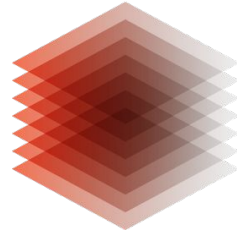


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How Do Open Knowledge Graphs Contribute to Understanding COVID-19 Related Treatments?

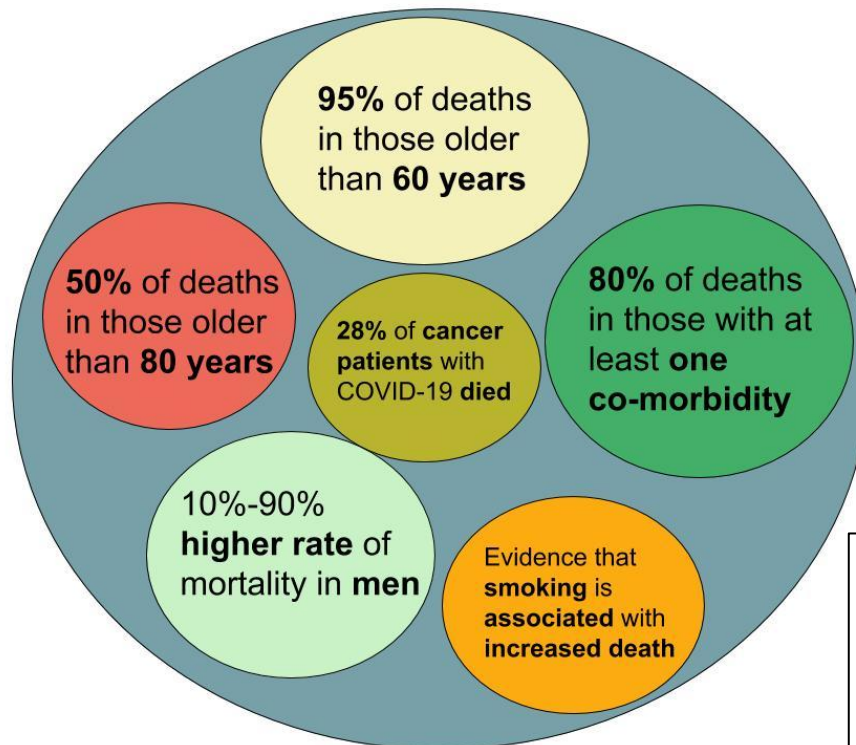


Maria-Esther Vidal
Scientific Data Management Group (TIB)

08.09.2020

Motivation

SARS-CoV-2 Fatality in Trends



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

CORD-19

COVID-19 Open Research Dataset

The Semantic Scholar team at the Allen Institute for AI has partnered with leading research groups to provide CORD-19, a free resource of more than 130,000 scholarly articles about the novel coronavirus for use by the global research community.

Open Dataset of COVID-19 Scientific Publications

Discover

Quickly explore the latest literature using these open tools built by the team at Allen Institute for AI.

Download CORD-19

The COVID-19 Open Research Dataset (CORD-19) is a growing resource of scientific papers on COVID-19 and related historical coronavirus research.

Download →

Adaptive Research Feed

Personalize your free AI-powered Research Feed to get coronavirus research recommendations.

Stay Up To Date →

Recent Research

Query the Semantic Scholar corpus for the latest COVID-19 research sorted by recency.

View Research →

SPIKE-CORD

A powerful sentence-level, context aware, linguistically informed system for extracting important information from a large corpus of COVID-19-related text.

View SPIKE-CORD →

SciSight

Visually investigate associations between concepts appearing in the scientific literature contained in CORD-19.

View SciSight →


SciFact

Find out whether published scientific research supports or contradicts claims about COVID-19.

View SciFact →

Discover More Resources


<https://www.semanticscholar.org/cord19>



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

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

Human readable representation of a scientific publication

Scientific Databases Describing Drugs

Drugs

Hydroxychloroquine

Targets (4)

Enzymes (3)

Carriers (2)

Transporters (2)

Scientific Database with information about drugs

IDENTIFICATION

Name	Hydroxychloroquine	Accession Number	DB01611
------	--------------------	------------------	---------

Description	Hydroxychloroquine is a racemic mixture consisting of an R and S enantiomer. ² Hydroxychloroquine is an aminoquinoline like chloroquine . ¹³ It is a commonly prescribed medication in the treatment of uncomplicated malaria, rheumatoid arthritis, chronic discoid lupus erythematosus, and systemic lupus erythematosus. ¹³ Hydroxychloroquine is also used for the
-------------	---

INTERACTIONS

Drug Interactions ⓘ

This information should not be interpreted without the help of a healthcare provider. If you believe you are experiencing an interaction, contact a healthcare provider immediately. The absence of an interaction does not necessarily mean no interactions exist.

APPROVED VET APPROVED NUTRACEUTICAL ILLICIT WITHDRAWN INVESTIGATIONAL EXPERIMENTAL ALL DRUGS

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.

Scientific Databases Describing Drugs

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Hydroxychloroquine

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INTERACTIONS

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

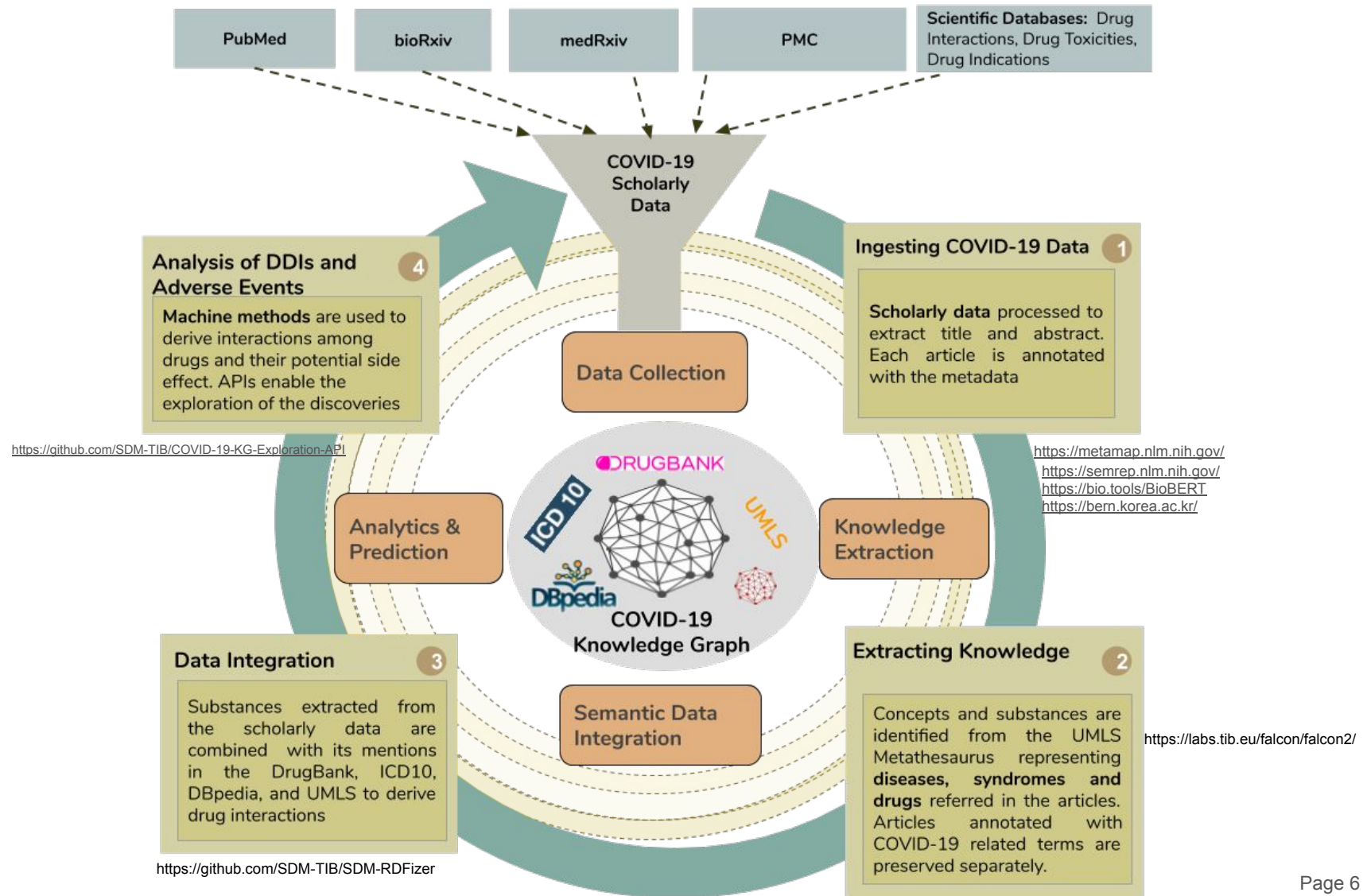
What is the **risk of prescribing a COVID-19** treatment to patients with comorbidities?

“Manual work” for checking scientific publications and databases for answering research questions

Azithromycin

The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Azithromycin.

Our Approach: Transforming Data into Knowledge



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

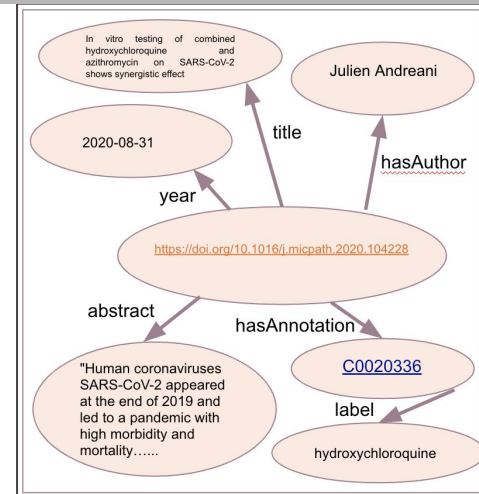
Entities and **relationships** are both first-class citizens in a **graph data model**.

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

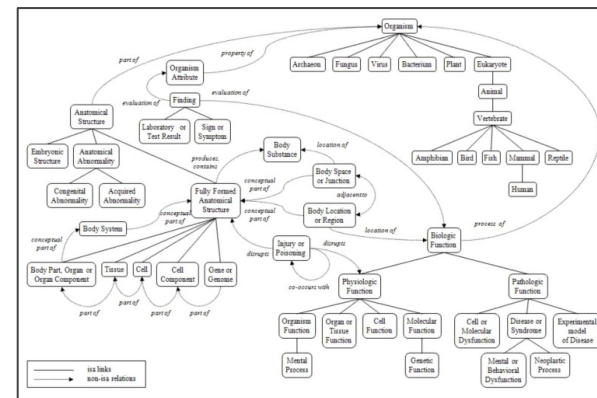
Metadata represents meaning of **entities** and **relationships**.

- Provenance
- Taxonomies
- Languages

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



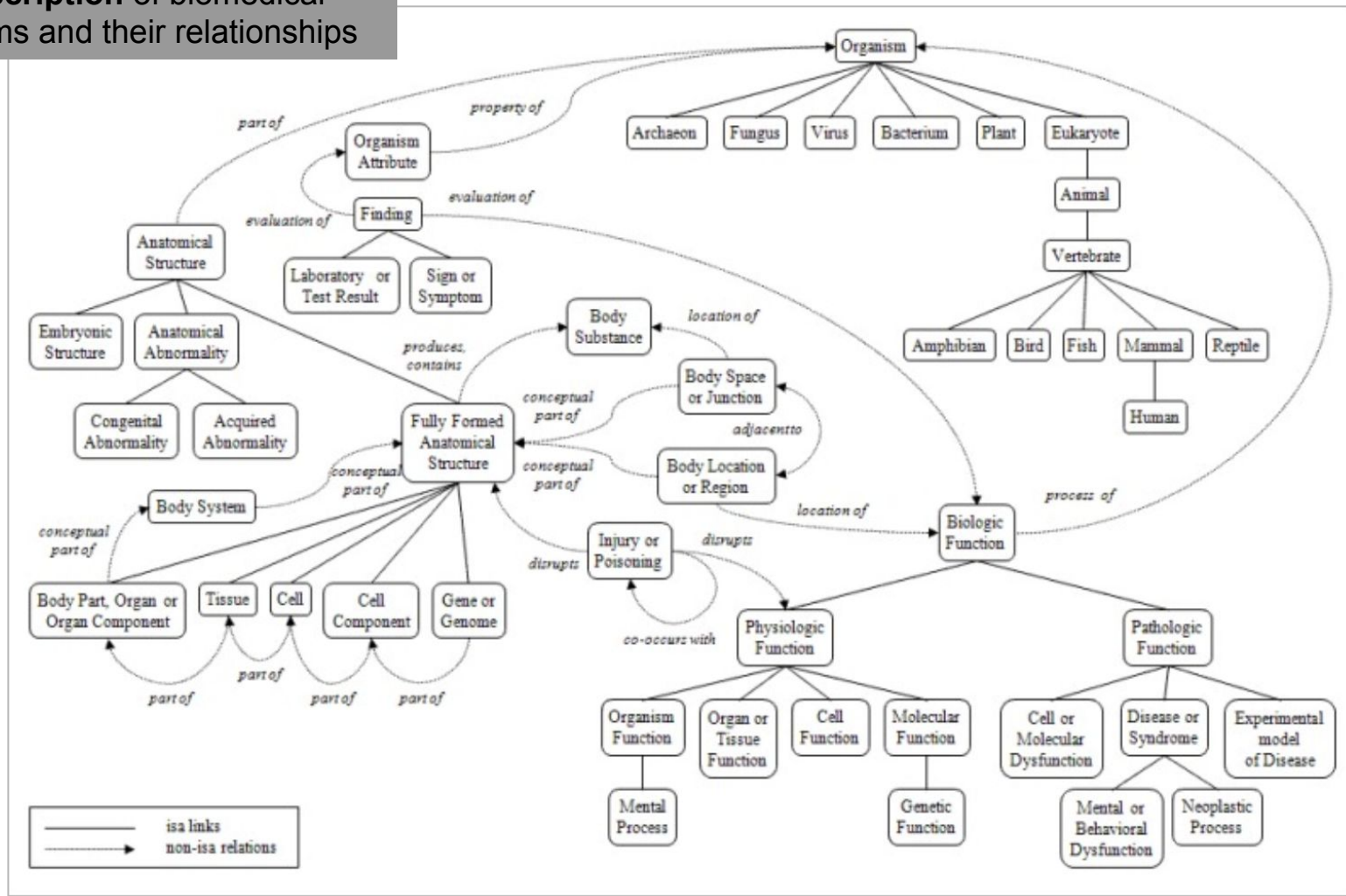
Data



Metadata


Controlled Vocabularies (Metadata)

UMLS provides a formal description of biomedical terms and their relationships



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**

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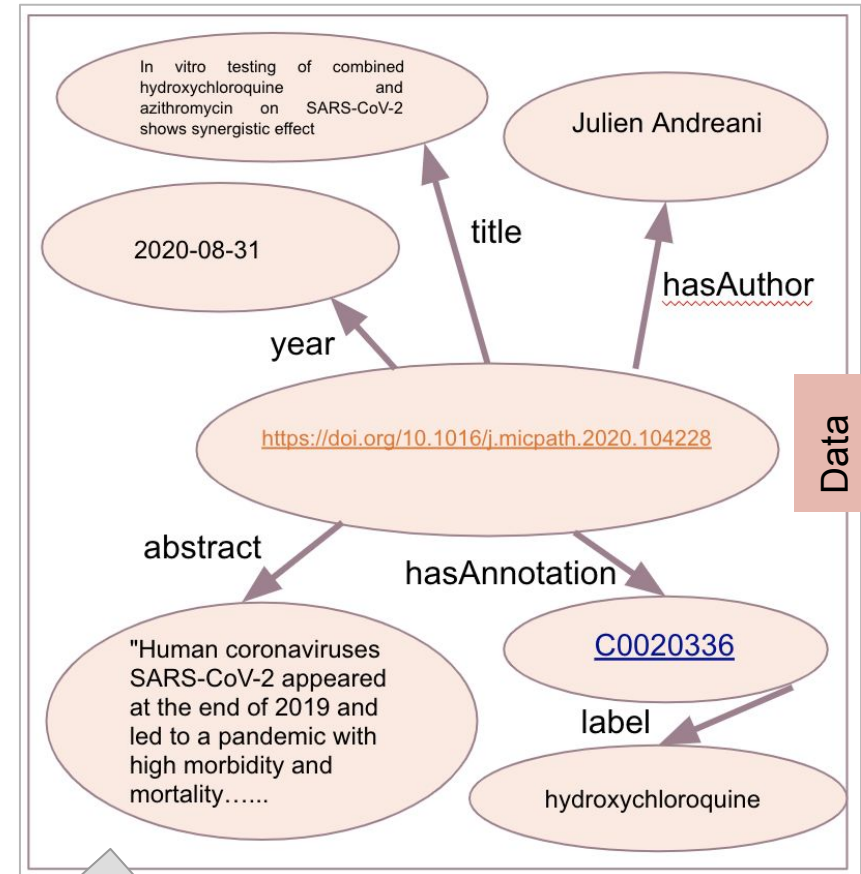
ABSTRACT

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.

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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

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Human readable representation of drug-drug interactions

Interactions

• Drug Interactions

Food Interactions

Products

Categories

Chemical Identifiers

References

Clinical Trials

Atomoxetine

Atropine

Azacitidine

Azatadine

Azathioprine

Azelastine

Azimilide

Azithromycin

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.

The metabolism of Atomoxetine can be decreased when combined with Hydroxychloroquine.

The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Atropine.

The risk or severity of adverse effects can be increased when Azacitidine is combined with Hydroxychloroquine.

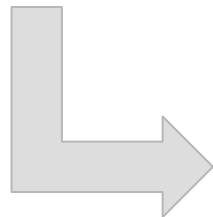
The risk or severity of QTc prolongation can be increased when Azatadine is combined with Hydroxychloroquine.

The risk or severity of adverse effects can be increased when Azathioprine is combined with Hydroxychloroquine.

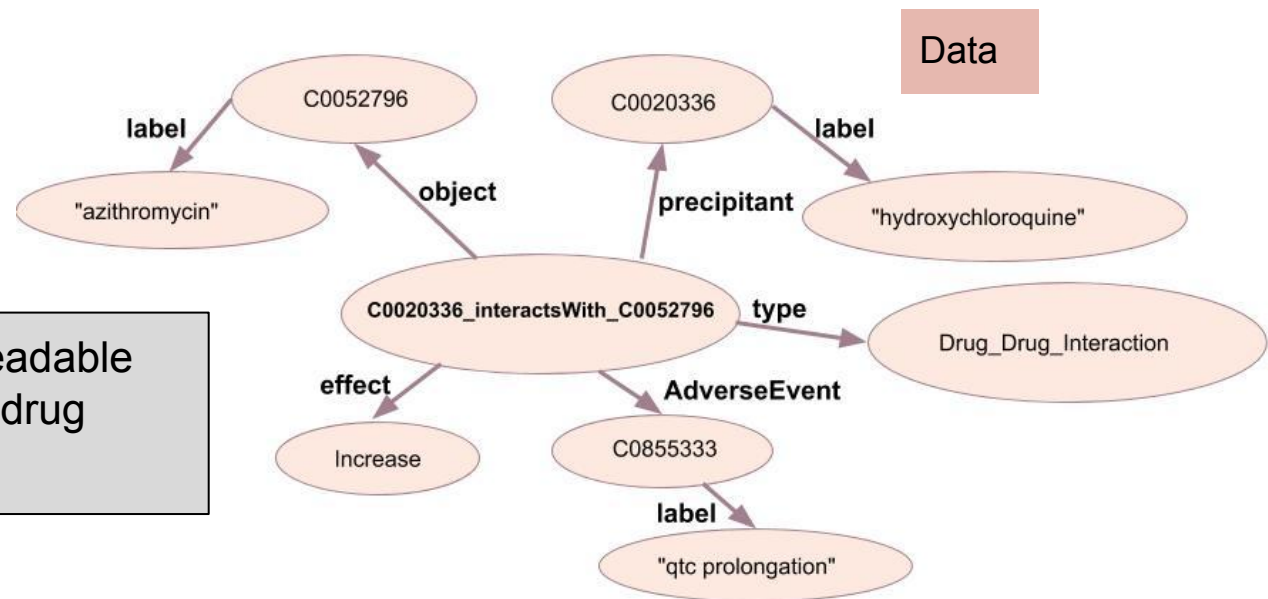
The metabolism of Azelastine can be decreased when combined with Hydroxychloroquine.

The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Azimilide.

The risk or severity of QTc prolongation can be increased when Hydroxychloroquine is combined with Azithromycin.



Machine and human readable representation of drug-drug interactions



Relationships Extracted From Publications

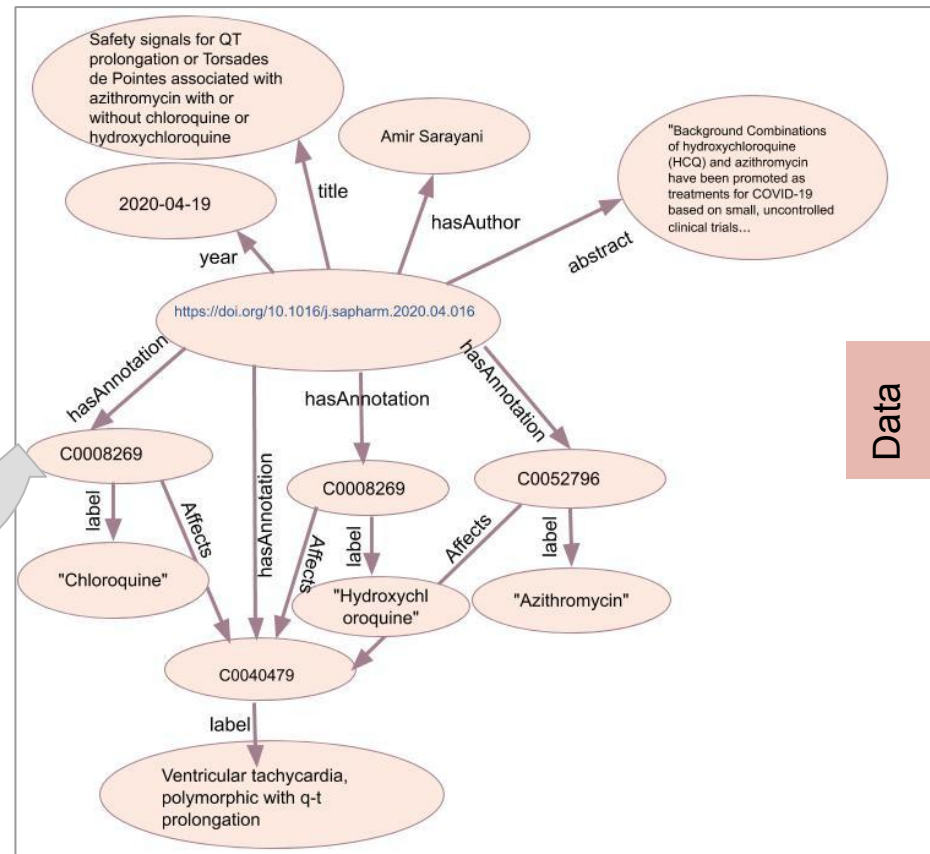
Research in Social & Administrative Pharmacy
Elsevier

Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine

Amir Sarayani, Brian Cicali, [...], and Joshua D. Brown

Additional article information

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



Data

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

Relationships Extracted From Publications

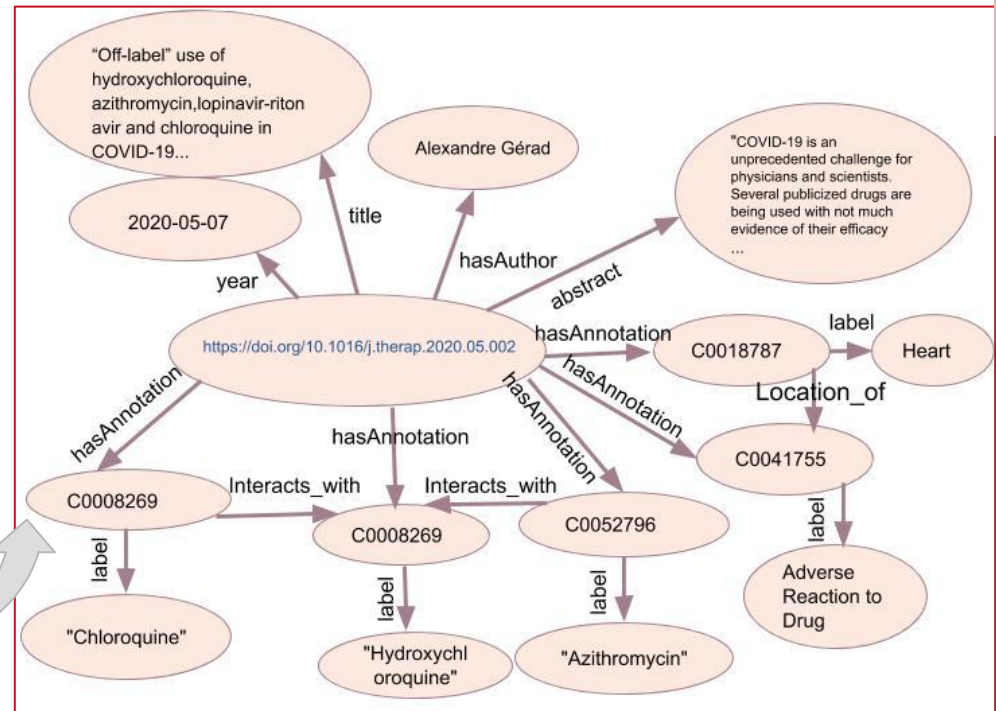
Thérapie

Elsevier

"Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers

Alexandre Gérard, Serena Romani, [...], and French Network of Pharmacovigilance Centers

[Additional article information](#)

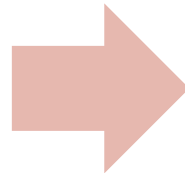
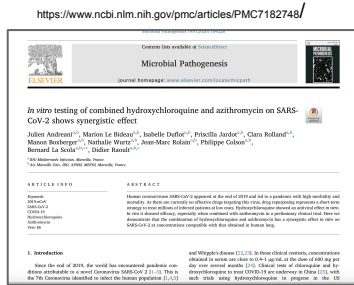


Data

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

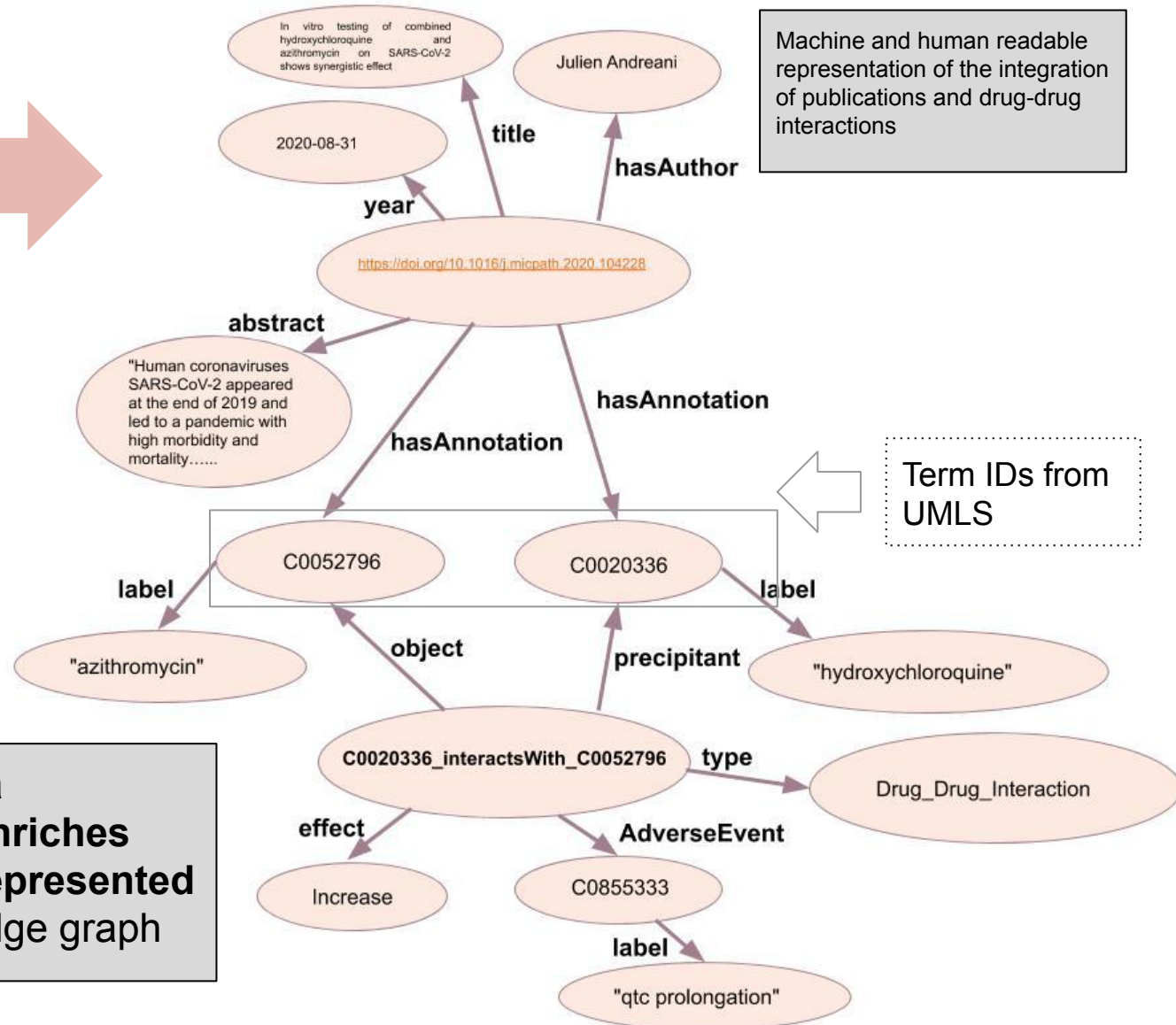
Extracted entities and predicate from scientific publications represent that Chloroquine, Hydroxychloroquine, and Azithromycin interact and cause adverse reactions in the heart

Semantic Data Integration into a Knowledge Graph



Human readable representation of publications and drug-drug interactions

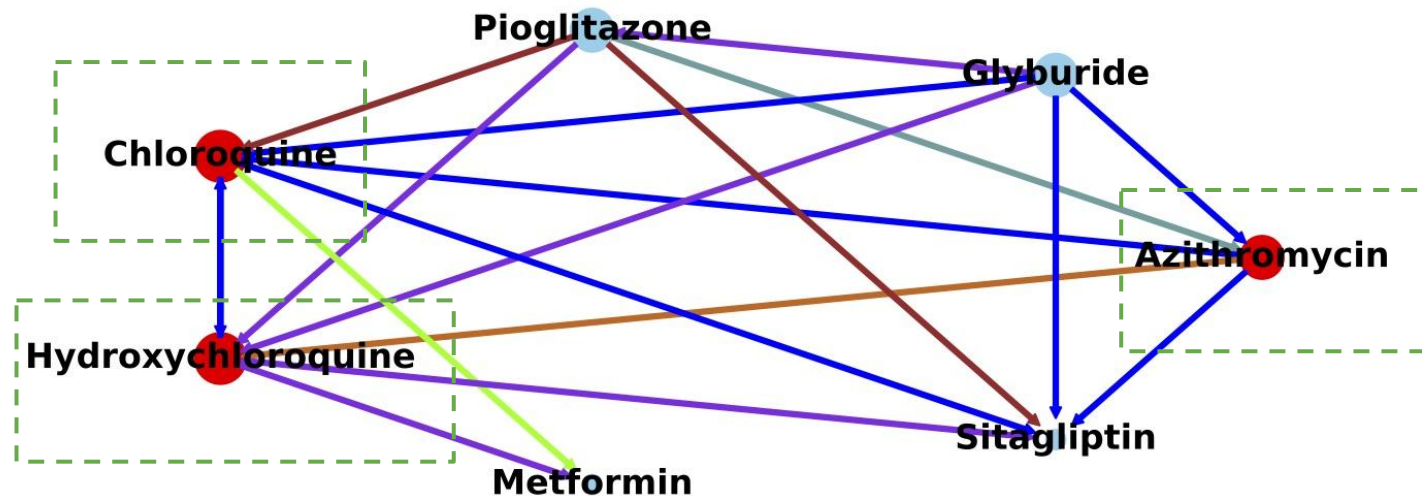
Semantic data integration enriches knowledge represented in the knowledge graph



Pattern Extraction from DDIs in the KG

Use Case: Hydroxychloroquine, Chloroquine and Azithromycin with Type 2 diabetes drugs

- | | |
|---------------------------------|---|
| — serum_concentration_increase | — metabolism_increase |
| — therapeutic_efficacy_increase | — excretion_rate_decrease |
| — metabolism_decrease | — risk_or_severity_of_qtc_prolongation_increase |



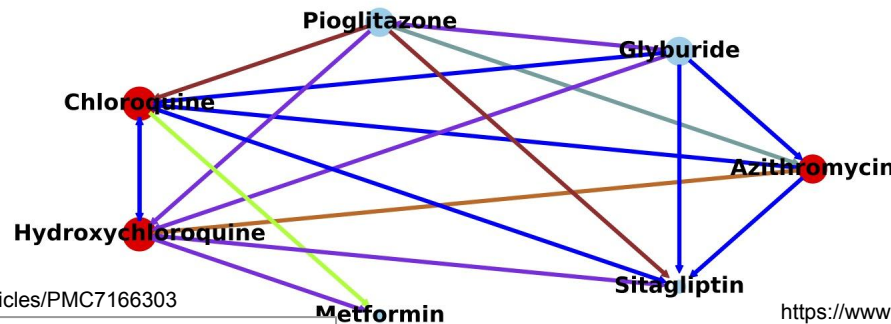
Drug-drug interactions (DDIs) among the COVID-19 treatment Hydroxychloroquine, Chloroquine, and Azithromycin and drugs commonly prescribed to treat diabetes

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

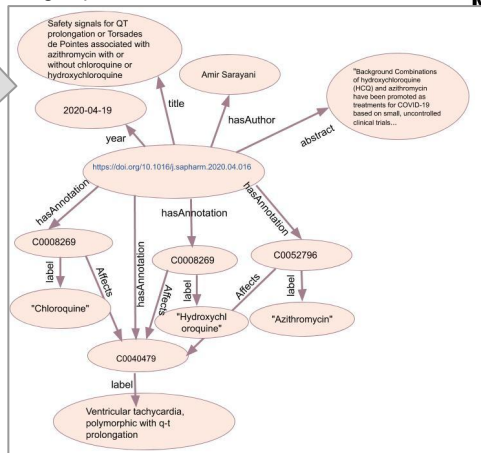
Explanations of the Extracted Patterns from KG

Use Case: Hydroxychloroquine, Chloroquine and Azithromycin with
Type 2 diabetes drugs

- serum_concentration_increase
- therapeutic_efficity_increase
- metabolism_decrease
- metabolism_increase
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- risk_or_severity_of_qtc_prolongation_increase

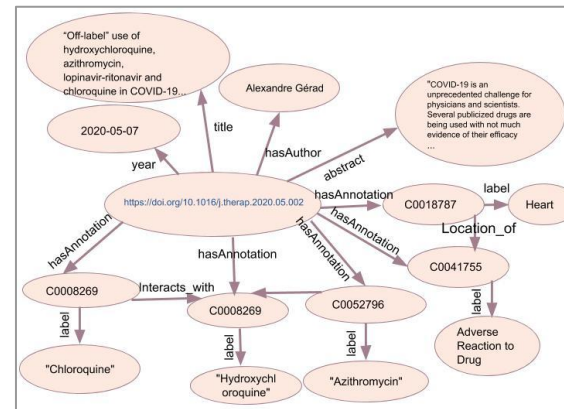


<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7166303>



Data

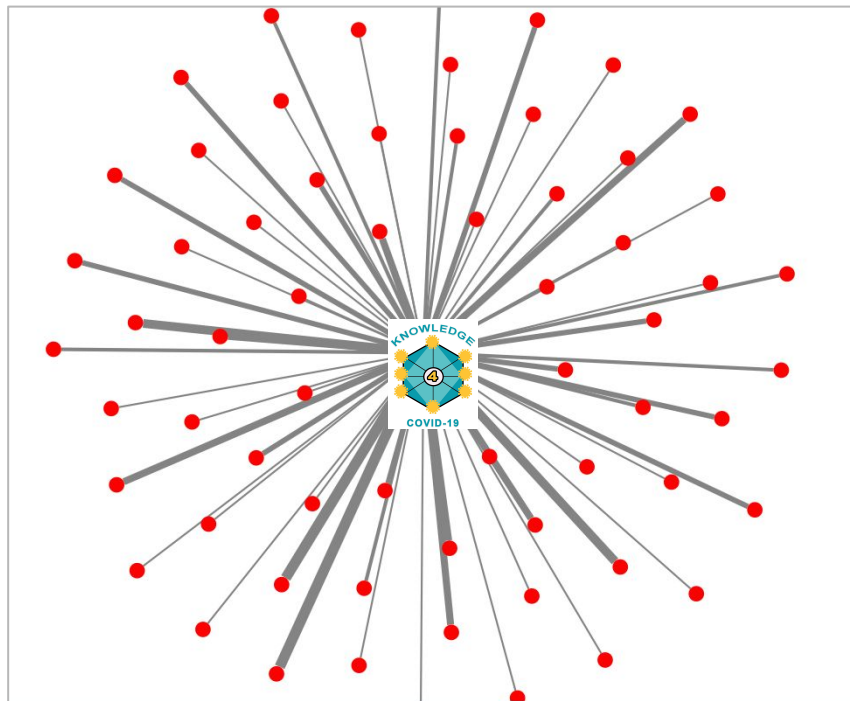
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7204701/>



Data

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

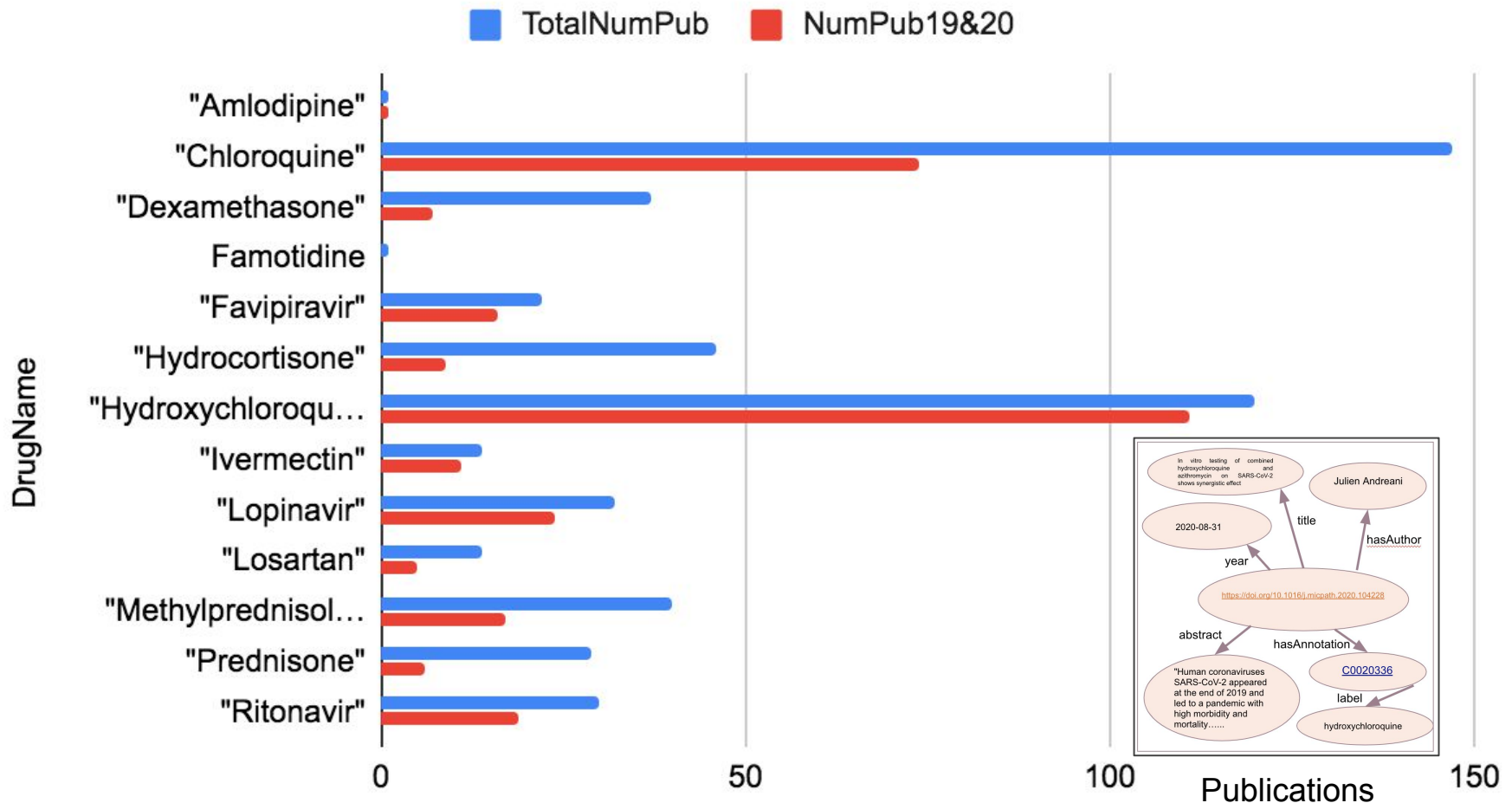


<https://f0ffbb86.ngrok.io/sparql>

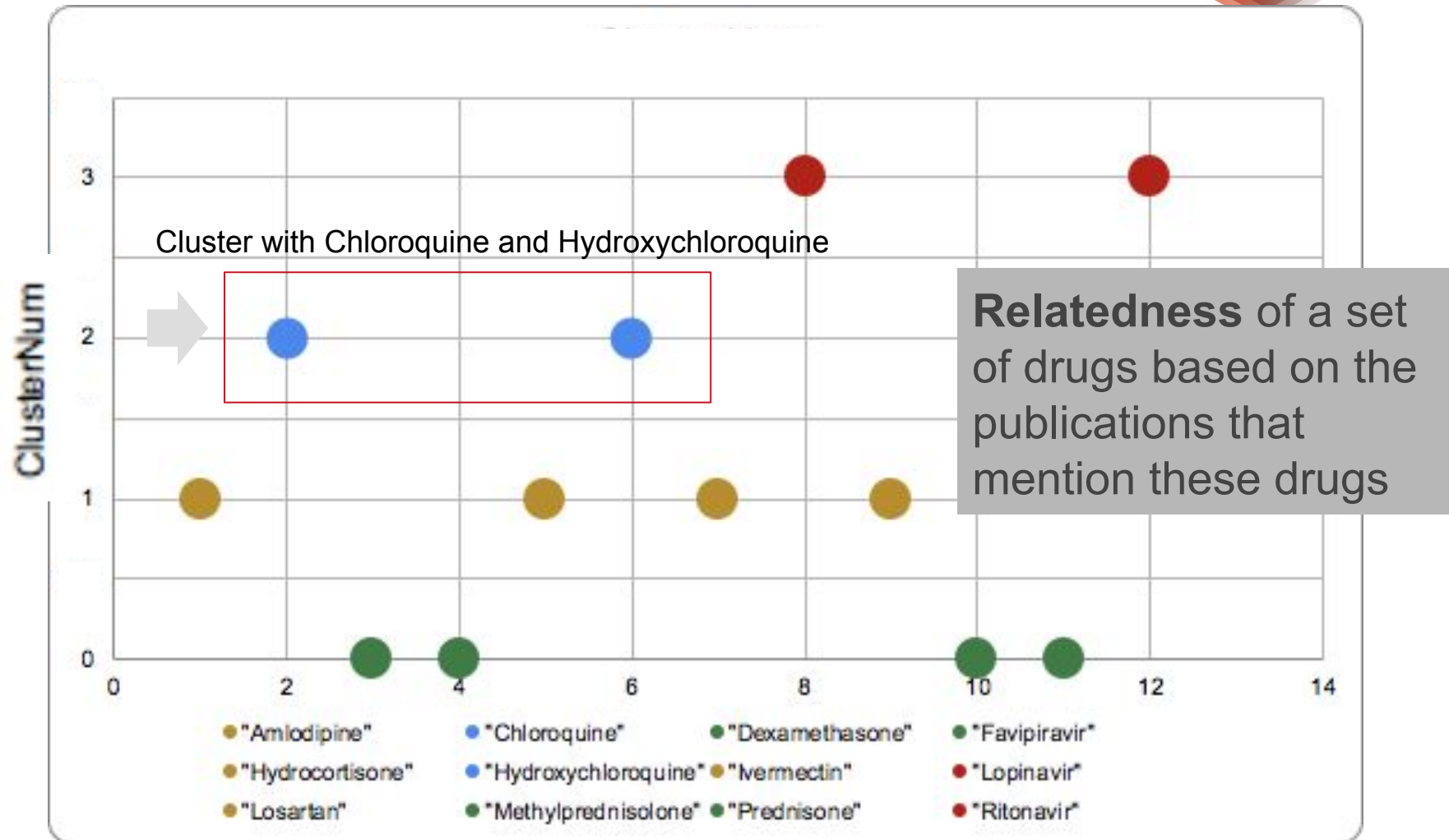
The Knowledge4COVID-19 Knowledge Graph	Value
Biomedical Entities	5,255,992
Relations between Biomedical Entities	27,158,885
Scientific Publications	51,868
Substances	4,162
Syndrome	2,012
Drug Toxicities	5,965
Links to DBpedia RDF Graph	5,905
Links to Bio2RDF RDF Graph	7,262
Links to DrugBank RDF Graph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

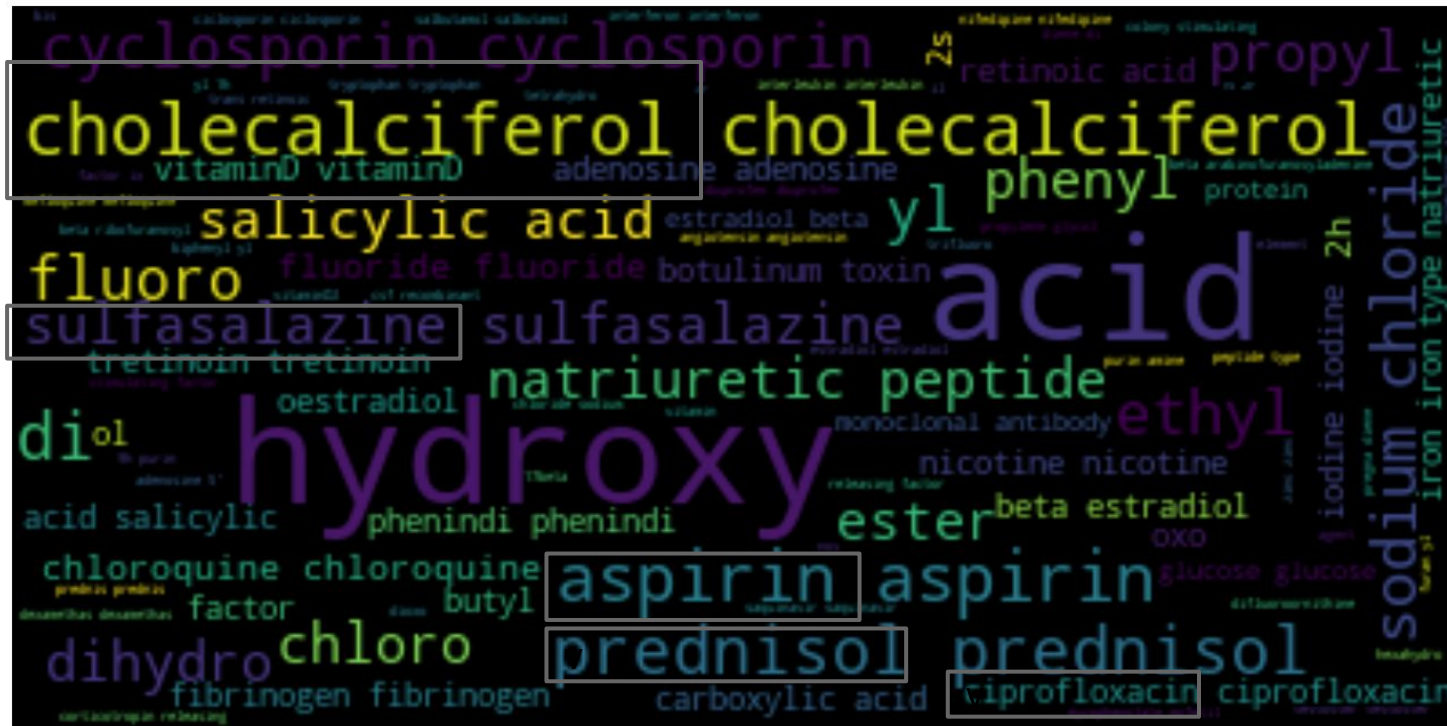


Clustering of Drugs based on Scientific Publications

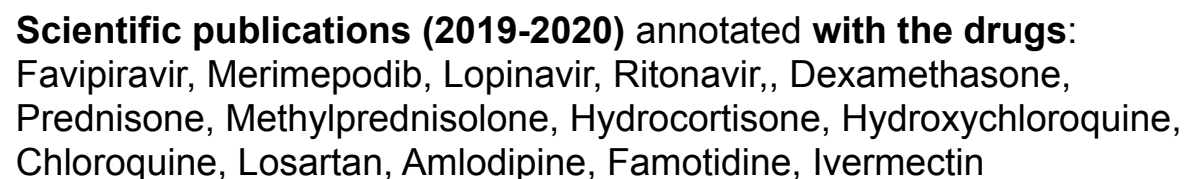


KMeans clustering based on Scientific publications (2019-2020) annotated with the drugs:
 Favipiravir, Merimepodib, Lopinavir, Ritonavir, Dexamethasone, Prednisone, Methylprednisolone, Hydrocortisone, Hydroxychloroquine, Chloroquine, Losartan, Amlodipine, Famotidine, Ivermectin

The Top Frequent Drugs in Scientific Publications

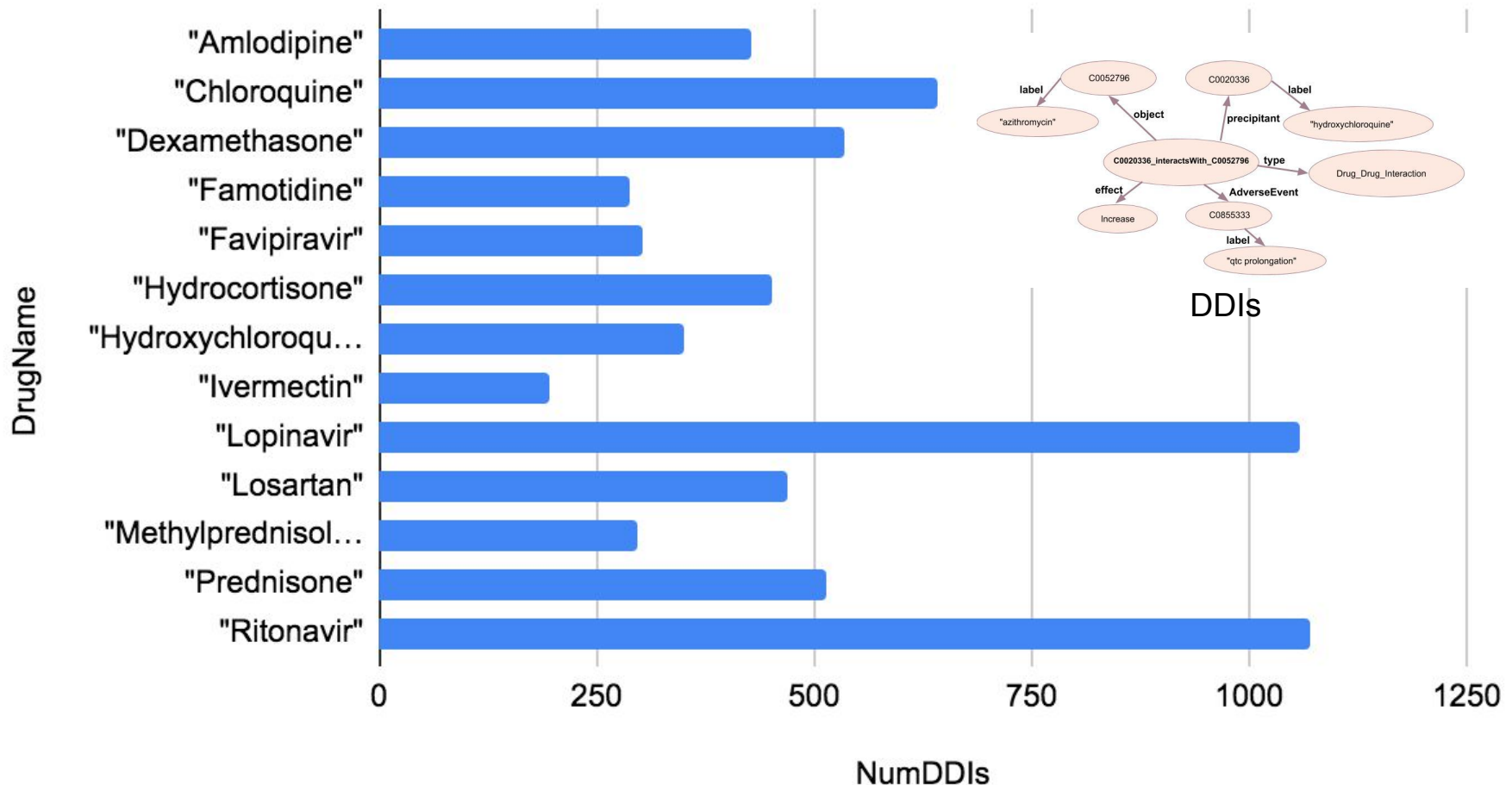


Scientific publications (2019-2020) annotated with the drugs:
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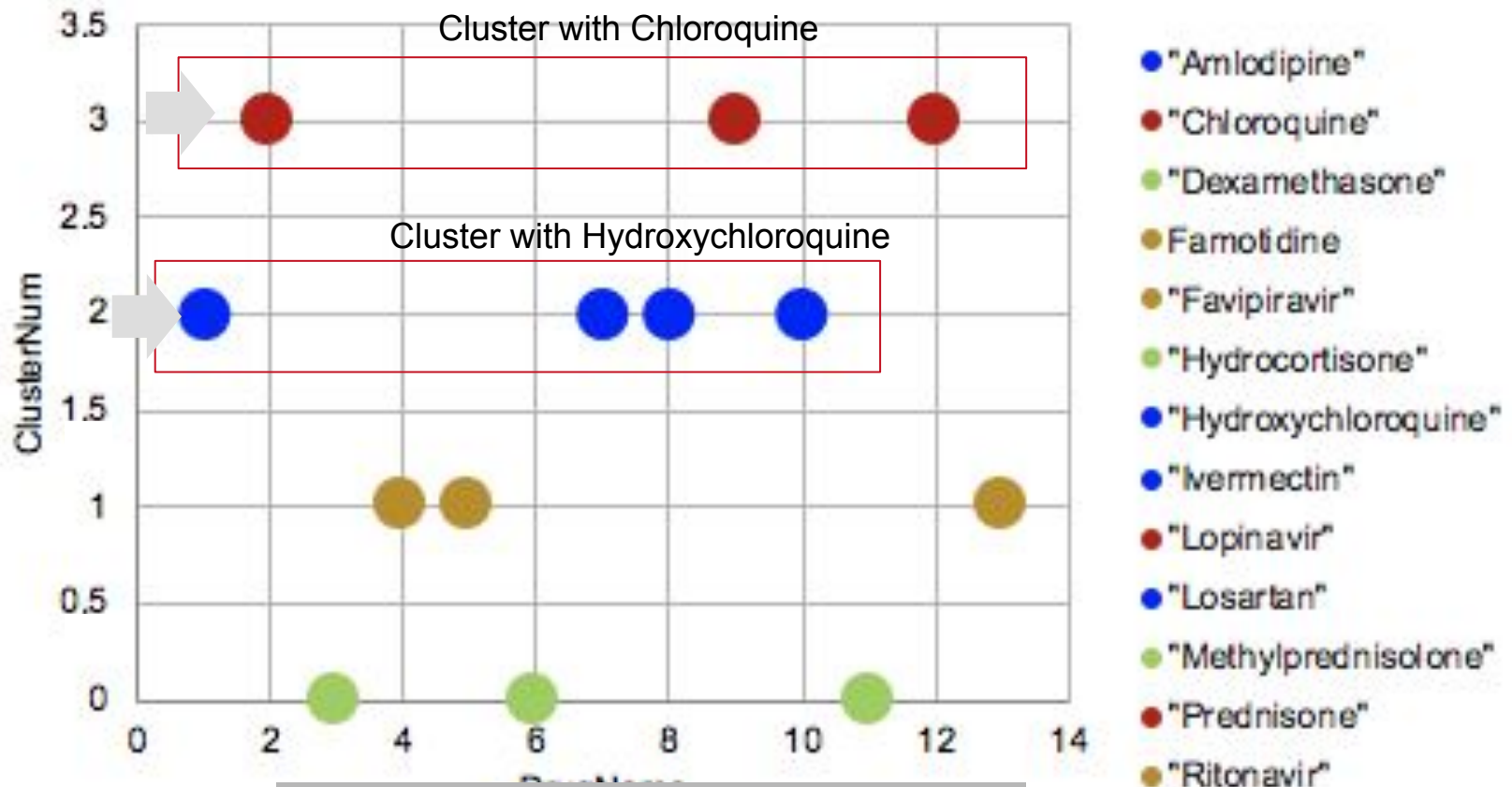


Drug-Drug Interactions (DDIs) per Drug

Number of drug-drug interactions per drug

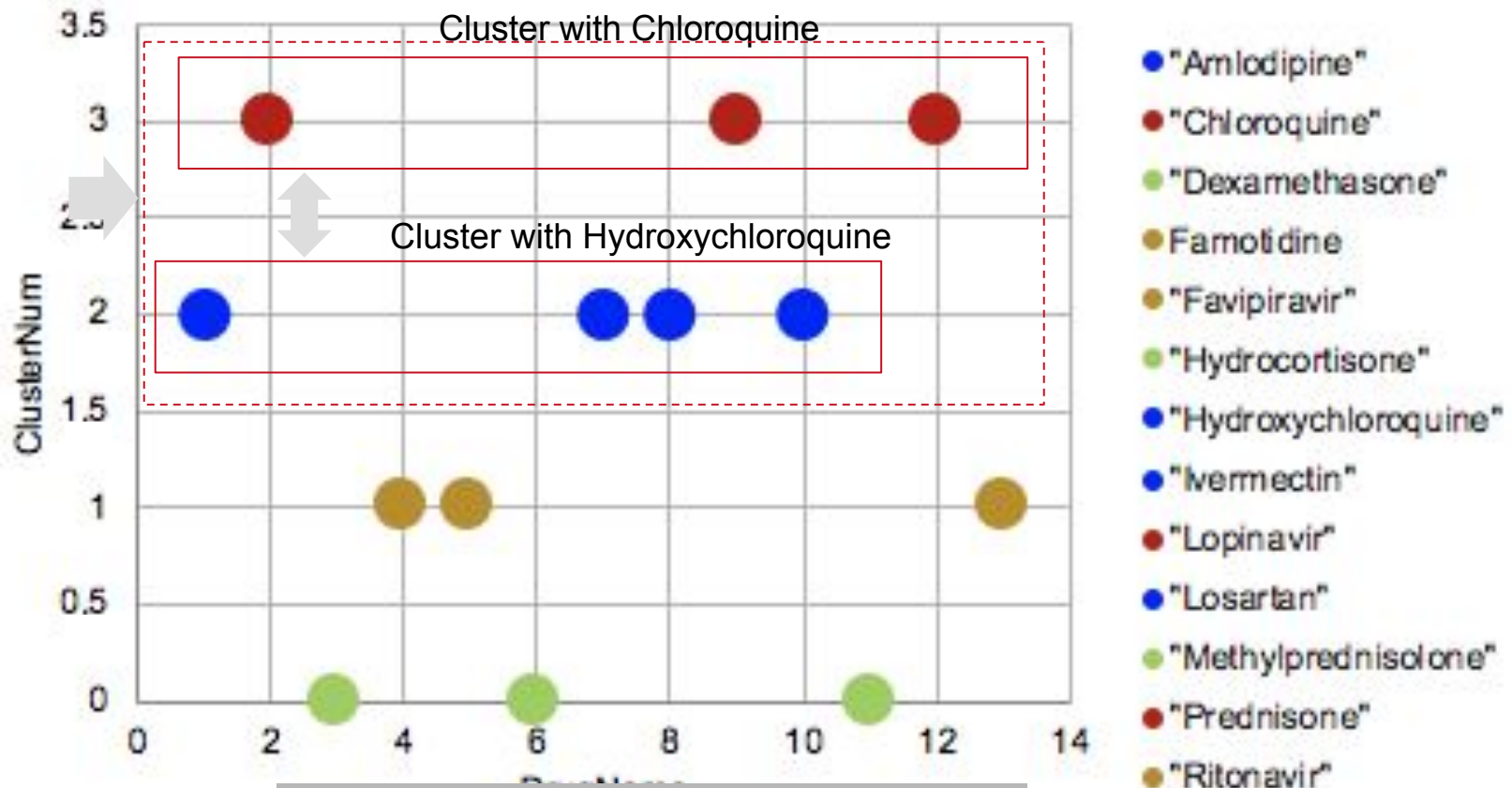


Clustering of Drugs based on Drug-Drug Interactions



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

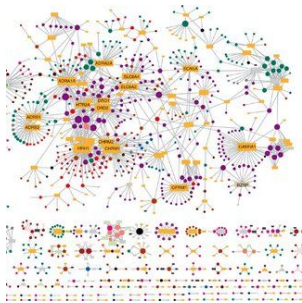


<https://eit.europa.eu/news-events/events/registration-extended-24-april-euvsvirus-pan-european-hackathon>

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

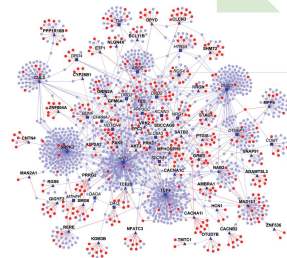
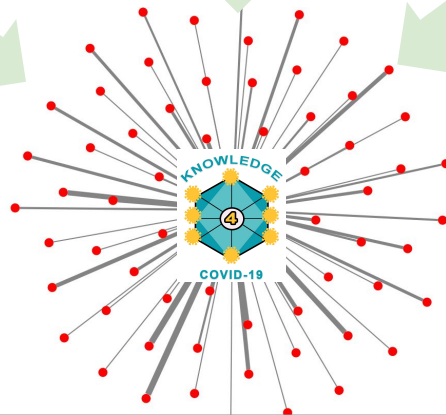
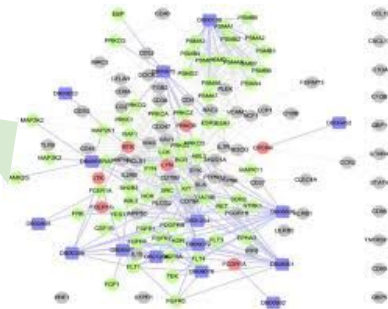
Drug-Gene Networks



Clinical Data

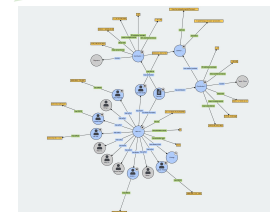


Drug-Target Networks

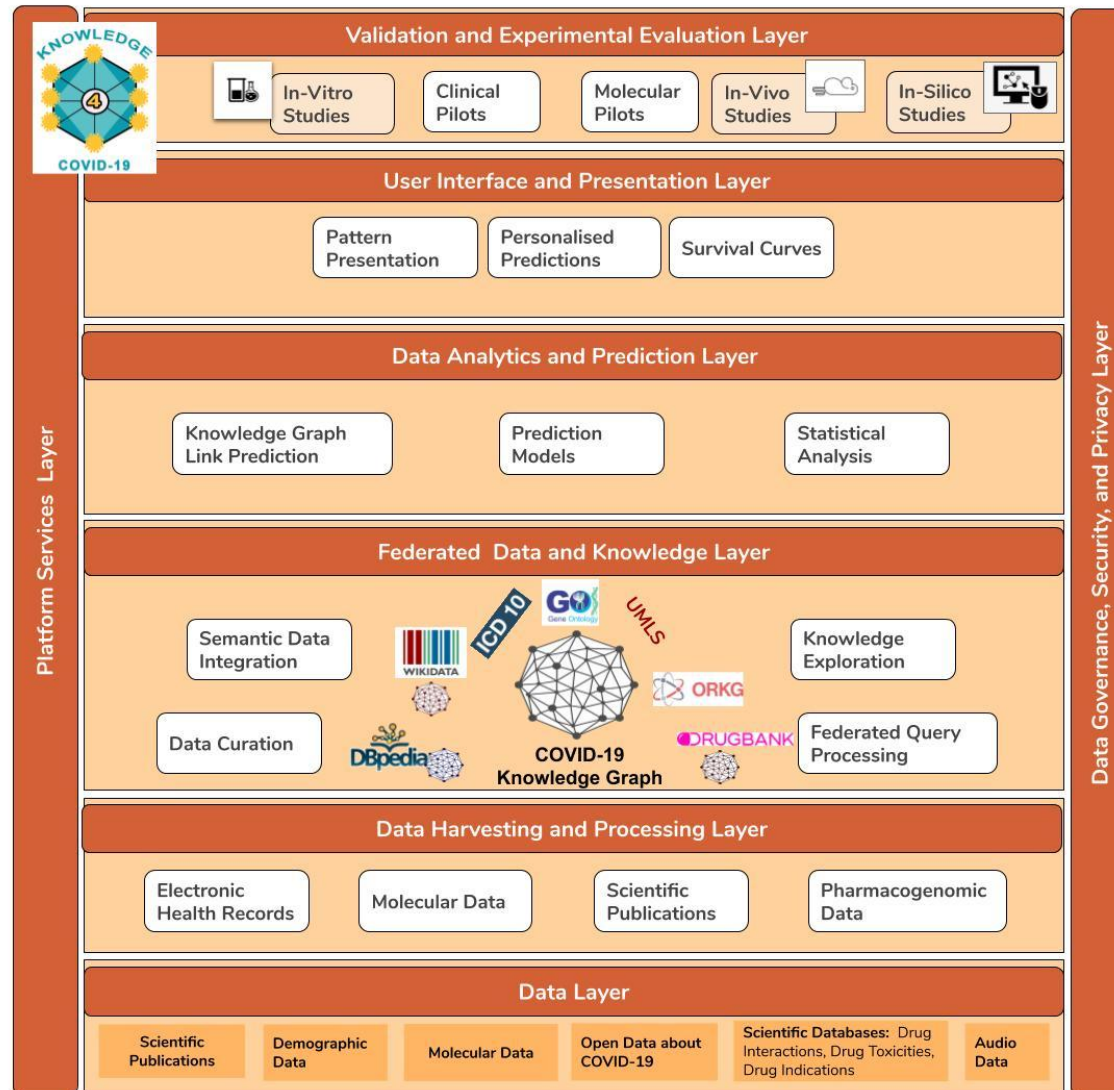


Protein-Protein Networks

Genomic Data



Next Steps: A Hybrid Framework



Our Team at the Scientific Data Management Group



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



Katja Bartel



Dr. Ingo Keck



Kemele Endris



Farah Karim

Senior Researcher



Akhilesh Vyas

Research Assistants



Samaneh
Jozashoori



Ariam
Rivas



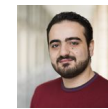
Maria Isabel
Castellanos



Philipp
Rohde



Emetis
Niazmand



Ahmad
Sakor

Master Student Assistants



Enrique
Iglesias



Monica
Figuera



Gabriela
Ydler



Supreetha
Hanasoge



Mohammad
Torabinejad



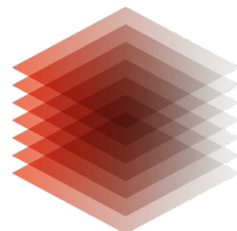
Anery Patel



NATIONAL CENTRE FOR
SCIENTIFIC RESEARCH "DEMOKRITOS"

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

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2020

MANY THANKS

Questions?

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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: **Towards 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

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