

PERSPECTIVE

Crippling life support for SARS-CoV-2 and other viruses through synthetic lethality

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With the rapid global spread of SARS-CoV-2, we have become acutely aware of the inadequacies of our ability to respond to viral epidemics. Although disrupting the viral life cycle is critical for limiting viral spread and disease, it has proven challenging to develop targeted and selective therapeutics. Synthetic lethality offers a promising but largely unexploited strategy against infectious viral disease; as viruses infect cells, they abnormally alter the cell state, unwittingly exposing new vulnerabilities in the infected cell. Therefore, we propose that effective therapies can be developed to selectively target the virally reconfigured host cell networks that accompany altered cellular states to cripple the host cell that has been converted into a virus factory, thus disrupting the viral life cycle.

Introduction

Infectious viruses continue to threaten our way of life. For example, every year, seasonal influenza causes 3,000,000 to 5,000,000 cases of severe disease and 290,000 to 650,000 deaths globally (World Health Organization, 2020). Dengue, an enveloped, positive-sense RNA flavivirus, is endemic in more than 100 countries and infects more than 390,000,000 people per year (Bhatt et al., 2013; Messina et al., 2019). In the past five years alone, the RNA viruses Ebola and Zika have caused several widespread epidemics. And at the time of writing, we are in the midst of a devastating global pandemic caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV)-2. The changing world mediated by the interconnected nature of our societies, coupled with environmental changes and human encroachment into natural ecosystems, only serve to magnify the threat.

Most epidemics over the past decade have been caused by RNA viruses, which include the coronaviruses (e.g., SARS-CoV-1, Middle East Respiratory Syndrome [MERS], and SARS-CoV-2), filoviruses (e.g., Ebola), flaviviruses (e.g., dengue, Zika, yellow fever, and West Nile), orthomyxoviruses (e.g., influenza), and paramyxoviruses (e.g., measles and mumps; Table 1; Heaton, 2019). The remarkable evolvability of RNA viruses contributes to their success as infectious agents and their frequent ability to

cross species barriers (Osterhaus, 2001; Carrasco-Hernandez et al., 2017). RNA viruses are prone to recombination and, in some cases such as influenza, reassortment of gene segments, whereby cells infected with two different viral strains can generate a hybrid strain with novel features (Van Poelvoorde et al., 2020). The generation of hybrid strains, coupled with rapid mutational adaptation to new hosts, enables cross-species transmission of lethal variants into naive populations. SARS-CoV-1, MERS, and perhaps SARS-CoV-2 transitioned from bats, which are reservoirs for thousands of coronavirus strains, to humans through an intermediary host, recombining with an endogenous strain of coronavirus of the intermediary host organism (Graham et al., 2013; Menachery et al., 2017; Cui et al., 2019; Boni et al., 2020; Lam et al., 2020; Liu et al., 2020b; Tse et al., 2020; Ye et al., 2020). Influenza is particularly adept at generating new strains and zoonotic transfer by reassortment of its segmented genome, as demonstrated by the flu pandemics of 1918–1919, 1957–1958, and 2009–2011. The avian and swine variants of hemagglutinin and neuraminidase in particular are associated with severe disease (Table 1; Castro et al., 2020; Van Poelvoorde et al., 2020). Most RNA viruses also lack a proof-reading replicative polymerase, leading to increased mutation rates that can drive diversity and the emergence of new serotypes (Bell et al., 2019; Durham et al., 2019) and drug resistance.

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Table 1. RNA virus outbreaks resulting in death from 2000 to 2020

Virus family	Virus	Outbreak	Date	Location	Deaths	Reference
<i>Arenaviridae</i>	Lassa mammarenavirus	Hemorrhagic fever	2000	Germany, The Netherlands, UK, West Africa	4	WHO
			2012	Nigeria	70	WHO
			2015–2016	Benin, Liberia, Nigeria, Togo	193	WHO
			2017–present	Nigeria	246	WHO
<i>Coronaviridae</i>	MERS	MERS	2012–present	Worldwide	862	WHO
	SARS-CoV-1	SARS	2002–2004	Worldwide	774	WHO
	SARS-CoV-2	COVID-19	2019–present	Worldwide	650,000+	WHO
<i>Filoviridae</i>	Ebola	Sudan	2004	Sudan	7	WHO
		Mweka epidemic	2007	DR Congo	187	WHO
		Uganda	2007	Uganda	37	WHO
		West Africa epidemic	2013–16	Worldwide	11,325	CDC/WHO
		Kivu epidemic	2018–present	DR Congo, Uganda	2,262	WHO
<i>Flaviviridae</i>	Chikungunya		2013–15	Americas	1,310+	CDC/WHO
	Dengue	Central America	2000	Central America	37	PAHO/WHO
			2004	Indonesia	658	WHO
			2005	Singapore	27	WHO
			2006	India, Pakistan	91+	WHO
			2006–2007	Philippines	2,307	GOVPH
			2007–2008	Americas	250	PAHO/WHO
				South Asia	1,000+	GOVPH/WHO
			2009	Bolivia	18	PAHO/WHO
			2011	Pakistan	350	WHO
			2013	Lao PDR	92	OCHA
			2016	Americas	1,032	PAHO/WHO
		Peshawar	2017	Pakistan	69	WHO
			2019–present	Asia-Pacific, Americas	3,930+	PAHO/WHO
		Japanese encephalitis	2017	India	1,317	WHO
		Yellow fever	2012	Sudan	171	WHO
			2016	Angola, DR Congo, China, Kenya	100+	WHO
	Zika		2015–16	Worldwide	53	CDC/PAHO/WHO
			2020	Brazil	1	PAHO
<i>Hepeviridae</i>	Hepatitis E	Kitgum District outbreak	2007–2009	Uganda	160	WHO
		Maban County outbreak	2012–2013	Sudan	88	WHO
		Biratnagar	2014	Nepal	9	WHO
			2019	Namibia	56	WHO
<i>Orthomyxoviridae</i>	Influenza	H5N1 “avian” flu	2003–present	Southeast Asia, Egypt	455	WHO
		H1N1/9 “swine” flu	2009–10	Worldwide	151,700–575,400	CDC/WHO
		H7N9 “avian” flu	2013–present	China, Malaysia, Canada	616	FAO
		H1N1 “swine” flu	2015	India	2,035	WHO
		Seasonal	2017–18	USA	45,000–90,000	CDC
<i>Paramyxoviridae</i>	Measles		2010–14	DR Congo	4,500+	WHO
			2013–14	Vietnam	142	WHO
			2019–present	DR Congo	6,400+	WHO

Table 1. RNA virus outbreaks resulting in death from 2000 to 2020 (Continued)

Virus family	Virus	Outbreak	Date	Location	Deaths	Reference
		Pacific Island countries and areas	2019–present	Samoa	83	WHO
	Nipah virus	Outbreak in Kerala	2018	India	17	WHO
<i>Picornaviridae</i>	Hepatitis A	Multistate outbreak in USA	2016–present	USA	332	CDC

CDC, Centers for Disease Control and Prevention; DR Congo, Democratic Republic of the Congo; FAO, Food and Agriculture Organization of the United States; GOVPH, Philippines Department of Health; Lao PDR, Lao People's Democratic Republic; OCHA, United Nations Office for the Coordination of Humanitarian Affairs; PAHO, Pan American Health Organization; UK, United Kingdom; USA, United States of America.

Interestingly, coronaviruses have an alternative error-correction mechanism encoded in nonstructural protein 14, which may help explain the relatively low mutation rate of SARS-CoV-2 (Denison et al., 2011; Ferron et al., 2018; Wang et al., 2020a).

The diversity, adaptability, and evolutionary dynamics of RNA viruses are subject to selective pressures associated with ecosystem changes, stability, infection, transmission, and host susceptibility (Pontremoli et al., 2016) and can present formidable challenges for vaccine development and the utility of broadly effective drugs. Despite decades of effort, there is still no universal vaccine against influenza. The vaccine to seasonal influenza must be updated annually to stay current with the antigenic drift of the virus (Castro et al., 2020). For dengue, achieving vaccine efficacy has been hampered by the presence of four different serotypes. Dengue is notorious for using host immunity to its advantage in a process termed antibody-dependent enhancement (Halstead and O'Rourke, 1977; Peiris and Porterfield, 1979) in which antibodies to one serotype can bind weakly to a different serotype to mediate widespread viral uptake through Fc receptors, raising the risk of severe disease including hemorrhagic fever, shock syndrome, and death (Pierson and Diamond, 2020). This effect can also occur between different flavivirus species, as shown for enhancement of Zika virus infections by prior dengue virus infection in some circumstances (Rodriguez-Barraquer et al., 2019; Whitehead and Pierson, 2019). While concerns about similar antibody-dependent enhancement effects have been raised for SARS-CoV-1 (Jaume et al., 2011; Wang et al., 2016) and SARS-CoV-2 (Eroshenko et al., 2020), perhaps more serious are concerns of the variable magnitude, durability, and protective capacity of the immune response. For seasonal coronaviruses, and possibly SARS-CoV-2, the nature of immunity can be short-lived and insufficient to prevent new infection (Alshukairi et al., 2016; Hamre and Beem, 1972; Isaacs et al., 1983; Long et al., 2020; Mo et al., 2006). Collectively, these uncertainties underscore the need for new approaches to rapidly discover and deploy new antiviral small molecule therapeutics.

Virus-directed therapeutics

Antiviral drugs complement vaccines, and have the potential advantage of rapid deployment during an outbreak. Most current antivirals directly inhibit virus-encoded enzymes that are essential for infection and/or replication. The largest class of

antiviral drugs is nucleoside analogues and nonnucleoside inhibitors that target viral replicative polymerases, whether RNA-dependent RNA polymerases or reverse transcriptases (De Clercq, 2009; Hoofnagle, 2012). Remdesivir is a nucleoside triphosphate analogue that has broad-spectrum activities against RNA viruses such as Ebola, MERS, and SARS-CoV-1 in cell culture and animal models. It has recently been shown to shorten the recovery time of hospitalized COVID-19 patients (Beigel et al., 2020; Ferner and Aronson, 2020; Li and De Clercq, 2020; Scavone et al., 2020). Protease inhibitors form a second major category and prevent the processing of viral polyproteins by virus-encoded proteases (Hoofnagle, 2012; Agbowuro et al., 2018). Although there are no clinically approved inhibitors of coronavirus-encoded proteases, pre-clinical inhibitors active against the main protease of SARS-CoV-1 nonstructural protein 5 (nsp5, also called M^{pro} or 3CL^{pro}) have been reported (Yang et al., 2005). Other viral enzymatic functions that have been successfully targeted include integrases, ion channels, and cap-dependent endonuclease activities (De Clercq, 2009; Hayden et al., 2018; Hoofnagle, 2012; Ison et al., 2020). Non-enzymatic functions can also be interdicted, for example by binding viral entry factors or disrupting RNA-based activities that can affect viral RNA replication and virion assembly (Liu et al., 2015).

Drug discovery in the wake of SARS-CoV-2 includes screening small molecule libraries (Riva et al., 2020; Zhou et al., 2020), machine learning-aided computational drug design approaches (Wang, 2020), and/or concerted medicinal chemistry efforts against various virus-encoded targets (Ghosh et al., 2020). Such targets include the nsp5 protease (Dai et al., 2020; Freitas et al., 2020; Jin et al., 2020a,b; Ma et al., 2020; Rut et al., 2020; Ton et al., 2020; Zhang et al., 2020), RNA-dependent RNA polymerase (Hillen et al., 2020; Wang et al., 2020b; Yin et al., 2020), exo- and endoribonucleases (Kim et al., 2020), and RNA cap nucleotide methyltransferases (Viswanathan et al., 2020). The interaction between spike and angiotensin converting enzyme 2 (ACE2) is a top priority nonenzymatic target (Lan et al., 2020; Monteil et al., 2020; Walls et al., 2020; Yan et al., 2020). Candidate molecules for therapeutic and/or prophylactic use include decoy fragments of ACE2 (Monteil et al., 2020), convalescent sera (Casadevall and Pirofski, 2020; Casadevall et al., 2020), monoclonal antibodies cloned from COVID-19 patients (Liu et al., 2020a; Pinto et al., 2020; Robbani et al., 2020; Rogers et al., 2020; Seydoux et al., 2020) and nanobodies, single-domain antibody fragments derived from the variable heavy domain

region of an IgG subclass of camelid antibodies (Fridy et al., 2014; Huo et al., 2020; Wrapp et al., 2020; Wu et al., 2020). Discovery of inhibitors of SARS-CoV-2-encoded targets is enabled by a wealth of x-ray crystallography and cryo-EM structural data that has become available since January 2020 with a protein structure determined for over half of the SARS-CoV-2 proteins or one of their constituent domains (Ghosh et al., 2020; Zhou et al., 2020).

Most antiviral drugs are developed in a virus-specific fashion and tend to be only marginally effective as monotherapies, in part because it is difficult to fully inhibit viral replication in patients due to dose-limiting toxicity (Jefferson et al., 2014) and in part because of the rapid emergence of resistance (Van Poelvoorde et al., 2020). An effective strategy to overcome these hurdles is to combine multiple drugs against different viral targets, with highly active antiretroviral combination therapies against human immunodeficiency virus (HIV) and hepatitis C virus being successful examples (Hofmann et al., 2009). Unfortunately, the antiviral drug combinations can only be explored after long-term development against multiple targets encoded by a particular pathogen. The difficulties inherent to antiviral drug development are underscored by a stark statistic: while there are currently 214 RNA viruses known to infect humans, U.S. Food and Drug Administration-approved antiviral therapeutics exist for only eight of these pathogens (Chaudhuri et al., 2018; Heaton, 2019; Woolhouse and Brierley, 2018).

Identifying host cell dependencies

As obligate pathogens, viruses require the host machinery for replication and propagation. Viruses exploit various host cell functions, including natural host receptors, endocytic machinery, organellar compartments, primary metabolism, RNA and protein synthesis, protein homeostasis, membrane biogenesis, and the endomembrane secretory system, among other functions. Viruses may also interdict innate antiviral responses, block host cell proliferation, and suppress cell death. Given the reliance on a myriad of host processes, host-based targets dramatically increase the potential search space for antiviral compounds.

Host genes in virally infected cells on which the virus is dependent are termed host-dependency factors and can be revealed as host-virus genetic interactions. Systematic loss-of-function genetic screens identify two main classes of genes that affect viral replication. The first class contains host genes that a virus needs to initiate and complete its life cycle, termed proviral genes because loss of function renders the host cell resistant to infection. The second class encompasses genes that have antiviral activity because loss of function sensitizes cells to the effects of infection. Antiviral gene function may be direct, such as for innate immunity genes, or may indirectly buffer and suppress the adverse effects of infection, for instance ER chaperones that help the host cell cope with the massive secretory flux imposed during virion biogenesis (Table 2). Loss of direct-acting antiviral genes increases viral replication and enhances infectivity, whereas loss of indirect-acting genes increases susceptibility to host cell death and may limit infectivity. These indirect antiviral functions manifest as synthetic lethality, as will be discussed.

Early RNAi screens hinted at the promise of genetic approaches to understand host dependencies (Krishnan et al., 2008) but were plagued by high false-positive and false-negative rates (Chung et al., 2014; Hart et al., 2014; Mohr et al., 2010). With the advent of genome-wide CRISPR knockout screens using complex pooled gRNA libraries that efficiently target every human gene, system-level interrogation of virus-host cell dependencies has the potential to define broad and virus-specific host genetic dependencies (Hart et al., 2015; Wang et al., 2015).

To date, most genome-wide CRISPR screens have been performed in a positive selection format that allows recovery only of gene knockouts that prevent the cytopathic effect and cell death caused by viral infection (Table 2). Phenotypic screens for noncytolytic viruses that employ sorting strategies to enrich for factors that enhance or inhibit persistence have also been performed (Puschnik et al., 2017). While screens revealed some common host pathways that mediate infection, many differences between viruses are evident. In addition, CRISPR screens with the same virus in different cell lines reveal cell type-specific dependencies (Table 2; Li et al., 2019; Savidis et al., 2016). Initial results from a genome-wide CRISPR screen for pro- and antiviral host genes for SARS-CoV-2 identified components of the TGF- β signaling pathway, the switch/sucrose nonfermenting chromatin remodeling complex, histone demethylases, ACE2, and the cathepsin L protease as proviral (Table 2; Wei et al., 2020). Antiviral host genes include components of the histone H3.3 chaperone complex, nucleosome remodeling factor complex, transcription factor IIH complex, and small nuclear ribonucleoprotein chaperone complex (Table 2; Wei et al., 2020). Further systematic identification of host-coronavirus genetic interactions in relevant human cell types will almost certainly yield a plethora of new candidate antiviral targets for SARS-CoV-2.

Host-directed antivirals

Several host-based antiviral therapeutics have been developed that modulate the host immune response (Kaufmann et al., 2018), and in doing so aim to dampen virus-induced pathology and buy the immune system time to mount a strong antiviral response. For example, imiquimod activates the toll-like receptor TLR7 during human papilloma virus infection to activate the host innate immune response through production of the cytokines IFN- α , interleukins 1 and 6, and TNF- α (Bilu and Sauder, 2003; Kaufmann et al., 2018). In another example, the retinoic acid derivative acitretin stimulates the cytosolic pattern recognition receptor, RIG-I, in cells with reactivated latent HIV, thereby inducing an IFN response, triggering apoptosis and depletion of the viral reservoir (Kaufmann et al., 2018; Li et al., 2016). Dexamethasone, a glucocorticoid receptor agonist with anti-inflammatory and immunosuppressant effects, reduced mortality for COVID-19 patients receiving invasive mechanical ventilation or oxygen support (Horby et al., 2020). Potential host-directed, immune-modulating antivirals that may be repurposed against SARS-CoV-2 also include acitretin, the C-C chemokine receptor type 1 antagonist MLN-3897, and apilimod (Gordon et al., 2020a; Riva et al., 2020). However, nonspecific

Table 2. CRISPR screens identify host dependency factors of viruses

RNA/DNA virus	Family, genus	Virus	Host factor genes	Host processes	References
RNA	<i>Flaviviridae</i> , <i>Flavivirus</i>	West Nile	EMC2, EMC3, SEL1L, DERL2, UBE2G2, UBE2J1, HRD1, STT3A, SEC63, SPCS1, SPC3	ERAD, endoplasmic reticulum-associated signal peptidase complex (SPCS)	(Ma et al., 2015); (Zhang et al., 2016)
	<i>Flaviviridae</i> , <i>Flavivirus</i>	Dengue	STT3A, STT3B, OSTC, EMC2, EMC4, EMC3, SSR1, SSR2, SSR3, SEC61A1, OST4, MAGT1	ERAD, SPCS, OST	(Marceau et al., 2016); (Lin et al., 2017)
	<i>Flaviviridae</i> , <i>Flavivirus</i>	Yellow fever	IFI6, IFNAR1, IFNAR2, IRF9, TYK2, JAK1, STAT2, PCBP1, ECD, SNRPF, PCF11, SNRPD1, HSPA5	IFN-stimulated genes (ISG)/IFN pathway, RNA processing	(Richardson et al., 2018)
	<i>Flaviviridae</i> , <i>Flavivirus</i>	Zika	AXL, EMC1, EMC2, EMC3, SSR3, RABGEF1, MMGT1	Viral entry, ERAD, SPCS, endocytosis	(Savidis et al., 2016); (Li et al., 2019)
	<i>Flaviviridae</i> , <i>Hepacivirus</i>	Hepatitis C	CD81, CLDN1, OCLN, MIR122, PPIA, RFK, FLAD ELAVL1, SSRD	Viral entry, RNA-binding proteins/ mRNA stabilization, FAD metabolism, peptidyl-prolyl isomerase	(Marceau et al., 2016)
	<i>Filoviridae</i> , <i>Ebolavirus</i>	Zaire Ebola	NPC1, SPNS1, SLC30A1, VPS16, VPS18, VPS33A, KLHDC3, STARD13, GNPTAB	Viral entry, lysosomal transport, multisubunit tethering complexes (MTCs) in the endolysosomal pathway (HOPS complex)	(Flint et al., 2019)
	<i>Caliciviridae</i> , <i>Norovirus</i>	Murine norovirus	CD300lf, CD300ld	Viral entry	(Orchard et al., 2016); (Haga et al., 2016)
	<i>Picornaviridae</i> , <i>Enterovirus</i>	Rhinovirus	SETD3, PLA2G16, CSDE1	ISG/IFN pathway, viral entry, translation (IRES)	(Diep et al., 2019)
	<i>Picornaviridae</i> , <i>Hepatovirus</i>	Hepatitis A	GNE, CMAS, SLC35A1, UGCG, ST3GAL5, VPS4A, UFM1, UBA5, UFL1, UFC1, UFSP2, PAPD5, PAPD7, ZCCHC14, PTBP1, EIF4B, EIF3C, EIF3CL	Sialic acid and ganglioside biosynthesis, translation initiation, IRES-mediated translation, endosomal sorting (ESCRT), Trf4/5-Air1/2-Mtr4 polyadenylation (TRAMP) complex, UFMylation, polyadenylation	(Kulsuptrakul et al., 2020)
	<i>Orthomyxoviridae</i> , <i>Alphainfluenzavirus</i>	Influenza A	SLC35A1, WDR7, EXOC4, VHL, TMEM38A, ATP6AP1 DPAGT1, cap methyltransferase 1 (CMTR1), SRP19,	Sialic acid biosynthesis and transport, N-glycan biosynthesis, UPS, v-type-ATPase, RNA processing, protein export	(Han et al., 2018); (Li et al., 2020)
	<i>Coronaviridae</i> , <i>Betacoronavirus</i>	SARS-CoV-2	ACE2, CTSL, switch/sucrose nonfermenting-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (SMARCA4), ARID1A, SMARCE1, KDM6A, DYRK1A, UBXN7, small body size/ mothers against the decapentaplegic 4 (SMAD4), HMGB1-like; HIRA ^a , CABIN ^a , ASF1A ^a	Viral entry and processing, chromatin remodeling, histone methylation, UPS, TGF- β signaling, alarmin	(Wei et al., 2020)
RNA, retrovirus	<i>Retroviridae</i> , <i>Lentivirus</i>	HIV	CD4, CCR5, TPST2, SLC35B2, ALCAM, myc-induced nuclear antigen 53 (MINA53) ^a	Viral entry, post-translational modification (sulfation), cell-cell adhesion, histone modification, latency	(Park et al., 2017); (Huang et al., 2019)
DNA	<i>Hepadnaviridae</i> , <i>Orthohepadnavirus</i>	Hepatitis B	ZCCHC14, (PAPD5, PAPD7), NXT1, ENY2, DCAF7 ^a , UBE2J1 ^a , UBE2J2 ^a , RNF139 ^a	Polyadenylation, nuclear export, UPS	(Hyrina et al., 2019)
	<i>Herpesviridae</i> , <i>Lymphocryptovirus</i>	Epstein-Barr	CD19 ^b , CD81 ^b , IRF2 ^b , IRF4 ^b , SYK ^b , BATF ^b , CFLAR ^b , RBPJ ^b , RelA ^b , RNF31 ^b , CCND2 ^b , CDK6 ^b , CDK4 ^c , CCND3 ^c , BCL6 ^c	Cell cycle, LMP1/LMP2a signaling, PI3K/AKT signaling, tumor suppression pathways	(Ma et al., 2017)

Genes listed are proviral unless annotated as antiviral (^a) genes. Screens for Epstein-Barr virus were performed in lymphoblastoid (^b) or Burkitt lymphoma (^c) cell lines.

immune modulators can lead to unintended side effects. A key to solving this problem may lie in targeting attributes of the viral-infected cell that are not shared with the uninfected cell and exploiting these features for therapeutic intervention.

Virus-induced vulnerability

As viruses infect cells, they execute control programs and hijack the host machinery to serve the viruses' goal of producing thousands of virions. They do so by using a relatively small number of precise control elements to subvert host cell functions (Ravindran et al., 2019). With a compact but highly adaptable toolset at their disposal, viruses continuously evolve to redirect the function of hundreds of host molecules to optimize viral fitness, thus rewiring the host cell. These radical changes create a novel genetic architecture that is specific to the virus-infected state (Gulbahce et al., 2012).

Rewiring cellular functions by virus-host protein-protein interactions involves co-opting so-called "driver" or "control" nodes that have greater influence on the host network function (Liu et al., 2011; Ravindran et al., 2019). These interactions can inhibit existing functions, redirect host proteins to other locations, or generate new targets and functionalities, which may lead to other downstream network effects. Because viruses depend on these host functions usurped by protein-protein interactions, targeting the interfaces between virus and host proteins directly has been proposed as a mechanism to inhibit the viral life cycle (Basler et al., 2019; Carpp et al., 2014; Gordon et al., 2020a; Heaton, 2019; Luo et al., 2016). However, we propose that the susceptible state induced by these interactions may be best targeted by chemically exploiting the genetic concept of synthetic lethality.

Synthetic lethality

Genetic interactions, typically observed by the synthetic combination of loss of function alleles in two genes, expose the functional organization of a cell and are broadly classified as either positive or negative (Costanzo et al., 2019). Negative genetic interactions reveals functional dependencies within cells and result when the combination of loss-of-function alleles in the same cell leads to a greater than multiplicative phenotype, the extreme form of which is synthetic lethality (Hartwell et al., 1997; Costanzo et al., 2019). Synthetic suppression, a type of positive genetic interaction, occurs when the combination results in a less severe phenotype than either of the single mutant alleles. Cell viability or growth is commonly used as a readout for genetic interactions, but any quantitative phenotype can be used to detect genetic interactions. The nonlinear interaction of two mutant alleles that results in synthetic lethality often reflects the genetic buffering that is inherent to biological systems: loss or reduction in functionality of either gene is not strongly deleterious due to genetic redundancy, but loss of both functions causes inviability (Fig. 1). Systematic genetic screens in the budding yeast *Saccharomyces cerevisiae* have revealed nearly 1,000,000 binary synthetic lethal and synthetic suppressive relationships, which far exceeds the approximately 1,000 single essential genes in this organism (Costanzo et al., 2019). At the molecular level, synthetic lethality can reflect the operation of

two parallel pathways that perform the same function, the redundant contribution of nonessential subunits to essential protein complexes, or damage prevention-response relationships (Bader et al., 2003). For example, in yeast, the essential nuclear pore complex can often survive the removal of one but usually not two nonessential subunits (Fabre and Hurt, 1997; Kim et al., 2018).

The phenomenon of synthetic lethality can be exploited to target specific disease states. For example, synthetic lethal drug-gene mutation interactions have been identified that exploit the genetic vulnerabilities of cancer cells (Fig. 1; Ashworth et al., 2011; Hartwell et al., 1997; Kaelin, 2005; Mendes-Pereira et al., 2009; Turner et al., 2008; Wiltshire et al., 2010). In a paradigm-shifting example, cells bearing mutations in the breast cancer type 1 susceptibility gene BRCA1 were found to rely on an alternative poly-ADP ribose polymerase pathway for homologous recombination, and hence to be exquisitely sensitive to poly-ADP ribose polymerase inhibitors (Lord and Ashworth, 2017). Numerous other examples of genetic vulnerabilities have been identified in cancer and other disease states (Huang et al., 2020; Mair et al., 2019), and this concept is readily extended to infectious disease (Mast et al., 2014; Tyers and Wright, 2019).

Viruses are dependent on the redundancies present within the host cell that allow it to survive for enough time to produce new virions despite infection. These redundancies may be targeted using the principle of synthetic lethality (Fig. 1). Applying the principle of synthetic lethality to viral infection requires identifying the viral-induced vulnerabilities and then targeting the redundancy and buffering capacity of cells in the infected state, thus killing or crippling both the host cell and the virus. Systems biology approaches, such as comprehensive identification and characterization of host-pathogen interactions, offer an unprecedented opportunity to exploit host vulnerabilities after sensitization by the virus (Eckhardt et al., 2020). With comprehensive functional system maps (Krogan et al., 2015; Mast et al., 2014), it may be possible to identify drug targets whose modulation kills or otherwise disrupts infected cells selectively during viral infection. The existing protein-protein interaction network (PPI) and drug repurposing data already provide ample resources for screening for potential synthetic lethal drug and gene candidates (Gordon et al., 2020a; Zhou et al., 2020). Below we discuss strategies to uncover viral-induced vulnerabilities and how to exploit these vulnerabilities for antiviral therapeutics.

Exploiting known virus biology

The accumulated wealth of information on functional interaction of viruses with host cells provides a rich source of candidate host processes that might be targeted in a synthetic lethal strategy. Many of the genes required for these processes are not strictly essential in the host cell and thus present viable therapeutic windows, particularly for chemical inhibitors that have passed safety criteria in human clinical trials for other indications. A nonexhaustive list of examples follows.

Virus-induced proteolysis. Many viruses target host proteins for degradation either directly or indirectly by usurping the

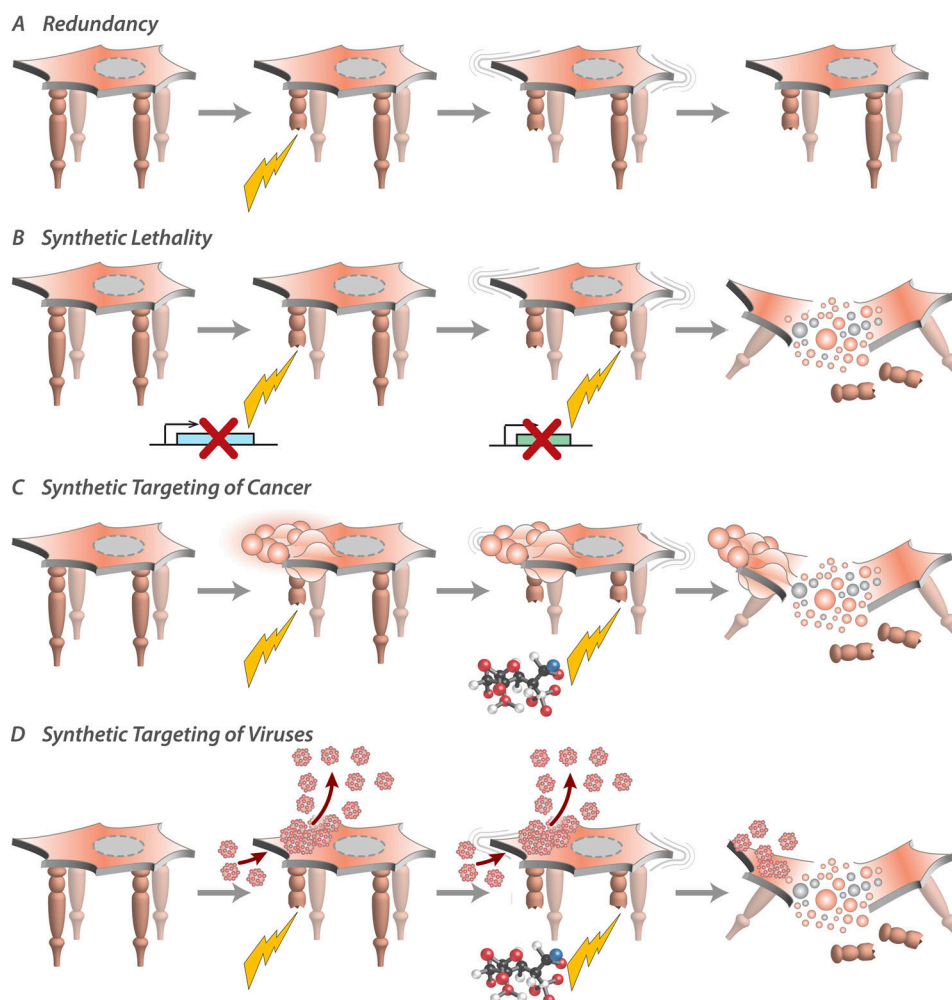


Figure 1. Synthetic lethality. We use the analogy of a table being supported by four legs to illustrate the concept of synthetic lethality and its application to druggable targets. **(A)** Redundancy is a normal feature of cells, which have many redundant systems (the legs of the table) that continue to support viability, even in the event of inhibition or removal of one system (lightning bolt truncating one leg). **(B)** Synthetic lethality in a classic genetic system is where disruption of one gene (lightning bolt truncating one leg) does not kill the cell as other redundant systems (legs) take over, but removal of any of those other systems (lightning bolt truncating another leg) leads to lethality (collapse and breakage of the table). **(C)** Synthetic targeting of cancer is a variant of the classic situation, where, in this case, oncogenic changes (blebbing) alter the cell's networks to such an extent as to effectively alter one system (lightning bolt truncating one leg), such that a drug that targets a redundant system (molecule with lightning bolt truncating another leg), whose inhibition would not normally kill a cell, now leads to lethality specifically of that cancer cell. **(D)** Synthetic targeting of viruses is a variant of synthetic lethality, where viral infection alters the infected cell (lightning bolt truncating one leg) to expose new vulnerabilities that can be targeted (molecule with lightning bolt truncating another leg) to cripple the host cell virus factory.

host's degradation machinery. Enteroviruses are known to target host cell proteins with viral proteases (Laitinen et al., 2016; Lamphear et al., 1993; Lloyd, 2016). As an example, coxsackievirus 2A, a viral-encoded protease, cleaves translation initiation factor 4G and the poly-A binding protein (Lamphear et al., 1993). The depletion of these two proteins in virus-infected cells results in shutting down cap-dependent translation by preventing engagement of the messenger ribonucleoprotein to the small ribosomal subunit (Laitinen et al., 2016; Lloyd, 2016). Because enteroviruses use cap-independent translation, the translation machinery shifts to viral transcripts. In another example, coxsackievirus B3, viral-encoded protease, cleaves dystrophin, a protein whose disruption leads to cardiomyopathies, demonstrating the resulting phenotypic consequences of viral proteolysis (Badorff et al., 2000). SARS-CoV-2 nsp5 interacts with

histone deacetylase 2 and tRNA methyltransferase 1, which have putative nsp5-specific cleavage sites (Gordon et al., 2020a). Degradation of histone deacetylase 2 might suppress host inflammatory and immune signaling responses (Comalada et al., 2010; Guise et al., 2013; Roger et al., 2011), while loss of tRNA methyltransferase 1 may impair host-protein translation and redox homeostasis (Dewe et al., 2017). Loss of either protein would sensitize SARS-CoV-2-infected cells to drugs targeting their synthetic lethal partners.

In addition, the ubiquitin proteasome system is exploited by some viruses to deplete host proteins by proteolysis in a more indirect fashion (Isaacson and Ploegh, 2009), as exemplified by degradation of p53 upon human papilloma virus infection (Laitinen et al., 2016). Numerous other host cell proteins are targeted for proteolysis upon viral infection (Laitinen et al.,

2016), effectively rewiring the host cell network as functional proteins are depleted or attenuated. For example, the SARS-CoV-2 papain-like PL^{pro} cysteine protease nonstructural protein (nsp)3 has deubiquitinase and de-(IFN-stimulated gene 15)-ylase activity in vitro, suggesting potential activity in further altering cell proteostasis (Freitas et al., 2020). Experiments in yeast and other model systems demonstrate that reduced gene expression (and consequent reduced functional protein levels) renders the cell more vulnerable to targeted therapeutic treatment (Andrusiak et al., 2012; Cokol et al., 2011). In the case of viral-induced proteolysis that reduces host protein function below a critical level, synthetic lethal dependencies may be targeted to cripple the host cell and disrupt the viral life cycle.

Virus-induced adaptive network states. Studies in bacteria treated with antimicrobials and in cancer cells treated with chemotherapeutics have demonstrated that all cells elicit protective transcriptional responses to better tolerate cytotoxic drug effects (Huang et al., 2020; Niepel et al., 2017). Secondary drugs targeting new vulnerabilities within active regulatory and metabolic networks of the tolerant state can potentiate the cytotoxic effect of the primary drug (Cokol et al., 2018; Ma et al., 2019; Peterson et al., 2016; Plaisier et al., 2016). Similarly, we posit that new vulnerabilities in the regulatory and metabolic networks of a virus-infected cell can be targeted with drugs that will have no cytotoxicity to uninfected cells. Common transcriptional responses of virally infected cells include innate immune responses as well as cellular stress responses such as the unfolded protein response, which may suggest specific targets for host-directed antivirals that can be designed to either selectively disable infected cells or support antiviral activity of the innate cellular, and perhaps the coupled adaptive immune, response to infection (Banerjee et al., 2020; Ferreira et al., 2020; Netea et al., 2020).

Virus-induced protein-protein interactions. Viruses use their limited proteomes to bind to host cell proteins, altering PPIs (Basler et al., 2019; Lum and Cristea, 2016). Each viral protein can interact with numerous host cell proteins. The large repertoire of host-interacting proteins is enhanced by the presence of short linear motifs in numerous viral proteins that mediate interactions (Davey et al., 2011). These interactions can have many effects, from controlling signaling and host responses to viral infection, to reorganizing structures such as the secretory system to enable viral replication. Drugs that target these host proteins of the PPIs have been shown to disrupt the viral life cycle (Carpp et al., 2014), most notably with viral entry inhibitors that prevent interaction between host cell surface receptors and viral coat proteins (Kaufmann et al., 2018). However, these druggable targets are limited in number and often essential in humans (Heaton, 2019).

Exploiting the synthetic lethal concept with PPI networks may be an effective host-based antiviral strategy. As an example, consider the effect of a virus-dependent PPI usurping the normal function of a host protein. Once recruited, this host protein may become less able to perform its normal function, compromising that function. This recruited protein may be considered a viral-induced “hypomorph” due to its reduced, but not abolished, functionality. Consequently, the cell becomes more

dependent on proteins with which the viral-induced hypomorph functionally interacts or with proteins that perform overlapping functions. This dependence sensitizes the infected cell to drugs that target these protein partners of the viral-induced hypomorph. Typically, these partner proteins are numerous (Carpp et al., 2014; Luo et al., 2016; Shah et al., 2018). Studies in yeast show that the average gene participates in ~100 negative and ~65 positive interactions (Costanzo et al., 2016), each one of which, in the case of viral-induced hypomorphs, potentially presents a new host-based drug target. As with other viral-induced vulnerabilities, these targets are only exposed as a result of a viral infection, and such drugs should therefore have little effect on uninfected cells. It should also be possible to identify or predict “synthetic lethal” partners of the viral-induced hypomorph based on CRISPR screen, PPI, and genetic network and emerging human synthetic lethal data (Benstead-Hume et al., 2019).

Virus-induced targeting of common pathways. Analysis of PPI data from viral infection models suggest that many viruses target common proteins, networks, or processes (de Chassey et al., 2014; Meyniel-Schicklin et al., 2012; Pfefferle et al., 2011). Viral proteins often interact with “hubs” in PPI networks (Heaton, 2019; Ravindran et al., 2019; Shah et al., 2018). There is a correlation between the number of protein interactions a protein has and its synthetic lethal partners (Costanzo et al., 2016), suggesting that common druggable targets should be present in these networks. Different viruses also target the same host pathways via targeting different protein members of the pathway. Borrowing from what has been learned from yeast, genes in the same pathway have correlated genetic interactions, suggesting common targets can be identified. However, direct translation from yeast remains challenging due to the added complexities of multicellularity and genetic diversity in humans.

For example, the host translational machinery is required by viruses to synthesize viral proteins at the expense of host proteins. Many viruses target the signaling proteins that regulate host protein synthesis to ease ribosome demand by the host, in turn allowing enhanced virus protein production. Enveloped viruses must all take advantage of the ER translocon and chaperone machinery, by redirecting host lipid synthesis and glycosylation machineries to become properly enveloped with functional and mature surface proteins. Several members of the flaviviruses target the ER stress response to ensure the production of new virions in specialized subdomains of the ER (Shah et al., 2018; Zhang et al., 2016). They also target autophagy, with both responses contributing to lengthening the lifespan of the infected cell, while minimizing detection by host immune surveillance and clearance and redirecting membrane resources in support of viral production. During replication, viruses retarget host proteins to replication complexes to assist in chaperoned folding, packaging, and assembly of new virions (Coyaud et al., 2018; Zhang et al., 2016). In the case of membrane-bound virions, a reconfiguration of the host secretory pathway occurs to support virion trafficking and budding from the cell. Such large-scale morphological changes may rely on the buffering capacity of cells and reveal specific vulnerabilities that could be targeted by synthetic lethal approaches.

Furthermore, redistribution of critical host factors may contribute to a virus-induced state that could be selectively targeted by synthetic lethality, such as the movement of the endosomal sorting complex required for transport (ESCRT)-III to sites of flavivirus replication in the ER (Tabata et al., 2016) that leads to a reduced capacity of ESCRT-III function elsewhere in the cell. Thus, commonly reconfigured networks could be harnessed for developing broad-spectrum therapeutics against many different viruses by targeting conserved synthetic lethal partners of common interactors and processes.

Results from CRISPR screens also support the notion of broad-spectrum viral targets (Li et al., 2020; Savidis et al., 2016; Shah et al., 2018; Zhang et al., 2016). A comparison of the top 100 highest scoring hits in studies performed to date reveals that some genes are important not only for closely related viruses but also for unrelated clades. Among the highest scoring vulnerabilities are multiple subunits of the chaperone ER-membrane protein complex (EMC) that are essential for West Nile, dengue, Zika, rhino, influenza A, and hepatitis B viral infections (Barrows et al., 2019; Ngo et al., 2019). The EMC is a highly conserved transmembrane domain complex and loss of the EMC results in accumulation of misfolded membrane proteins (Jonikas et al., 2009). The EMC physically interacts with components of the ER-associated protein degradation (ERAD) pathway, which is also often essential for virus replication, as exemplified requirements for the ubiquitin conjugating enzymes UBE2J1 and UBE2G2 in Epstein-Barr, dengue, and West Nile virus replication. Other common host factor dependency pathways include components of the oligosaccharyltransferase complex (OST; Harada et al., 2019) and the vacuolar ATPase (Ho et al., 2017; Perreira et al., 2015). The dependence of these different viruses on these common processes suggests the existence of common druggable targets on which different viruses may be directly or indirectly dependent through viral-induced vulnerability.

From host dependency factor genes to antiviral drugs

Pharmacological inhibition of host dependency factors identified in CRISPR screens should phenocopy resistant to infection and/or replication, and in instances where preexisting drugs are available, present immediate opportunities for drug repurposing. Several examples support this strategy. In a screen with Zaire Ebola virus (EBOV), knockout of the N-acetylglucosamine-1-phosphate transferase GNPTAB impaired infection, likely due to loss of cathepsin B activity, a known EBOV entry factor (Flint et al., 2019). GNPTAB activity requires proteolytic processing by the subtilisin kexin isozyme-1/site-1 protease, and correspondingly, inhibition of subtilisin kexin isozyme-1/site-1 protease with the small molecule PF-429242 also impaired EBOV infection (Flint et al., 2019). Similarly, loss of poly(A) RNA polymerase associated domain containing proteins 5 and 7, two subunits of the Trf4/5-Air1/2-Mtr4 polyadenylation complex, impairs hepatitis A replication and phenocopied the inhibitor RG7834 (Mueller et al., 2018, 2019). The histone demethylase inhibitor JIB-04 was able to phenocopy the loss of myc-induced nuclear antigen 53 in a model of HIV infection and latency, and it exhibited synergy with other HIV latency-reversing agents

(Huang et al., 2019). This new therapeutic strategy may help purge HIV-1 viral reservoirs. Small molecule inhibitors of proviral targets identified for SARS-CoV-2 block virus-induced cell death and viral replication in cell culture. These compounds include the switch/sucrose nonfermenting-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (SMARCA4) inhibitor PFI3, and SIS2, an inhibitor of the mothers against the decapentaplegic homolog 4 (SMAD4)/TGF- β pathway (Wei et al., 2020). Finally, even in the absence of known inhibitors, antiviral gene-drug interactions can validate new targets. For example, a host dependency factor identified in an influenza A screen, the mRNA cap methyltransferase 1, exhibits strong and highly specific synergy with the U.S. Food and Drug Administration-approved influenza A endonuclease inhibitor baloxavir (Li et al., 2020). Building on these successes, further CRISPR-based screens against SARS-CoV-2 and many other viruses, combined with synthetic lethal concepts, should enable new antiviral drugs.

The path forward

The development of therapeutics for targeting viral-induced vulnerabilities based on synthetic lethality presents an exciting opportunity to identify therapeutics that are specific for virally infected cells. Unlike viral targets, host targets are not subjected to powerful mutational selection for resistance and may inhibit a spectrum of viral pathogens that rely on common host systems. Importantly, complete ablation of the host target may not be required to achieve a dramatic negative effect on the virus-infected cell. Less potent drugs that are still effective should be a lot easier to develop and may also have fewer side effects in uninfected cells. Furthermore, combining synergistic drugs at what would otherwise be subtherapeutic levels may be an effective antiviral strategy (Tyers and Wright, 2019). Moreover, approved drugs or advanced preclinical candidates discovered through efforts originally aimed at other indications may be rapidly repurposed as antivirals.

CRISPR-based genetic profiles for all major human viral pathogens will help identify viral-induced vulnerabilities and guide the development of inhibitors that are broadly effective against sets of related viruses as front-line interventions. However, as demonstrated in the development of synthetic lethal cancer therapeutics, care with respect to genetic diversity and the differences between cell culture and more physiologically relevant disease environments remains an important consideration (Huang et al., 2020). Interactions dependent on a particular genetic background can become irrelevant in different genetic backgrounds, cell lines, or model systems. Beyond screening, systems-based models that capture the network dynamics of the viral life cycle, infection, and host responses can help to predict and prioritize synthetic lethal interactions among host genes, drug combinations, and their potential synergy or other complex interactions that will be robust to genetic and physiological idiosyncrasies. Exploration of drug combinations based on the concept of genetic interactions is already underway (Eckhardt et al., 2020; Gordon et al., 2020b) and, as demonstrated by synthetic lethal cancer therapeutics (Huang et al., 2020), holds promise as an effective solution. In addition to

targeting infected cells, host-based antivirals can target the subsequent immune response that is often associated with pathology. Therapeutics should target the early stages of infection to promote cell death, limit viral release, minimize dysregulation of the host inflammatory response and host tissue damage, and ideally promote immune surveillance and clearance of infected cells. Of course, as with any pharmacological agent, side effects that arise by on-or-off target effects must be balanced with efficacy.

Quantitative multiscale models that address the multiscale nature of infection will guide the development of therapeutics that are effective and minimize unintended negative impacts on the host. Computing such models is difficult, in part because of the limited amount, relevance, and quality of the data. However, integrative modeling methods may help us address some of these challenges (Calhoun et al., 2018; Rout and Sali, 2019). Moreover, emerging data on virus-mediated network remodeling, including host-viral protein interactions, and global phosphorylation dynamics in SARS-CoV-2 infections (Bouhaddou et al., 2020; Gordon et al., 2020a), host responses to infection and viral-induced morphological changes, genetic interactions, and host dependency factors augers well for the rapid development and deployment of novel therapeutic strategies to combat new and old viruses that plague humankind (Benstead-Hume et al., 2019).

Conclusions

By increasing the diversity of targets and explicitly addressing the challenge of drug specificity, synthetic lethal approaches that target viral-induced vulnerabilities of the host cell can help us respond to the pressing challenge of outbreaks caused by viruses. Identifying solutions to infectious disease through the familiar prism of genetic interactions has the potential to illuminate numerous new drug targets, rationally repurpose existing drugs, and define mechanisms of action for drugs discovered through unbiased screening approaches. By working now to identify common host functions used by many viruses and to develop synthetic lethal drug approaches based on these targets, we may be able to more rapidly and comprehensively counter future global outbreaks.

Acknowledgments

The authors gratefully acknowledge support from the National Institutes of Health: U19 AI100627 (A. Aderem), R01 AI032972 (A. Aderem), U19 AI135976 (A. Aderem, J.D. Aitchison, N.S. Baliga), U19 AI111276 (J.D. Aitchison), P41 GM109824 (J.D. Aitchison, M.P. Rout, A. Sali, B.T. Chait), R01 GM112108 (J.D. Aitchison, M.P. Rout), R01 AI141953 (N.S. Baliga, J.D. Aitchison), R01 AI128215 (N.S. Baliga), GM 109824 (B.T. Chait), R01 CA228351 (M.P. Rout), U19AI135990 (A. Sali), R01GM083960 (A. Sali), P01 AI138398-S1 (C.M. Rice), U19 AI111825 (C.M. Rice), R01 AI091707 (C.M. Rice), R21 AI151344 (A. Kaushansky), and R01 GM101183 (A. Kaushansky); the Canadian Institutes for Health Research: FDN-167277 (M. Tyers); The G. Harold and Leila Y. Mathers Charitable Foundation (J.D. Aitchison, M.P. Rout, B.T. Chait, C.M. Rice); and a George Mason University Fast Grant (C.M. Rice).

The authors declare no competing financial interests.

Author contributions: J.D. Aitchison, F.D. Mast, and A.T. Navare wrote the original draft of the manuscript. F.D. Mast, A.T. Navare, A.M. van der Sloot, J. Coulombe-Huntinton, M.P. Rout, N.S. Baliga, A. Kaushansky, B.T. Chait, A. Aderem, C.M. Rice, A. Sali, and J.D. Aitchison contributed ideas and examples to expand and define the scope of applying the synthetic lethal concept to viral infections. All authors commented on and edited the manuscript.

Submitted: 25 June 2020

Revised: 28 July 2020

Accepted: 28 July 2020

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