FRONTEO
～COMBAT COVID-19～
⑤探索結果（1）　TOP1阻害剤

FRONTEO AI

Kibit & concept Encoder

MAY. 2020

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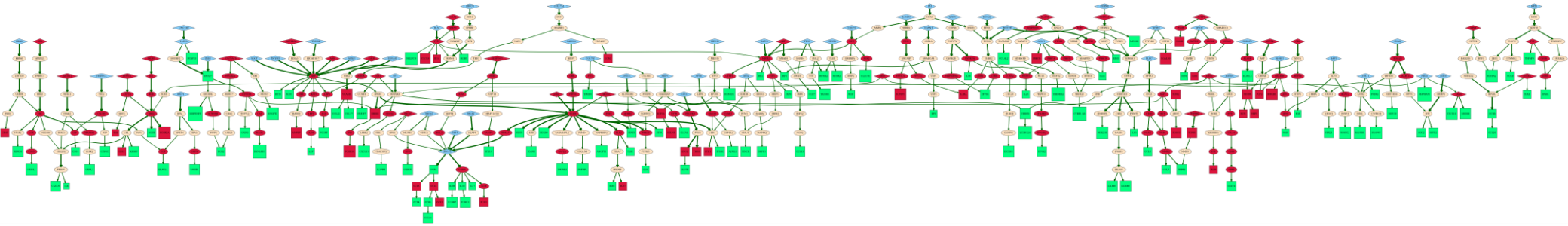
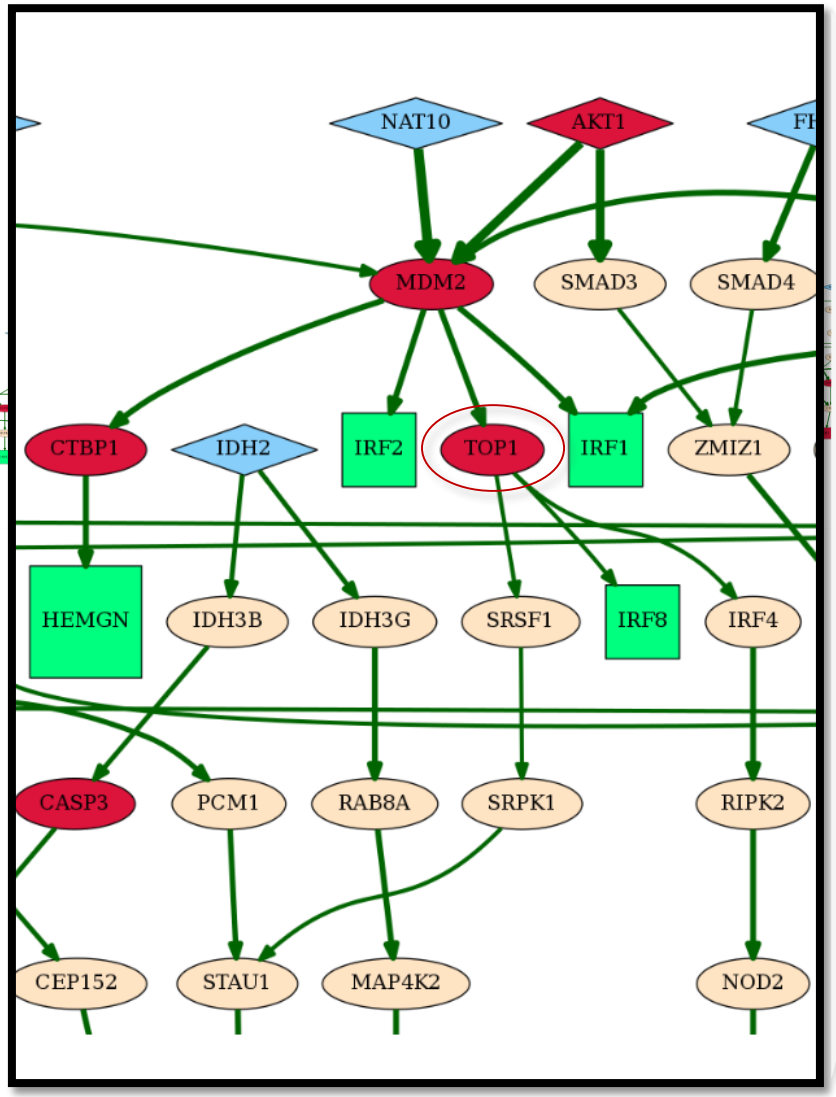
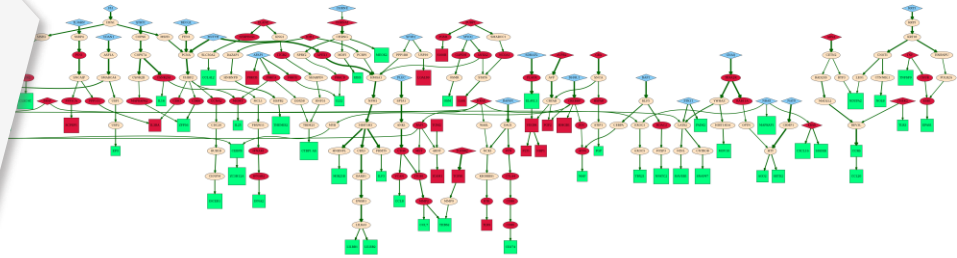
既存薬の標的分子



赤色は、既存の薬もしくはツール化合物
のターゲットになっている分子

既存薬ターゲット　TOP1（トポイソメラーゼ）





TOP1

抗がん剤や抗生物質のターゲットとして知られる分子

TOP1をターゲットとする既存薬

イリノテカン

ルカンソン

エドテカリン

カンプトテシン

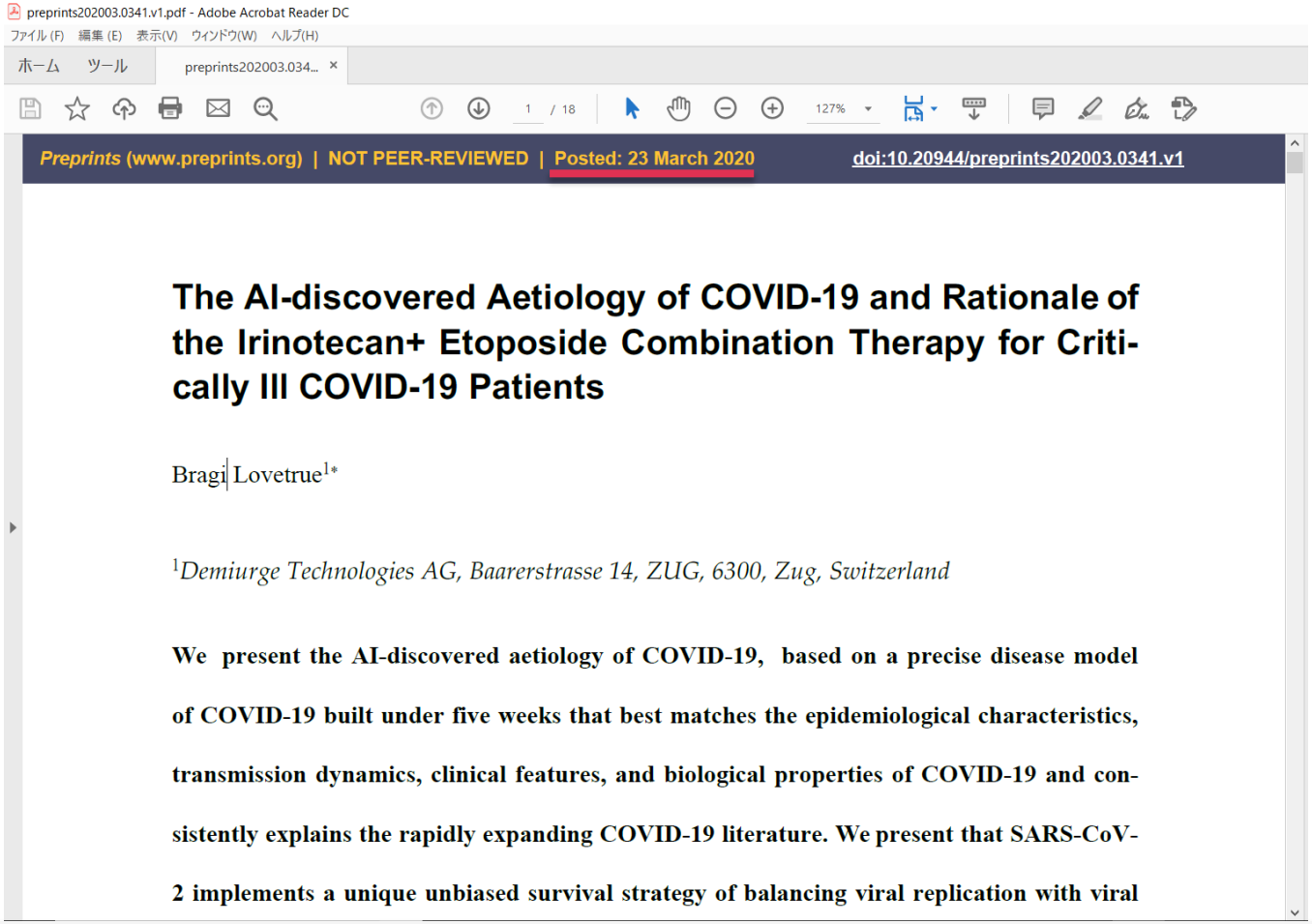
Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation

Science. Author manuscript; available in PMC 2017 May 27

Here, we show that the enzyme topoisomerase 1 (Top1) exerts an activating role on the transcriptional response against infection in cells and at the organismal level. This effect is achieved via Top1-assisted transcriptional activation of proinflammatory genes. We demonstrate that chemical inhibition, as well as reduced expression of Top1, limits the overexpression of inflammatory genes characteristic of infection with influenza and Ebola viruses and bacterial products. Notably, Top1 inhibition rescues mortality in mouse models of lethal inflammation caused by over-exposure to bacterial and viral PAMPs. Our results suggest that Top1 inhibitors offer therapeutic efficacy for the treatment of diseases characterized by exacerbated innate immune responses.

炎症により瀕死のマウスにトポイソメラーゼ1（TOP1）阻害剤を投与したケースに関する論文。
マウスの死亡を回避することができたことから、TOP1阻害剤は炎症作用の抑制に効果的であることがわかっている

AIによる解析根拠：TOP1阻害剤　イリノテカンとは



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The AI-discovered Aetiology of COVID-19 and Rationale of the Irinotecan+ Etoposide Combination Therapy for Critically Ill COVID-19 Patients

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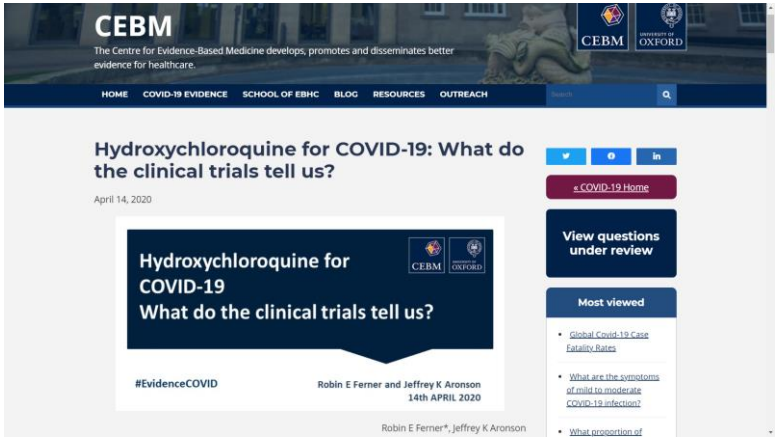
We present the AI-discovered aetiology of COVID-19, based on a precise disease model of COVID-19 built under five weeks that best matches the epidemiological characteristics, transmission dynamics, clinical features, and biological properties of COVID-19 and consistently explains the rapidly expanding COVID-19 literature. We present that SARS-CoV-2 implements a unique unbiased survival strategy of balancing viral replication with viral

他社のAIでも同様の研究結果を発表。
イリノテカンとエトポサイド（TOP2阻害剤）の合剤によるCOVID-19への効果が報告されている。

Lucanthone Is a Novel Inhibitor of Autophagy That Induces Cathepsin D-mediated Apoptosis*

Received for publication, June 3, 2010, and in revised form, November 3, 2010 Published, JBC Papers in Press, December 10, 2010, DOI 10.1074/jbc.M110.151324

Cellular stress induced by nutrient deprivation, hypoxia, and exposure to many chemotherapeutic agents activates an evolutionarily conserved cell survival pathway termed autophagy. This pathway enables cancer cells to undergo self-digestion to generate ATP and other essential biosynthetic molecules to temporarily avoid cell death. Therefore, disruption of autophagy may sensitize cancer cells to cell death and augment chemotherapy-induced apoptosis. Chloroquine and its analog hydroxychloroquine are the only clinically relevant autophagy inhibitors. Because both of these agents induce ocular toxicity, novel inhibitors of autophagy with a better therapeutic index are needed. Here we demonstrate that the small molecule lucanthone inhibits autophagy, induces lysosomal membrane permeabilization, and possesses significantly more potent activity in breast cancer models compared with chloroquine. Exposure to lucanthone resulted in processing and recruitment of microtubule-associated protein 1 light chain 3 (LC3) to autopha-



TOP1の阻害剤でもありながら、オートファジーの阻害剤でもある
同じくオートファジー阻害剤であるクロロキン、ハイドロキシクロロキンと比較されており、COVID-19の臨床で効果が確認されている。また、オートファジーに関してはルカンソンの方が効果が高いといわれている。

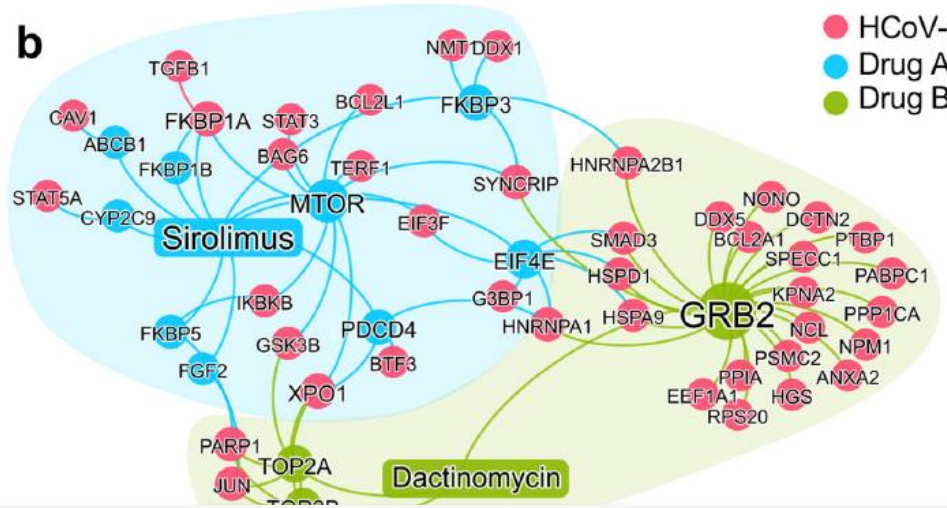
ARTICLE Open Access

Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2

Yadi Zhou[1], Yuan Hou[1], Jiayu Shen[1], Yin Huang[1], William Martin[1] and Feixiong Cheng[1,2,3]

Zhou et al. *Cell Discovery* (2020)6:14
https://doi.org/10.1038/s41421-020-0153-3

Cell Discovery
www.nature.com/celldisc



inhibit both mTOR signaling and RNA synthesis pathway (including DNA topoisomerase 2-alpha (TOP2A) and DNA topoisomerase 2-beta (TOP2B)) in HCoV-infected cells (Fig. 6b).

オートファジーの中心的な分子mTORに関する論文（Cell Discoveryに掲載）。
オートファジー阻害剤がCOVID-19に効果を発揮することが示唆されている。

AIによる解析根拠：他のコロナウイルスに対するトポイソメラーゼ阻害剤の有効性

Medicine & Health Sciences | Emerging Preeminent Program

Researchers target cell's own machinery in fight against COVID-19

By JoAnn Adkins

April 13, 2020 at 1:48pm

In an effort to help stop the spread of COVID-19, a team of researchers is trying to block a key enzyme in the human cell that the virus needs to thrive.

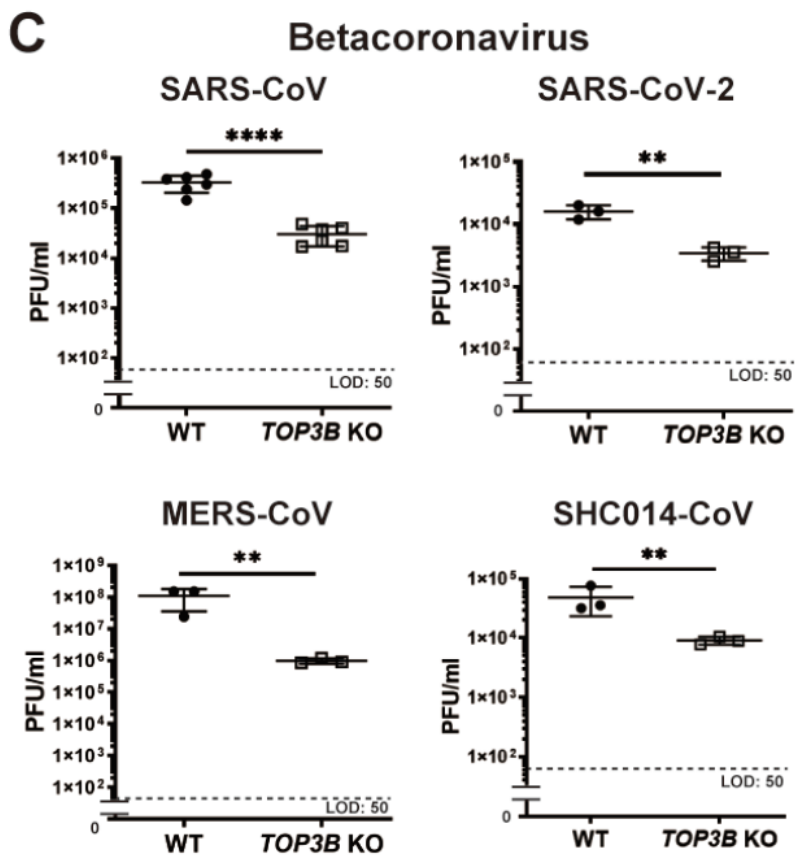
FIU Biomolecular Sciences Institute Director Yuk-Ching Tse-Dinh and Associate Director Prem Chapagain have teamed up with researchers at the University of Texas Medical Branch (UTMB) at Galveston and National Cancer Institute. The team is searching for potential treatment leads, hoping at least one of them will reduce the spread of the virus in infected individuals. Currently there are no evidence-based treatments for COVID-19 or any other coronaviruses.

Last month, Dr. Mariano Garcia-Blanco from UTMB reported in BioRxiv his discovery that coronaviruses rely on the enzyme Topoisomerase III-ß (TOP3B) as a host factor. Normally, topoisomerases aid in DNA replication within human cells. But when certain viruses, including Dengue, Zika and COVID-19, latch on to TOP3B, they use the enzyme to help assemble new copies of the virus, turning infected cells into virus factories.

Upon this discovery, Garcia-Blanco enlisted the help of Tse-Dinh, an internationally known expert in topoisomerases, to start screening for a drug that could block the enzyme and prevent COVID-19 from multiplying in high numbers in a person's body.

"We approached FIU as a place where the best inhibitors can come from," Garcia-Blanco said.

Tse-Dinh is starting with drugs already approved by the Food and Drug Administration because she is looking for a treatment that can be tested quickly on patients.



SARS、MERS等のコロナウイルスに対する実験でTOP3阻害剤が効果があったことが分かっている。

この資料は下記により作成されました。

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