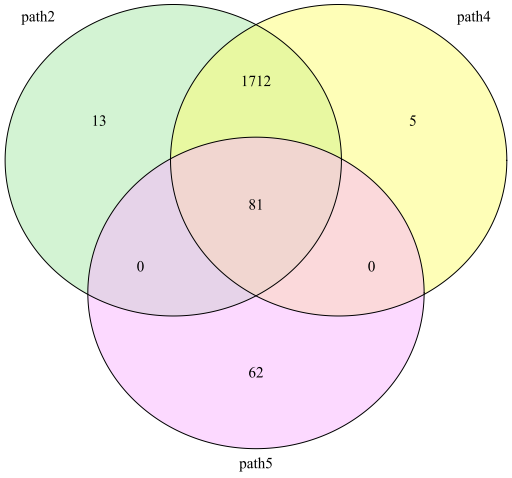
SM 2—Path intersections

Supplementary Table 6. Number of drugs obtained from each path.

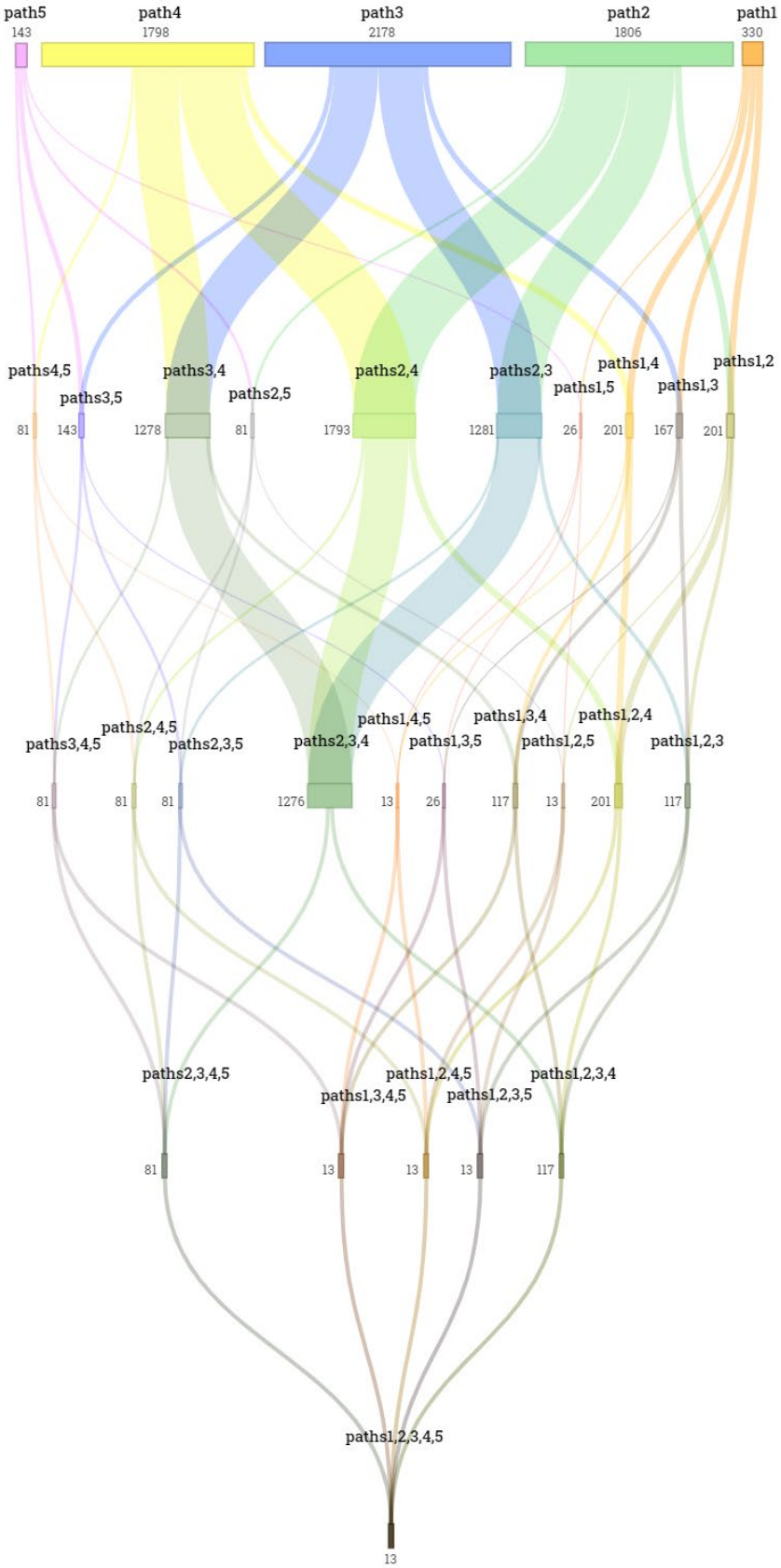
Path	Number of drugs
Path 1	330
Path 2	1,806
Path 3	2,178
Path 4	1,798
Path 5	143
Intersection of paths 1 to 5	13



Supplementary Figure 2: Venn diagram showing the number of drugs that intersect between every DR path. 13 drugs are shared by the five DR paths.



Supplementary Figure 3: Venn diagram showing the number of drugs that intersect between paths 2, 4, and 5. These three paths were chosen because they were the most specific ones. The three routes have 81 drugs in common.



Supplementary Figure 4: Diagram displaying the total number of drugs shared in every path intersection. It is worth noting that path intersections 1, 2, 5 and 1, 4, 5 share the same 13 drugs that converge in the final five-way intersection (intersection 1, 2,3, 4, 5).

SM 3—Mechanisms of action of the intersecting drugs

Supplementary Table 7. COVID-19-related mechanisms of action of the drugs that intersect in the five proposed repurposing paths.

Drugs	Mechanism of action
Aldesleukin	Aldesleukin is a human recombinant interleukin-2 (IL2) product that promotes the proliferation, differentiation, and recruitment of T and B cells, natural killer cells, and thymocytes. It also causes cytolytic activity in a subset of lymphocytes and subsequent interactions between the immune system and malignant cells. It can stimulate lymphokine-activated killer cells and tumor-infiltrating lymphocyte cells. Recombinant IL2 has been shown to have potent, dose-dependent immunomodulatory and antitumor activity. These observations led to the development of high-dose IL-2 regimens for use in patients with metastatic melanoma and cell renal carcinoma.
Cefazolin	Cefazolin is a first-generation cephalosporin antibiotic. It inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins, which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thereby inhibiting cell wall biosynthesis. Bacteria eventually lyse due to the ongoing activity of cell wall autolytic enzymes while cell wall assembly is arrested.
Epinephrine	Epinephrine or adrenalin is a sympathomimetic amine that has potent beta-1 adrenergic receptor activity and moderate beta-2 and alpha-1 adrenergic receptor effects. The effect on these receptors causes vasoconstrictor, inotropic and positive chronotropic, bronchodilator, and hyperglycemic activities. This drug is most often used for the treatment of anaphylaxis, and as a second-line agent in septic shock, acute asthma, cardiac arrest, and cardiopulmonary resuscitation.
Everolimus and sirolimus	Everolimus and sirolimus are a type of immunosuppressant: mTOR kinase inhibitors. Sirolimus inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production. It binds to FK binding protein-12 (FKBP-12), an intracellular protein, to form an immunosuppressive complex that inhibits the regulatory kinase, mTOR (mechanistic target of rapamycin). This inhibition suppresses cytokine-mediated T-cell proliferation, halting progression from the G_1 to the S phase of the cell cycle. It inhibits acute rejection of allografts and prolongs graft survival. Everolimus is a macrolide immunosuppressant and an mTOR inhibitor that has antiproliferative and antiangiogenic properties, and also reduces lipoma volume in patients with angiomyolipoma. Like sirolimus, everolimus reduces protein synthesis and cell proliferation by binding to FKBP-12, forming a complex that inhibits the activation of mTOR. Everolimus also reduces angiogenesis by inhibiting the expression of vascular endothelial growth factor and hypoxia-inducible factor. Both drugs are used in rejection prophylaxis in transplant

	patients.
Hydroxychloroquine	Hydroxychloroquine is an aminoquinoline, an antimalarial agent that shares the same mechanism of action as chloroquine. As an antimalarial, it interferes with the digestive vacuole function within sensitive malarial parasites by increasing the pH and interfering with the lysosomal degradation of hemoglobin, inhibits the locomotion of neutrophils and the chemotaxis of eosinophils, and impairs complement-dependent antigen-antibody reactions. This drug may inhibit SARS-CoV-2 *in vitro*; the immunomodulatory effect of hydroxychloroquine may be useful in controlling the cytokine storm that occurs in the late phase in critically ill patients with SARS-CoV-2. However, accumulating data from controlled trials suggest that hydroxychloroquine does not provide a clinical benefit for patients with COVID-19. In a randomized, blinded, placebo-controlled trial of 479 hospitalized patients with COVID-19, hydroxychloroquine did not improve 14-day clinical status or 28-day mortality (10.4% versus 10.6%; adjusted OR 1.07, 95% CI 0.54–2.09) when compared with placebo. The trial was terminated early because of this lack of benefit.
Losartan and candesartan cilexetil	As a selective and competitive, nonpeptide angiotensin II (ATII) receptor antagonist, losartan blocks the vasoconstrictor and aldosterone-secreting effects of ATII; it interacts reversibly with the angiotensin I (ATI) and ATII receptors of many tissues. Candesartan is an angiotensin receptor antagonist, binds the ATI receptors, and has the same effects as losartan.
Enalapril and ramipril	Enalapril and ramipril are prodrugs belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications. ACE is the enzyme responsible for the conversion of ATI to ATII. ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS).
Minocycline	Minocycline is a tetracycline antibiotic. The tetracyclines enter the bacterial cell wall in two ways: by passive diffusion and through an energy-dependent active transport system, which is probably mediated in a pH-dependent fashion. Once inside the cell, tetracyclines bind reversibly to the 30S ribosomal subunit at a position that blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA–ribosome complex. Protein synthesis is ultimately inhibited, leading to a bacteriostatic effect.
Sitagliptin and vildagliptin	Sitagliptin and validagliptin are inhibitors of the DPP4 protein (DPP-4i). DPP-4i are a class of oral diabetes drugs that inhibit the enzyme DPP-4. DPP-4 is a ubiquitous enzyme that is expressed on the surface of most cell types. This enzyme deactivates a variety of other bioactive peptides, including glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1; therefore, its inhibition could potentially affect glucose regulation through multiple effects.