- WHO. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. 2014. http://apps.who.int/iris/rest/ bitstreams/604045/retrieve (accessed Feb 20, 2020)
- Arabi Y, Balkhy H, Hajeer AH. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus 2015; 4: 709
- Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011; 52: 447-56
- Hung IFN, To KKW, Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 2013; **144**: 464-73
- Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211:80-90

- 10 Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 2006; 145: 599-609
- 15 Schoofs T, Klein F, Braunschweig M, et al. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. Science 2016; 352: 997-1001.
- 12 Lu CL, Murakowski DK, Bournazos S, et al. Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 in vivo. Science 2016; 352: 1001-04.
- 13 WHO, Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020. https://www.who. int/docs/default-source/coronaviruse/clinical-management-of-novel-cov. pdf (accessed Feb 20, 2020).
- 14 Clark DR, Jonathan EM, JKB. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; published online Feb 7. https://doi.org/10.1016/S0140-6736(20)30317-2.



(W) COVID-19: combining antiviral and anti-inflammatory treatments

Published Online February 27, 2020 https://doi.org/10.1016/ 51473-3099(20)30132-8 Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms.^{1,2} In our previous Correspondence to The Lancet,3 we described how BenevolentAl's proprietary artificial intelligence (AI)-derived knowledge graph,4 queried by a suite of algorithms, enabled identification of a target and a potential therapeutic against SARS coronavirus 2 (SARS-CoV-2; the causative organism in COVID-19). We identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells (appendix). The drug targets are members of the numb-associated kinase (NAK) family-including AAK1 and GAK-the inhibition of which has been shown to reduce viral infection in vitro.^{5,6} Baricitinib was identified as a NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrinmediated endocytosis. We suggested that this drug could be of use in countering SARS-CoV-2 infections, subject to appropriate clinical testing.

To take this work further in a short timescale, a necessity when dealing with a new human pathogen, we re-examined the affinity and selectivity of all the approved drugs in our knowledge graph to identify those with both antiviral and anti-inflammatory properties. Such drugs are predicted to be of particular importance in the treatment of severe cases of COVID-19, when the host inflammatory response becomes a major cause of lung damage and subsequent mortality. Comparison of the properties of the three best candidates are shown in the table. Baricitinib, fedratinib, and ruxolitinib are potent and selective IAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful antiinflammatories that, as JAK-STAT signalling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon-γ) typically observed in people with COVID-19.2 Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.7 The most significant side-effect seen over 4214 patientyears in the clinical trial programmes used for European Medicines Agency registration was a small increase in upper respiratory tract infections (similar to that observed with methotrexate), but the incidence of serious infections (eg, herpes zoster) over 52 weeks' dosing was small (3.2 per 100 patient-years), and similar to placebo. Use of this agent in patients with COVID-19 over 7-14 days, for example, suggests side-effects would be trivial.

Other AI-algorithm-predicted NAK inhibitors include a combination of the oncology drugs sunitinib and

See Online for appendix

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	400
Affinity and efficacy: K_d or IC_{50} , nM^*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C _{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

See regulatory approval documents for further information on these drugs. K_u =dissociation constant. IC_{so} =half-maximal inhibitory concentration. C_{max} =maximum serum concentration. *All values are IC_{so} except the cell free values for AAK1, GAK, and BIKE; "cell free" values indicate inhibitory activity against purified protein in biochemical assay; "cell" values indicate enzyme-inhibitory activity inside a cell. †In the absence of direct measurements of drug inhibition in cells, the predicted cell affinity and efficacy values are derived from the ratio of each compound for their primary target; for example, for baricitinib, IC_{so} AAK1[cell] = (IC_{so} AK1[cell]/ IC_{so} AK1[cell free]) × IC_{so} AAK1[cell free].

Table: Properties of three antiviral and anti-inflammatory candidate drugs

erlotinib, shown to reduce the infectivity of a wide range of viruses, including hepatitis C virus, dengue virus, Ebola virus, and respiratory syncytial virus. However, sunitinib and erlotinib would be difficult for patients to tolerate at the doses required to inhibit AAK1 and GAK. By contrast, at therapeutic doses used for the treatment of patients with rheumatoid arthritis, the free plasma concentrations of baricitinib are predicted to be sufficient to inhibit AAK1, and potentially GAK, in cell-based assays.

The predicted inhibition of clathrin-mediated endocytosis by baricitinib is unlikely to be observed

with other anti-arthritic drugs or JAK inhibitors. Our analysis of the closely related JAK inhibitors ruxolitinib and fedratinib (table) illustrates that the predicted unbound plasma exposure required to inhibit the enzymes needed for clathrin-mediated endocytosis greatly exceeds the currently tolerated exposures used therapeutically. These drugs are, therefore, unlikely to reduce viral infectivity at tolerated doses, although they might reduce the host inflammatory response through JAK inhibition. Intriquingly, another JAK inhibitor, tofacitinib, shows no detectable inhibition of AAK1. The high affinity of baricitinib for NAKs, its antiinflammatory properties, and its ability to ameliorate associated chronic inflammation in interferonopathies,8 together with its advantageous pharmacokinetic properties, appear to make it a special case among the approved drugs.

In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. Furthermore, there is the potential for combining baricitinib with the direct-acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drugmetabolising enzymes. Combinations of baricitinib with these direct-acting antivirals could reduce viral infectivity, viral replication, and the aberrant host inflammatory response. This work demonstrates that the use of an Al-driven knowledge graph can facilitate rapid drug development.

JS is editor-in-chief of *Oncogene*. JS has previously sat on a number of scientific advisory boards, including BenevolentAl, and consults with Lansdowne partners and Vitruvian; he now sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. All other authors are employees of BenevolentAl. Events in relation to the COVID-19 outbreak are evolving rapidly, and we make our initial thoughts available in this Comment in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or

*Justin Stebbing, Anne Phelan, Ivan Griffin, Catherine Tucker, Olly Oechsle, Dan Smith, Peter Richardson j.stebbing@imperial.ac.uk

Department of Surgery and Cancer, Imperial College London, London W12 0NN, UK (JS); and Benevolent AI, London, UK (AP, IG, CT, OO, DS, PR)

- Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak or coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003; 361: 1767–72.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

Comment

- 3 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395**: 497–506.
- 4 Segler MHS, Preuss M, Waller P. Planning chemical syntheses with deep neural networks and symbolic Al. *Nature* 2018; **555**: 604–10.
- 5 Bekerman E, Neveu G, Shulla A, et al. Anticancer kinase inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects. J Clin Invest 2017; 127: 1338–52.
- Pu S-Y, Xiao F, Schor S, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment.

 Antiviral Res 2018; 155: 67–75.
- 7 European Medicines Agency. Olumiant: summary of product characteristics. https://www.ema.europa.eu/en/documents/productinformation/olumiant-epar-product-information_en.pdf (accessed Feb 24, 2020).
- 8 Sanchez GAM, Reinhardt A, Ramsey S et al., JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018; 128: 3041–52