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Opinion

SLiM-binding pockets: an attractive target for broad-spectrum antivirals

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Short linear motif (SLiM)-mediated interactions offer a unique strategy for viral intervention due to their compact interfaces, ease of convergent evolution, and key functional roles. Consequently, many viruses extensively mimic host SLiMs to hijack or deregulate cellular pathways and the same motif-binding pocket is often targeted by numerous unrelated viruses. A toolkit of therapeutics targeting commonly mimicked SLiMs could provide prophylactic and therapeutic broad-spectrum antivirals and vastly improve our ability to treat ongoing and future viral outbreaks. In this opinion article, we discuss the therapeutic relevance of SLiMs, advocating their suitability as targets for broad-spectrum antiviral inhibitors.

Highlights

Short linear motifs (SLiMs) are compact interaction interfaces indispensable for a variety of cellular processes.

Accumulated evidence points at SLiM-binding pockets as a common target for viral hijacking via viral mimicry of host motifs.

Recent studies have revealed that blocking SLiM-binding pockets can significantly disrupt the viral life cycle.

Targeting human SLiM-binding pockets hijacked by multiple viruses spanning many viral families could allow the development of broad-spectrum antiviral drugs.

Exploiting viral reliance on host pathways

Viral disease causes huge personal, societal, and economic distress worldwide. HIV has resulted in almost 40 million deaths worldwide since emerging in the early 1980s, influenza A virus (IAV) causes hundreds of thousands of respiratory deaths each year, and almost 300 million people are living with hepatitis C virus (HCV) worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the latest severe viral outbreak of the 21st century after SARS-CoV, H1N1 influenza virus, Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus, and Zika virus [1]. Many endemic viruses have attracted huge investment for drug development and several of these diseases are now treatable, with HIV and HCV being particular success stories. However, sporadic outbreaks of understudied viruses have revealed a failure of a reactive drug development pipeline where drugs are developed with a significant lag. During the SARS-CoV-2 pandemic, initial drug development work focused on repurposing drugs previously approved for other microbial and non-microbial diseases with limited success [2,3]. Given the development and approval time for novel drugs, it may be a decade before specific SARS-CoV-2-targeting small-molecule therapeutics are widely available [4]. Fortunately, the rapid development of SARS-CoV-2 vaccines lessened the catastrophic impact and minimised the loss of life. However, reactive development of therapies inevitably results in societal disruption during the early months of an outbreak. This advocates for a transition to a proactive development model of an extensive toolkit of antiviral molecules for pre- and post-infection drugs to allow prophylactic and therapeutic intervention [5,6].

Given the finite research capacity of academia and industry, the majority of drug development focuses on a few viruses that cause diseases of significant societal and economic impact. As a result, antiviral drugs are available for only a handful of viral pathogens and no targeted therapeutic interventions exist for the vast majority of viruses. Furthermore, antiviral drugs are generally targeted at a single virus or a limited range of closely related viruses, a strategy colloquially known as the 'one drug/one bug' approach. There have been extensive efforts to discover druggable commonalities between viruses; however, broad-spectrum viral therapeutic avenues

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analogous to commonly used antibiotics remain elusive [7–9]. The major problem for broadly acting viral drug development is viral diversity; there are uncountable numbers of distinct existing and potential human viral pathogens, especially when their rapid evolution is considered.

One fundamental requirement of virus infection is the extensive interaction of viral proteins with the host proteome to hijack and deregulate cellular processes. Key points in the human proteome will be targeted by multiple distinct viruses; consequently, viral diversity issues can be avoided by therapeutic targeting of host mechanisms shared across multiple viruses. The host-targeting strategy has the added advantage of being more robust to the generation of drug-resistant viruses, although there is a possibility of mutations optimising the affinity of the viral interface to outcompete the drug. Despite these appealing properties, successful host targets remain elusive [10], and to date the vast majority of clinical antiviral drugs are virus targeted. However, most of the potential host search space for viral therapeutics remains unexplored. As we learn more about virus biology, we reveal novel common host targets for therapeutic intervention to exploit the viruses' reliance on our own pathways and proteins. If we can overcome the barrier of negative on-target effects on host cell physiology while inhibiting viral replication, the development of an extensive toolkit of broad-spectrum antiviral molecules may be achievable.

Short linear motifs (SLiMs) are ubiquitous compact interaction interfaces that direct fundamental cellular processes by acting as enzyme docking sites, localisation signals, degradation motifs, transactivation domains, and binding sites in dynamic complexes [11]. The key attribute of SLiMs distinguishing them from other interface classes is their compact footprint, which usually contains three or four key affinity- and specificity-determining residues encoded in a protein region of fewer than ten amino acids in length [12] (Figure 1). Several additional distinctive attributes result from their compact degenerate interfaces, including the transient nature of their interactions [13], their simple *ex nihilo* evolution by random mutation [14], and their extensive regulation by post-translational modification [15]. SLiMs are ubiquitous in higher eukaryotic proteomes and hundreds of examples of viral mimicry of host SLiMs have been validated (Table 1 and Figure 1C) [13,16]. For example, it has previously been shown that approximately one-third of characterised human SLiM-binding pockets have an example of hijacking by viral mimicry [17]. The extreme case of the archetypal multifunctional viral protein E1A from adenovirus has validated motifs for 14 distinct host motif-binding pockets (Figure 2A) [18].

For many SLiM classes, there is widespread usage across diverse viral clades as the requirements of many viruses overlap and in many cases they convergently evolve the same easily evolvable solution (Figure 2B) [17]. Our current snapshot of the landscape of viral motif mimicry, collected through decades of low-throughput experiments, is expected to be only the tip of the iceberg [13]. It is likely that the majority of viral SLiMs remain to be discovered and SLiM-binding pockets with validated examples of viral mimicry will be shown to be extensively targeted once high-throughput motif discovery approaches are widely applied. For example, large-scale screening of ~140 SLiM-binding domains with a proteomic phage display (ProP-PD) library encoding tiled overlapping coronavirus peptides discovered several novel examples of SLiM mimicry by SARS-CoV-2 [19]. As such data accumulates over the coming years, the true scale of viral mimicry of host SLiMs will be revealed. In this perspective, we advocate exploiting our growing understanding of viral SLiM mimicry to develop broad-spectrum antiviral drugs effective against multiple viruses across many viral families.

Why are SLiMs extensively mimicked by viruses?

Decades of basic biology has revealed extensive detail on the life cycle of multiple viruses. Of the major groups of infectious microbes, viruses rely most heavily on the host's cellular machinery to

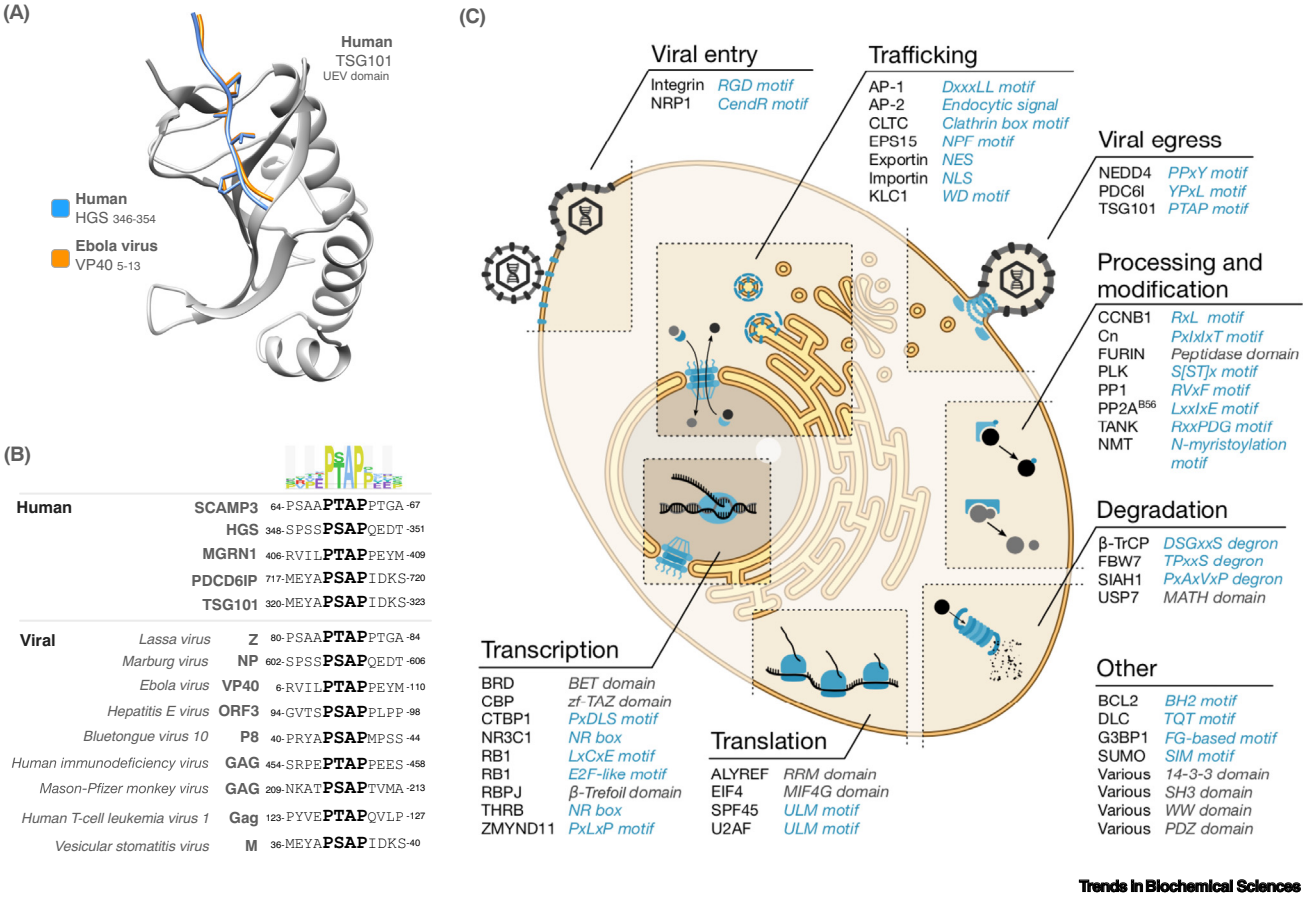

Figure 1. Widespread viral hijacking of cellular pathways by mimicry of host SLiMs. (A) Structures of the PTAP motifs of the Ebola virus matrix protein VP40 (PDB ID: 4EJE; orange) and human hepatocyte growth factor-regulated tyrosine kinase substrate (HGS) (PDB ID: 3OBQ; blue) bound to the PTAP motif-binding pocket of the human tumour susceptibility gene 101 protein (TSG101) (grey) UEV domain showing mimicry at the structural level. (B) Examples of validated PTAP motifs in viral and human proteins demonstrating mimicry of the SLiM at the sequence level. The panel includes a logo of the major specificity determinants derived from all validated instances of the motif. (C) Representative examples showing the diversity of pathways and SLiM-binding pockets targeted by motif mimicry derived from curation and the Eukaryotic Linear Motif (ELM) resource [13].

complete their life cycle. Host pathways required for successful viral replication will be extensively targeted by viruses (Figure 1C). Functional modules allowing a virus to hijack these pathways represent attractive targets for viral acquisition either by mimicry or horizontal transfer of an existing host interface or through the evolution of novel binding interfaces. SLiMs have high evolvability as a result of the limited number of residues in direct contact in the interface of SLiM-mediated interactions and most SLiMs are predicted to have evolved *ex nihilo* solely by the accumulation of random mutations [14]. The relative ease of *de novo* SLiM evolution by viral proteins can simplify the formation of novel interactions with important host proteins. This simple mechanism of motif acquisition coupled to the key role of SLiMs in the cell makes them ideal interfaces for viral subversion of cellular processes. Furthermore, the spatial efficiency of SLiMs permits increased functional density in spatially restricted viral proteomes.

Are viral SLiM-mediated interactions therapeutically relevant?

There are three major mechanisms by which viruses utilise host SLiMs: (i) to use endogenous motif-recruited functionality; (ii) to redirect the motif-encoded functionalities to novel host proteins; and (iii) to deregulate the host function of a SLiM by acting as motif-binding pocket

Table 1. Representative examples of viral mimicry of host motifs

Host protein	Host domain	Motif class	Peptide	Virus protein	Virus	Refs
Viral entry						
Integrins	FG-GAP	RGD motif	$_{764}$RGD$_{766}$	Genome polyprotein (VP1)	Human parechovirus 1	[30]
Neuropilin-1 (NRP1)	F5/8 type C 1	CendR motif	$_{683}$RAR$_{685}$	Spike glycoprotein (S)	SARS-CoV-2	[31]
Trafficking						
AP-2 complex subunit mu (AP2M1)	Adaptor complex medium subunit	Endocytic signal	$_{136}$YIPL$_{139}$	Core protein	HCV genotype 1a	[32]
Importins	Arm	Nuclear localisation signal	$_{121}$PRPKRARV$_{128}$	Transcriptional regulator ICP22 (ICP22)	Human herpesvirus 1	[33]
Exportins	Exportin-1-like	Nuclear export signal	$_{82}$LSAQLYSSLSLD$_{93}$	Protein Rex	Human T cell leukemia virus 1	[34]
Viral egress						
Programmed cell death 6-interacting protein (PDCD6IP)	ALIX V-shaped domain	YPxL motif	$_{16}$AIYPVRSN$_{23}$	Matrix protein VP40 (VP40)	Zaire ebolavirus	[35]
Tumour susceptibility gene 101 protein (TSG101)	UEV	PTAP motif	$_{454}$EPTAPP$_{459}$	Gag polyprotein (gag)	HIV type 1	[36]
E3 ubiquitin-protein ligase NEDD4 (TSG101)	WW	PPxY motif	$_{94}$PPPY$_{97}$	RING finger protein Z (Z)	Lassa virus	[37]
Transcription						
Retinoblastoma-associated protein (RB1)	RB A/B	E2F-like motif	$_{41}$PTLHELYDL$_{49}$	Early E1A protein	Human adenovirus C serotype 5	[38]
Zinc finger MYND domain-containing protein 11 (ZMYND11)	zf-MYND	PxLxP motif	$_{113}$PNLVP$_{117}$	Early E1A protein	Human adenovirus C serotype 5	[39]
C-terminal-binding protein 1 (CTBP1)	2-Hacid dh	PxDLS motif	$_{856}$EALDLSI$_{862}$	Epstein–Barr nuclear antigen 3 (EBNA3)	Epstein–Barr virus	[40]
Translation						
THO complex subunit 4 (ALYREF)	RRM	ALYREF motif	$_{105}$WSRLGARR$_{112}$	ICP27 (UL54)	Human herpesvirus 1	[41]
Splicing factor U2AF 65 kDa subunit (U2AF2)	RRM	UHM ligand motif (ULM)	$_{41}$RRRRWR$_{46}$	Protein Rev (rev)	HIV type 1	[42]
Degradation						
Ubiquitin carboxyl-terminal hydrolase 7 (USP7)	MATH	MATH	$_{39}$PSRSE$_{43}$	VIRF-1	Human herpesvirus 8 type P	[43]
E3 ubiquitin-protein ligase SIAH1 (SIAH1)	Sina	PxAxVxP degron	$_{312}$PAVAAVVP$_{319}$	E3 ubiquitin-protein ligase ICP0 (RL2)	Human herpesvirus 2	[44]
F-box/WD repeat-containing protein 1A (BTRC)	WD40	DSGxxS degron	$_{479}$DSGISDVE$_{486}$	Non-structural protein 1	Rotavirus A	[45]
Processing and modification						
Phosphatase 2A 56 kDa (PPP2R5C)	B56	LxxIxE motif	$_{562}$LTPINE$_{567}$	Nucleoprotein (NP)	Zaire ebolavirus	[21]
Poly [ADP-ribose] polymerase tankyrase-1 (TNKS)	Ank	RxxPDG motif	$_{75}$KRPSCIGC$_{82}$	Epstein–Barr nuclear antigen 1 (EBNA1)	Epstein–Barr virus	[46]
Cyclin A2 (CCNA2)	Cyclin	RxL motif	$_{34}$GVKRKLFAE$_{42}$	Probable ganciclovir kinase (U69)	Human herpesvirus 6A	[47]

Table 1. (continued)

Host protein	Host domain	Motif class	Peptide	Virus protein	Virus	Refs
Other						
Small ubiquitin-related modifier 1 (SUMO1)	Ubiquitin-like	SIM motif	$_{195}$GCIVISDSE$_{206}$	Viral transcription factor IE2 (UL122)	Human cytomegalovirus	[48]
Ras GTPase-activating protein-binding protein 1 (G3BP1)	NTF	FG-based motif	$_{1828}$LTFGDF$_{1833}$	Polyprotein P1234	Chikungunya virus	[49]
Dynein light chain 1 (DLC1)		TQT motif	$_{142}$EDKSTQT$_{148}$	Phosphoprotein (P)	Rabies virus	[50]

inhibitors. The first two hijacking approaches are clearly vulnerable to therapeutic intervention and the third approach, although more nuanced, will be targetable in some cases. Numerous studies have applied mutational or deletional analyses to show the importance of motifs to the life cycle of viruses, and in many of these cases disabling the motif was shown to have a strong effect on the ability of a virus to control host cell physiology resulting in a large decrease in virulence (Table 1) [13,17]. More recently, several authors have gone a step further by using SLiM-containing peptides to mimic the inhibitory effect of small molecules targeting motif-binding pockets in the context of a viral infection [19,20]. These studies demonstrated that blocking a motif-binding pocket can inhibit viral recruitment of host SLiM-binding proteins and have a deleterious effect on the virulence. For example, studies using genetically encoded peptide inhibitors have shown that

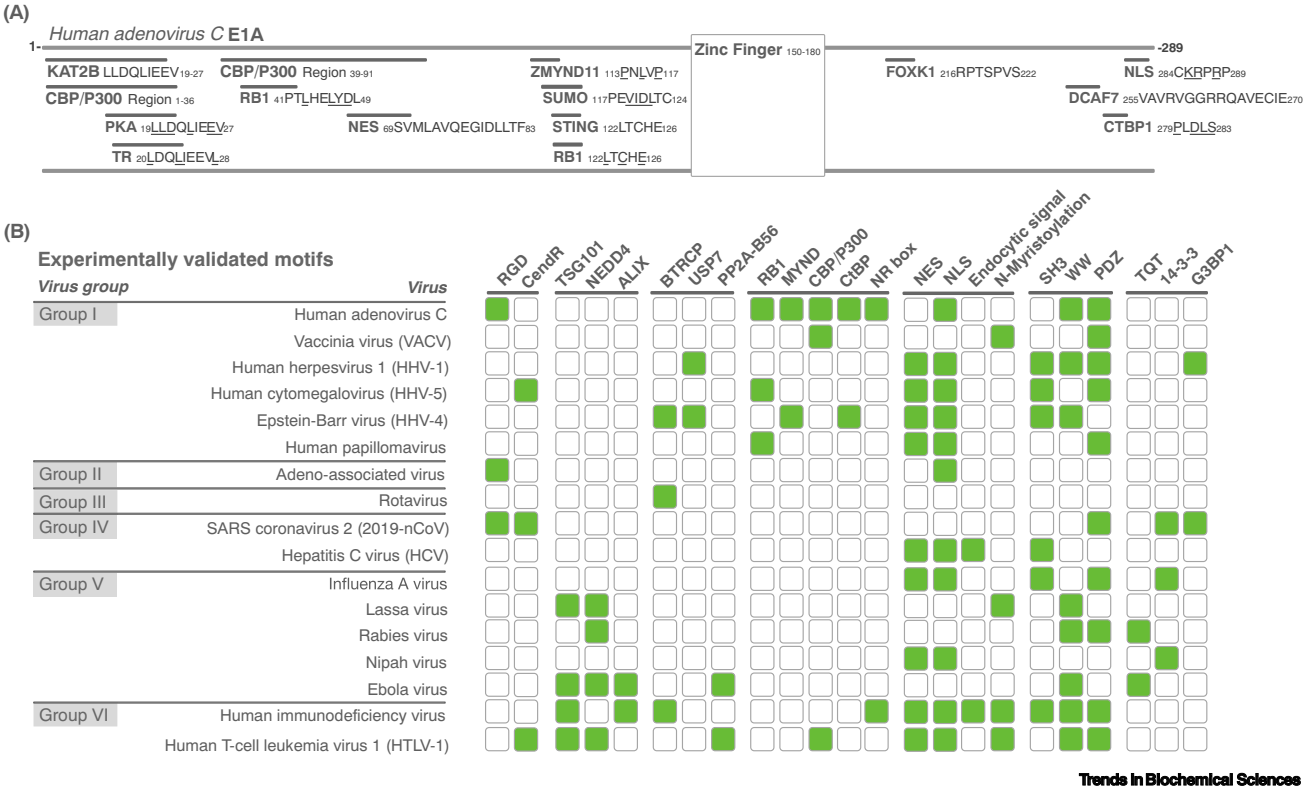

Figure 2. Extensive mimicry of host SLiMs by viral proteins and proteomes. (A) Modular architecture of adenovirus E1A protein showing the extensive mimicry of host motifs [13,17,18]. (B) Representative examples of the commonalities in motif mimicry across several commonly studied viral proteomes derived from manual curation and the Eukaryotic Linear Motif (ELM) resource [13].

inhibition of the LxxIxE motif-binding pocket of $PP2A^{B56}$ suppresses Ebola virus transcription [20,21] and inhibition of the FG-based motif pocket of G3BP1 dampens SARS-CoV-2 infection [19]. Recently, a molecule based on a cyclic motif, cilengitide, which targets the α_v integrin RGD motif-binding pocket, was shown to inhibit SARS-CoV-2 spike protein binding to human endothelial cells and has been suggested as a potential pre-exposure prophylactic for SARS-CoV-2 [22].

Are viral SLiM-mediated interactions druggable?

A key argument against targeting host interactions is the potential for on-target effects resulting in drug-related adverse events and toxicity. Chemical toxicity is not specific to host-targeted drugs, but unexpected or undesirable effects caused by antivirals could be increased by the usage of host-targeted therapeutics. Given that SLiMs mimicked by viral proteins are regulating key cellular pathways, therapeutic targeting of these interactions is likely to lead to some degree of on-target deleterious effects. This possibility has been emphasised by recent work showing that many viral SLiM targets are highly expressed, highly connected, and essential motif-binding proteins in the human proteome [23]. However, the level of toxicity of SLiM-pocket inhibition can be characterised prior to target development and such analyses can be included in the target validation pipeline. It is important to note that safe and effective SLiM-binding pocket drugs are achievable. Small-molecule inhibitors have been produced for many motif-binding pockets, proving undeniably that SLiM-mediated interactions are 'druggable' [24]. MDM2 degron and RGD motif pocket inhibitors have previously reached late-stage clinical trials after showing tolerable safety profiles [22,25] and SLiM-pocket inhibitors such as the apoptosis regulator Bcl-2 (BCL2) inhibitor venetoclax are in clinical use [26]. To date, most issues for SLiM-binding pocket inhibitors in late-stage clinical trials are related to efficacy rather than toxicity or potency; for example, the failure of MDM2 inhibitors to pass Phase 3 clinical trials [25]. If the deleterious effect of inhibition of host interactions mediated through a given pocket are not tolerated, combination therapy with lower doses targeting multiple SLiMs in the virus, or in combination with other antivirals, could be applied [27]. Furthermore, given the limited timeframe for the usage of these drugs, long-term toxicity may not be an issue.

Many SLiM-binding pockets or specific motif-mediated viral–host interactions may not be targetable by antiviral inhibitors. First, it may not be possible to develop a specific and highly potent inhibitor for a proportion of motif-binding pockets. Second, the binding strength of a given viral–host motif interaction is likely to be case specific and dependent on many factors including the local abundance and binding strength of host motif-containing proteins, the expression levels of the viral and host motif-binding proteins, the oligomeric state of the viral protein, the functional role of the motif, and the reason for motif mimicry (i.e., motif-binding protein deregulation versus use of the endogenous functionality encoded by the motif). Consequently, although the low-micromolar affinity ranges of most SLiM-mediated interactions make these interactions amenable to inhibition, a subset of motif-mediated viral–host interactions will be relatively strong compared with other host and viral instances and therefore represent difficult targets requiring higher inhibitor concentrations or alternative approaches. In cases where inhibition of a SLiM-binding pocket or specific motif-mediated interaction is not achievable, an interesting strategy is the development of antiviral proteolysis targeting chimeras (PROTACs) to degrade the host SLiM-binding pocket containing protein [28].

Concluding remarks

The SARS-CoV-2 pandemic has reemphasised the personal, societal, and economic impact of viral disease. Furthermore, it highlighted that the global public health system is underequipped to control viral infection using pharmacotherapeutic intervention. A key missing weapon is antivirals capable of targeting multiple viruses across many viral families equivalent to broad-spectrum

Outstanding questions

Understanding the potential of therapeutic targeting of SLiM-binding pockets

- How many virus-targeted SLiM-binding pockets have tolerable on-target toxicity and are druggable by antiviral inhibitors or PROTACs?
- How many druggable SLiM-binding pockets are therapeutically relevant for multiple viruses?
- For emerging viruses, can we predict the correct set of drugs based on the SLiM content of the viral proteome or the virally targeted pathways?
- Can combination therapies targeting multiple SLiM-binding pockets act synergistically?
- Can SLiM-targeting PROTACs be leveraged to target host pockets inaccessible to high-affinity small-molecule inhibitors?
- What is the polypharmacological potential of virus-targeting SLiM-binding pocket inhibitors for use as antibacterial, anticancer, and antineurodegenerative drugs?
- How many SLiM-pocket-targeting drugs do we need in our antiviral armoury for panviral protection and to be prepared for future pandemics?

Understanding the challenges of therapeutic targeting of SLiM-binding pockets

- What are the properties of SLiM-binding pockets druggable by small molecule inhibitors or PROTACs?
- What are the on- and off-target negative effects of inhibiting host SLiM-binding pockets?
- How likely are viral mutations that result in resistance to SLiM-binding pocket inhibitors, most notably mutations increasing the affinity of the viral SLiM, to allow the virus to outcompete the drug?
- Are there approaches that can minimise the prohibitive time and costs of the target validation and drug development pipeline?
- What is the most efficient path to characterise the therapeutic relevance of the full SLiM pocket search space?
- How can we convince funding sources to support the farsighted

antibiotics [5,6]. However, to date shared viral vulnerabilities have been elusive and most antiviral therapies still target specific viral proteins. Host SLiMs are commonly mimicked by viral proteins due to their compact interfaces, ease of convergent evolution, and key functional roles. Over one-third of known human SLiM-binding pockets have evidence for deregulation by viral SLiMs and many SLiM classes are mimicked across numerous viral clades [17]. Consequently, a toolkit of therapeutics targeting commonly mimicked SLiMs could provide broad-spectrum antivirals.

Recent studies have shown that SLiM-based peptide inhibitors can severely disrupt viral life cycles and drugs such as venetoclax, nutlin, and cilengitide have provided proof of principle that SLiM-mediated interaction interfaces are targetable by small molecules, suggesting that the development of such a therapeutic toolkit is achievable. Recent developments in the field of PROTACs has further expanded the range of therapeutically targetable SLiM-binding pockets [29]. Given that the SLiM-recruited pathways and their associated functionality are often the focus of viral hijacking, and multiple avenues for hijacking are often available, SLiM-based drugs inhibiting the function of these key virally targeted pathways may affect virulence even in the absence of inhibition of a direct viral–host interaction.

SLiM-targeting strategies could result in therapeutics for both well-studied and neglected viruses, improve our preparedness for future pandemics, and potentially be applied to other human diseases including bacterial infection, cancer, and neurodegeneration. Effective cooperation between funding agencies, academia, and industry will be required to successfully explore the potential of SLiM inhibitors as broad-spectrum antiviral therapeutics. However, the implications for untreatable viruses currently in circulation, and the world's preparedness for future pandemics, are worth the considerable cost and effort. There are numerous considerations to be weighed given the advantages and challenges of SLiM pocket inhibition as broad-spectrum viral therapeutics (see Outstanding questions). The key initial question is how many SLiM-binding pockets can be targeted with tolerable drug-related adverse events and high antiviral activity. Once this question has been answered, the next step is likely to come down to economics: how many SLiM-pocket-targeting drugs do we need in our antiviral armoury to be prepared for future pandemics and does the benefit of developing such a resource provide recompense for the significant investment? In our opinion, SLiM-binding pockets are an important potential target for the discovery of broad-spectrum antiviral therapeutics and this drug development opportunity should be explored extensively.

and significant investment required for the development of drugs for viruses that have not yet, or may not ever, become a problem?

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Declaration of interests

None are declared.

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