LEIBNIZ-INFORMATIONSZENTRUM
TECHNIK UND NATURWISSENSCHAFTEN
UNIVERSITÄTSBIBLIOTHEK

TIB

Bibliothek des Jahres 2020

How Do Open Knowledge Graphs Contribute to Understanding COVID-19 Related Treatments?

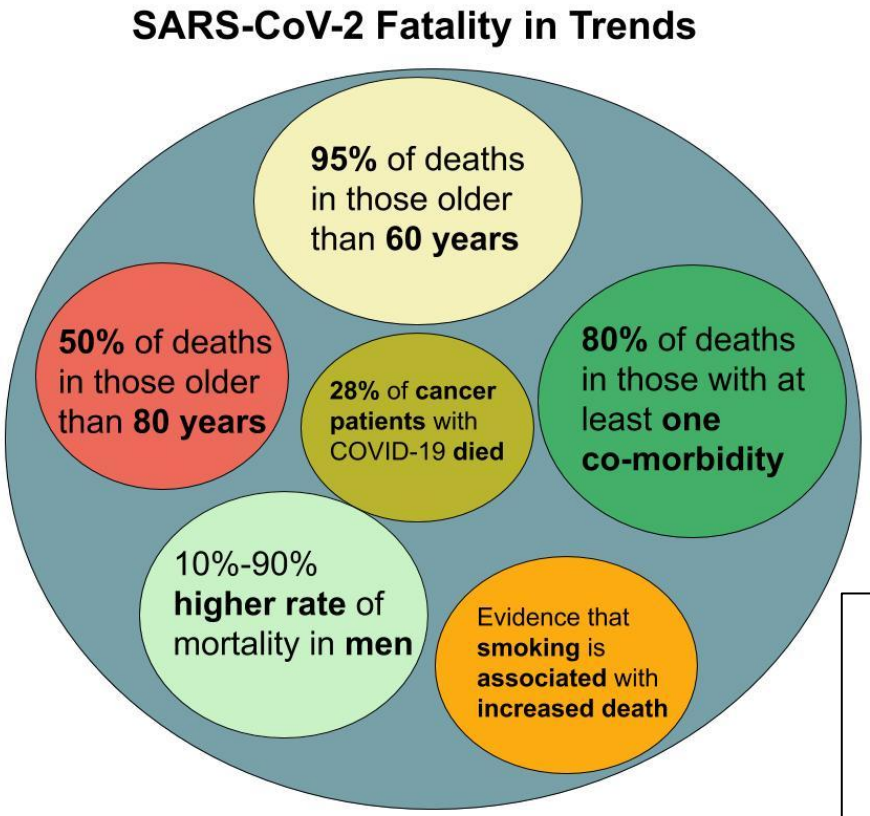
Maria-Esther Vidal

Scientific Data Management Group (TIB)

08.09.2020

Leibniz Association

Motivation



What are potential **adverse effects** of a group of COVID-19 drugs?

What is the **risk of prescribing a COVID-19** treatment to patients with comorbidities?

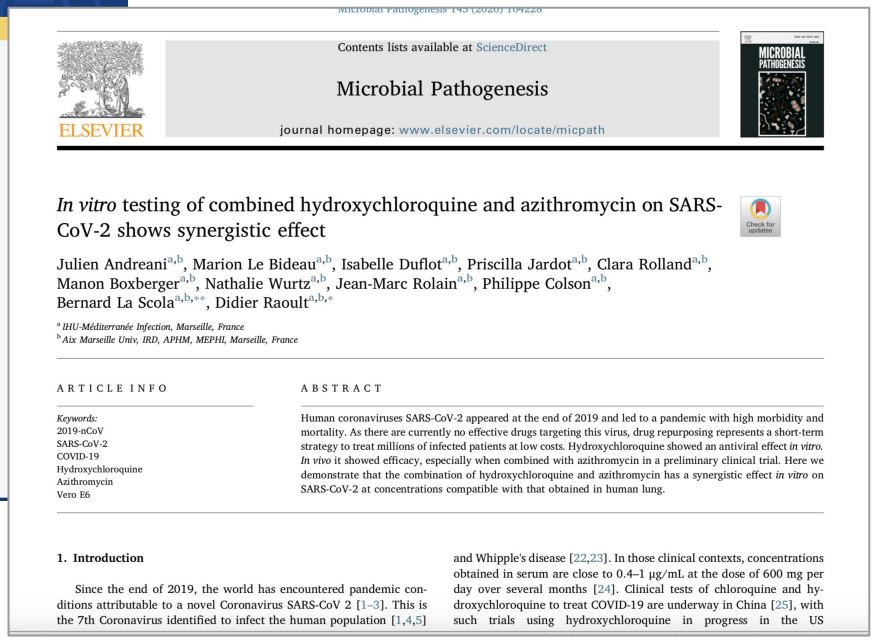
Objectives:

- Improve **patients' treatments** and outcomes;
- Anticipate and prevent **new infections** with informed processes, protocols, and policies; and
- Equip **healthcare systems** to respond more effectively to new **medical challenges**.

Dataset of COVID-19 Scientific Publications

Open Dataset of COVID-19 Scientific Publications

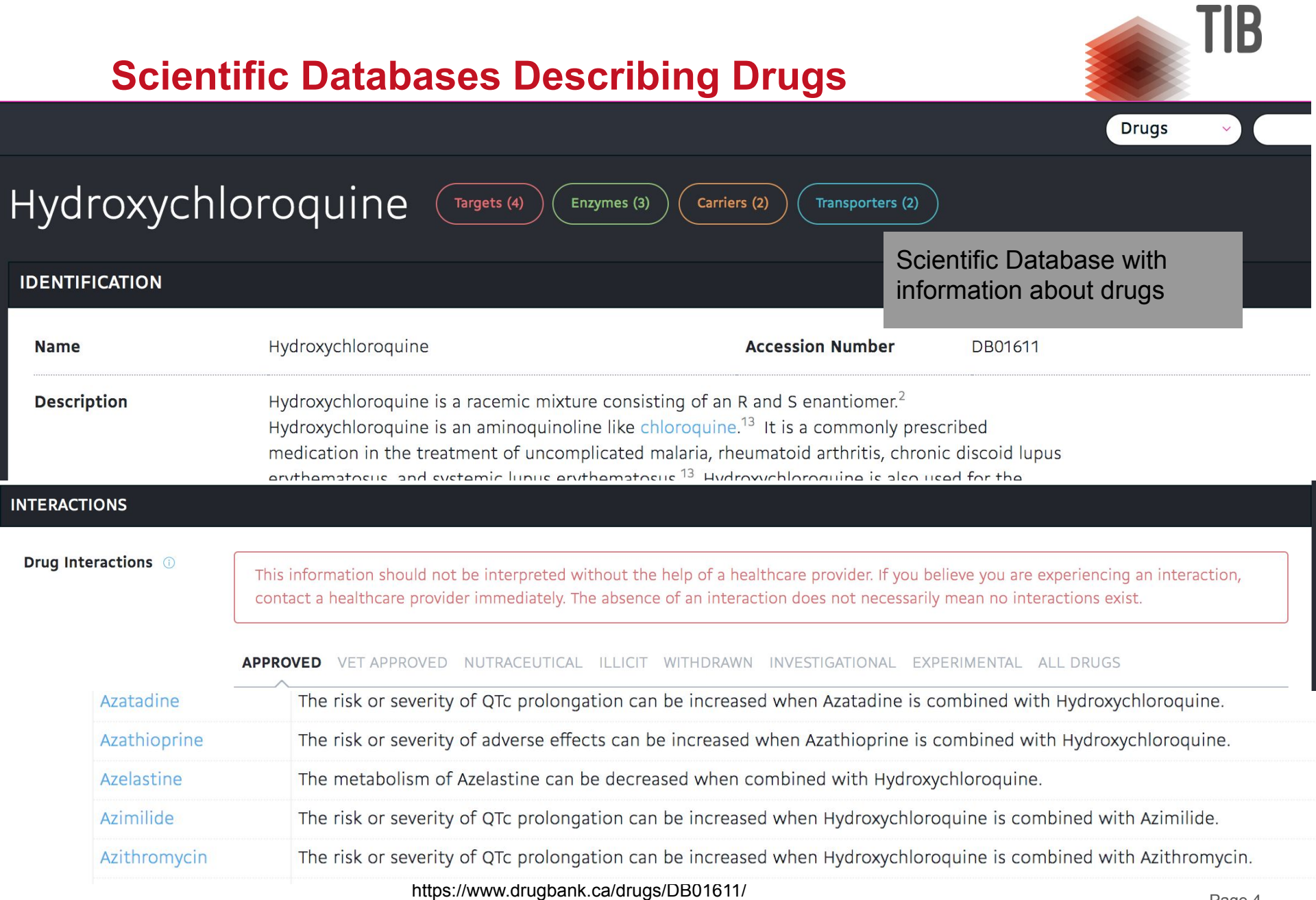
https://www.semanticscholar.org/cord19



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7182748/

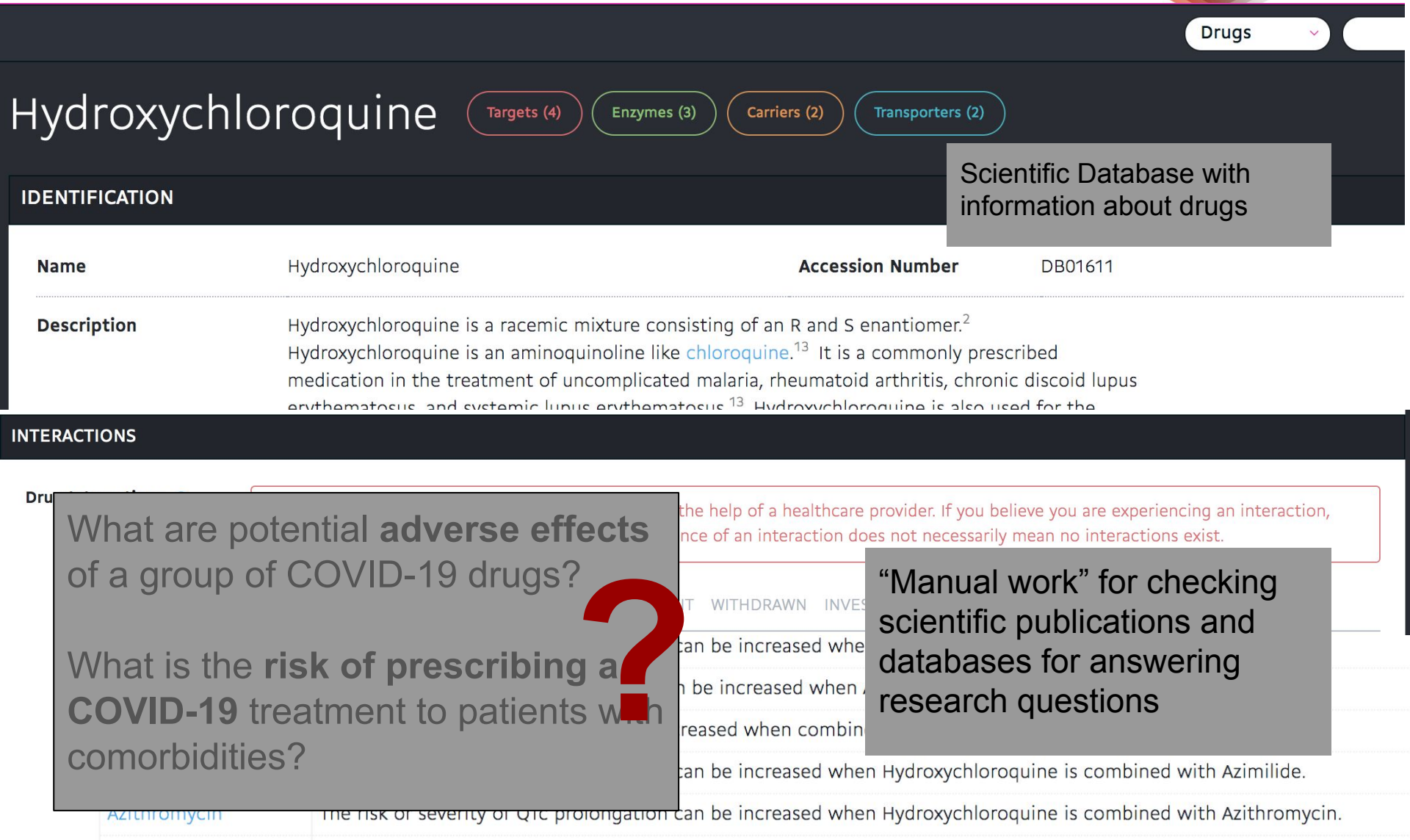
Human readable representation of a scientific publication

Scientific Databases Describing Drugs



https://www.drugbank.ca/drugs/DB01611/

Scientific Databases Describing Drugs



Scientific Database with information about drugs

What are potential **adverse effects** of a group of COVID-19 drugs?

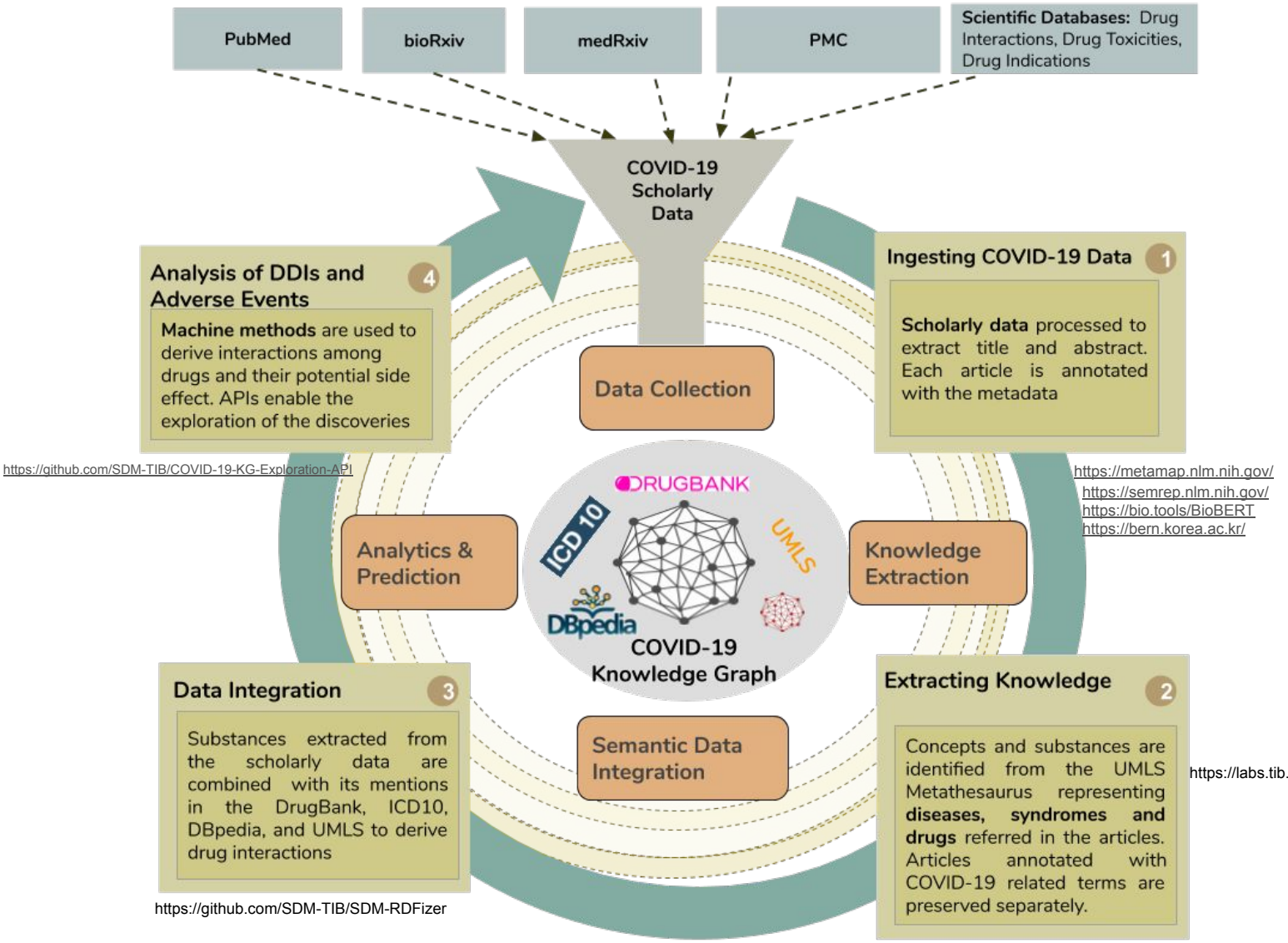
What is the **risk of prescribing a COVID-19** treatment to patients with comorbidities?

?

"Manual work" for checking scientific publications and databases for answering research questions

https://www.drugbank.ca/drugs/DB01611/

Our Approach: Transforming Data into Knowledge



https://github.com/SDM-TIB/COVID-19-KG-Exploration-API

https://metamap.nlm.nih.gov/
https://semrep.nlm.nih.gov/
https://bio.tools/BioBERT
https://bern.korea.ac.kr/

https://labs.tib.eu/falcon/falcon2/

https://github.com/SDM-TIB/SDM-RDFizer

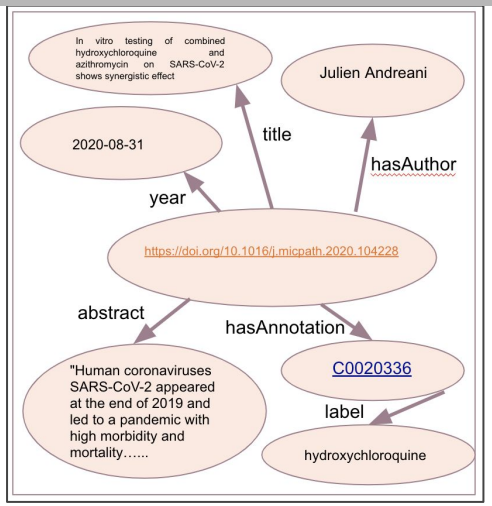
What are Knowledge Graphs?

Knowledge graphs are data structures that represent **factual knowledge** using the graph data model.

- Provide a **formal specification** of biomedical knowledge (metadata)
- Model **taxonomies** of entities and relationships
- Develop a **common understanding of the meaning** of the entities of a certain universe of discourse
- **Enable knowledge** management and discovery

Entities and **relationships** are both first-class citizens in a **graph data model.**

- **Natural representation** of a large number of relationships between entities
- Enable easy traversal along those connections

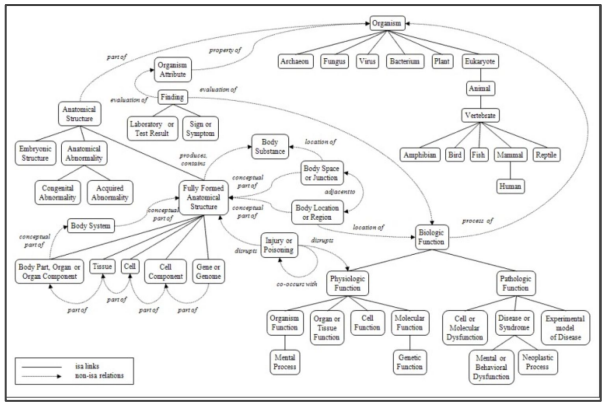


Data

Metadata represents meaning of entities and **relationships.**

- Provenance
- Taxonomies
- Languages

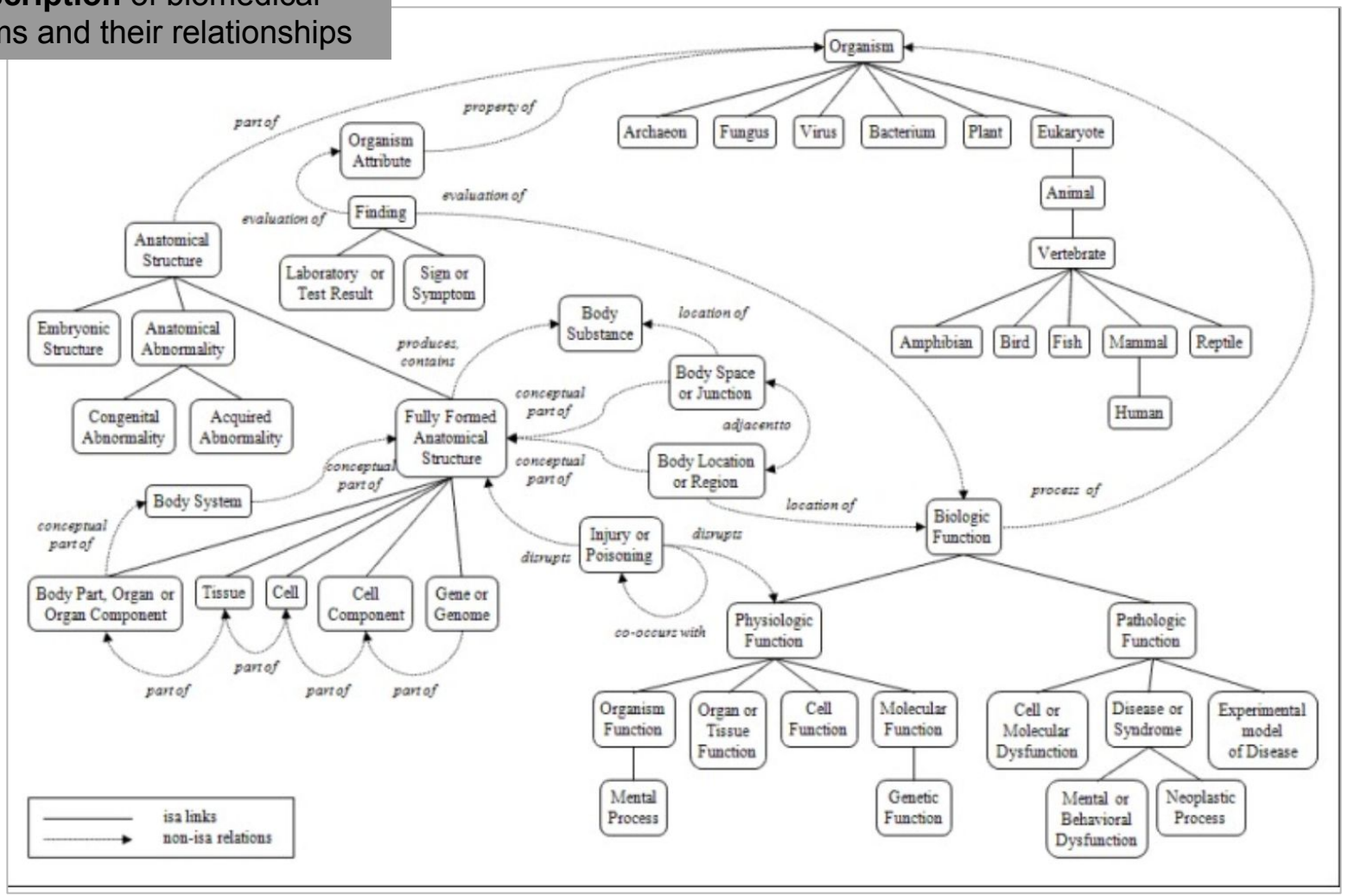
Metadata is empowered with inference processes to **deduce new facts**.



Metadata

Controlled Vocabularies (Metadata)

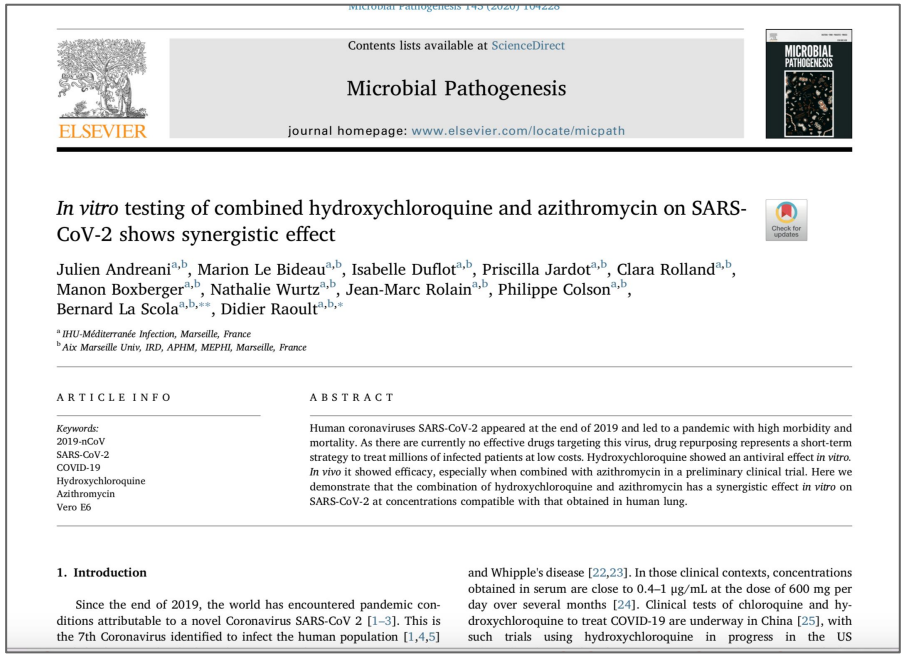
UMLS **provides** a **formal description** of biomedical terms and their relationships



https://www.ncbi.nlm.nih.gov/books/NBK9679/figure/ch05.F3/

Fine-Grained Semantic Description

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7182748/



Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect

Julien Andreani[a,b], Marion Le Bideau[a,b], Isabelle Duflot[a,b], Priscilla Jardot[a,b], Clara Rolland[a,b], Manon Boxberger[a,b], Nathalie Wurtz[a,b], Jean-Marc Rolain[a,b], Philippe Colson[a,b], Bernard La Scola[a,b,**], Didier Raoult[a,b,*]

[a] IHU-Méditerranée Infection, Marseille, France
[b] Aix Marseille Univ, IRD, APHM, MEPHI, Marseille, France

ARTICLE INFO

Keywords:
2019-nCoV
SARS-CoV-2
COVID-19
Hydroxychloroquine
Azithromycin
Vero E6

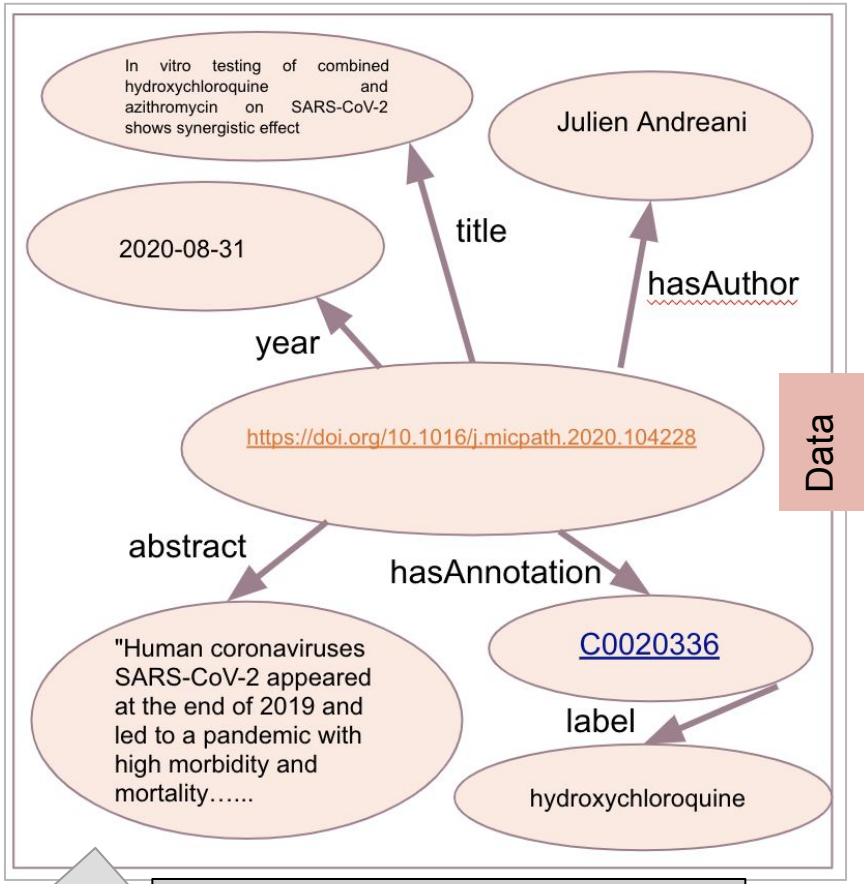
ABSTRACT

Human coronaviruses SARS-CoV-2 appeared at the end of 2019 and led to a pandemic with high morbidity and mortality. As there are currently no effective drugs targeting this virus, drug repurposing represents a short-term strategy to treat millions of infected patients at low costs. Hydroxychloroquine showed an antiviral effect *in vitro*. *In vivo* it showed efficacy, especially when combined with azithromycin in a preliminary clinical trial. Here we demonstrate that the combination of hydroxychloroquine and azithromycin has a synergistic effect *in vitro* on SARS-CoV-2 at concentrations compatible with that obtained in human lung.

1. Introduction

Since the end of 2019, the world has encountered pandemic conditions attributable to a novel Coronavirus SARS-CoV 2 [1–3]. This is the 7th Coronavirus identified to infect the human population [1,4,5] and Whipple's disease [22,23]. In those clinical contexts, concentrations obtained in serum are close to 0.4–1 μg/mL at the dose of 600 mg per day over several months [24]. Clinical tests of chloroquine and hydroxychloroquine to treat COVID-19 are underway in China [25], with such trials using hydroxychloroquine in progress in the US

Human readable representation of a scientific publication



Graph-based, machine and human readable representation of a scientific publication

Fine-Grained Description Drug-Drug Interactions

https://www.drugbank.ca/drugs/DB01611 Hydroxychloroquine

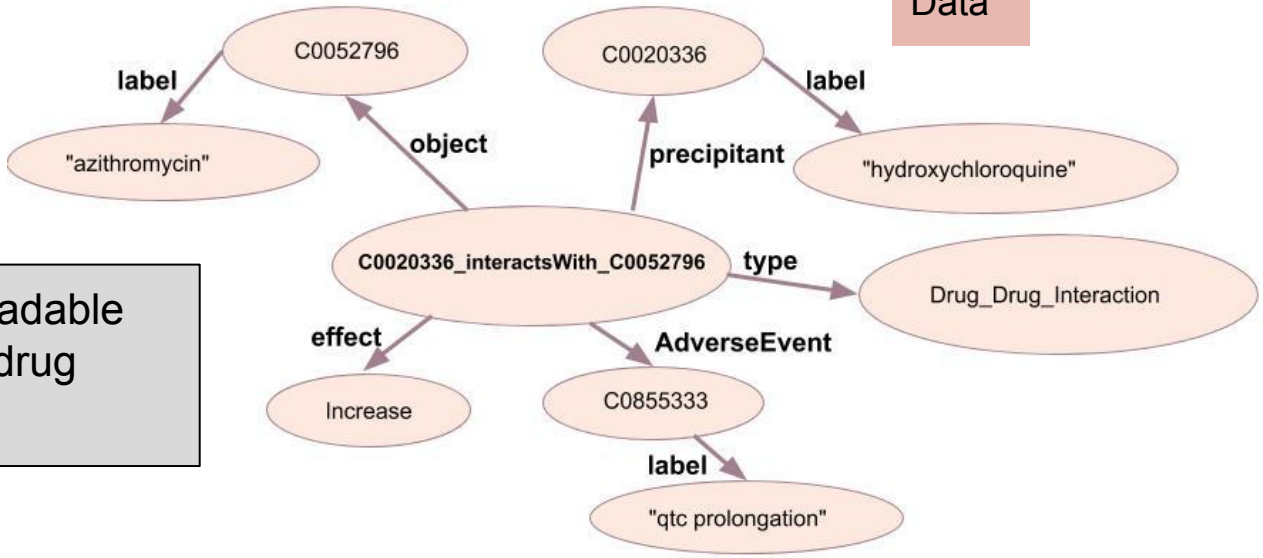
DRUGBANK | Browse | COVID-19 | Search | Downloads | Commercial Data | Help | About

Human readable representation of drug-drug interactions

- Interactions
- Drug Interactions
- Food Interactions
- Products
- Categories
- Chemical Identifiers
- References
- Clinical Trials

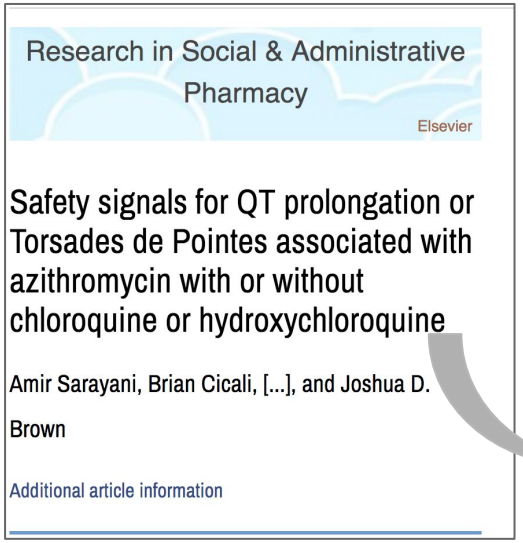
	The metabolism of Astemizole can be decreased when combined with Hydroxychloroquine.
	The metabolism of Asunaprevir can be decreased when combined with Hydroxychloroquine.
	The risk or severity of QTc prolongation can be increased when Atazanavir is combined with Hydroxychloroquine.
	The risk or severity of QTc prolongation can be decreased when Hydroxychloroquine is combined with Atenolol.
Atomoxetine	The metabolism of Atomoxetine can be decreased when combined with Hydroxychloroquine.
Atropine	The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Atropine.
Azacitidine	The risk or severity of adverse effects can be increased when Azacitidine is combined with Hydroxychloroquine.
Azatadine	The risk or severity of QTc prolongation can be increased when Azatadine is combined with Hydroxychloroquine.
Azathioprine	The risk or severity of adverse effects can be increased when Azathioprine is combined with Hydroxychloroquine.
Azelastine	The metabolism of Azelastine can be decreased when combined with Hydroxychloroquine.
Azimilide	The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Azimilide.
Azithromycin	The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Azithromycin.

Data

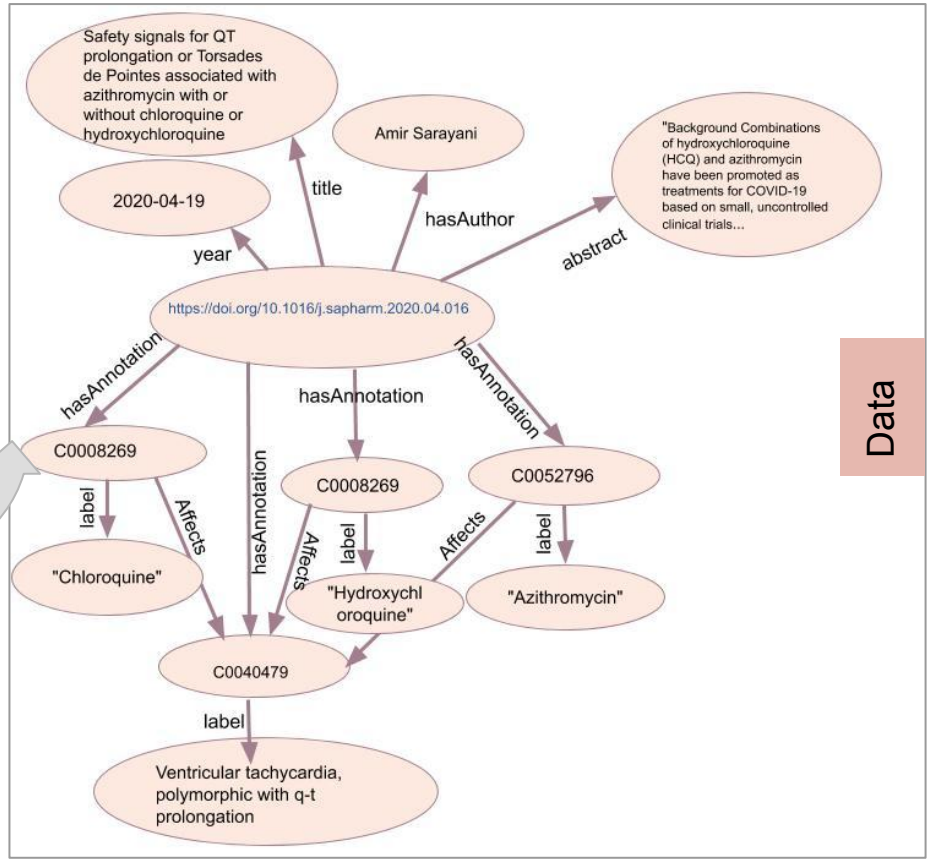


Machine and human readable representation of drug-drug interactions

Relationships Extracted From Publications



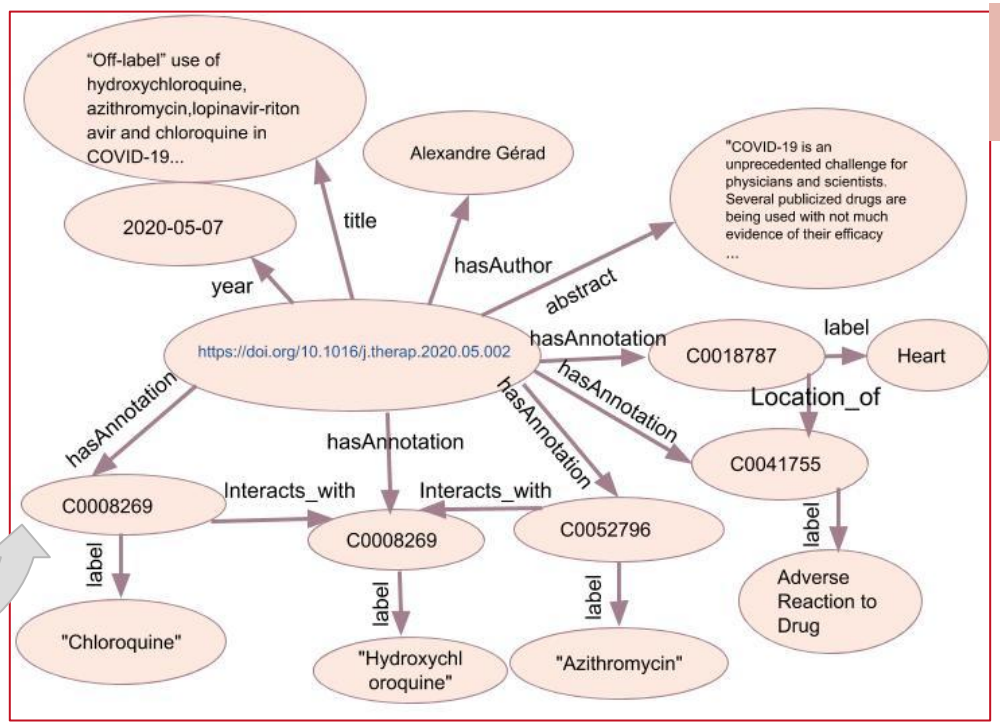
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7166303/



Extracted entities and predicate from scientific publications represent that Chloroquine, Hydroxychloroquine, and Azithromycin Affect QT prolongation

Relationships Extracted From Publications

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204701/

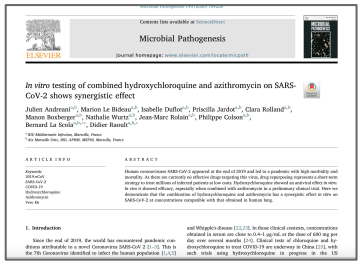


Data

Extracted entities and predicate from scientific publications represent that Chloroquine, Hydroxychloroquine, and Azithromycin interact and cause adverse reactions in the heart

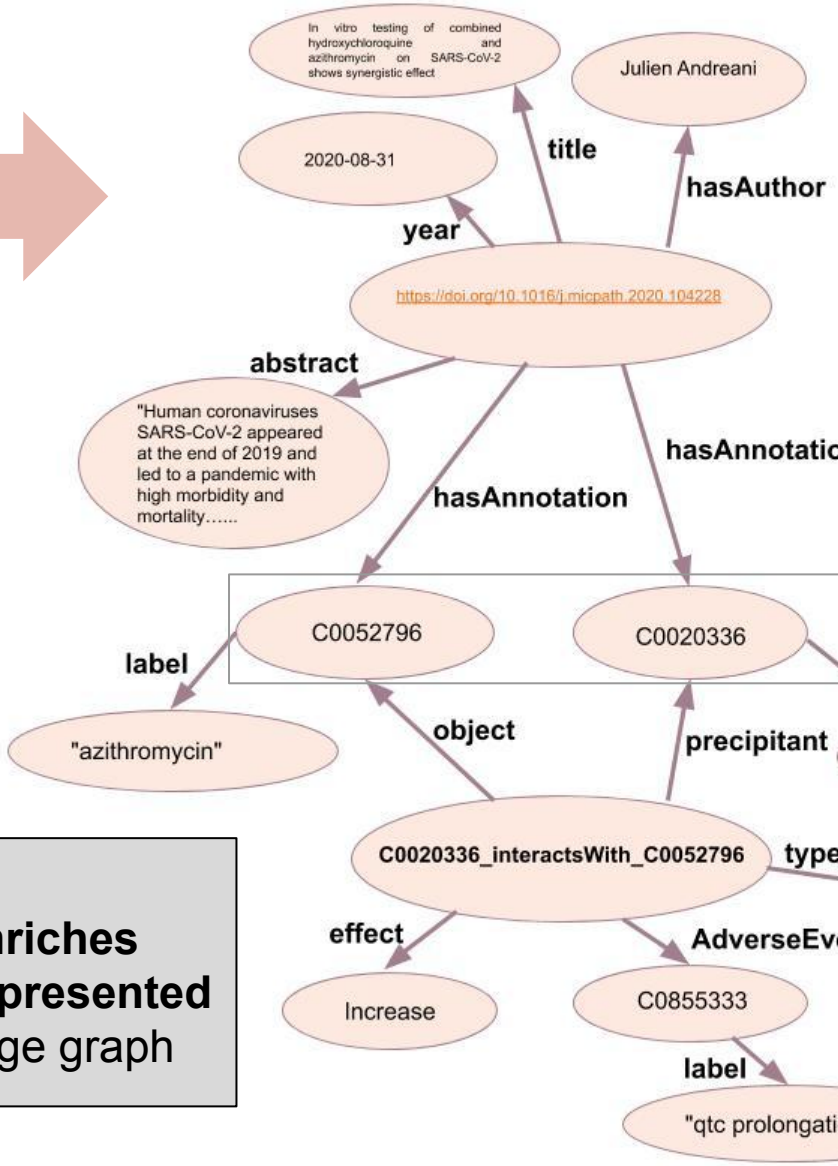
Semantic Data Integration into a Knowledge Graph

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7182748/



https://www.drugbank.ca/drugs/DB01611/

Human readable representation of publications and drug-drug interactions

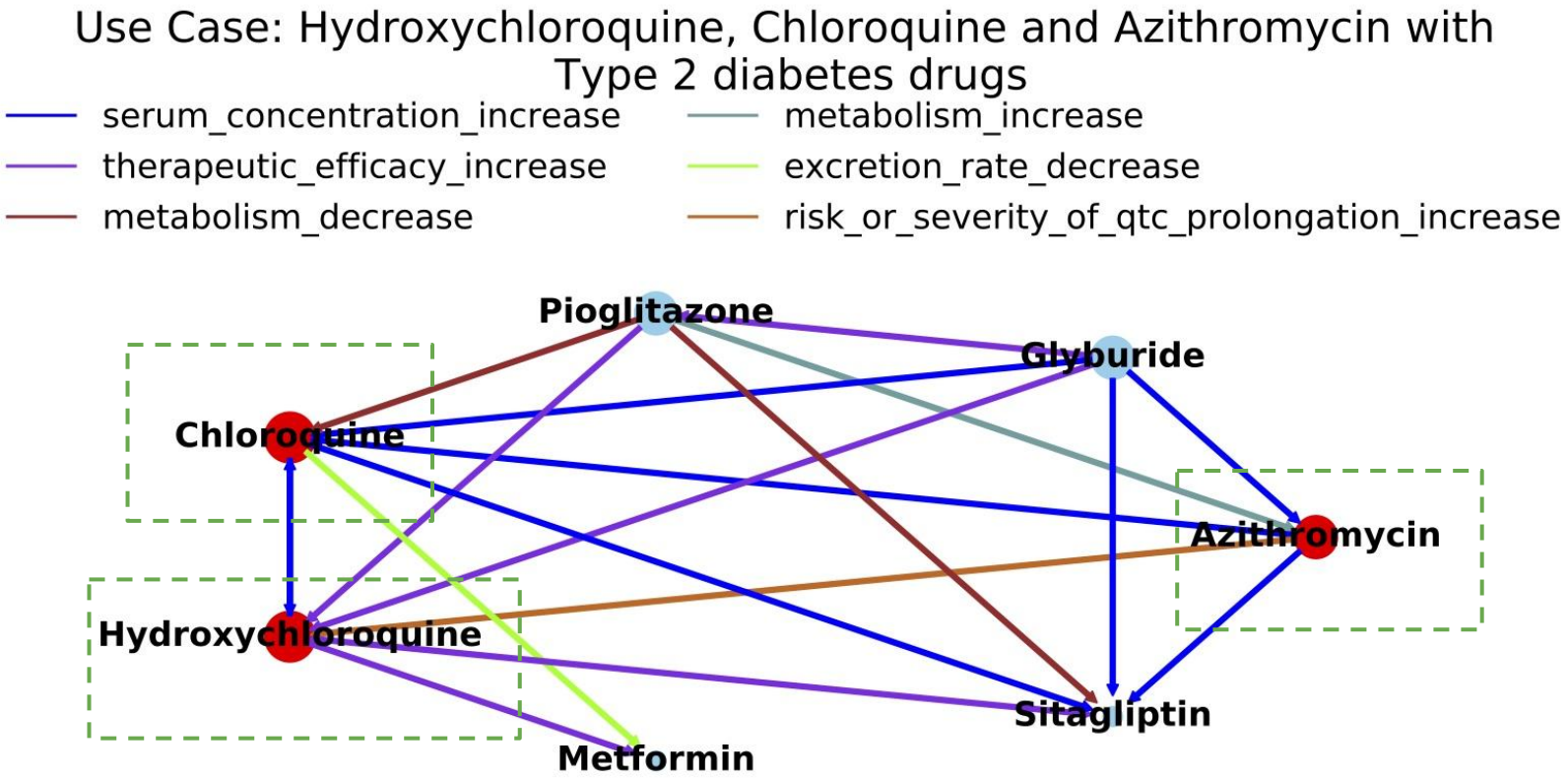


Machine and human readable representation of the integration of publications and drug-drug interactions

Term IDs from UMLS

Semantic data **integration enriches knowledge represented** in the knowledge graph

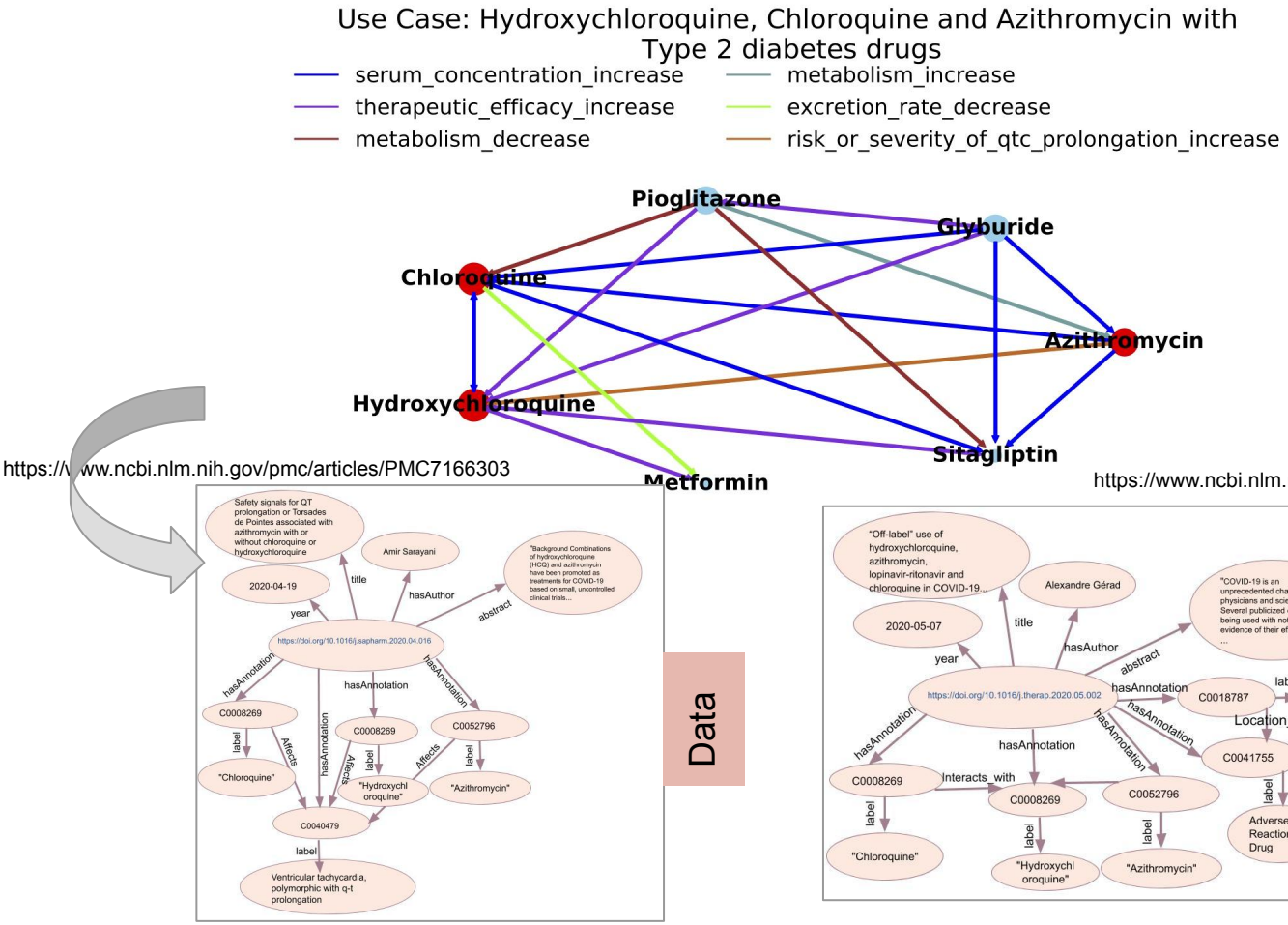
Pattern Extraction from DDIs in the KG



Drug-drug interactions (DDIs) among the COVID-19 treatment Hydroxychloroquine, Chloroquine, and Azithromycin and drugs commonly prescribed to treat diabetes

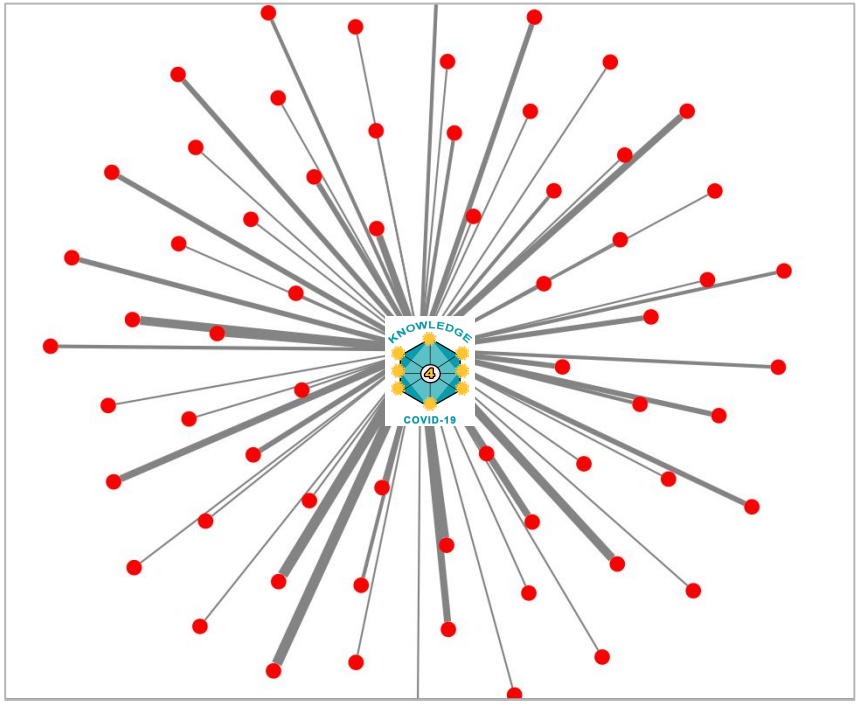
According to **entities and predicates extracted from Drugbank**

Explanations of the Extracted Patterns from KG



Drug-drug interactions (DDIs) among the COVID-19 treatment Hydroxychloroquine, Chloroquine, and Azithromycin and drugs commonly prescribed to treat diabetes, can be **explained** not only based on what **extracted from Drugbank** but also in terms of what is **extracted from the related publications**

Our Knowledge4COVID-19 KG in Numbers

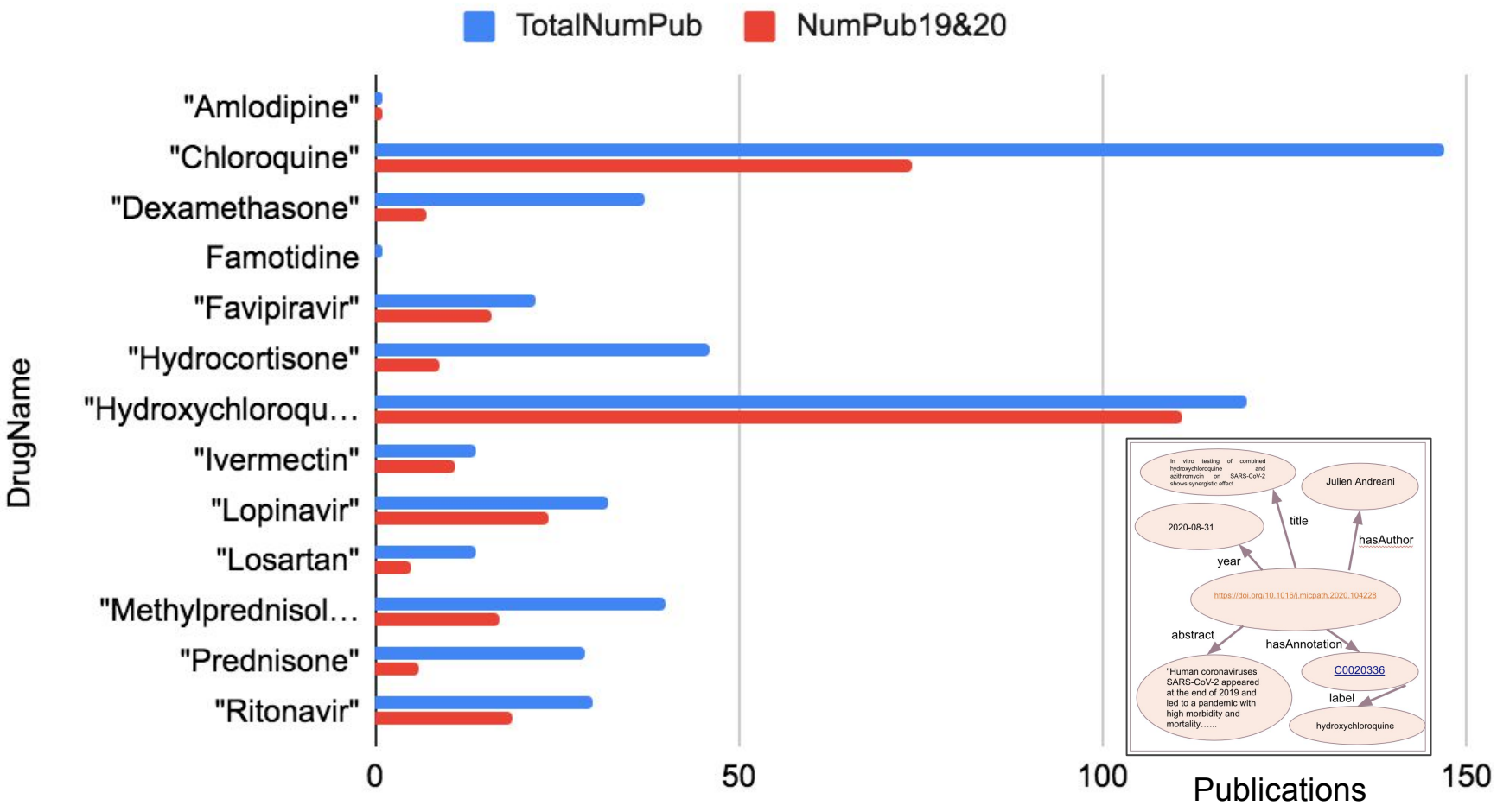


https://f0ffbb86.ngrok.io/sparql

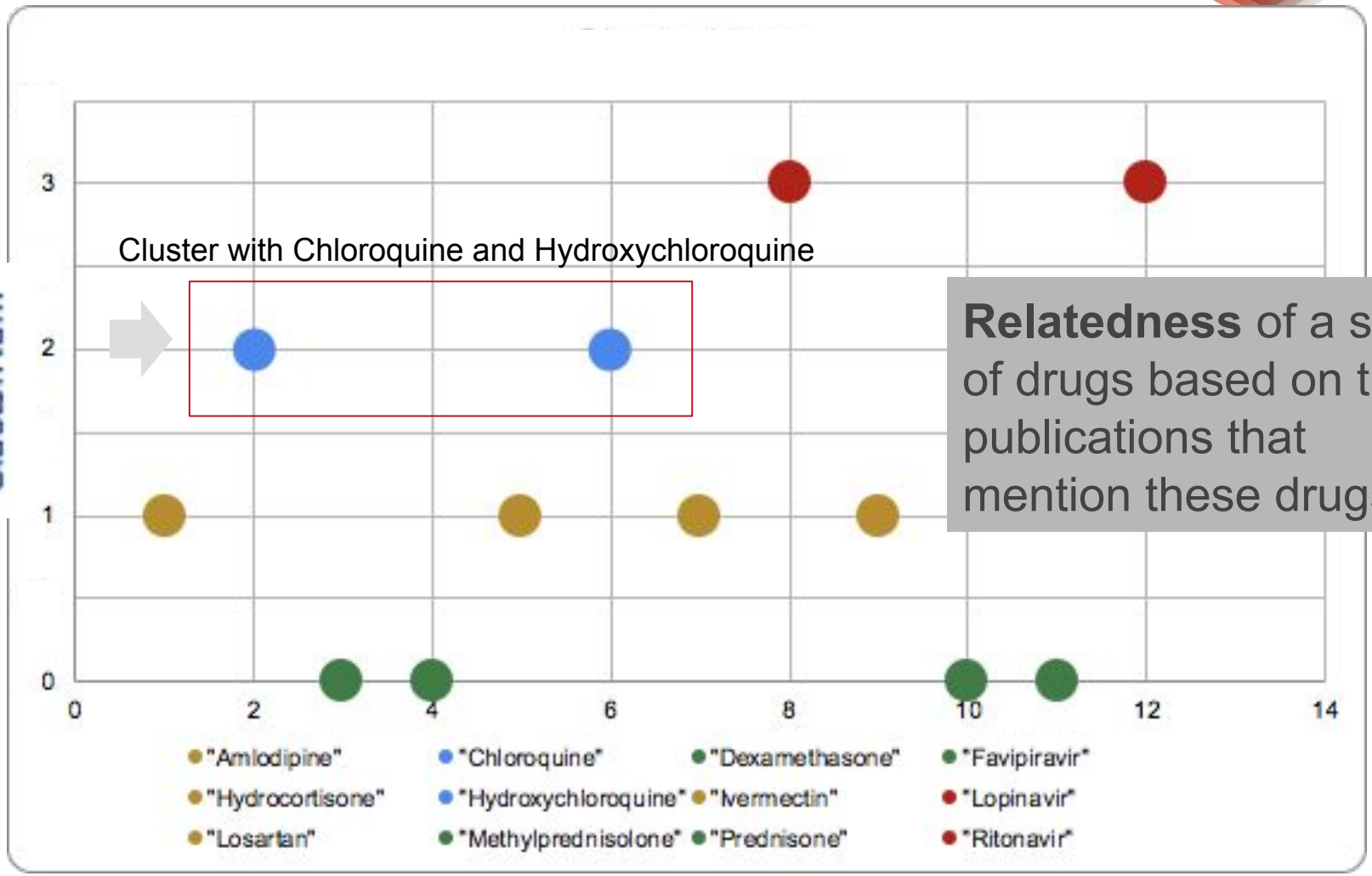
The Knowledge4COVID-19 Knowledge Graph	Value
Biomedical Entities	5,255,992
Relations between Biomedical Entities	27,158,885
Scientific Publications	51,868
Substances	4,162
Syndrome	2,012
Drug Toxicities	5,965
Links to DBpedia RDF Graph	5,905
Links to Bio2RDF RDF Graph	7,262
Links to DrugBank RDF Graph	14,524
Drug-Drug Interactions	2,205,099
Predicted Drug-Drug Interactions	22,346

Number of Publications per Drug

Total number of publication and publications in 2019 and 2020



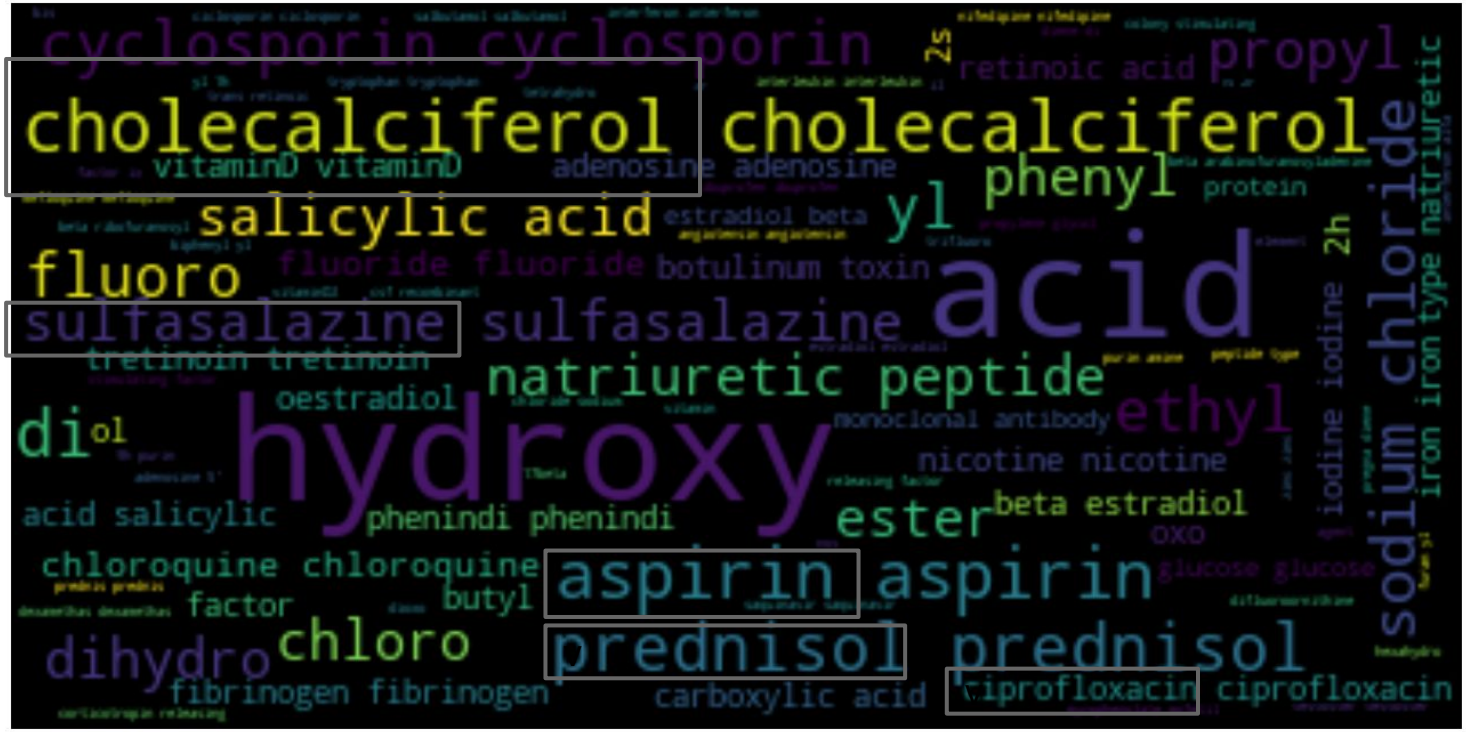
Clustering of Drugs based on Scientific Publications



Relatedness of a set of drugs based on the publications that mention these drugs

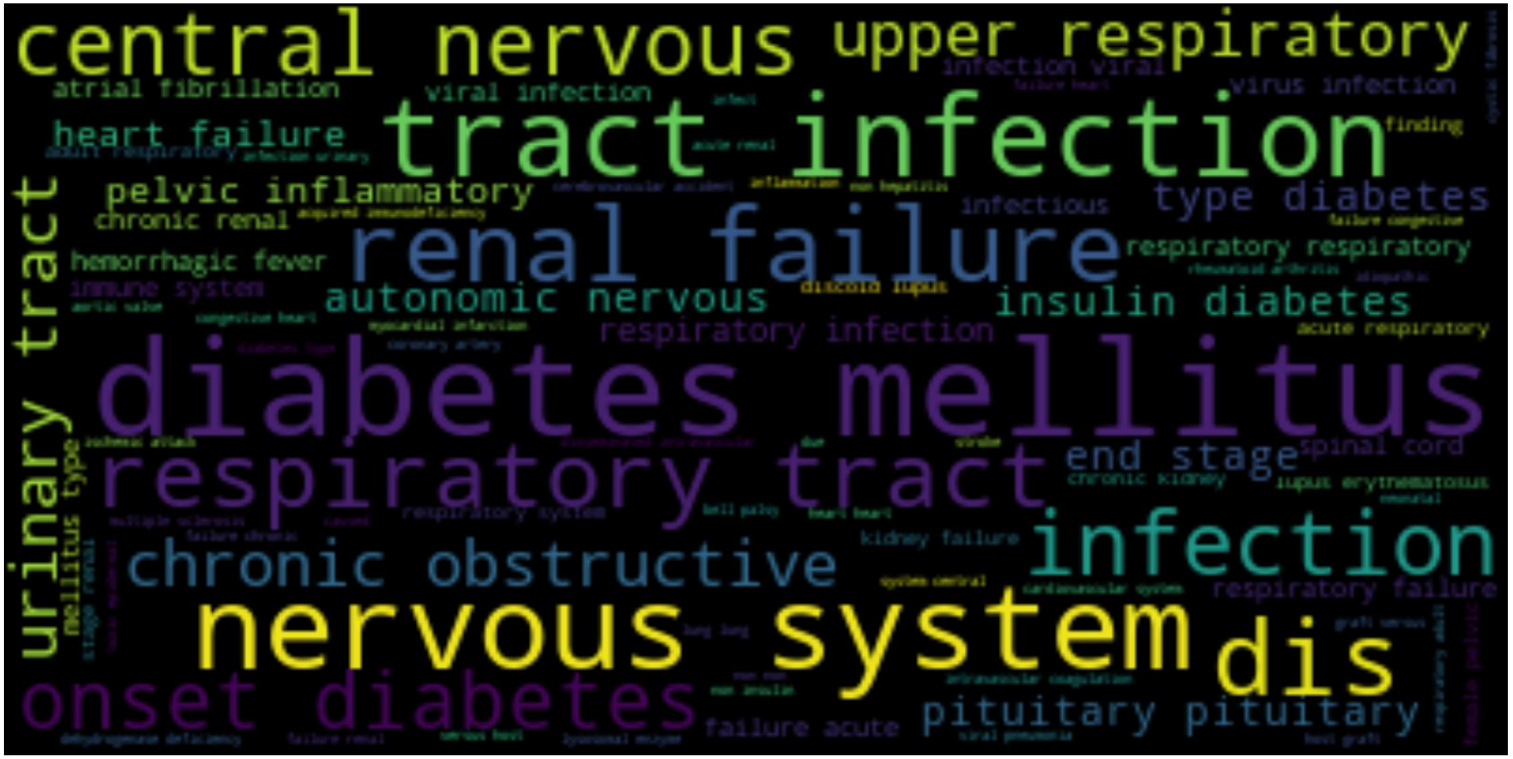
KMeans clustering based on Scientific publications (2019-2020) annotated **with the drugs**: Favipiravir, Merimepodib, Lopinavir, Ritonavir,, Dexamethasone, Prednisone, Methylprednisolone, Hydrocortisone, Hydroxychloroquine, Chloroquine, Losartan, Amlodipine, Famotidine, Ivermectin

The Top Frequent Drugs in Scientific Publications



Scientific publications (2019-2020) annotated **with the drugs**:
Favipiravir, Merimepodib, Lopinavir, Ritonavir,, Dexamethasone, Prednisone, Methylprednisolone, Hydrocortisone, Hydroxychloroquine, Chloroquine, Losartan, Amlodipine, Famotidine, Ivermectin

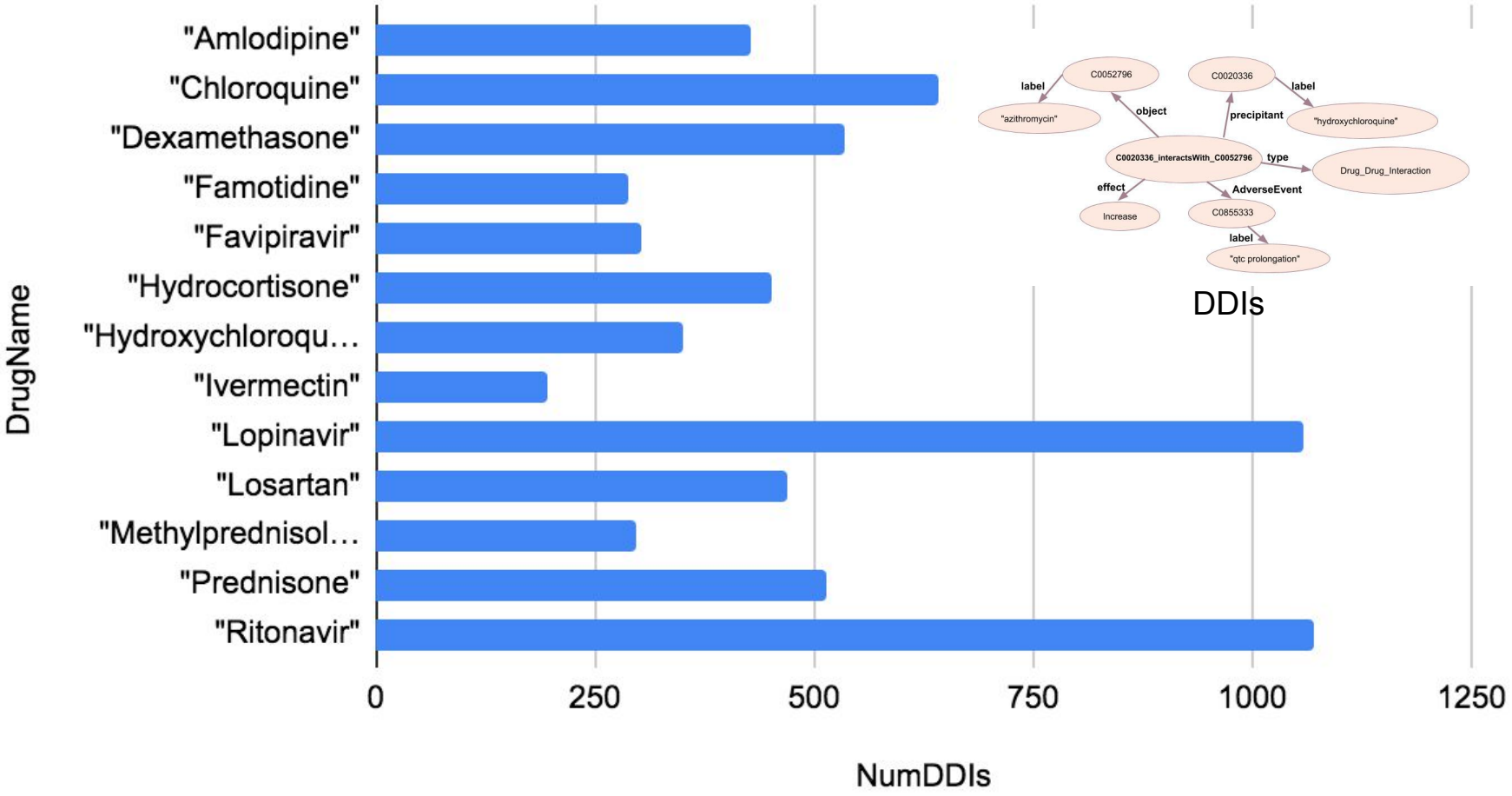
The Top Frequent Conditions in Scientific Publications



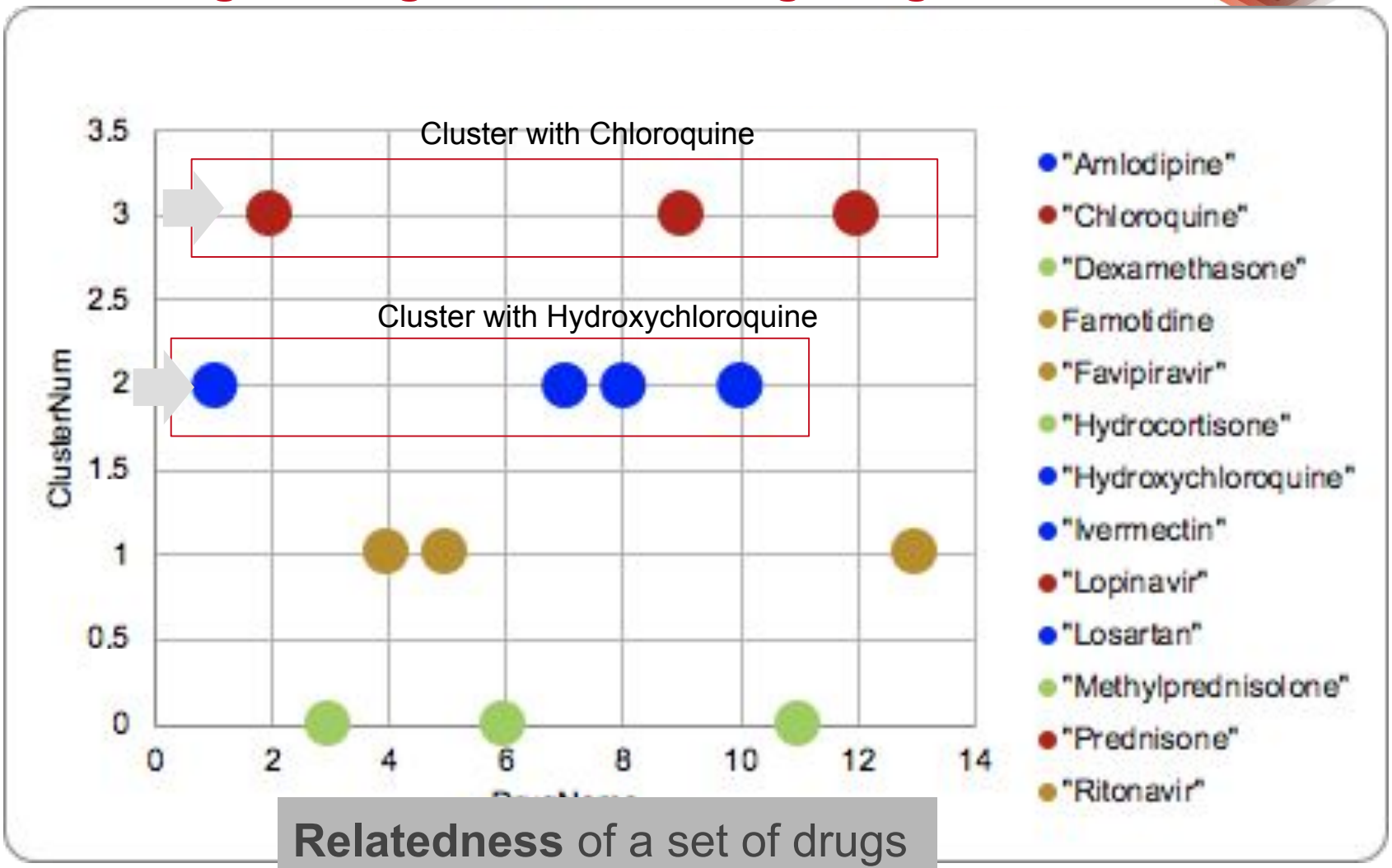
Scientific publications (2019-2020) annotated **with the drugs**:
Favipiravir, Merimepodib, Lopinavir, Ritonavir,, Dexamethasone, Prednisone, Methylprednisolone, Hydrocortisone, Hydroxychloroquine, Chloroquine, Losartan, Amlodipine, Famotidine, Ivermectin

Drug-Drug Interactions (DDIs) per Drug

Number of drug-drug interactions per drug

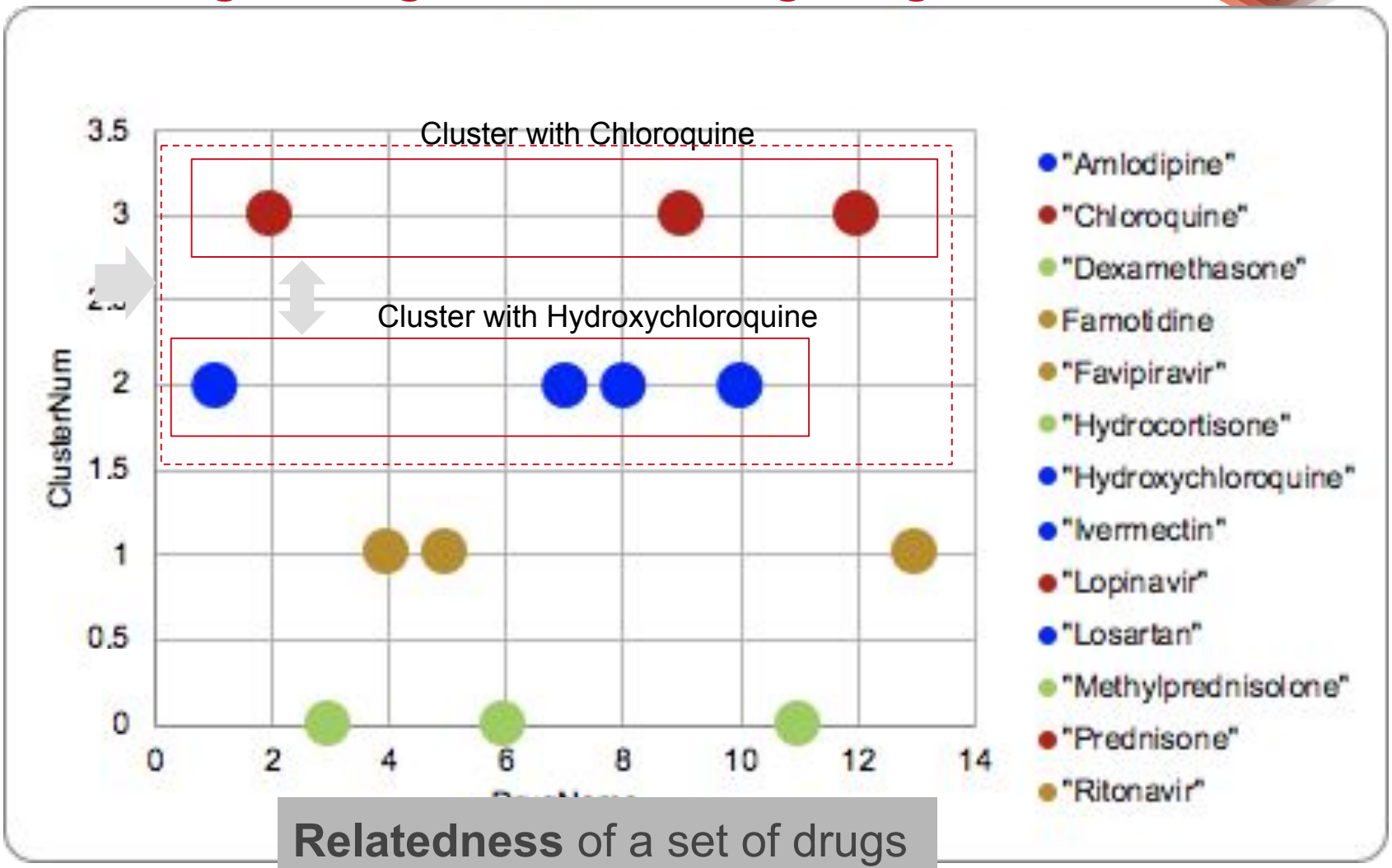


Clustering of Drugs based on Drug-Drug Interactions



Relatedness of a set of drugs based on the drug-drug interactions of these drugs

Clustering of Drugs based on Drug-Drug Interactions



Relatedness of a set of drugs based on the drug-drug interactions of these drugs

Participation in Events

#t_covid19kg_bzym2m12njf

TIB team: Ahmad Sakor, Ariam Rivas, Anery Patel, Vitalis Wiens, and Maria-Esther Vidal. Germany

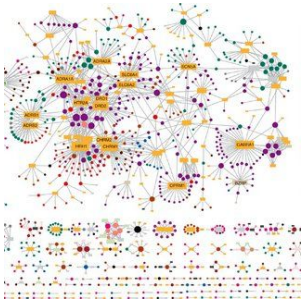
NCSR team: Kostantinos Bougiatiotis, Fotis Aisopos, Anastasia Krithara, and George Paliouras. Greece

https://eit.europa.eu/news-events/events/registration-extended-24-april-euvsvirus-pan-european-hackathon

The Pan-European hackathon #EUvsVirus (From 24 to 26 April 2020) organized with the aim of connecting experts, investors, and civilian organizations to devise together innovative solutions to the coronavirus outbreak. Citizens of all over the world responded to the call, and more than 2,160 proposals were submitted in 37 challenges.

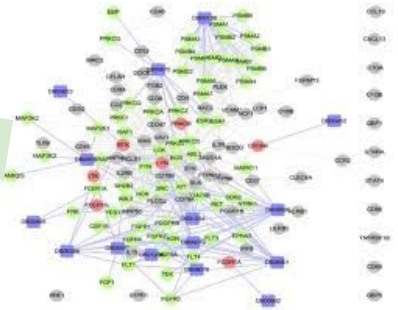
Next Steps: Data to be Integrated

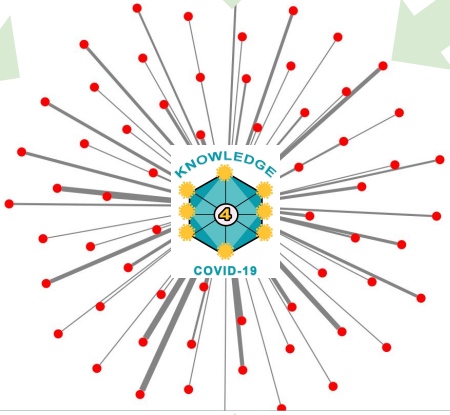
Drug-Gene Networks

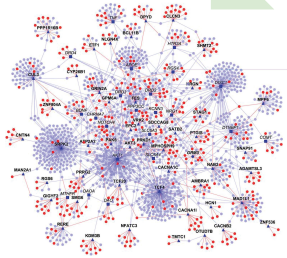


Clinical Data

Drug-Target Networks

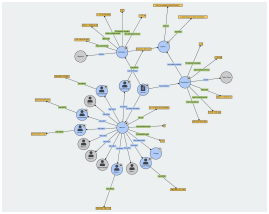






Protein-Protein Networks

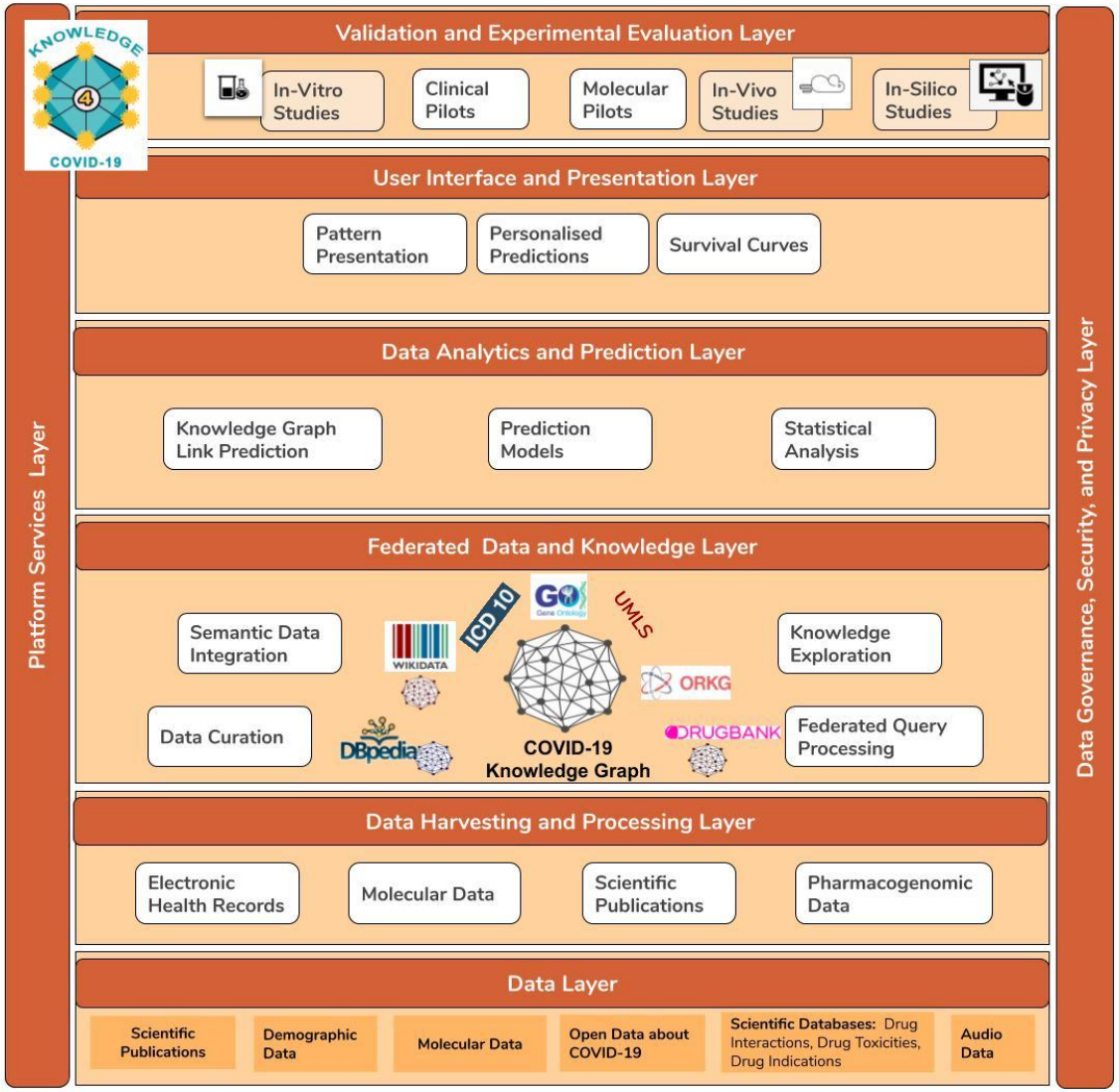
Genomic Data



ORKG

https://www.orkg.org/orkg/

Next Steps: A Hybrid Framework



Our Team at the Scientific Data Management Group

Prof.(Uni. Simon Bolivar)
Dr. Maria-Esther Vidal

Katja Bartel

PostDocs

Dr. Ingo Keck

Kemele Endris

Farah Karim

Senior Researcher

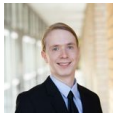
Akhilesh Vyas

Research Assistants

Samaneh Jozashoori

Ariam Rivas

Maria Isabel Castellanos



Philipp Rohde

Emetis Niazmand

Ahmad Sakor

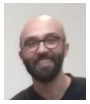
Master Student Assistants

Enrique Iglesias

Monica Figuera

Gabriela Ydler

Supreetha Hanasoge



Mohammad Torabinejad

Anery Patel

NATIONAL CENTRE FOR SCIENTIFIC RESEARCH "DEMOKRITOS"

NCSR team: Kostantinos Bougiatiotis, Fotis Aisopos, Anastasia Krithara, and George Paliouras. Greece

LEIBNIZ INFORMATION CENTRE
FOR SCIENCE AND TECHNOLOGY
UNIVERSITY LIBRARY

TIB

Bibliothek des Jahres 2020

MANY THANKS

Questions?

Contact:

Maria-Esther Vidal
Maria.Vidal@tib.eu
@MEVidalSerodio

Creative Commons Attribution 3.0 Germany
https://creativecommons.org/licenses/by/3.0/de/deed.en

Leibniz Association

Recent Publications

Maria-Esther Vidal, Kemele M. Endris, Samaneh Jazashoori, Ahmad Sakor, Ariam Rivas
Transforming Heterogeneous Data into Knowledge for Personalized Treatments - A Use Case. Datenbank-Spektrum 19(2): 95-106 (2019)

Anastasia Krithara, et al. iASiS: T**owards Heterogeneous Big Data Analysis for Personalized Medicine.** CBMS 2019

Ahmad Sakor, Isaiah Onando Mulang, Kuldeep Singh, Saeedeh Shekarpour, Maria-Esther Vidal, Jens Lehmann, Sören Auer. **Old is Gold: Linguistic Driven Approach for Entity and Relation Linking of Short Text.** NAACL-HLT 2019

Ahmad Sakor, Anery Patel, Kuldeep Singh, Maria-Esther Vidal.
Falcon 2.0: An Entity and Relation Linking Tool over Wikidata. ACM International Conference on information and Knowledge Management (CIKM). 2020.

Samaneh Jozashoori, Maria-Esther Vidal. **MapSDI: A Scaled-Up Semantic Data Integration Framework for Knowledge Graph Creation.** CooPIS 2019

David Chaves-Fraga, Kemele M. Endris, Enrique Iglesias, Óscar Corcho, Maria-Esther Vidal: **What Are the Parameters that Affect the Construction of a Knowledge Graph?** ODBASE 2019

Enrique Iglesias, Samaneh Jozashoori, David Chaves-Fraga, Diego Collarana, Maria-Esther Vidal. **SDM-RDFizer: An RML Interpreter for the Efficient Creation of RDF Knowledge Graphs.** ACM CIKM 2020.

Samaneh Jozashoori, David Chaves-Fraga, Enrique Iglesias, Maria-Esther Vidal and Oscar Corcho.
FunMap: Efficient Execution of Functional Mappings for Scaled-Up Knowledge Graph Creation. ISWC 2020