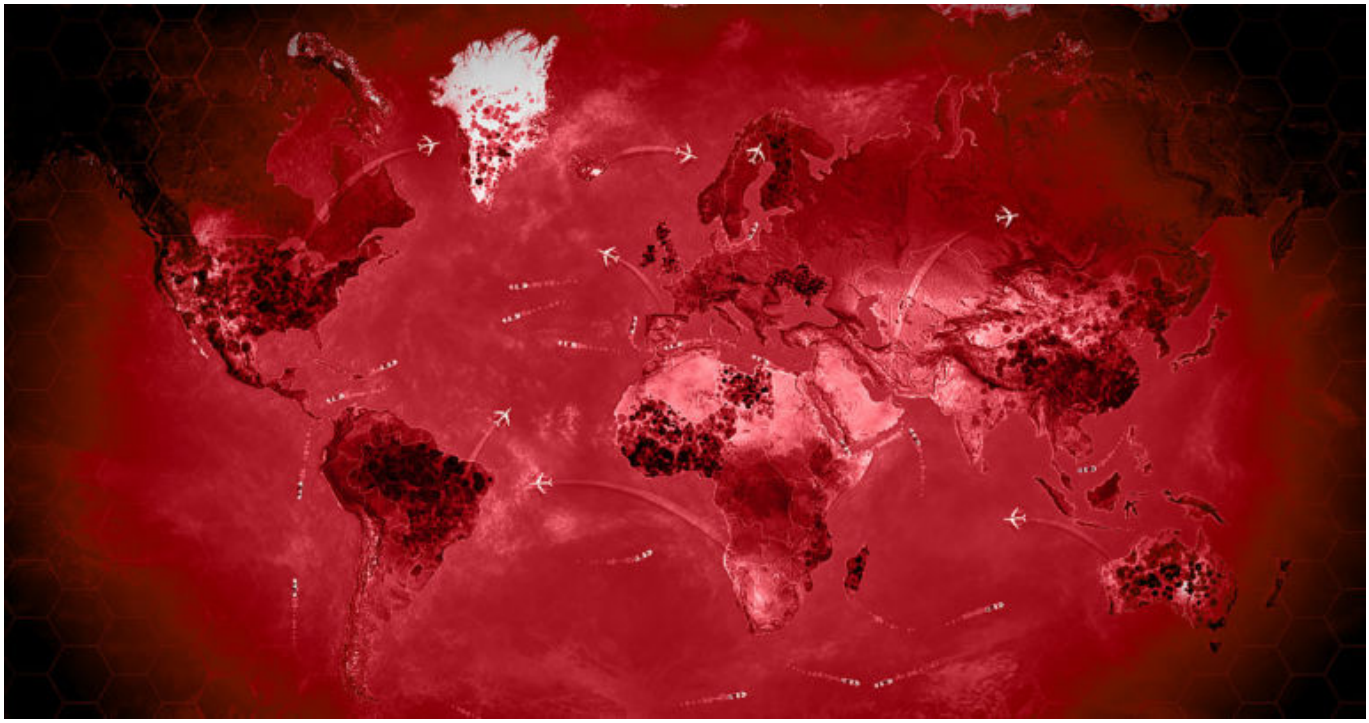
Web Scraping science papers from site: bioRxiv on the topic - "Coronavirus 2019-nCoV".



Machine learning-based analysis of genomes suggests associations between Wuhan 2019-nCoV and bat Betacoronaviruses

https://www.biorxiv.org/content/10.1101/2020.02.03.932350v1

As of February 3, 2020, the 2019 Novel Coronavirus (2019-nCoV) spread to 27 countries with 362 deaths and more than 17000 confirmed cases. 2019-nCoV is being compared to the infamous SARS coronavirus outbreak. Between November 2002 and July 2003, SARS resulted in 8098 confirmed cases worldwide with a 9.6% death rate and 774 deaths. Mainland China alone suffered 349 deaths and 5327 confirmed cases. Though 2019-nCoV has a death rate of 2.2% as of 3 February, the 17489 confirmed cases in a few weeks (December 8, 2019 to February 3, 2020) are alarming. Cases are likely under-reported given the comparatively longer incubation period. Such outbreaks demand rapid elucidation and analysis of the virus genomic sequence for timely treatment plans. We classify the 2019-nCoV using MLDSP and MLDSP-GUI, alignment-free methods that use Machine Learning (ML) and Digital Signal Processing (DSP) for genome analyses. Genomic sequences were mapped into their respective genomic signals (discrete numeric series) using a two-dimensional numerical representation (Chaos Game Representation). The magnitude spectra were computed by applying Discrete Fourier Transform on the genomic signals. The Pearson Correlation Coefficient was used to calculate a pairwise distance matrix. The feature vectors were constructed from the distance matrix and used as an input to the supervised machine learning algorithms. 10-fold cross-validation was applied to compute the average classification accuracy scores. The trained classifier models were used to predict the labels of 29 2019-nCoV sequences. The classification strategy used over 5000 genomes and tested associations at taxonomic levels of realm to species. From our machine learning-based alignment-free analyses using MLDSP-GUI, we corroborate the current hypothesis of a bat origin and classify 2019-nCoV as Sarbecovirus, within Betacoronavirus.

Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov

https://www.biorxiv.org/content/10.1101/2020.01.26.919985v1

A novel coronavirus (2019-nCov) was identified in Wuhan, Hubei Province, China in December of 2019. This new coronavirus has resulted in thousands of cases of lethal disease in China, with additional patients being identified in a rapidly growing number internationally. 2019-nCov was reported to share the same receptor, Angiotensin-converting enzyme 2 (ACE2), with SARS-Cov.

Here based on the public database and the state-of-the-art single-cell RNA-Seq technique, we analyzed the ACE2 RNA expression profile in the normal human lungs. The result indicates that the ACE2 virus receptor expression is concentrated in a small population of type II alveolar cells (AT2). Surprisingly, we found that this population of ACE2-expressing AT2 also highly expressed many other genes that positively regulating viral reproduction and transmission. A comparison between eight individual samples demonstrated that the Asian male one has an extremely large number of ACE2-expressing cells in the lung. This study provides a biological background for the epidemic investigation of the 2019-nCov infection disease, and could be informative for future anti-ACE2 therapeutic strategy development.

The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells

https://www.biorxiv.org/content/10.1101/2020.01.31.929042v1

The emergence of a novel, highly pathogenic coronavirus, 2019-nCoV, in China, and its rapid national and international spread pose a global health emergency. Coronaviruses use their spike proteins to select and enter target cells and insights into nCoV-2019 spike (S)-driven entry might facilitate assessment of pandemic potential and reveal therapeutic targets. Here, we demonstrate that 2019-nCoV-S uses the SARS-coronavirus receptor, ACE2, for entry and the cellular protease TMPRSS2 for 2019-nCoV-S priming. A TMPRSS2 inhibitor blocked entry and might constitute a treatment option. Finally, we show that the serum form a convalescent SARS patient neutralized 2019-nCoV-S-driven entry. Our results reveal important commonalities between 2019-nCoV and SARS-coronavirus infection, which might translate into similar transmissibility and disease pathogenesis. Moreover, they identify a target for antiviral intervention.

2019-20 Wuhan coronavirus outbreak: Intense surveillance is vital for preventing sustained transmission in new locations

https://www.biorxiv.org/content/10.1101/2020.01.24.919159v1

The outbreak of pneumonia originating in Wuhan, China, has generated 830 confirmed cases, including 26 deaths, as of 24 January 2020. The virus (2019-nCoV) has spread elsewhere in China and to other countries, including South Korea, Thailand, Japan and USA. Fortunately, there has not yet been evidence of sustained human-to-human transmission outside of China. Here we assess the risk of sustained transmission whenever the coronavirus arrives in other countries. Data describing

the times from symptom onset to hospitalisation for 47 patients infected in the current outbreak are used to generate an estimate for the probability that an imported case is followed by sustained human-to-human transmission. Under the assumptions that the imported case is representative of the patients in China, and that the 2019-nCoV is similarly transmissible to the SARS coronavirus, the probability that an imported case is followed by sustained human-to-human transmission is 0.37. However, if the mean time from symptom onset to hospitalisation can be halved by intense surveillance, then the probability that an imported case leads to sustained transmission is only 0.005. This emphasises the importance of current surveillance efforts in countries around the world, to ensure that the ongoing outbreak will not become a large global epidemic.

Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China

https://www.biorxiv.org/content/10.1101/2020.01.24.919183v2

Emerging and re-emerging infectious diseases, such as SARS, MERS, Zika and highly pathogenic influenza present a major threat to public health1â€“3. Despite intense research effort, how, when and where novel diseases appear are still the source of considerable uncertainly. A severe respiratory disease was recently reported in the city of Wuhan, Hubei province, China. At the time of writing, at least 62 suspected cases have been reported since the first patient was hospitalized on December 12nd 2019. Epidemiological investigation by the local Center for Disease Control and Prevention (CDC) suggested that the outbreak was associated with a sea food market in Wuhan. We studied seven patients who were workers at the market, and collected bronchoalveolar lavage fluid (BALF) from one patient who exhibited a severe respiratory syndrome including fever, dizziness and cough, and who was admitted to Wuhan Central Hospital on December 26th 2019. Next generation metagenomic RNA sequencing4 identified a novel RNA virus from the family Coronaviridae designed WH-Human-1 coronavirus (WHCV).

Highly Distinguished Amino Acid Sequences of 2019-nCoV (Wuhan Coronavirus)

https://www.biorxiv.org/content/10.1101/2020.01.31.929497v1

Using a method for pathogen screening in DNA synthesis orders, we have identified a number of amino acid sequences that distinguish 2019-nCoV (Wuhan Coronavirus) from all other known viruses in Coronaviridae. We find three main regions of unique sequence: two in the 1ab polyprotein QHO60603.1, one in surface glycoprotein QHO60594.1.

The 2019-new coronavirus epidemic: evidence for virus evolution

https://www.biorxiv.org/content/10.1101/2020.01.24.915157v1

There is concern about a new coronavirus, the 2019-nCoV, as a global public health threat. In this article, we provide a preliminary evolutionary and molecular epidemiological analysis of this new virus. A phylogenetic tree has been built using the 15 available whole genome sequence of 2019-nCoV and 12 whole genome sequences highly similar sequences available in gene bank (5 from SARS, 2 from MERS and 5 from Bat SARS-like Coronavirus). FUBAR analysis shows that the Nucleocapsid and the Spike Glycoprotein has some sites under positive pressure while homology modelling helped to explain some molecular and structural differences between the viruses. The phylogenetic tree showed that 2019.nCoV significantly clustered with Bat SARS-like Coronavirus sequence isolated in 2015, whereas structural analysis revealed mutation in S and nucleocapsid proteins. From these results, 2019nCoV could be considered a coronavirus distinct from SARS virus, probably transmitted from bats or another host where mutations conferred upon it the ability to infect humans.

Fast assessment of human receptor-binding capability of 2019 novel coronavirus (2019-nCoV)

https://www.biorxiv.org/content/10.1101/2020.02.01.930537v2

The outbreaks of 2002/2003 SARS, 2012/2015 MERS and 2019/2020 Wuhan respiratory syndrome clearly indicate that genome evolution of an animal coronavirus (CoV) may enable it to acquire human transmission ability, and thereby to cause serious threats to global public health. It is widely accepted that CoV human transmission is driven by the interactions of its spike protein (S-protein) with human receptor on host cell surface; so, quantitative evaluation of these interactions may be used to assess the human transmission capability of CoVs. However, quantitative methods directly using viral genome data are still lacking. Here, we perform large-scale protein-protein docking to quantify the interactions of 2019-nCoV S-protein receptor-binding domain (S-RBD) with human receptor ACE2, based on experimental SARS-CoV S-RBD-ACE2 complex structure. By sampling a large number of thermodynamically probable binding conformations with Monte Carlo algorithm, this approach successfully identified the experimental complex structure as the lowest-energy receptor-binding conformations, and hence established an experiment-based strength reference for evaluating the receptor-binding affinity of 2019-nCoV via comparison with SARS-CoV. Our results show that this binding affinity is about 73% of that of SARS-CoV, supporting that 2019-nCoV may

cause human transmission similar to that of SARS-CoV. Thus, this study presents a method for rapidly assessing the human transmission capability of a newly emerged CoV and its mutant strains, and demonstrates that post-genome analysis of protein-protein interactions may provide early scientific guidance for viral prevention and control.

MRCA time and epidemic dynamics of the 2019 novel coronavirus

https://www.biorxiv.org/content/10.1101/2020.01.25.919688v3

The 2019 novel coronavirus (2019-nCoV) have emerged from Wuhan, China. Studying the epidemic dynamics is crucial for further surveillance and control of the outbreak. We employed a Bayesian framework to infer the time-calibrated phylogeny and the epidemic dynamics represented by the effective reproductive number (Re) changing over time from 33 genomic sequences available from GISAID. The time of the most recent common ancestor (MRCA) was December 17, 2019 (95% HPD: December 7, 2019 â€“ December 23, 2019). The median estimate of Re shifted from 1.6 to 1.1 on around January 1, 2020. This study provides an early insight of the 2019-nCoV epidemic. However, due to limited amount of data, one should be cautious when interpreting the results at this stage.

Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation

https://www.biorxiv.org/content/10.1101/2020.01.27.921627v1

2019-nCov has caused more than 80 deaths as of 27 January 2020 in China, and infection cases have been reported in more than 10 countries. However, there is no approved drug to treat the disease. 2019-nCov Mpro is a potential drug target to combat the virus. We built homology models based on SARS Mpro structures, and docked 1903 small molecule drugs to the models. Based on the docking score and the 3D similarity of the binding mode to the known Mpro ligands, 4 drugs were selected for binding free energy calculations. Both MM/GBSA and SIE methods voted for nelfinavir, with the binding free energy of âˆ’24.69Â±0.52 kcal/mol and âˆ’9.42Â±0.04 kcal/mol, respectively. Therefore, we suggested that nelfinavir might be a potential inhibitor against 2019-nCov Mpro.

Genomic and protein structure modelling analysis depicts the origin and infectivity of

2019-nCoV, a new coronavirus which caused a pneumonia outbreak in Wuhan, China

https://www.biorxiv.org/content/10.1101/2020.01.20.913368v2

Detailed genomic and structure-based analysis of a new coronavirus, namely 2019-nCoV, showed that the new virus is a new type of bat coronavirus and is genetically fairly distant from the human SARS coronavirus. Structure analysis of the spike (S) protein of this new virus showed that its S protein only binds weakly to the ACE2 receptor on human cells whereas the human SARS coronavirus exhibits strongly affinity to the ACE receptor. These findings suggest that the new virus does not readily transmit between humans and should theoretically not able to cause very serious human infection. These data are important to guide design of infection control policy and inform the public on the nature of threat imposed by 2019-nCov when results of direct laboratory tests on this virus are not expected to be available in the near future.

Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin

https://www.biorxiv.org/content/10.1101/2020.01.22.914952v2

Since the SARS outbreak 18 years ago, a large number of severe acute respiratory syndrome related coronaviruses (SARSr-CoV) have been discovered in their natural reservoir host, bats. Previous studies indicated that some of those bat SARSr-CoVs have the potential to infect humans. Here we report the identification and characterization of a novel coronavirus (nCoV-2019) which caused an epidemic of acute respiratory syndrome in humans, in Wuhan, China. The epidemic, started from December 12th, 2019, has caused 198 laboratory confirmed infections with three fatal cases by January 20th, 2020. Full-length genome sequences were obtained from five patients at the early stage of the outbreak. They are almost identical to each other and share 79.5% sequence identify to SARS-CoV. Furthermore, it was found that nCoV-2019 is 96% identical at the whole genome level to a bat coronavirus. The pairwise protein sequence analysis of seven conserved non-structural proteins show that this virus belongs to the species of SARSr-CoV. The nCoV-2019 virus was then isolated from the bronchoalveolar lavage fluid of a critically ill patient, which can be neutralized by sera from several patients. Importantly, we have confirmed that this novel CoV uses the same cell entry receptor, ACE2, as SARS-CoV.

Preliminary identification of potential vaccine targets for 2019-nCoV based on SARS-CoV immunological studies

https://www.biorxiv.org/content/10.1101/2020.02.03.933226v1

The beginning of 2020 has seen the emergence of the 2019 novel coronavirus (2019-nCoV) outbreak. Since the first reported case in the Wuhan city of China, 2019-nCoV has spread to other cities in China as well as to multiple countries across four continents. There is an imminent need to better understand this novel virus and to develop ways to control its spread. In this study, we sought to gain insights for vaccine design against 2019-nCoV by considering the high genetic similarity between 2019-nCoV and the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), and leveraging existing immunological studies of SARS-CoV. By screening the experimentally-determined SARS-CoV-derived B cell and T cell epitopes in the immunogenic structural proteins of SARS-CoV, we identified a set of B cell and T cell epitopes derived from the spike (S) and nucleocapsid (N) proteins that map identically to 2019-nCoV proteins. As no mutation has been observed in these identified epitopes among the available 2019-nCoV sequences (as of 29 January 2020), immune targeting of these epitopes may potentially offer protection against 2019-nCoV. For the T cell epitopes, we performed a population coverage analysis of the associated MHC alleles and proposed a set of epitopes that is estimated to provide broad coverage globally, as well as in China. Our findings provide a screened set of epitopes that can help guide experimental efforts towards the development of vaccines against 2019-nCoV.

Breaking down of healthcare system: Mathematical modelling for controlling the novel coronavirus (2019-nCoV) outbreak in Wuhan, China

https://www.biorxiv.org/content/10.1101/2020.01.27.922443v2

Background

A novel coronavirus pneumonia initially identified in Wuhan, China and provisionally named 2019-nCoV has surged in the public. In anticipation of substantial burdens on healthcare system following this human-to-human spread, we aim to scrutinise the currently available information and evaluate the burden of healthcare systems during this outbreak in Wuhan.

Methods and Findings

We applied a modified SIR model to project the actual number of infected cases and the specific burdens on isolation wards and intensive care units (ICU), given the scenarios of different diagnosis rates as well as different public health intervention efficacy. Our estimates suggest, assuming 50% diagnosis rate if no public health interventions were implemented, that the actual number of infected

cases could be much higher than the reported, with estimated 88,075 cases (as of 31st January, 2020), and projected burdens on isolation wards and ICU would be 34,786 and 9,346 respectively The estimated burdens on healthcare system could be largely reduced if at least 70% efficacy of public health intervention is achieved.

Conclusion

The health system burdens arising from the actual number of cases infected by the novel coronavirus appear to be considerable if no effective public health interventions were implemented. This calls for continuation of implemented anti-transmission measures (e.g., closure of schools and facilities, suspension of public transport, lockdown of city) and further effective large-scale interventions spanning all subgroups of populations (e.g., universal facemask wear) aiming at obtaining overall efficacy with at least 70% to ensure the functioning of and to avoid the breakdown of health system.

The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes

https://www.biorxiv.org/content/10.1101/2020.01.30.927806v1

Since December 2019, a newly identified coronavirus (2019 novel coronavirus, 2019-nCov) is causing outbreak of pneumonia in one of largest cities, Wuhan, in Hubei province of China and has draw significant public health attention. The same as severe acute respiratory syndrome coronavirus (SARS-CoV), 2019-nCov enters into host cells via cell receptor angiotensin converting enzyme II (ACE2). In order to dissect the ACE2-expressing cell composition and proportion and explore a potential route of the 2019-nCov infection in digestive system infection, 4 datasets with single-cell transcriptomes of lung, esophagus, gastric, ileum and colon were analyzed. The data showed that ACE2 was not only highly expressed in the lung AT2 cells, esophagus upper and stratified epithelial cells but also in absorptive enterocytes from ileum and colon. These results indicated along with respiratory systems, digestive system is a potential routes for 2019-nCov infection. In conclusion, this study has provided the bioinformatics evidence of the potential route for infection of 2019-nCov in digestive system along with respiratory tract and may have significant impact for our healthy policy setting regards to prevention of 2019-nCoV infection.

Functional assessment of cell entry and receptor usage for lineage B Î²-coronaviruses,

including 2019-nCoV

https://www.biorxiv.org/content/10.1101/2020.01.22.915660v1

Over the past 20 years, several coronaviruses have crossed the species barrier into humans, causing outbreaks of severe, and often fatal, respiratory illness. Since SARS- CoV was first identified in animal markets, global viromics projects have discovered thousands of coronavirus sequences in diverse animals and geographic regions. Unfortunately, there are few tools available to functionally test these novel viruses for their ability to infect humans, which has severely hampered efforts to predict the next zoonotic viral outbreak. Here we developed an approach to rapidly screen lineage B betacoronaviruses, such as SARS-CoV and the recent 2019-nCoV, for receptor usage and their ability to infect cell types from different species. We show that host protease processing during viral entry is a significant barrier for several lineage B viruses and that bypassing this barrier allows several lineage B viruses to enter human cells through an unknown receptor. We also demonstrate how different lineage B viruses can recombine to gain entry into human cells and confirm that human ACE2 is the receptor for the recently emerging 2019-nCoV.

Molecular Modeling Evaluation of the Binding Abilities of Ritonavir and Lopinavir to Wuhan Pneumonia Coronavirus Proteases

https://www.biorxiv.org/content/10.1101/2020.01.31.929695v1

An anti-HIV drug named Kaletra, composed of two protease inhibitors, ritonavir and lopinavir, might have therapeutic effect on coronavirus diseases like Wuhan pneumonia. In this study, we built the structure models of two Wuhan pneumonia coronavirus proteases, coronavirus endopeptidase C30 and papain like viral protease, by homology modeling, followed by docking ritonavir and lopinavir to the protease models, respectively. In all the simulations, the binding between ritonavir and coronavirus endopeptidase C30 was most suitable. In addition, both ritonavir and lopinavir seemed more suitable to bind to coronavirus endopeptidase C30 than papain like viral protease. According to these results, we suggest that the therapeutic effect of Kaletra on Wuhan pneumonia, might be mainly due to the inhibitory effect of ritonavir on coronavirus endopeptidase C30.

A mathematical model for simulating the transmission of Wuhan novel Coronavirus

https://www.biorxiv.org/content/10.1101/2020.01.19.911669v1

As reported by the World Health Organization, a novel coronavirus (2019-nCoV) was identified as the causative virus of Wuhan pneumonia of unknown etiology by Chinese authorities on 7 January,

2020. In this study, we developed a Bats-Hosts-Reservoir-People transmission network model for simulating the potential transmission from the infection source (probable be bats) to the human infection. Since the Bats-Hosts-Reservoir network was hard to explore clearly and public concerns were focusing on the transmission from a seafood market (reservoir) to people, we simplified the model as Reservoir-People transmission network model. The basic reproduction number (R0) was calculated from the RP model to assess the transmissibility of the 2019-nCoV.

Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak

https://www.biorxiv.org/content/10.1101/2020.01.23.916395v2

Backgrounds An ongoing outbreak of a novel coronavirus (2019-nCoV) pneumonia hit a major city of China, Wuhan, December 2019 and subsequently reached other provinces/regions of China and countries. We present estimates of the basic reproduction number, R0, of 2019-nCoV in the early phase of the outbreak.

Genomic variance of the 2019-nCoV coronavirus

https://www.biorxiv.org/content/10.1101/2020.02.02.931162v2

There is rising global concern for the recently emerged novel Coronavirus (2019-nCov). Full genomic sequences have been released by the worldwide scientific community in the last few weeks in order to understand the evolutionary origin and molecular characteristics of this virus. Taking advantage of all the genomic information currently available, we constructed a phylogenetic tree including also representatives of other coronaviridae, such as Bat coronavirus (BCoV) and SARS. We confirm high sequence similarity (>99%) between all sequenced 2019-nCoVs genomes available, with the closest BCoV sequence sharing 96.2% sequence identity, confirming the notion of a zoonotic origin of 2019-nCoV. Despite the low heterogeneity of the 2019-nCoV genomes, we could identify at least two hyper-variable genomic hotspots, one of which is responsible for a Serine/Leucine variation in the viral ORF8-encoded protein. Finally, we perform a full proteomic comparison with other coronaviridae, identifying key aminoacidic differences to be considered for antiviral strategies deriving from previous anti-coronavirus approaches.

Transmission dynamics of 2019 novel coronavirus (2019-nCoV)

https://www.biorxiv.org/content/10.1101/2020.01.25.919787v1

Background Since December 29, 2019, pneumonia infection with 2019-nCoV has rapidly spread out from Wuhan, Hubei Province, China to most others provinces and other counties. However, the transmission dynamics of 2019-nCoV remain unclear.

Evolution and variation of 2019-novel coronavirus

https://www.biorxiv.org/content/10.1101/2020.01.30.926477v1

Background The current outbreak caused by novel coronavirus (2019-nCoV) in China has become a worldwide concern. As of 28 January 2020, there were 4631 confirmed cases and 106 deaths, and 11 countries or regions were affected.

Beware of asymptomatic transmission: Study on 2019-nCoV prevention and control measures based on extended SEIR model

https://www.biorxiv.org/content/10.1101/2020.01.28.923169v1

Background The 2019 new coronavirus, â€œ2019-nCoVâ€•, was discovered from Wuhan Viral Pneumonia cases in December 2019, and was named by the World Health Organization on January 12, 2020. In the early stage, people knows little about the 2019-nCoV virus was not clear, and the spread period was encountering Chinaâ€™s annual spring migration, which made the epidemic spread rapidly from Wuhan to almost all provinces in China.

Insights into Cross-species Evolution of Novel Human Coronavirus 2019-nCoV and Defining Immune Determinants for Vaccine Development

https://www.biorxiv.org/content/10.1101/2020.01.29.925867v2

Novel Coronavirus (nCoV) outbreak in the city of Wuhan, China during December 2019, has now spread to various countries across the globe triggering a heightened containment effort. This human pathogen is a member of betacoronavirus genus carrying 30 kilobase of single positive-sense RNA genome. Understanding the evolution, zoonotic transmission, and source of this novel virus would help accelerating containment and prevention efforts. The present study reported detailed analysis of 2019-nCoV genome evolution and potential candidate peptides for vaccine development. This nCoV genotype might have been evolved from a bat-CoV by accumulating non-synonymous mutations, indels, and recombination events. Structural proteins Spike (S), and Membrane (M) had

extensive mutational changes, whereas Envelope (E) and Nucleocapsid (N) proteins were very conserved suggesting differential selection pressures exerted on 2019-nCoV during evolution. Interestingly, 2019-nCoV Spike protein contains a 39 nucleotide sequence insertion relative to SARS-like bat-SL-CoVZC45/2017. Furthermore, we identified eight high binding affinity (HBA) CD4 T-cell epitopes in the S, E, M and N proteins, which can be commonly recognized by HLA-DR alleles of Asia and Asia-Pacific Region population. These immunodominant epitopes can be incorporated in universal subunit CoV vaccine. Diverse HLA types and variations in the epitope binding affinity may contribute to the wide range of immunopathological outcomes of circulating virus in humans. Our findings emphasize the requirement for continuous surveillance of CoV strains in live animal markets to better understand the viral adaptation to human host and to develop practical solutions to prevent the emergence of novel pathogenic CoV strains.

Nucleotide Analogues as Inhibitors of Viral Polymerases

https://www.biorxiv.org/content/10.1101/2020.01.30.927574v1

Coronaviruses such as the newly discovered virus from Wuhan, China, 2019-nCoV, and the viruses that cause SARS and MERS, have resulted in regional and global public health emergencies. Based on our molecular insight that the hepatitis C virus and the coronavirus use a similar viral genome replication mechanism, we reasoned that the FDA-approved drug EPCLUSA (Sofosbuvir/Velpatasvir) for the treatment of hepatitis C will also inhibit the above coronaviruses, including 2019-nCoV. To develop broad spectrum anti-viral agents, we further describe a novel strategy to design and synthesize viral polymerase inhibitors, by combining the ProTide Prodrug approach used in the development of Sofosbuvir with the use of 3â€™-blocking groups that we have previously built into nucleotide analogues that function as polymerase terminators.

Genome Detective Coronavirus Typing Tool for rapid identification and characterization of novel coronavirus genomes

https://www.biorxiv.org/content/10.1101/2020.01.31.928796v1

Summary Genome Detective is a web-based, user-friendly software application to quickly and accurately assemble all known virus genomes from next generation sequencing datasets. This application allows the identification of phylogenetic clusters and genotypes from assembled genomes in FASTA format. Since its release in 2019, we have produced a number of typing tools for emergent viruses that have caused large outbreaks, such as Zika and Yellow Fever Virus in Brazil.

Here, we present The Genome Detective Coronavirus Typing Tool that can accurately identify novel coronavirus (2019-nCoV) sequences isolated in China and around the world. The tool can accept up to 2,000 sequences per submission and the analysis of a new whole genome sequence will take approximately one minute. The tool has been tested and validated with hundreds of whole genomes from ten coronavirus species, and correctly classified all of the SARS-related coronavirus (SARSr-CoV) and all of the available public data for 2019-nCoV. The tool also allows tracking of new viral mutations as the outbreak expands globally, which may help to accelerate the development of novel diagnostics, drugs and vaccines.

Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody

https://www.biorxiv.org/content/10.1101/2020.01.28.923011v1

The newly identified 2019 novel coronavirus (2019-nCoV) has caused more than 800 laboratory-confirmed human infections, including 25 deaths, posing a serious threat to human health. Currently, however, there is no specific antiviral treatment or vaccine. Considering the relatively high identity of receptor binding domain (RBD) in 2019-nCoV and SARS-CoV, it is urgent to assess the cross-reactivity of anti-SARS-CoV antibodies with 2019-nCoV spike protein, which could have important implications for rapid development of vaccines and therapeutic antibodies against 2019-nCoV. Here, we report for the first time that a SARS-CoV-specific human monoclonal antibody, CR3022, could bind potently with 2019-nCoV RBD (KD of 6.3 nM). The epitope of CR3022 does not overlap with the ACE2 binding site within 2019-nCoV RBD. Therefore, CR3022 has the potential to be developed as candidate therapeutics, alone or in combination with other neutralizing antibodies, for the prevention and treatment of 2019-nCoV infections. Interestingly, some of the most potent SARS-CoV-specific neutralizing antibodies (e.g., m396, CR3014) that target the ACE2 binding site of SARS-CoV failed to bind 2019-nCoV spike protein, indicating that the difference in the RBD of SARS-CoV and 2019-nCoV has a critical impact for the cross-reactivity of neutralizing antibodies, and that it is still necessary to develop novel monoclonal antibodies that could bind specifically to 2019-nCoV RBD.

Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event

https://www.biorxiv.org/content/10.1101/2020.01.26.920249v1

Background A novel coronavirus (2019-nCoV) associated with human to human transmission and severe human infection has been recently reported from the city of Wuhan in China. Our objectives were to characterize the genetic relationships of the 2019-nCoV and to search for putative recombination within the subgenus of sarbecovirus.

Therapeutic Drugs Targeting 2019-nCoV Main Protease by High-Throughput Screening

https://www.biorxiv.org/content/10.1101/2020.01.28.922922v2

2019 Novel Coronavirus (2019-nCoV) is a virus identified as the cause of the outbreak of pneumonia first detected in Wuhan, China. Investigations on the transmissibility, severity, and other features associated with this virus are ongoing. Currently, there is no vaccine or therapeutic antibody to prevent the infection, and more time is required to develop an effective immune strategy against the pathogen. In contrast, specific inhibitors targeting the key protease involved in replication and proliferation of the virus are the most effective means to alleviate the epidemic. The main protease of SARS-CoV is essential for the life cycle of the virus, which showed 96.1% of similarity with the main proteaseof 2019-nCoV, is considered to be an attractive target for drug development. In this study, we have identified 4 small molecular drugs with high binding capacity with SARS-CoV main protease by high-throughput screening based on the 8,000 clinical drug libraries, all these drugs have been widely used in clinical applications with guaranteed safety, which may serve as promising candidates to treat the infection of 2019-nCoV.

Pattern of early human-to-human transmission of Wuhan 2019-nCoV

https://www.biorxiv.org/content/10.1101/2020.01.23.917351v1

On December 31, 2019, the World Health Organization was notified about a cluster of pneumonia of unknown aetiology in the city of Wuhan, China. Chinese authorities later identified a new coronavirus (2019-nCoV) as the causative agent of the outbreak. As of January 23, 2020, 655 cases have been confirmed in China and several other countries. Understanding the transmission characteristics and the potential for sustained human-to-human transmission of 2019-nCoV is critically important for coordinating current screening and containment strategies, and determining whether the outbreak constitutes a public health emergency of international concern (PHEIC). We performed stochastic simulations of early outbreak trajectories that are consistent with the epidemiological findings to date. We found the basic reproduction number, R0, to be around 2.2 (90% high density interval 1.4â€”3.8), indicating the potential for sustained human-to-human

transmission. Transmission characteristics appear to be of a similar magnitude to severe acute respiratory syndrome-related coronavirus (SARS-CoV) and the 1918 pandemic influenza. These findings underline the importance of heightened screening, surveillance and control efforts, particularly at airports and other travel hubs, in order to prevent further international spread of 2019-nCoV.

A database resource for Genome-wide dynamics analysis of Coronaviruses on a historical and global scale

https://www.biorxiv.org/content/10.1101/2020.02.05.920009v1

The recent outbreak of a new zoonotic origin Coronavirus has ring the bell for the potential spread of epidemic Coronavirus crossing the species. With the urgent needs to assist the control of the Coronavirus spread and to provide valuable scientific information, we developed a coronavirus database (CoVdb), an online genomics and proteomics analysis platform. Based on public available coronavirus genomic information, the database annotates the genome of every strain and identifies 780 possible ORFs of all strains available in Genebank. In addition, the comprehensive evaluation of all the published genomes of Coronavirus strains, including population genetics analysis, functional analysis and structural analysis on a historical and global scale were presented in the CoVdb. In the database, the researcher can easily obtain the basic information of a Coronavirus gene with the distribution of the gene among strains, conserved or high mutation regions, possible subcellular location and topology of the gene. Moreover, sliding windows for population genetics analysis results is provided, thereby facilitating genetics and evolutional analysis at the genomic level. CoVdb can be accessed freely at http://covdb.popgenetics.net.

Potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig

https://www.biorxiv.org/content/10.1101/2020.02.01.929976v2

2019-nCoV, which is a novel coronavirus emerged in Wuhan, China, at the end of 2019, has caused at least infected 11,844 as of Feb 1, 2020. However, there is no specific antiviral treatment or vaccine currently. Very recently report had suggested that novel CoV would use the same cell entry receptor, ACE2, as the SARS-CoV. In this report, we generated a novel recombinant protein by connecting the extracellular domain of human ACE2 to the Fc region of the human immunoglobulin IgG1. An ACE2 mutant with low catalytic activity was also used in the study. The fusion proteins were then characterized. Both fusion proteins has high affinity binding to the receptor-binding

domain (RBD) of SARS-CoV and 2019-nCoV and exerted desired pharmacological properties. Moreover, fusion proteins potently neutralized SARS-CoV and 2019-nCoV in vitro. As these fusion proteins exhibit cross-reactivity against coronaviruses, they could have potential applications for diagnosis, prophylaxis, and treatment of 2019-nCoV.

Machine intelligence design of 2019-nCoV drugs

https://www.biorxiv.org/content/10.1101/2020.01.30.927889v1

Wuhan coronavirus, called 2019-nCoV, is a newly emerged virus that infected more than 9692 people and leads to more than 213 fatalities by January 30, 2020. Currently, there is no effective treatment for this epidemic. However, the viral protease of a coronavirus is well-known to be essential for its replication and thus is an effective drug target. Fortunately, the sequence identity of the 2019-nCoV protease and that of severe-acute respiratory syndrome virus (SARS-CoV) is as high as 96.1%. We show that the protease inhibitor binding sites of 2019-nCoV and SARS-CoV are almost identical, which means all potential anti-SARS-CoV chemotherapies are also potential 2019-nCoV drugs. Here, we report a family of potential 2019-nCoV drugs generated by a machine intelligence-based generative network complex (GNC). The potential effectiveness of treating 2019-nCoV by using some existing HIV drugs is also analyzed.

Predicting commercially available antiviral drugs that may act on the novel coronavirus (2019-nCoV), Wuhan, China through a drug-target interaction deep learning model

https://www.biorxiv.org/content/10.1101/2020.01.31.929547v1

The infection of a novel coronavirus found in Wuhan of China (2019-nCoV) is rapidly spreading, and the incidence rate is increasing worldwide. Due to the lack of effective treatment options for 2019-nCoV, various strategies are being tested in China, including drug repurposing. In this study, we used our pretrained deep learning-based drug-target interaction model called Molecule Transformer-Drug Target Interaction (MT-DTI) to identify commercially available drugs that could act on viral proteins of 2019-nCoV. The result showed that atazanavir, an antiretroviral medication used to treat and prevent the human immunodeficiency virus (HIV), is the best chemical compound, showing a inhibitory potency with Kd of 94.94 nM against the 2019-nCoV 3C-like proteinase, followed by efavirenz (199.17 nM), ritonavir (204.05 nM), and dolutegravir (336.91 nM). Interestingly, lopinavir, ritonavir, and darunavir are all designed to target viral proteinases. However, in our prediction, they may also bind to the replication complex components of 2019-nCoV with an

inhibitory potency with Kd < 1000 nM. In addition, we also found that several antiviral agents, such as Kaletra, could be used for the treatment of 2019-nCoV, although there is no real-world evidence supporting the prediction. Overall, we suggest that the list of antiviral drugs identified by the MT-DTI model should be considered, when establishing effective treatment strategies for 2019-nCoV.

Interpretable detection of novel human viruses from genome sequencing data

https://www.biorxiv.org/content/10.1101/2020.01.29.925354v2

Viruses evolve extremely quickly, so reliable methods for viral host prediction are necessary to safeguard biosecurity and biosafety alike. Novel human-infecting viruses are difficult to detect with standard bioinformatics workflows. Here, we predict whether a virus can infect humans directly from next-generation sequencing reads. We show that deep neural architectures significantly outperform both shallow machine learning and standard, homology-based algorithms, cutting the error rates in half and generalizing to taxonomic units distant from those presented during training. We propose a new approach for convolutional filter visualization to disentangle the information content of each nucleotide from its contribution to the final classification decision. Nucleotide-resolution maps of the learned associations between pathogen genomes and the infectious phenotype can be used to detect virulence-related genes in novel agents, as we show here for the 2019-nCoV coronavirus, unknown before it caused a pneumonia outbreak in December 2019.

Host and infectivity prediction of Wuhan 2019 novel coronavirus using deep learning algorithm

https://www.biorxiv.org/content/10.1101/2020.01.21.914044v3

The recent outbreak of pneumonia in Wuhan, China caused by the 2019 Novel Coronavirus (2019-nCoV) emphasizes the importance of detecting novel viruses and predicting their risks of infecting people. In this report, we introduced the VHP (Virus Host Prediction) to predict the potential hosts of viruses using deep learning algorithm. Our prediction suggests that 2019-nCoV has close infectivity with other human coronaviruses, especially the severe acute respiratory syndrome coronavirus (SARS-CoV), Bat SARS-like Coronaviruses and the Middle East respiratory syndrome coronavirus (MERS-CoV). Based on our prediction, compared to the Coronaviruses infecting other vertebrates, bat coronaviruses are assigned with more similar infectivity patterns with 2019-nCoVs. Furthermore, by comparing the infectivity patterns of all viruses hosted on vertebrates, we found mink viruses show a closer infectivity pattern to 2019-nCov. These consequences of infectivity

pattern analysis illustrate that bat and mink may be two candidate reservoirs of 2019-nCov.These results warn us to beware of 2019-nCoV and guide us to further explore the properties and reservoir of it.

Structure-Guided Mutagenesis Alters Deubiquitinating Activity and Attenuates Pathogenesis of a Murine Coronavirus

https://www.biorxiv.org/content/10.1101/782409v2

Coronaviruses express a multifunctional papain-like protease, termed PLP2. PLP2 acts as a protease that cleaves the viral replicase polyprotein, and a deubiquitinating (DUB) enzyme which removes ubiquitin moieties from ubiquitin-conjugated proteins. Previous in vitro studies implicated PLP2 DUB activity as a negative regulator of the host interferon (IFN) response, but the role of DUB activity during virus infection was unknown. Here, we used X-ray structure-guided mutagenesis and functional studies to identify amino acid substitutions within the ubiquitin-binding surface of PLP2 that reduced DUB activity without affecting polyprotein processing activity. We engineered a DUB mutation (Asp1772 to Ala) into a murine coronavirus and evaluated the replication and pathogenesis of the DUB mutant virus (DUBmut) in cultured macrophages and in mice. We found that the DUBmut virus replicates similarly as the wild-type virus in cultured cells, but the DUBmut virus activates an IFN response at earlier times compared to the wild-type virus infection in macrophages, consistent with DUB activity negatively regulating the IFN response. We compared the pathogenesis of the DUBmut virus to the wild-type virus and found that the DUBmut-infected mice had a statistically significant reduction ($p<0.05$) in viral titer in livers and spleens at day 5 post-infection, albeit both wild-type and DUBmut virus infections resulted in similar liver pathology. Overall, this study demonstrates that structure-guided mutagenesis aids the identification of critical determinants of PLP2-ubiquitin complex, and that PLP2 DUB activity plays a role as an interferon antagonist in coronavirus pathogenesis.

Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines

https://www.biorxiv.org/content/10.1101/2020.01.29.924100v1

Starting from December 2019, a novel coronavirus, named 2019-nCoV, was found to cause Severe Acute Respiratory (SARI) symptoms and rapid pandemic in China. With the hope to identify candidate drugs for 2019-nCoV, we adopted a computational approach to screen for available

commercial medicines which may function as inhibitors for the Mpro of 2019-nCoV. Up to 10 commercial medicines that may form hydrogen bounds to key residues within the binding pocket of 2019-nCoV Mpro were identified, which may have higher mutation tolerance than lopinavir/ritonavir and may also function as inhibitors for other coronaviruses with similar Mpro binding sites and pocket structures.

Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection

https://www.biorxiv.org/content/10.1101/2020.02.03.931766v1

A newly identified coronavirus, 2019-nCoV, has been posing significant threats to public health since December 2019. ACE2, the host cell receptor for severe acute respiratory syndrome coronavirus (SARS), has recently been demonstrated in mediating 2019-nCoV infection. Interestingly, besides the respiratory system, substantial proportion of SARS and 2019-nCoV patients showed signs of various degrees of liver damage, the mechanism and implication of which have not yet been determined. Here, we performed an unbiased evaluation of cell type specific expression of ACE2 in healthy liver tissues using single cell RNA-seq data of two independent cohorts, and identified specific expression in cholangiocytes. The results indicated that virus might directly bind to ACE2 positive cholangiocytes but not necessarily hepatocytes. This finding suggested the liver abnormalities of SARS and 2019-nCoV patients may not be due to hepatocyte damage, but cholangiocyte dysfunction and other causes such as drug induced and systemic inflammatory response induced liver injury. Our findings indicate that special care of liver dysfunction should be installed in treating 2019-nCoV patients during the hospitalization and shortly after cure.

Modelling the epidemic trend of the 2019 novel coronavirus outbreak in China

https://www.biorxiv.org/content/10.1101/2020.01.23.916726v1

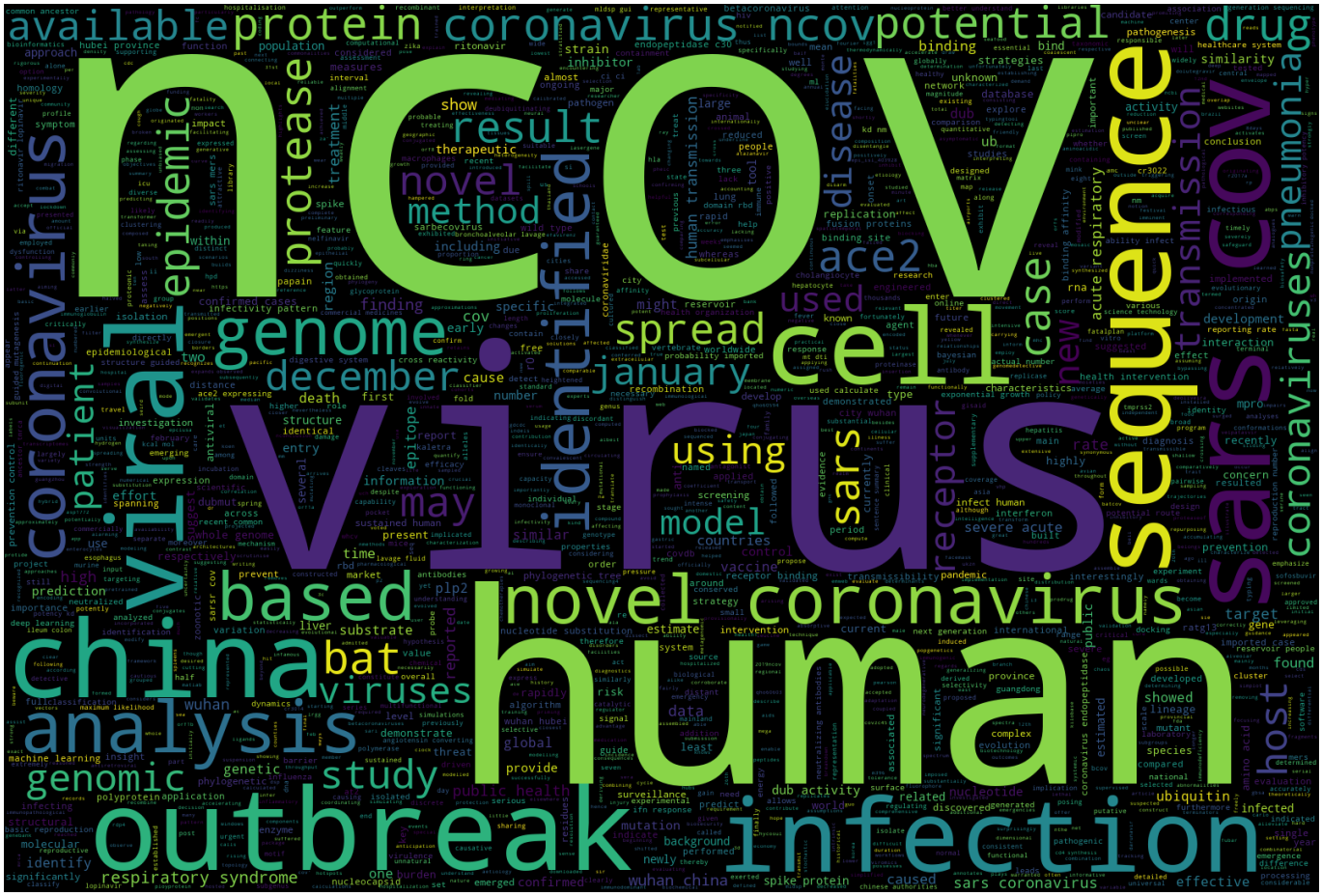
We present a timely evaluation of the Chinese 2019-nCov epidemic in its initial phase, where 2019-nCov demonstrates comparable transmissibility but lower fatality rates than SARS and MERS. A quick diagnosis that leads to case isolation and integrated interventions will have a major impact on its future trend. Nevertheless, as China is facing its Spring Festival travel rush and the epidemic has spread beyond its borders, further investigation on its potential spatiotemporal transmission pattern and novel intervention strategies are warranted.

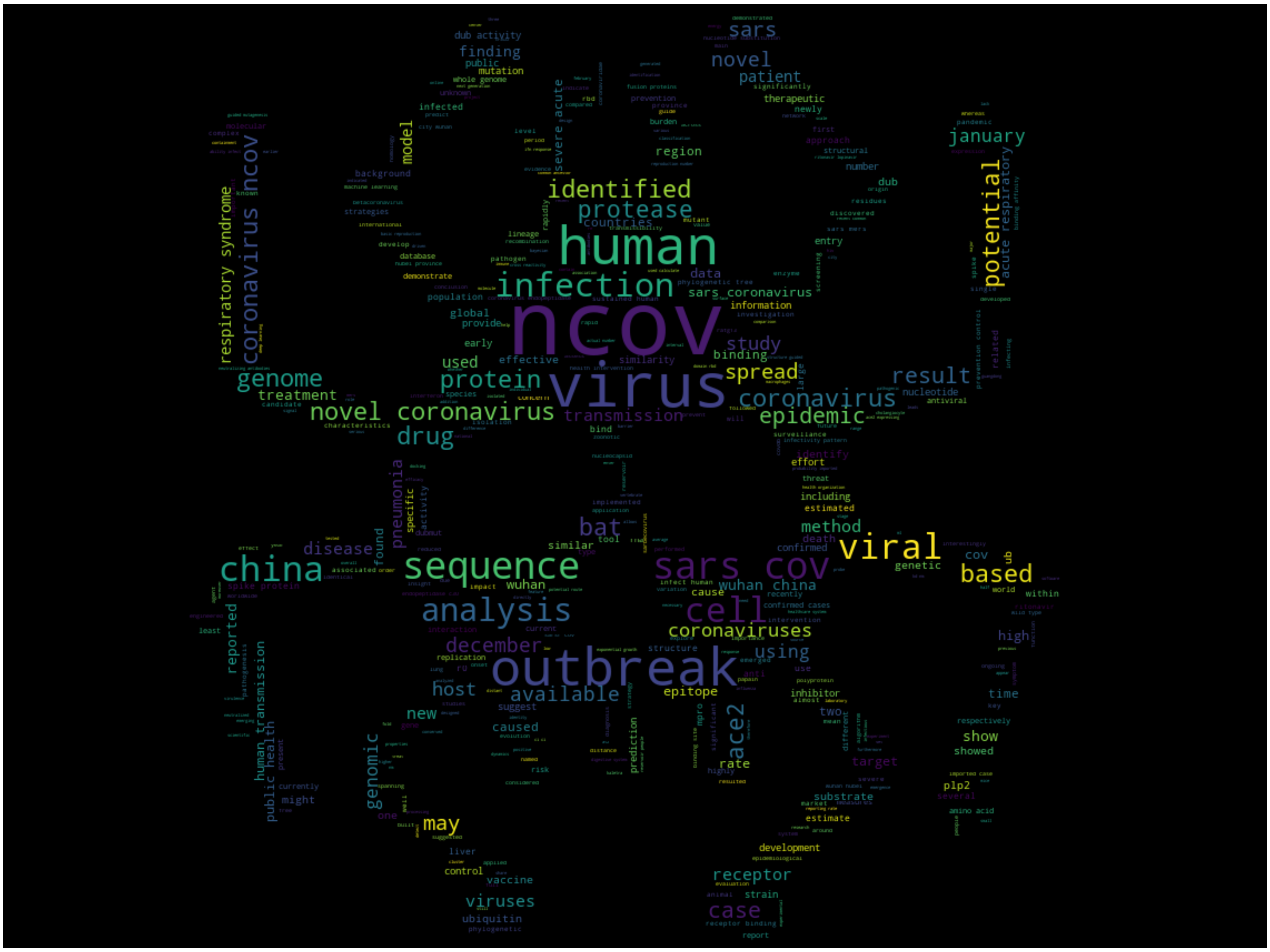
Engineered unnatural ubiquitin for optimal detection of deubiquitinating enzymes

https://www.biorxiv.org/content/10.1101/2020.01.30.926881v1

Deubiquitinating enzymes (DUBs) are responsible for removing ubiquitin (Ub) from its protein conjugates. DUBs have been implicated as attractive therapeutic targets in the treatment of viral diseases, neurodegenerative disorders and cancer. The lack of selective chemical tools for the exploration of these enzymes significantly impairs the determination of their roles in both normal and pathological states. Commercially available fluorogenic substrates are based on the C-terminal Ub motif or contain Ub coupled to a fluorophore (Z-LRGG-AMC, Ub-AMC); therefore, these substrates suffer from lack of selectivity. By using a hybrid combinatorial substrate library (HyCoSuL) and a defined P2 library containing a wide variety of nonproteinogenic amino acids, we established a full substrate specificity profile for two DUBsâ€”MERS PLpro and human UCH-L3. Based on these results, we designed and synthesized Ub-based substrates and activity-based probes (ABPs) containing selected unnatural amino acids located in the C-terminal Ub motif. Biochemical analysis and cell-based experiments confirmed the activity and selectivity of engineered Ub-based substrates and probes. Using this approach, we propose that for any protease that recognizes Ub and Ub-like substrates, a highly active and selective unnatural substrate or probe can be engineered.

Top Words Cloud

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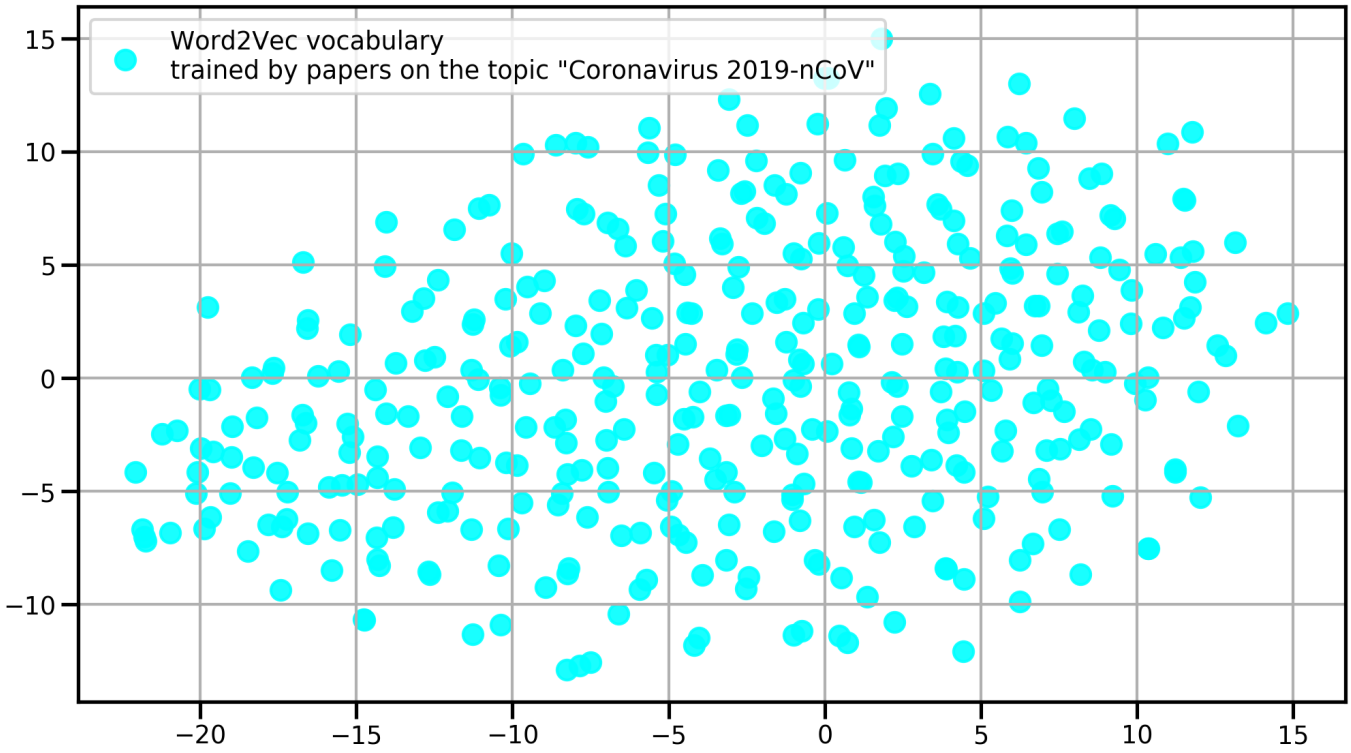
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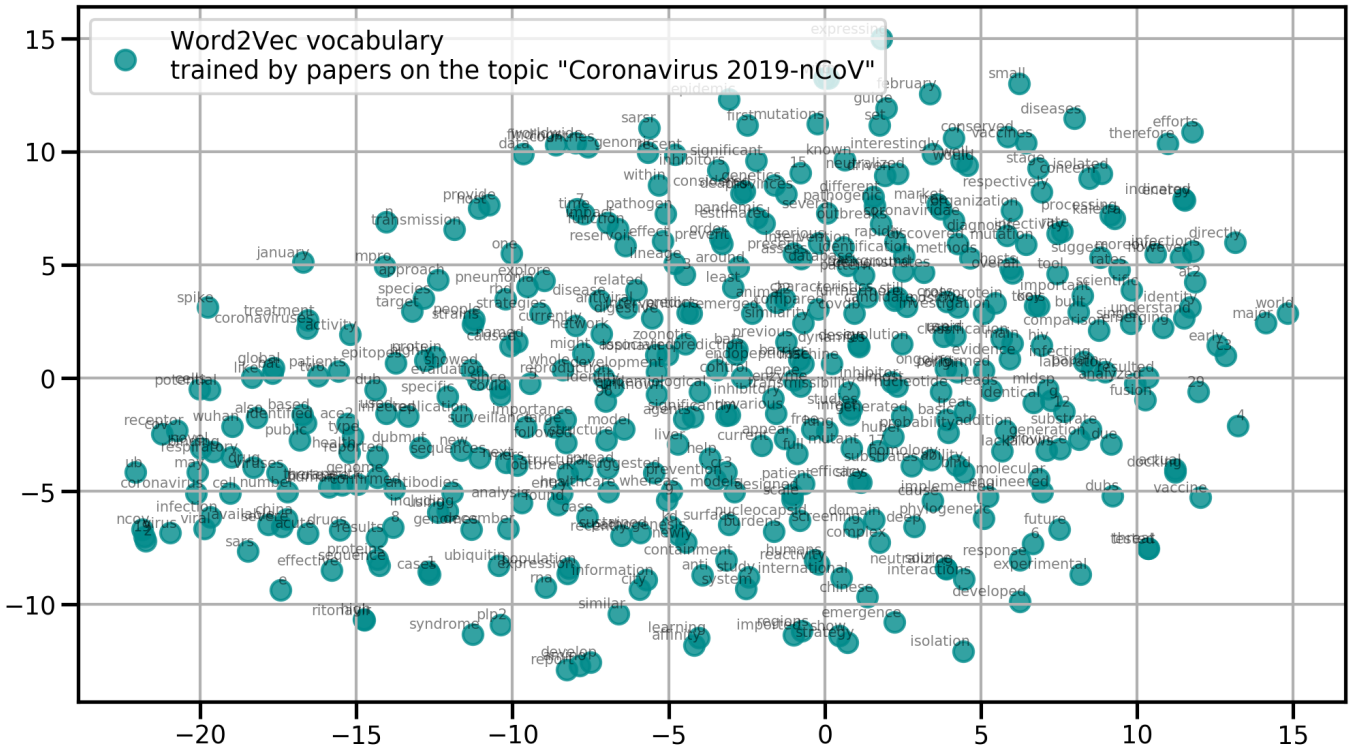
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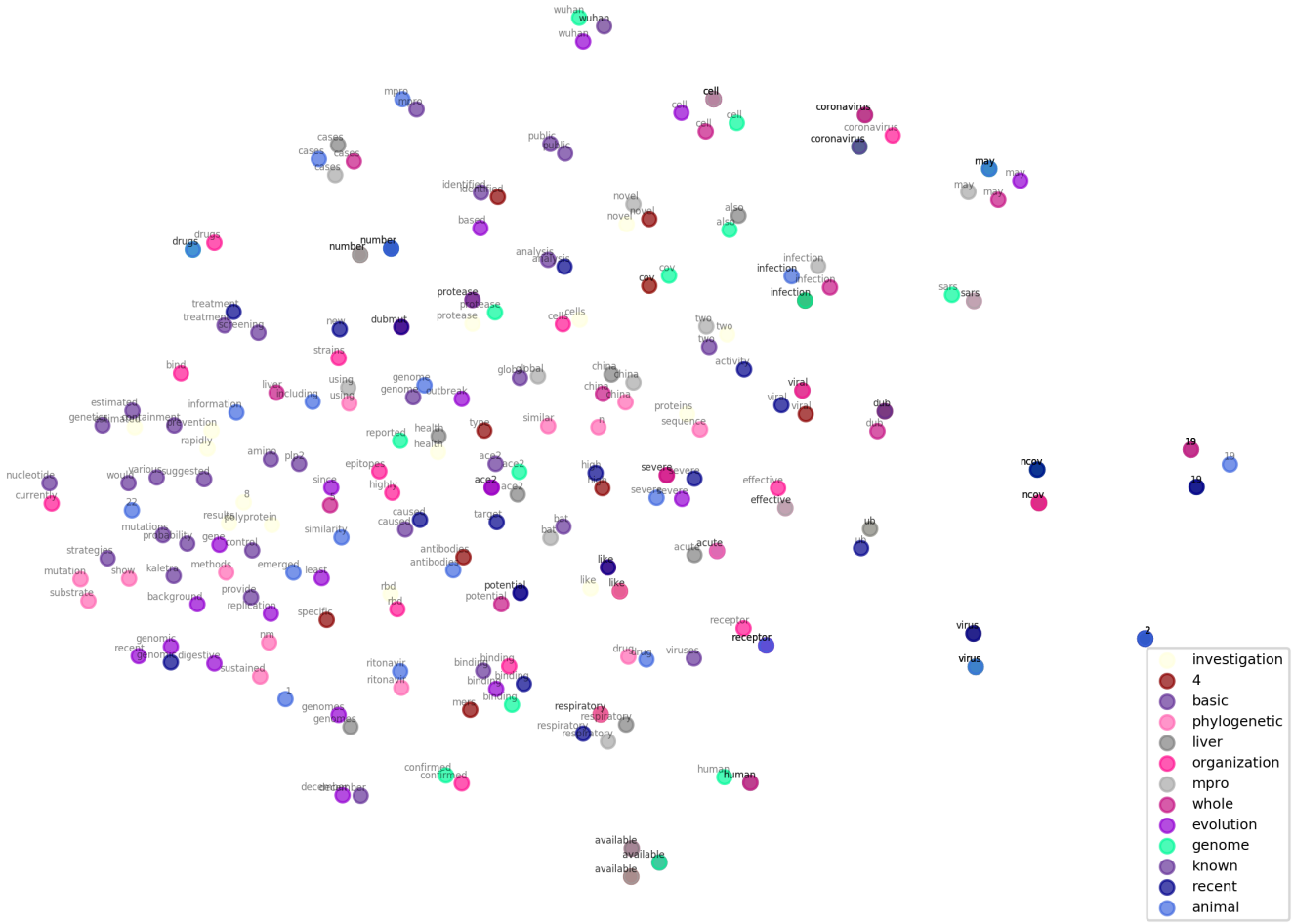
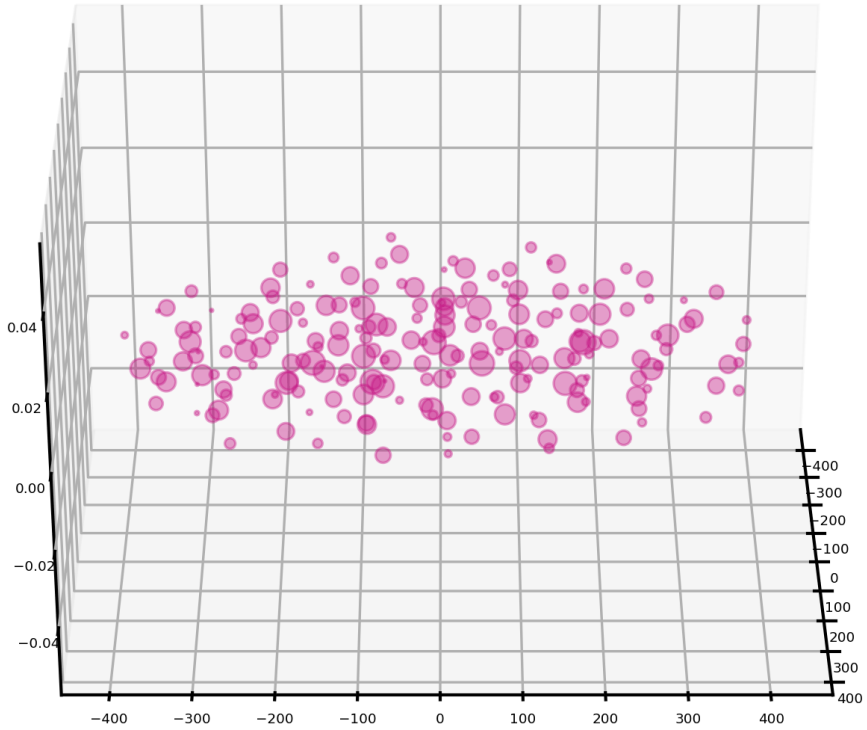


Visualizing Word Embeddings using t-SNE



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