

Ronja Meyer Simonsen

# Broad-Spectrum Antiviral monotherapies: *in silico* drug repositioning against emergent viruses

Database expansion and generation of BSA-  
scoring system

Master's thesis in Molecular Medicine

Supervisor: Denis Kainov

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Norwegian University of Science and Technology  
Faculty of Medicine and Health Sciences  
Department of Clinical and Molecular Medicine



Kunnskap for en bedre verden



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*RonjaMS*

Ronja Meyer Simonsen

Trondheim, May 2022

## Publications

The work that has been conducted in this thesis resulted in being part of the following scientific publications:

- Aleksandr Ianevski, Ronja M. Simonsen, Vegard Myhre, Tanel Tenson, Valentyn Oksenysh, Magnar Bjørås, Denis E. Kainov, DrugVirus.info 2.0: an integrative data portal for broad-spectrum antivirals (BSA) and BSA-containing drug combinations (BCCs). *Nucleic Acid Research*, 2022. <https://doi.org/10.1093/nar/gkac348>, Accepted.
- Aleksandr Ianevski, Rouan Yao, Ronja M. Simonsen, Vegard Myhre, Erlend Ravlo, Gerda D. Kaynova, Eva Zusinaite, Judith M. White, Stephen J. Polyak, Valentyn Oksenysh, Marc P. Windisch, Qiuwei Pan, Eglė Lastauskienė, Astra Vitkauskienė, Algimantas Matukevičius, Tanel Tenson, Magnar Bjørås, Denis E. Kainov, Mono- and combinational drug therapies for global viral pandemic preparedness. *iScience*, Volume 25, Issue 4, 2022, 104112, ISSN 2589-0042, <https://doi.org/10.1016/j.isci.2022.104112>.

## Abstract

Animal viruses, such as SARS-CoV-2, have demonstrated the current reality of global viral threats. SARS-CoV-2 crossed species barriers and caused an unpredictable pandemic within the human population. Antivirals are medications with activity against a specific virus. Several antivirals have demonstrated a profound activity, supporting the importance of further antiviral elaboration in viral disease management. Currently, the emphasis is on broad-spectrum antivirals (BSAs), compounds with activity against a broad range of viruses and their drug-resistant strains and variants. The favorable method of BSA development is drug repositioning. Drug repositioning displays a rapid, cost-efficient, and reduced-risk approach in the search for new indications of already available medications. The most critical phase of drug repositioning is *in silico* discovery of a new indication of BSAs. To perform *such* discoveries, researchers need a database summarizing BSA activities. BSA databases could help identify the most promising few of thousands of potential BSAs to prioritize their development during the critical period between the identification of a new virus and the development of virus-specific vaccines, drugs, and therapeutic antibodies.

My aim was to assemble a resource for the exploration and analysis of BSAs and to develop a new method to identify the most promising BSAs for viral pandemic preparedness.

Here, I describe the integrative and interactive DrugVirus.info 2.0 portal that allows exploration and analysis of BSAs. I further describe a new method of selecting the most promising BSAs among 255 drugs present in the DrugVirus.info database based on BSA-target relevance, routes of administration, phylogeny- and structure-activity relationship, and immunomodulatory properties analyses. Thus, my study promoted the discovery and development of promising broadly-effective antiviral therapies.

## Sammendrag

Utbruddet av SARS-CoV-2 har demonstrert realiteten av globale virale trusler. SARS-CoV-2 krysset arts barrierer og forårsaket en pandemi som verden ikke var forberedt på. Antiviraler er medikamenter som hemmer formeringen av ett spesifikt virus. Flere slike antiviraler har bevist utslagsgivende effekt mot virus. Dette illustrerer viktigheten av forskning på antivirale medikamenter, som i fremtiden vil være viktige forkjempere i kampen mot virus-relaterte sykdommer. Det nåværende fokuset er på utviklingen av bredt-spektrert antivirale legemidler (BSA), som er medikamenter med effekt mot et bredt spekter av virus og deres medikamentresistente varianter. Den mest utbredte metoden for utvikling av BSA er reposisjonering av medikamenter. Denne metoden utgjør en rask og kostnadseffektiv tilnærming med redusert risiko i søken etter nye indikasjoner av eksisterende medikamenter. *In silico* oppdagelse av disse nye indikasjonene er den første og viktigste fasen innen reposisjonering av medikamenter. For å kunne avdekke nye indikasjoner er man avhengig av databaser som integrerer mulige BSA aktiviteter. Slike databaser vil være verdifulle i identifiseringen av de mest lovende BSAene fra en samling av flere tusen mulige BSAer. Disse forberedelsene vil gjøre det mulig å prioritere utviklingen av lovende BSAer i den kritiske perioden mellom identifikasjon av et nytt virus og fremstillingen av virus-spesifikke vaksiner, medisiner og terapeutiske antistoffer.

Formålet med masteroppgaven var å utarbeide en ressurs som samler og analyserer BSAer, samt å etablere metoder for å identifisere de mest lovende BSAene som forberedelser mot fremtidige globale virale trusler.

I denne masteroppgaven beskriver jeg den integrerende og interaktive DrugVirus.info 2.0 databasen som muliggjør analyse og visualisering av BSA aktivitet. Videre beskriver jeg en ny metode for å selektere de mest lovende BSAene innad i DrugVirus.info databasen. Denne metoden er basert på evaluering av BSA komponenter som påvirker antiviral aktivitet; BSAenes målgrupper av gener og proteiner, administrasjonsveier, fylogeni- og struktur-aktivitetsforhold, og immunomodulatoriske egenskaper. På denne måten bidro studiet mitt til oppdagelse av potensielle bredt-spektrede antivirale medikamenter.



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## Abbreviations

AIDS	Acquired immune deficiency syndrome	MAPK	Mitogen-activated protein kinase
AP-1	Activator protein 1	MDA5	Melanoma differentiation-associated protein 5
BC	Baltimore Classification	MF	Macrophage
BCC	BSA-containing drug combination	NF- $\kappa$ B	Nuclear factor kappa-light-chain enhancer of activated B cells
BSA	Broad-Spectrum antiviral	NK	Neutral killer
DAMPs	Damage associated molecular patterns	NTRI	Nucleoside reverse transcriptase inhibitor
DC	Dendritic cells	PAMP	Pathogen-associated molecular pattern
DSS	Drug sensitivity score	Phyl	Phylogeny
CC <sub>50</sub>	Half maximal cytotoxic concentration	PRRs	Pattern recognition receptors
CFR	Case fatality rate	PSC	Pluripotent stem cells
DAMP	Damage associated molecular pattern	RdRp	RNA-dependent RNA polymerase
DdDp	DNA-dependent DNA polymerase	RIG-I	Retinoic acid inducible gene I
DDS	Drug developmental status	RLR	RIG-I like receptor
DGIdb	Drug Gene Interaction database	RoA	Route of Administration
dsDNA	Double stranded deoxyribonucleic acid	RT	Reverse transcriptase
EC <sub>50</sub>	Half maximal effective concentration	SAR	Structure-activity relationship
ESC	Embryonic stem cell	SI	Selectivity index
FDA	U.S Food and Drug Administration	TGF $\beta$	Transforming growth factor beta
GWAS	Genome-wide association study	T <sub>h</sub>	T-helper cells
HAART	Highly Active Antiretroviral therapy	TLR	Toll-like receptor
IP	Immunomodulatory properties	TNF	Tumor necrosis factor
IC <sub>50</sub>	Half maximal inhibitory concentration	TR	Target relevance
ICTV	International Committee on Taxonomy of Viruses	TTD	Therapeutic Target database
IFN	Interferon	T <sub>h</sub>	T-helper cells
IL	Interleukin	Voi	Virus of interest
iPSC	Induced pluripotent stem cell		

# 1 Introduction

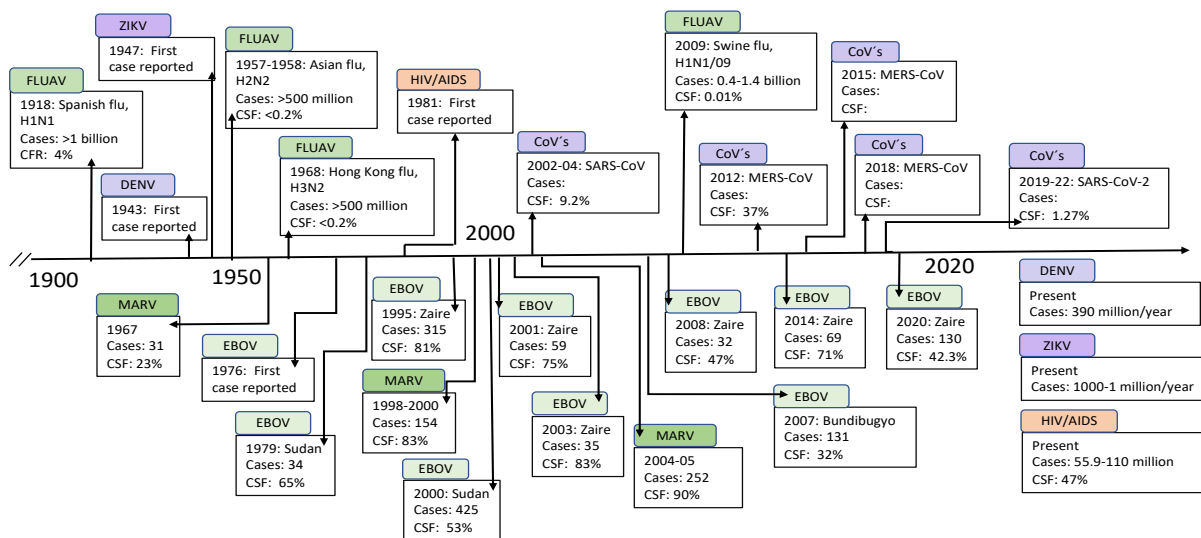
## 1.1 The scope of past and presently virology

### 1.1.1 Emerging viral strains

Humans had faced viruses long before our kind evolved into its modern form. For certain viral diseases, antiviral drugs and vaccines have assisted in reducing viral pathogenesis and spread, and even contributed to the total eradication of viral pathogens. The development of Highly Active Antiretroviral Therapy (HAART) in managing Acquired immune deficiency syndrome (AIDS) has made it possible for infected individuals to live with the causative virus, human immunodeficiency virus (HIV) (1). Further, the development of the Smallpox vaccine resulted in entire eradication of the variola virus (2).

Contempt historical successes, outbreaks of severe viral pandemics during the twenty-first century demonstrate that viral diseases still are a significant health burden worldwide. Viruses have the potential to spread to a specific geographic area or globally, causing epidemics and pandemics, respectively (3, 4). Emerging viruses include recently discovered viruses with increased incidence or potential to increase in incidence (3). Such Emerging viral infections cover both newly emerging and re-emerging viral diseases (4).

Most of the emerging viruses are zoonotic viruses spilled over from animals to humans, causing disease in the human population (5). Such zoonotic viral diseases, zoonoses, appear when people contact animals carrying the disease. Indeed, zoonoses are at high risk of causing pandemics and endemics, potentially introducing an uncharacterized pathogen into the population (6, 7). Emerging zoonotic viruses such as Influenza A (FLUAV) (8-12), Ebola virus (EBOV), Marburg virus (MARV) (4, 13-15), and Zika virus (ZIKV)(16, 17), comes to the surface from natural reservoirs regularly, representing global threats (4, 18-20). Another example of zoonosis is the recently emerging Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and former endemic causing coronaviruses such as SARS-CoV and Middle east respiratory syndrome coronavirus (MERS-CoV) (4, 21). Further, the vector-borne transmitted Dengue virus (DENV) is known for causing recurrent endemics (16, 22). Also, the ongoing HIV/AIDS pandemic in African regions costs several million lives yearly (Figure 1) (4, 23).



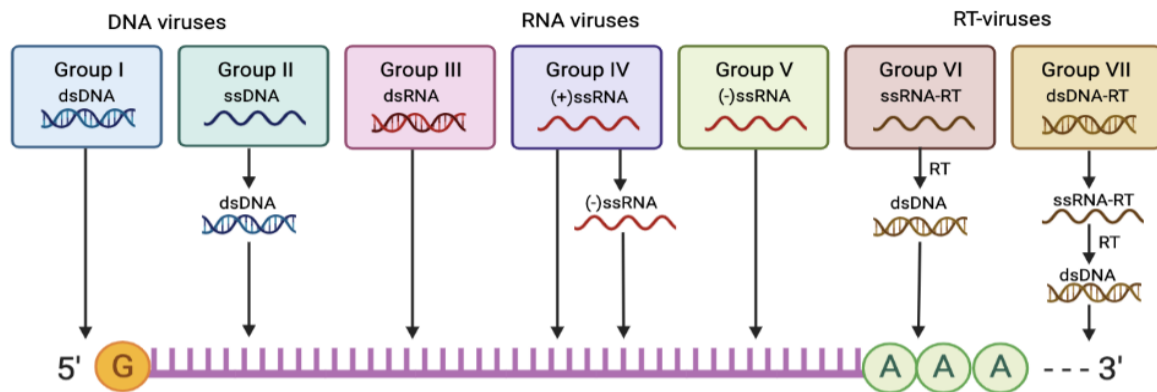
**Figure 1: Timeline of past and present emerging viral strains.** Presented is the time of outbreak, number of cases, and case fatality rate (CFR), when applicable. *Upper part:* FLUAV pandemics: 1918 Influenza A/Spanish flu (H1N1 subtype); Asian flu (H2N2 subtype); 1968 flu pandemic/Hong Kong flu (H3N2 subtype); and 2009 flu pandemic/Swine flu (H1N1/09 subtype). Current circulating FLUAV strains appear as seasonal epidemics, mainly caused by H2N2 and H1N1/09 subtypes. Emergent coronaviruses (CoVs) include SARS-CoV initially identified in 2002, and MERS-CoV in 2012, both causing endemics. Also designated is the recent pandemic of SARS-CoV-2. Further, the timeline shows the first detection of ZIKV, DENV, and HIV/AIDS, which still have incidences in the human population. *Lower part:* shows MARV and EBOV endemic outbreaks. MARV was first recognized in 1967 and EBOV in 1976, followed by regional epidemics.

### 1.1.2 Classification of viruses

Once a viral outbreak emerges, a specified classification of the new virus is crucial. Accordingly, new viruses are introduced into the pool of previously announced viruses, generating a framework for connecting viral strains. Therefrom, predications of virus properties can be made, and potential evolutionary relationships can be revealed (24). The international committee on Taxonomy of Viruses (ICTV) provides a universal taxonomic classification and nomenclature of viruses as guidelines for specific naming conventions (25, 26). Such taxonomy allows arrangements of an emerged virus into realm, kingdom, phylum, class, order, family, and genus (26).

Alongside ICTV, Baltimore classification (BC) is a system that organizes viruses based on the structure of the virion nucleic acid and replication of their virus genome (Figure 2) (27). Group I and II comprise deoxyribonucleic acid (DNA) viruses with double-stranded DNA (dsDNA) and single-stranded DNA (ssDNA) genomes, respectively. (27-29). Group III, VI and V cover ribonucleic acid (RNA) viruses. Group III include dsRNA, meanwhile, group IV, and V comprise viruses with positive-sense ssRNA ((+)ssRNA) and negative-sense ssRNA

((-ssRNA) genome, respectively. Furthermore, the last two groups consist of viruses which produces an intermediate in their replication cycle. Group VI include ssRNA viruses with a DNA intermediate (ssRNA-RT) and group VII contains dsDNA viruses with an RNA intermediate (dsDNA-RT) (27, 28).



**Figure 2: Baltimore classification.** The figure illustrates the seven BC groups (I-VII) with its replication strategy. Group I, dsDNA viruses have the same replication strategy as cellular life forms. Meanwhile, group II ssDNA viruses replicate through rolling-circle (circular genome) or rolling harpin (linear genome) mechanisms. The ssDNA genome must be transcribed into dsDNA by DNA-dependent DNA polymerases (DdDp). Group III contains dsRNA viruses, which transcribe the negative strand of dsRNA into mRNA by RNA-dependent RNA polymerase (RdRp). Group IV, (+)ssRNA viruses do not typically need transcription. However, (+)ssRNA viruses will produce positive-sense copies of the intermediate dsRNA genome, using a negative-sense strand as a template. Group V, (-)ssRNA viruses copy their genome directly from their negative-sense strand. Group VI and VII, ssRNA-RT, and dsDNA-RT viruses, use reverse transcription (RT) for replication. ssRNA-RT first transcribes their linear genome into dsDNA through RT. The dsDNA-RT group produces pregenomic RNA from dsDNA, followed by RT, resulting in newly produced dsDNA.

### 1.1.3 What happens when we get infected: our normal host immune response and inflammatory answer to viral infections

Host responses, such as Immune responses and inflammatory pathways are initiated by pattern recognition receptors (PRRs) which recognize specific components of viruses. This leads to signaling events and subsequently activation of innate immune cells and cytokines. The cytokine milieu generated decides the role of adaptive immune responses. Ideally, such immune responses and inflammatory stages favor viral clearance. However, the host response generated can cause damage to host self-cells. Thus, there is a fine balance of the immune system, where disruptions of this homeostasis can result in viral persistence or host tissue and cell damage (30). The following text explains briefly concepts of viral recognition, initiation of inflammation and adaptive responses to viral infections.

Once a virus enters a host, small molecular motifs such as pathogen- and damage-associated molecular patterns (PAMPs and DAMPs, respectively) are recognized by PRRs (31). The pattern of PRR activation determines the innate immune events, resulting in stereotyped inflammatory answers (31, 32). An example of PRRs includes Toll-like receptors (TLRs), which have vital roles in innate immune responses to viruses (30, 31, 33, 34). TLRs are expressed on a variety of innate immune cells, both on extracellular and endosomal compartments. TLR recognize different types of viruses (30, 35). TLR3 recognizes dsRNA viruses and viruses that generate dsRNA through their life cycle. TLR7 and TLR8 respond to ssRNA. Diversely, TLR9 recognizes dsDNA viruses (30, 35). Furthermore, TLR2 and TLR4 are implied in the detection of viral glycoproteins (30, 33, 35, 36). Cells also constitute cytoplasmic sensors, RIG-I-like receptors (RLRs). RLRs are RNA helicases, located in the interior of cells and recognize RNA viruses. Examples of RNA helicases are retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5). RIG-I recognizes 5-triphosphorylated ssRNA and short dsRNA. Contrarily, MDA5 recognizes longer dsRNA. (35, 37). Figure 3A illustrates PRR recognition of dsRNA, dsDNA and ssRNA viruses.

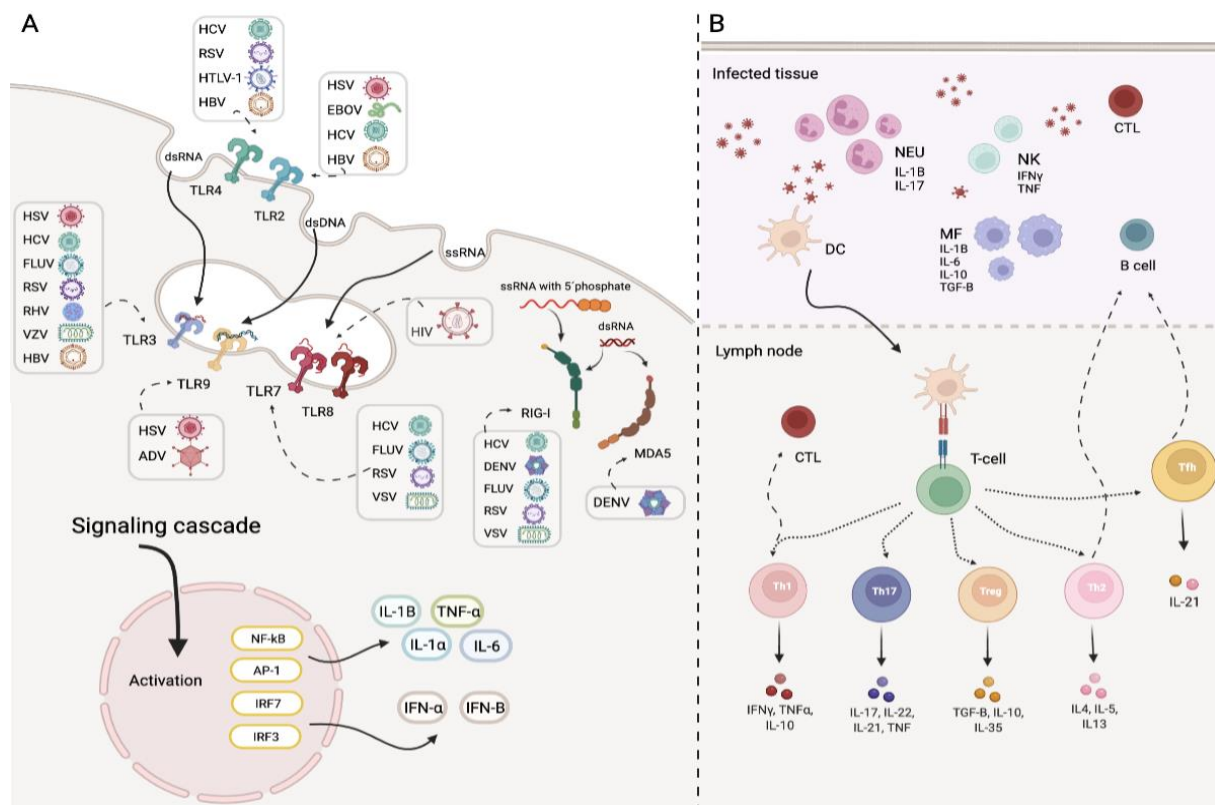
PRR signaling encourage the activation of the transcription factors NF- $\kappa$ B and AP-1 which results in the production of pro-inflammatory cytokines, such as interleukin 1 $\alpha$  (IL-1 $\alpha$ ), IL-1 $\beta$ , Tumor-necrosis factor  $\alpha$  (TNF- $\alpha$ ), and IL-6. These pro-inflammatory cytokines further stimulate the recruitment of immune cells. Furthermore, IRF7 and IRF3 result in type I interferon production, as IFN- $\alpha$  and IFN- $\beta$ . This Interferon production enhances the induction of interferon-stimulated genes (Figure 3A) (38, 39). All these contributions encourage the activation of inflammatory immune cells and pro-inflammatory cytokines.

Inflammation can cause damage to self-cells when the amount of pro-inflammatory cells and molecules exceeds a certain threshold. This overwhelming cytokine production is termed "cytokine storm" or "cytokine cascade" which occasionally lead to tissue damage (32, 40). Thus, blockade of PRRs might alleviate damaging inflammation associated with viral infections, such as those generated with SARS-CoV-2 (39). However, deficient immune activation and inflammatory responses would favor viral persistence.

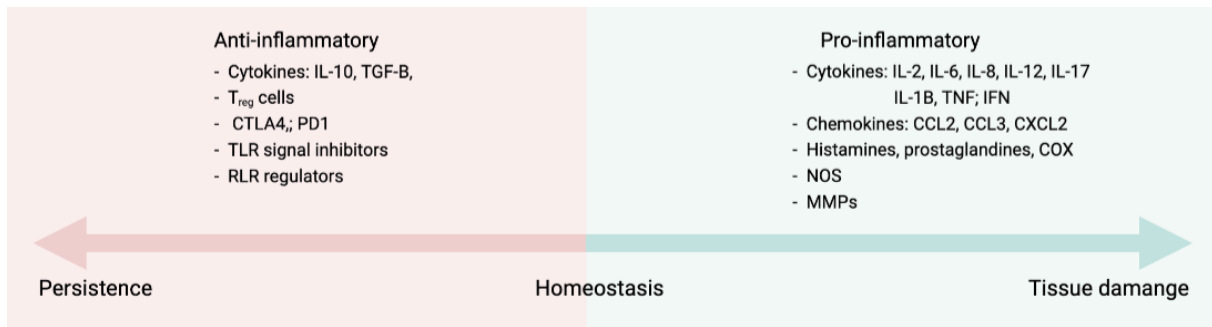
Some viruses trigger innate immune cells such as macrophages (MF), DC, and natural killer (NK) cells to produce anti-inflammatory molecules as IL-10 and transforming growth factor- $\beta$  (TGF $\beta$ ), which inhibits further inflammatory events. An anti-inflammatory milieu upon viral infection would favors viral pathogenesis (31). Accordingly, the balance of our immune system, including the inflammatory stage, is central to a successful host response to viral infections (Figure 4).



Innate immune responses initiate adaptive immune responses. Viral antigens are taken up by dendritic cells (DC) and presented to naïve CD4<sup>+</sup> T cells in draining lymph nodes. Depending on which cytokine milieu present, different T-helper cell (T<sub>H</sub>) responses are generated (Figure 3B) (31). This cytokine milieu varies extensively for different viruses, depending on route of infection, viral load, and host cell type infected (41-43). These Th subsets produce diverse cytokines, and have characteristic effects on immunological processes.



**Figure 3: Host responses during viral infection.** A. Common signaling receptors for dsRNA dsDNA, and ssRNA. Downstream signaling lead to the activation of the transcription factors IRF3, IRF7, NF-κβ and AP-1. These are involved in the generation of inflammatory processes. Inflammation is crucial immune defense in clearance of viral pathogens. In cases where innate immune responses fail to clear the virus, adaptive immune responses are generated. B. DCs present viral antigen to naïve CD4<sup>+</sup> T cells in draining lymph nodes, resulting in activation of different Th cell subsets, including Th1, Th17, Tregs, Th2 and Tfh cells. Th1 responses are most frequently observed against viral pathogens, involving the production of pro-inflammatory cytokines and cell-mediated immunity. Th2 and follicular T helper cells (Tfh) responses are important for activation of B-cell effector function and thus the production of neutralizing antibodies. Treg responses are on the other hand associated decline of inflammation. Th17 responses are important for recruiting neutrophils to the site of infection, but also avoidance of excessive immune responses.



**Figure 4: Factors affecting homeostasis of inflammation.** Several molecules are associated with anti-inflammatory and pro-inflammatory appearances. Cells producing cytokines such as IL-10 and TGF- $\beta$  contributes to an anti-inflammatory milieu. Also, T<sub>regs</sub>, and inhibitory receptors as CTLA4 and PD1 are associated with anti-inflammatory progressions. Cells producing cytokines such as IL-2, IL-6 and TNFs generate a pro-inflammatory milieu. Other components which enhance inflammation are matrix metalloproteinases (MMPs), chemical mediators as histamine and cyclooxygenases (COX) and several chemokines. An exaggerated inflammatory process is associated with tissue damage. On the other hand, the risk of viral persistence increases when components of the inflammatory process are inhibited.

## 1.2 Broad-spectrum Antivirals

Vaccines is a powerful tool for preventing incidences of emergent viruses once it has been described within the society, with potential to achieve widespread immunization in populations (44, 45). However, Vaccine targets remain undefined before an outbreak occurs (7). Therefore, a central challenge arises from vaccination: To predictively develop vaccines against emerging and resistant strains that might arise in the future (46). Another major hurdle is immunocompromised individuals, which will not respond robustly to vaccination (47).

This can be alleviated by using Antiviral drugs, a class of medications that targets specific viruses. Antivirals work by inhibiting the virus from multiplying but do not deactivate or destroy the virus particles (48-50). Antivirals can be divided into antiviral agents and antiviral drugs. Antiviral agents are molecules that have gone through preclinical stages for certain viruses, yet not approved for therapeutical use. On the other hand, antiviral drugs are approved for pharmacological use (46).

Antivirals selectively inhibit unique viral proteins, providing one drug, one bug solution. In contrast, Broad-spectrum antivirals (BSAs) can target multiple viruses and genotypes. Accordingly, BSAs inhibits common viral protein functions or common host factors required by several viruses (49). Nucleoside and nucleotide analogues are an excellent example of medications with antiviral activities, which inhibits replication and transcription of the viral genome (18, 50). They function by replacing viral nucleotides, terminating the synthesis. For example, Ribavirin works by inhibiting viral DNA or RNA synthesis. Ribavirin is approved

in the treatment of Hepatitis C virus (HCV), Respiratory syncytial virus (RSV), and FLUAV, and is implied in the treatment of vesicular stomatitis virus (VSV) (49, 51-54). Vidarabine, another nucleoside analogue, is currently approved to treat dsDNA viruses such as herpes simplex virus (HSV) and varicella-zoster virus (VZV). Other approved antiviral drugs include rimantadine, zanamivir, and oseltamivir for the treatment of influenza viruses (54). Also, contempt inconsistent proposals, FDA recently approved the use of remdesivir in hospitalized COVID-19 patients and in individuals with high-risk of hospitalization (55, 56) (Table 1).

**Table 1: Approved BSA drugs in clinical use.** FDA Approved antiviral drugs in the treatment of HSV, VZV, HBV, HIV, FLUV, human cytomegalovirus (HCMV), human papillomavirus (HPV) infections and SARS-CoV-2. The table includes antiviral name, brand drug name, approved clinical use, and if the antiviral is viral- or host-directed. The newest approved (remdesivir) and oldest approved (trifluridine) antivirals are shown from the top left panel to the bottom right panel. The information is retrieved from FDA, E.D.Clerq et al., and D.R.Tompa et al. (54, 57). ^ Discontinued monotherapies; \* Avigan (Japan), and Zostex against VZV (Europe).

BSA (Brand name)	Clinical use	Target	BSA (Brand name)	Clinical use	Target
Remdesivir (Veklury)	SARS-CoV-2	Viral	Valacyclovir (Valtrex)	HSV; VZV	Viral
Baloxavir marboxil	FLUV	Viral	Stavudine (Zerit)	HIV	Viral
Favipiravir (Avigan)*	FLUAV; FLUBV; FLUCV	Viral	Rimantadine (Flumadine)	FLUAV	Viral
Rilpivirine (Edurant)	HIV-1	Viral	Foscarnet (Foscavir)	HSV; HCMV	Viral
Etravirine (Intelence)	HIV-1	Viral	Didanosine (Videx)	HIV	Vira
Maraviroc (Selzentry)	HIV	Host	Famciclovir (Famvir)	HSV; VZV	Viral
Darunavir (Prezista)	HIV	Viral	Podofilox (Condylox)	HPV	Host
Tipranavir (Aptivus)	HIV-1	Viral	Ganciclovir (Cytovene)	HCMV	Viral
Emtricitabine (Emtriva)	HIV	Viral	IFN-a (Alferon N)	HPV	Host
Atazanavir (Reyataz)	HIV	Viral	IFN-a (Intron-A)	HCV; HBV; HPV	Host
Sofosbuvir	HCV	Viral	Zidovudine (Retrovir)	HIV	Viral
Adefovir dipivoxil (Hepsera)	HBV	Viral	Ribavirin (Copegus); (Virazole)	HCV; FLUV; RSV	Viral
IFN-a (Pegasys)	HCV; HBV	Host	Acyclovir (Zovirax)	HSV; VZV	Viral
IFN-a (Pegintron)	HCV	Host	Trifluridine (Viroptic)	HSV	Viral
Brivudine (Zostex)*	HSV-1; VZV	Viral	Amantadine (Symmetrel)^	FLUV	Viral
Docosanol (Abreva)	HSV	Viral	Idoxuridine (Dendrid)^	HSV	Viral
Zanamivir (Relenza)	FLUAV; FLUBV	Viral	Vidarabine (Vir-A)^	HSV; VZV	Viral
Oseltamivir (Tamifu)	FLUAV; FLUBV	Viral	Telbivudine (Tyzeka)^	HBV	Viral
Efavirenz (Sustiva)	HIV-1	Viral	Simeprevir (Olysio)^	HCV-1	Viral
Nelfinavir (Viracept)	HIV	Viral	Valganciclovir (Vistide)^	HCMV	Viral
Ritonavir (Norvir)	HIV	Viral	Cidofovir (Vistide)^	HCMV	Viral
Indinavir (Crixivan)	HIV	Viral	Zalcitabine (Hivid)^	HIV	Viral
Penciclovir (Denavir)	HSV	Viral	Amprenavir (Agenerase); (Symmetrel)^	HIV; FLUV	Viral
Saquinavir (Invirase)	HIV	Viral	IFN-a (Infergen)^	HCV-1	Host
Lamivudine (Epivir)	HIV; HBV	Viral	Boceprevir (Victrelis)^	HCV	Viral

These examples underline the importance of antivirals in viral disease management. Particularly, BSAs are favorable for treating viral co-infections, reducing the therapy complexity. BSAs can predictively be developed before an emergent strain appears in a population, thus having an advantage over vaccine development. Further, BSAs are propitious substitutes to vaccination programs, for instance, in immunocompromised individuals, meanwhile pending vaccine development, prophylaxis of acute viral infections, and demote pathogenesis once infected (18, 46, 47).

### 1.3 Prediction of BSA activity

#### 1.3.1 Drug target relevance: Host- and viral-directed BSA targets

BSA activity can be evaluated by investigation of several components. This includes for instance drug-target relevance (TR), which defines a BSA potential to target mechanisms important for viral replication. If a BSA target is associated with the replication of a virus of interest (Voi), the BSA is more likely to succeed in treatment strategies.

BSAs can be divided into virus-directed and host-directed BSAs (52, 58). Virus-directed BSAs target viral proteins essential for viral replication, such as proteins of the viral envelope or nucleic acids. Host-directed BSAs are those targeting cellular factors essential for viral replication (46). Virus-directed BSAs have less potential for toxicity compared to host-target BSAs (52). Further, host-directed BSAs are not selective and modulates the activity of major host-derived factors and pathways. Host-directed BSAs are therefore associated with a higher barrier to drug resistance than virus-directed BSAs (46, 52, 58-60).

RNA viruses encode an RNA-dependent RNA polymerase (RdRp) used for genome replication. Similar, viruses from BC groups VI and VII utilize viral derived reverse transcriptase (RT) for replication steps. BSAs targeting such viral proteins are therefore virus-directed BSAs (61).

Several viruses are dependent on Adenosine 5'-Triphosphatases (ATPases) for viral entry, commonly localized on the host endoplasmic reticulum and plasma membranes. Therefore, BSAs targeting ATPases are host-directed (62-64). Also, both dihydroorotate dehydrogenase (DHODH) and inosine monophosphate dehydrogenase (IMPDH) has been related to the virus life cycle of several RNA viruses (65, 66). Other host targets include Heat shock proteins (HSPs), necessary for various stages of the viral life cycle (67, 68). A selection of host derived BSA targets important for various virus strategies can be retrieved in Table 2.

**Table 2: Virus dependency on host targets.** The table shows host-derived targets, cellular functions, and their importance in virus pathogenesis. Virus and target abbreviations can be retrieved in supplementary Table S.1 and Table S.3.1, respectively.

Target	Cellular function	Virus	Target viral use
ABL	Regulation of cell proliferation, differentiation, and actin reorganization.	HCV	Viral entry (69).
ACE	Renin-angiotensin system; wound healing and inflammation	SARS-CoV-2	Viral entry (70, 71).
ADA	Purine metabolism	MERS-CoV	Inhibits viral entry (72).
		HIV; MeV; KSHV; EBV	Replication (73, 74).
ADRA	Regulation of neurotransmitter release	FLUV	Virus assembly (75).
AKT	PI3K-Akt signaling pathway	FLUV	Viral entry, internalization, and replication (76).
		EBV; HCV; HBV; HIV	Several (76).
		CPXV; VACV	Replication (77).
ATPases	Membrane transport	MHV; FIPV; VZV; CoVs; ZIKV	Viral entry (62-64, 78)
CCR	Inflammation	DENV	Replication (79).
		HIV	Viral entry (80).
CDKs	Cell division control; Modulation of transcription	HPV; hAdV; HIV; HSV; EBV; FLUAV; HTLV; ZIKV SARS-CoV-2; MERS-CoV; SARS-CoV	Several (81, 82).
CXCL8	Immunosuppression	HCV	Replication (83).
		HIV	Nuclear translocation (84).
DHODH	Pyrimidine synthesis	SARS-CoV-2; FLUAV; ZIKV; EBOV	Replication (65).
Eph-R	Regulate movement, survival, and proliferation	HCV; EBV; KSHV	Viral entry, several (85, 86)
ERBBs	Development	HCV; HBV	Viral entry (86, 87).
		VACV	Spread (77, 86).
FGFs	Development	HSV; ZIKV; FLUV; DENV	Replication (86, 88).
		HSV	Viral entry (86).
		EBV	Cell transformation (86).
		MERS-CoV	Lung cell apoptosis (86).
IMPDH	<i>de novo</i> synthesis of guanine nucleotides	CHIKV; JUNV; LASV; EBOV; ZIKV	Replication (66).
H-Ras	Regulation of cell division	HCV	Viral entry (87).
HSPs	Regulation of environmental stress	JEV; DENV; EV; VSV; hPIV; RSV; HCV	Replication (67, 68).
		HSV	Capsid transport (67, 68).
		HBV	Nuclear import and RT activity (67, 68).
JUN	Proliferation, apoptosis, and survival of cells	FLUAV (H5N1)	Viral pneumonia (89).
mTOR	Regulate cell growth and protein synthesis	hAdV	Replication (77).
		HCMV; BKPyV; KSHV	Several (90).
MYC	Regulation of cell proliferation and apoptosis	EBV	Replication, latency (91).

MAPKs	Directing cellular responses	AstV	Translation (77).
		CV-B3; JUNV	Replication (77).
		HCV	Genome synthesis (77).
NF-κB	Controlling transcription of DNA, cytokine production and cell survival	KSHV; MeV; RSV; WNV; HCV; EV; HSV; EBV; FLUAV; HBV; hRoV; POXV; VACV; VZV	Inactivate NF-κB (92).
		KSHV; HSV; HIV; HBV; HPV; hRoV	Activate NF-κB (92).
PDGFR	Regulating cell proliferation and differentiation	KSHV	Tumor progression (77).
		FLUV	Viral entry and internalization (86).
RAF	Regulatory link between Ras GTPases and MAPK cascade	HIV	Synthesis and release (77).
		B19B	Nuclear transport and capsid assembly (77).
SIRT	DNA repair; Proliferation; Metabolism	HIV; FLUAV; HSV; HPV; HBV; HCMV; VZV	Modulate histone modification on viral nucleosomes (93-95).
VEGF	Angiogenesis	ORFV	Replication (77).
		EBV; KSHV; DENV; HSV	Angiogenesis (96).

Most Host-directed BSAs work by inhibiting host factors. However, some host-directed BSAs work to activate innate immune responses against viruses, such as IFNs. IFNs are natural host-directed activators that result in cellular antiviral responses and subsequent attenuation of viral replication (46). Also, some BSAs have both host- and viral-directed activity. For instance, ribavirin targets both RNA-dependent RNA polymerase (RdRp) and inosine monophosphate dehydrogenase (IMPDH) (52, 97). Similar, suramin simultaneously target host and viral related factors. Furthermore, some BSAs are administered as prodrugs and are dependent on activation by either viral or host factors for exerting their antiviral effect (46).

### 1.3.2 Immunomodulatory BSAs

Immunomodulatory properties (IP) are important to predict prospective toxicity of investigated BSAs. Immunomodulatory antivirals cover all molecules with the potential to regulate components of our immune system. They work to either enhance or repeal immunological functions, specified as immunostimulatory or immunosuppressive drugs, respectively (98-100). Immunomodulatory drugs have been valuable in treating “cytokine storm syndromes”. Interestingly, the disease progression of many inflammatory syndromes shares similarities with viral pathogenesis. These features have been linked to FLUAV, HSV, HIV, MERS-CoV and SARS-CoV, but also implied in the recent emerging SARS-COV-2 (98, 101, 102).

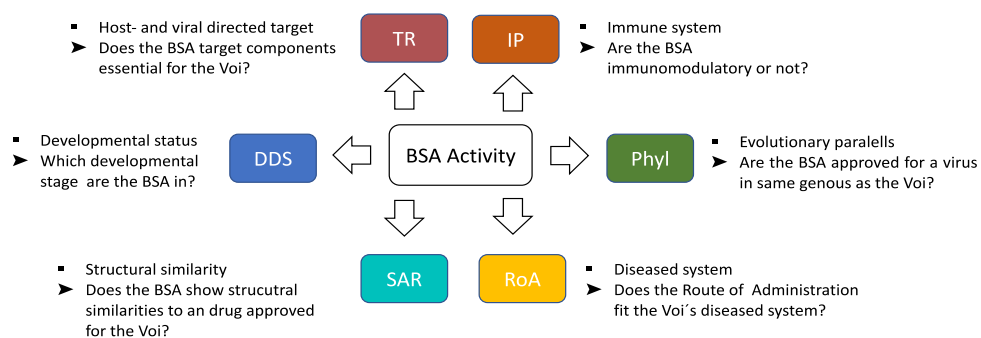
Immunosuppressive BSAs could be beneficial for the treatment of “cytokine storms”. However, such medications can prevent the development of adaptive immune responses,

allowing re-infections (58). Studies have shown a substantial correlation between a significant elevation of the pro-inflammatory cytokine IL-6 in severe COVID-19 cases (103). IL-6 are important for the recruitment of innate immune cells and the generation of inflammation. Accordingly, treatment of anti-inflammatory medications, such as anti-IL6 would prove beneficial for reducing adverse reactions seen in SARS-CoV-2. Similarly, the immunosuppressive agent hydroxychloroquine has been proposed as a potential treatment for severe COVID-19 cases. However, the risk of adverse effects outlines the potential clinical benefits (104). Like immunosuppressors, immunostimulatory medications are also related to adverse effects. Potent immunostimulatory BSAs could lead to the activation of cytokine storm events and subsequent tissue damage (58). Nevertheless, precise data on immunomodulatory activities are currently scarce (101).

### 1.3.3 Other components that can predict BSA activity

TR and IP are only a fraction of BSA activity components to be studied. BSAs can also be evaluated by Phylogeny- and structure- activity relationships. Structure-activity relationship (SAR) analysis reveal chemical structural similarities between BSAs, achieving clusters of comparable BSAs. Such analysis makes it possible to draw structural parallels between BSAs, but also the identification of compounds related to known BSAs. If the BSA is identical to a drug that has already been established against the Voi, the BSA is more likely to be profitable. Phylogenetic (Phyl) analyses are vital in virus exploration, especially in fields of viral epidemiology and diagnostics. Phylogeny investigates trait variations that can be measured for a group of viruses, thus revealing evolutionary parallels between viruses. For example, a BSA is more likely to be effective against a Voi if the BSA has already been approved for a virus closely related to the Voi (46).

Further, Drug developmental status (DDS) can predict a BSAs success. An investigational BSA identical to an approved drug is more likely to succeed than agents only passed *in vitro* testing. Also, BSAs require a Route of administration (RoA) that fits the viral pathogenesis and infection area. Typically, viruses tend to infect more than one specific organ system, thus having a widespread diseased system. For instance, EBV infections mainly affects the cardiovascular system (105). In this case, favorable BSAs are those administered intravenous, such as remdesivir. Most of the developed BSAs are only orally available, due to ease of development and distribution on the market (46). All these BSA activity components are crucial when evaluating a BSAs potential to produce a desired therapeutic effect in patients (Figure 5).



**Figure 5: Components of BSA activity prediction.** A variety of BSA components can be evaluated to assess BSA activity against a Voi. BSA target relevance (TR) involves the exploration of BSA targets, if a BSA target component(s) important for virus pathogenesis. By evaluation of Immunomodulatory properties (IP), BSA toxicity can be predicated. Potent immunomodulatory medications are commonly associated with adverse effects in patients. Thus, BSAs with no immunomodulation are likely to be beneficial. Furthermore, Phylogeny (phyl)- and structure-activity relationships (SAR) analysis connects evolutionary parallels between viruses and structural similarities between BSAs, respectively. Also, the Route of Administration (RoA) is essential when predicting BSA activity. A BSA must fit the Voi diseased system to be an efficient treatment alternative. Drug developmental status (DDS) denotes current developmental stage of the BSAs.

## 1.4 Drug development: from *in silico* explorative studies to clinical trials

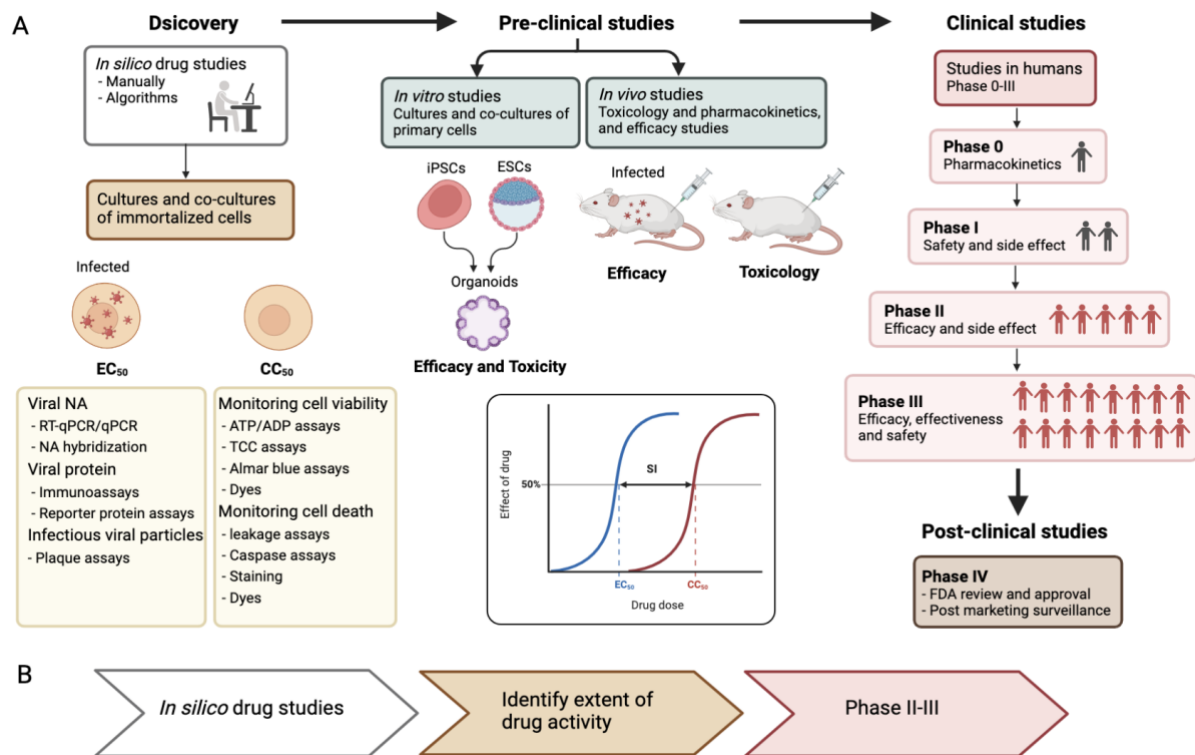
### 1.4.1 Traditional drug developmental phases

Before a drug can enter the pharmaceutical market as a licensed medicine, there are several authorization steps. It takes on average ten years for a new drug to complete the process from initial detection until its approval (106). Within this time frame, there are four essential steps. These include the discovery of the novel drug, pre-clinical studies, clinical trials, and post-clinical studies (Figure 6A).

The discovery of novel antiviral activities against a Voi is first explored in immortalized cells. Commonly, these cell cultures and co-cultures express suitable viral receptors for certain viruses, allowing the virus to enter the cells. Antiviral activities are further evaluated in pre-clinical stages, including *in vitro* and *in vivo* studies. *In vitro* studies comprise primary cells such as pluripotent stem cells (PSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) (18). Primary cells are isolated directly from tissue or blood and are highly specialized. iPSCs, ESCs, and other primary tissue cells are used to produce organoids, which are complex three-dimensional structures resembling organ-specific cell types. *In vivo* studies include immunocompetent or chemically immunocompromised animals. Here, the drug efficacy is elucidated by treating the animal with the drug and infecting it with the Voi (18, 106).



Clinical trials are the most time-consuming step in drug development. Phase 0 and I clinical trials include a few healthy volunteers. Participants in phase 0 are administered with subtherapeutic but pharmacologically active doses, assessing the bioavailability and half-life of the drug (51, 107). However, phase 0 is often skipped (51). Phase I establish a general safety of drug dosage. Further, phase II and III includes testing on patients with the viral disease in question. Phase II involves testing on more people than phase I. Participants are administered the ideal therapeutic dose, assessing the efficacy and side effects. Phase III involves the most participants, including placebos and double-blind studies. Phase III assesses the drug efficacy, effectiveness, and safety and are considered the longest phase in clinical trials. After completing phase III, the drug enters phases IV and V for approval or disapproval by U.S Food and Drug Administration (FDA) and post-market safety monitoring (51).



**Figure 6: Drug developmental steps and drug repositioning.** A. Drug development starts with the discovery of novel BSA activities. Novel antiviral activity is evaluated by Antiviral efficacy and cytotoxicity measurements of compounds. Positive results are further evaluated in pre-clinical studies. Pre-clinical studies include both studies in primary cells (*in vitro*) and animal models (*in vivo*). Further evaluation of a drug is performed in clinical studies (phase 0-III). Lastly, post-clinical studies involve post-marketing surveillance and examination of drug activity by the FDA. FDA decides if the drug should be approved for pharmaceutical use or discontinued, taken off the market. B. Drug repositioning makes it possible to skip time-consuming clinical phases 0-I.

#### 1.4.2 BSA discovery through repositioning

Developing new drugs is a time-consuming, expensive, and high-risk process (108). Therefore, many commonly known antivirals are a product of drug repositioning (or repurposing; redirecting; reprofiling), an evolving approach for drug development. Drug repositioning aims to redirect marketed drugs to target another use outside its original indication (46, 51). For instance, the pharmacological nature of a drug off-target might present the prospect of treating other disorders (57). Accordingly, new medical uses can be identified for approved or investigational drugs, giving additional value to existing medications.

Drug repositioning is a highly efficient process compared with traditional drug development and decreases the time cost significantly (57, 108, 109). Drug repositioning makes it possible to skip both pre-clinical stages and phase 0-I of clinical trials, as these stages are unspecific for any new indication of drug activity. Therefore, synthesis, manufacturing, safety profiling, pharmacokinetic evaluation in animal models, and early clinical developmental steps are already available (51, 57, 108, 109). Since safety profile of repositioned drugs are previously confirmed, drug repositioning holds a higher rewards with lower risk compared to traditional drug development (108). Further, by repositioning BSAs, the cost-effectiveness would increase even further, as the overall developmental cost can be distributed across many viral indications (46).

Normally, drug repositioning consists of three steps before potential approval of the candidate drug (Figure 6B). The first and most critical step includes "indication discovery", to detect drug candidates for a given indication. This step includes *in silico* explorative studies (110). *In silico* studies can be both manually and algorithm-based screening. Manually studies include literature review and database searches, to obtain evidence for potential drug candidates. This method gives low throughput and is highly time-consuming. Manually generated studies are often preferred when less data is available, for instance in cases of newly introduced viruses. Plenty of algorithm-based screening methods can be applied, including signature matching, computational molecular docking, pathway, network mapping and Genome-wide association studies (GWAS) (108, 110-112). This method gives higher throughput than manually based studies. Algorithm-based screening is preferred when much data is available, such as in case of well-established viruses (110, 111).

The following step includes experimental studies to confirm high-hit drug-virus interactions from phase 1, to identify the extent of antiviral activity of drug candidates for its new indication. Further, the BSA enter phase II and III, which assess the drug's efficacy, effectiveness, safety, and side effects in patients (111).

### 1.4.3 Measuring antiviral efficacy and cytotoxicity

The potential for a drug as an antiviral is often measured by the selectivity index (SI) or therapeutic index. These two parameters are relative to each other, giving the same relationship of measurements (this measurement is henceforward mentioned as SI). SI results from dividing antiviral cytotoxicity by antiviral efficacy (Equation 1) (113). Antiviral efficacy is often given by the half-maximal effective concentration ( $EC_{50}$ ), the concentration needed to obtain a 50% antiviral effect. Also, but less commonly, antiviral efficacy can be given as the half-maximum inhibitory concentration ( $IC_{50}$ ), which is a substance potency to inhibit 50% of viral replication. Cytotoxicity can also be given by  $IC_{50}$  but is furthermost given as the compound's half cytotoxic concentration ( $CC_{50}$ ), which is the concentration that reduces the cell viability by 50% (113, 114).

**Equation 1:** Selectivity index (SI).  $SI = \frac{CC_{50}}{EC_{50}}$

An ideal drug should have a low active concentration, and a relatively high cytotoxic concentration (113). Accordingly, the greater the value of SI, the drug are more likely to gain approval for development, and the drug is less likely associated with high-risk in patients (107). Thus, SI reflects the window between antiviral efficacy and cytotoxicity.

Antiviral efficacy can be measured experimentally by detecting viral nucleic acid, viral proteins, or infectious particles. The most used methods include plaque reduction assays, which detect infectious viral particles. These measurements designate viral infection for a variety of drug concentrations. Furthermore, cytotoxicity assays can be experimentally determined by monitoring cell viability or cell death. Cell viability assays include techniques such as metabolic assays and exclusion and reduction dyes. Likewise, cell death can be measured by apoptotic and metabolic assay, but also by staining and dye methods (51).

$EC_{50}$  and  $CC_{50}$  are often measured in cultures and co-cultures of immortalized cells in the exploratory phase of drug development. Pre-clinical *in vivo* studies measure the efficacy of antivirals by visualizing clinical signs and estimates the development of immunity and viral titers. Further, toxicological *in vivo* studies denote the maximum tolerated dose by measuring drug absorbance and duration (51).

Another parameter which indicates drug activity is drug sensitivity score (DSS). DSS represent the normalized version of area under the curve (AUC), whereas AUC describes the total drug exposure at function of time. Thus, DSS quantify the sum of response intensity, and thus a drug's sensitivity can be revealed across a broad range of viruses (115, 116).

## 2 Aims and Objectives of the project

Over the past years, humans have faced several major viral epidemics and pandemics unprepared. During widespread viral outbreaks, vaccines and antiviral drugs have shown to be influential on the outcome. However, several hurdles are associated with vaccine use, such as the appearance of vaccine-immune viral strains. Also, vaccine and drug development are highly time-consuming, which is not time matching when a pandemic has already emerged. This is solved by drug repositioning, which offers a rapid and low-cost approach against emergent viruses. As preparation for drug repositioning steps, databases summarizing material on antiviral research and methods for identifying the most promising BSAs are essential.

Subsequent to the SARS-CoV-2 emergence, the crowded material and information on antiviral activity became even harder to follow. To assemble and review BSA activity, my research team generated DrugVirus.info database containing safe-in-man BSAs. I aimed to enrich this BSA database, which facilitated the visualization and comparison of antiviral activities. Accordingly, we managed to expand the already available BSA information from DrugVirus.info and incorporated BSA-containing drug combinations (BCCs) into the portal ([DrugVirus.info 2.0](#)).

Furthermore, drug repositioning includes an initial and vigorous step: discovery and identification of new BSA attributes. For that purpose, we generated a six-component BSA scoring system to evaluate BSA activities. Thus, my aim was to examine components within the BSA-scoring system, to select promising BSAs for drug repositioning and for evaluation in combinations. To investigate promising BCCs, we developed a four-component BCC scoring system. Together, these scoring systems enabled the prediction of both BSAs and BCCs against potential pandemic viruses.

Accordingly, this thesis will address the following trends:

- Development of DrugVirus.info 2.0 BSA database by manual *in silico* curation of peer-reviewed scientific literature.
- Development of BSA scoring system for prediction of a few from 255 most promising BSAs.

### 3 Material and Methods

Data material for this thesis work was obtained through a comprehensive literature and database search in each section, divided into two parts: the generation of DrugVirus.info 2.0 database and a BSA scoring system. Each part consists of separate sections. Each section describes search strategy and selection criteria, and data curation. Snapshots of excel files were added as illustrations of data curation.

#### Part 1: DrugVirus.info 2.0 database

My contributions in developing the DrugVirus.info 2.0 database was to expand the initial BSA database and *in silico* assemblage of antiviral activities from published scientific papers. These two contributions were used to create the final DrugVirus.info BSA database.

#### 3.1 BSA database expansion

##### 3.3.1 Search strategy and selection criteria

The initial population of DrugVirus.info BSA database provided within my research group was expanded with experimental, investigational, approved, and withdrawn BSAs. To identify those BSAs, antivirals were inspected by their antiviral activity. Only antivirals with activity against more than two different viruses within two different viral families were included. Accordingly, antivirals with activity against less than two viral families were excluded from the database, as they do not meet the criteria for being BSA. Other exclusion factors include illicit drugs, mixtures, metals, and exclusively veterinary drugs.

##### 3.3.2 Curation of data output

For each BSA, the drug name(s), approval status, primary activity indication, potential target, mode of action, PubChem ID, DrugBank ID, and InChI key were recorded.

Drug	Other Names	Approval Status	Primary Indication	Potential target	Drug_Bank_ID	PubChem_CID	Mode_of_action	InChI_Key
25HC	25-Hydroxycholesterol	Experimental	Anticancer	Human membrane	DB04710	65094	Inhibits viral entry	INBG5XNNRGLWJU-ZHHJC
Digitoxin		Experimental	Antiarrhythmic	Human ion transporter	DB01396	441207	Inhibits viral entry	WDJUJZGPOPHGTGOT-XUDU
Sertraline		Approved	Antidepressant	Human serotonin transporter	DBSALT000808	68617	Mediates sodium-dependent	VGKDLMBJGBXTGI-SJCJKP
Tetrandrine	Fanchinine; Sinomenin	Experimental	Anti-inflammatory	Human ion channel	n.a.	73078	Prevents viral entry	WVTKBKWTSCPRNU-KYJU
Valacyclovir	Valaciclovir	Approved	Antiviral	Viral DNA pol; Viral RNA polymerase	DB00577	135398742	Inhibits viral DNA synthesis	HDOOVUKNUBWVHOX-QM
Verdinexor	KPT-335	Investigational	Antiviral	Human exportin 1	DB12207	71492799	Nuclear export inhibitor	OPAKEJZFFCECPN-XQRV

Further, drug-virus interactions were recorded. The viral target name and abbreviation, BC (virus group), virus family, and viral disease were recorded for each drug. Also Recorded was the developmental status of the drug-virus interactions.

Drug	Virus	Virus Group	Cell lines	Primary cells	Animal model	Phase I	Phase II	Phase III	Approved	Phase IV	Reference	Virus Family	Virus Name	Viral disease
25HC	ZIKV	(+)ssRNA	*								PMID: 2831	Flaviviridae	Zika virus	Zika virus disease
25HC	HIV-1	ssRNA-RT	*		*						PMID: 2327	Retroviridae	Human immunodeficiency virus	Acquired immunodeficiency syndrome
Digitoxin	CMV	dsDNA	*								PMID: 2932	Herpesviridae	Human cytomegalovirus	Mononucleosis
Digitoxin	SARS-CoV-2	(+)ssRNA	*								PMID: 3477	Coronaviridae	Severe acute respiratory syndrome coronavirus 2	COVID-19
Sertraline	PICV	(-)ssRNA	*								PMID: 3070	Arenaviridae	California mammarenavirus	No disease in humans
Sertraline	LASV	(-)ssRNA	*								PMID: 3070	Arenaviridae	Lassa mammarenavirus	Lassa hemorrhagic fever
Tetrandrine	HSV-1	dsDNA	*		*						PMID: 9326	Herpesviridae	Human alphaherpesvirus 1	Cold sores
Tetrandrine	EBOV	(-)ssRNA	*								PMID: 3180	Filoviridae	Zaire ebolavirus	Ebola hemorrhagic fever
Valacyclovir	EBV	dsDNA							*		CID:135398	Herpesviridae	Human gammaherpesvirus 4	Infectious mononucleosis
Valacyclovir	HBV	dsDNA-RT							*		CID:135398	Hepadnaviridae	Hepatitis B virus	Hepatitis B
Verdinexor	EBV	dsDNA				*					PMID: 3033	Herpesviridae	Human gammaherpesvirus 4	Infectious mononucleosis
Verdinexor	FLUAV	(-)ssRNA			*						PMID: 2789	Orthomyxoviridae	Influenza A virus	Influenza

This section was performed by all group members within my research group. Data assembled was added to the DrugVirus.info 2.0 BSA database, represented in a heat-map. This BSA collection was used in all further sections described in this thesis.

## 3.2 *In silico* assembly of antiviral activity

### 3.2.1 Search strategy and selection criteria

A manual literature search in PubMed was performed of all BSAs within our database. The searches included the respective BSAs and the following keywords: "EC50" and "CC50" or "IC50" and "CC50" or "selectivity index" or "antiviral activity" and "cytotoxicity". The searches were restricted to "antiviral activity" only to identify articles involving viral activity. Selected papers were reviewed, and the most applicable were included. Excluded papers include those not reporting the cell line used in measurements.

### 3.2.2 Curation of data output

For each unique drug, the drug name, target virus, cell line, antiviral efficacy values, cytotoxicity values, SI values, and PMID reference were recorded when available. All data was gathered and presented in an excel-table.

DrugName	Virus	Cell line	Antiviral efficacy	Cytotoxicity	SI	PMID
25HC	hRoV	MA104	0.16uM (0.12-0.2)	>150uM	>938.	30212801
Digitoxin	HSV-1	Vero	0.05uM	10.66uM	213.	18353452
Sertraline	EBOV	Huh7	3.79uM	22.61uM	5.97.	29939303
Tetrandine	hCoV-229E	MRC-5	0.33uM (+-0.03)	13.41uM (+	40.19.	31690059
Verdinexor	hAdV-5	HeLa	0.18uM	0.18uM	1.	30332435

Standardized converting methods were used for converting antiviral efficacy and cytotoxicity values. Nanomolar (nM), micromole per milliliter (umol/mL), nanomole per milliliter (nmol/mL), and millimolar (mM) into micromolar (uM). Further, gram per liter (g/L), nanogram per milliliter (ng/mL), microgram per milliliter (ug/mL), gram per liter (g/L), and milligrams per liter (mg/L) were all converted. The molecular weights used for the respective BSAs were retrieved from the PubChem database, given in g/mol. The BSAs and their corresponding molecular weight used can be found in supplementary Table S.2.2.

In cases where SI was not specified, BSA antiviral efficacy and cytotoxicity measurements were used to calculate SI, using Equation 1. Calculated SI was included for each BSA into the DrugVirus.info 2.0 BSA database.

## Part 2: BSA scoring system

My contributions to generating a BSA-scoring system were to evaluate BSA targets and immunomodulatory properties. Potential viral- and host targets have previously been investigated within my research group. This section was therefore indented as an expansion of already available information. Investigation of immunomodulatory properties was a new supplement to my research group. This, together with phylogeny- and structure-activity relationship analysis, route of administration, and developmental status assessed, were used to generate suitable scores for each BSA (46). The two following sections describes search strategy and data curation in examinations of drug target relevance and immunomodulatory properties, followed by stepwise explanation of BSA-scoring system generation.

### 3.3 Drug target relevance: BSA targets

#### 3.3.1 Search strategy and selection criteria

BSA targets were retrieved and evaluated from three following databases: DrugBank; Therapeutic Target Database (TTD); and Drug Gene Interaction database (DGIdb). There were no criteria selected for database searches within DrugBank and TDD. Within DGIdb, only drug-host target genes with an interaction score of more than 0.1 were assembled.

#### 3.3.2 Curation of data output

From DrugBank and TDD database, both viral proteins and host target genes were assembled. Viral proteins were recorded due to the lack of viral gene names. N.a. indicates when searches in DrugBank or TDD were not appearing or when the respective BSA did not have any reported targets. Furthermore, only host target genes were available within DGIdb. Within the DGIdb, N.a. indicates searches which were not appearing or when the drug-target interactions did not meet the search criteria.

BSA	DrugBank		DGIdb	TTD	
	Host target	Viral target	Host target	Host target	Viral target
25HC	N.a.	N.a.	N.a.	N.a.	N.a.
Digitoxin	ATP1A1 (inhibitor)	N.a.	ATP1A1, ATP1B2,	ATP1A1, ATP1A	N.a.
Etravirine	N.a.	gag-pol (HIV-1)	ABCC3, ABCG2, AB	N.a.	gag-pol (HIV-1,
Sertraline	SLC6A4 (inhibitor and b	N.a.	SLC6A4 (inhibitor,	SLC6A4 (inhibite	N.a.
Tetrandrine	ABCB1 (inhibitor)	N.a.	N.a.	N.a.	N.a.
Zanamivir	NEU2 (inhibitor)	NA (FLUAV A/B;	N.a.	N.a.	NA (FLUAV A/W

The targets were further evaluated based on their functionality. Targets that were found within the same protein family were clustered together. Both host and viral targets were illustrated in two manually made heat maps.

## 3.4 Immunomodulatory properties

### 3.4.1 Search strategy and selection criteria

Immunomodulatory properties were evaluated based on published scientific papers in PubMed. The manual PubMed searches included the BSA of interest and keywords such as "Immunomodulatory" and "Immunosuppressive" or "Immunostimulatory". Furthermore, DrugBank ATC classification of "Antineoplastic and immunomodulating agents" (L) were used to support the immune-modulatory indications of all BSAs from the PubMed searches. Within this classification, DrugBank ATC sub-classification of immunosuppressive compounds (L04) and immunostimulatory compounds (L03) were used.

### 3.4.2 Curation of data output

For each drug, immunomodulatory property (yes or no), implied activity, and its effect on the immune system or inflammation was recorded. If the BSA were specified with immunomodulatory activities on the first five pages on a PubMed search, the BSA was recorded with "yes". Similar, if the BSA was specified with no immunomodulatory appearances, the BSA were recorded with "No". If immunomodulating activities were not apparent, the BSA was assumed to have nonobvious immunomodulatory appearances, designated with N.a.

If a BSA were specified with "yes", its indicated activity was recorded. The indicated activity was recorded as either immunosuppressive or immunostimulatory, as central separation. Some BSAs were identified with minor suppression of the immune system or with unspecified suppressive activity. These BSAs were therefore classified as "implied immunosuppressive". BSAs with immunomodulatory properties that directly affected inflammation was specified with pro-inflammatory or anti-inflammatory activities. BSAs with overlapping activities were given more than one activity (e.g., immunosuppressive and anti-inflammatory, or anti-inflammatory and pro-inflammatory). Lastly, a more detailed description of the BSAs' effect on the immune system or inflammation was recorded.

BSA	Immunomodulator	Indicated activity	Effect on the immune system	Reference
25HC	Yes	Pro-inflammatory	Amplifies inflammatory signaling	PMID: 24994901
Alisporivir	No	N.a.	N.a.	PMID:32376613
Clotrimazole	Yes	Implied immunosuppressive	Inhibits IKCa1 channels in activation	PMID: 10884437
Digitoxin	N.a.	N.a.	N.a.	N.a.
Fluvastatin	Yes	Anti-inflammatory and pro-inflammatory	Induce IL-1beta release; trigger inflammation	PMID: 31573980;
Monensin	Yes	N.a.	Reduced IL-1beta secretion; inhibition of signaling	PMID: 26936096;
Sertraline	Yes	Immunosuppressive	Inhibitors of innate signaling pathways	PMID: 20382888
Sunitinib	Yes	Immunostimulatory	Reduce expression of immunosuppressive factors	PMID: 21716852;



### 3.5 Generation of BSA-scoring system

A six-component BSA scoring system was generated within my research group to identify the most promising monotherapies, covering different virus species within five Baltimore groups (group I, IV, V, VI, and VII). The BSAs scoring was based on giving each component a size, representing favorable and less favorable BSA properties. The following components (C) were used in the scoring system: Structure-activity relationship (SAR); Drug developmental status (DDS); Drug target relevance (TR); Drug immunomodulatory properties (IP); Route of administration (RoA); and Phylogeny (Phyl). Each of the respective BSAs was scored as follows (46):

- I. SAR component ( $C_{SAR}$ )
  - ⇒ If the BSA is identical to a drug which has been developed or is currently under development for the virus of interest (Voi),  $C_{SAR} = 1$ ;
  - ⇒ If the BSA is structurally similar to a drug which was developed or under development against the Voi,  $C_{SAR} = 0.5$ ;
  - ⇒ If the BSA has a distinct structure,  $C_{SAR} = 0$
- II. DDS component ( $C_{DDS}$ ), only applies to BSA with  $C_{SAR} = 1$ 
  - ⇒ If the BSA is approved or is in phase IV clinical trials against the Voi,  $C_{DDS} = 1$ ;
  - ⇒ If the BSA is in phase I-III clinical trials,  $C_{DDS} = 0.75$ ;
  - ⇒ If the BSA has been tested *in vivo*,  $C_{DDS} = 0.5$ ;
  - ⇒ If the BSA has been tested *in vitro*,  $C_{DDS} = 0.25$ ;
  - ⇒ If the BSA has not been tested,  $C_{DDS} = 0$ ;
- III. TR component ( $C_{TR}$ )
  - ⇒ If the confirmed primary target of the BSA in question is associated with Voi replication (the drug target is essential for Voi replication),  $C_{TR} = 1$ ;
  - ⇒ If not,  $C_{TR} = 0$
- IV. IP component ( $C_{IP}$ )
  - ⇒ If the BSA does not interfere with host immune response,  $C_{IP} = 1$ ;
  - ⇒ If the BSA is immunomodulatory,  $C_{IP} = 0$
- V. RoA component ( $C_{RoA}$ )
  - ⇒ If the Route of administration (RoA) of the BSA is well-suited for the diseased system (for example, inhalation of drug for treatment of respiratory viruses),  $C_{RoA} = 1$ ;
  - ⇒ If not,  $C_{RoA} = 0$
- VI. Phyl component ( $C_{Phyl}$ )
  - ⇒ If the Voi is in the same genus as the virus for which the BSA has been developed,  $C_{Phyl} = 1$ ;
  - ⇒ If the Voi is in the same family,  $C_{Phyl} = 0.5$ ;
  - ⇒ If the Voi is in a closely-related family,  $C_{Phyl} = 0.25$ ;
  - ⇒ If the Voi is distantly-related,  $C_{Phyl} = 0$

To calculate the final BSA score, the points across all six components were summated together, using the formula for BSA score:

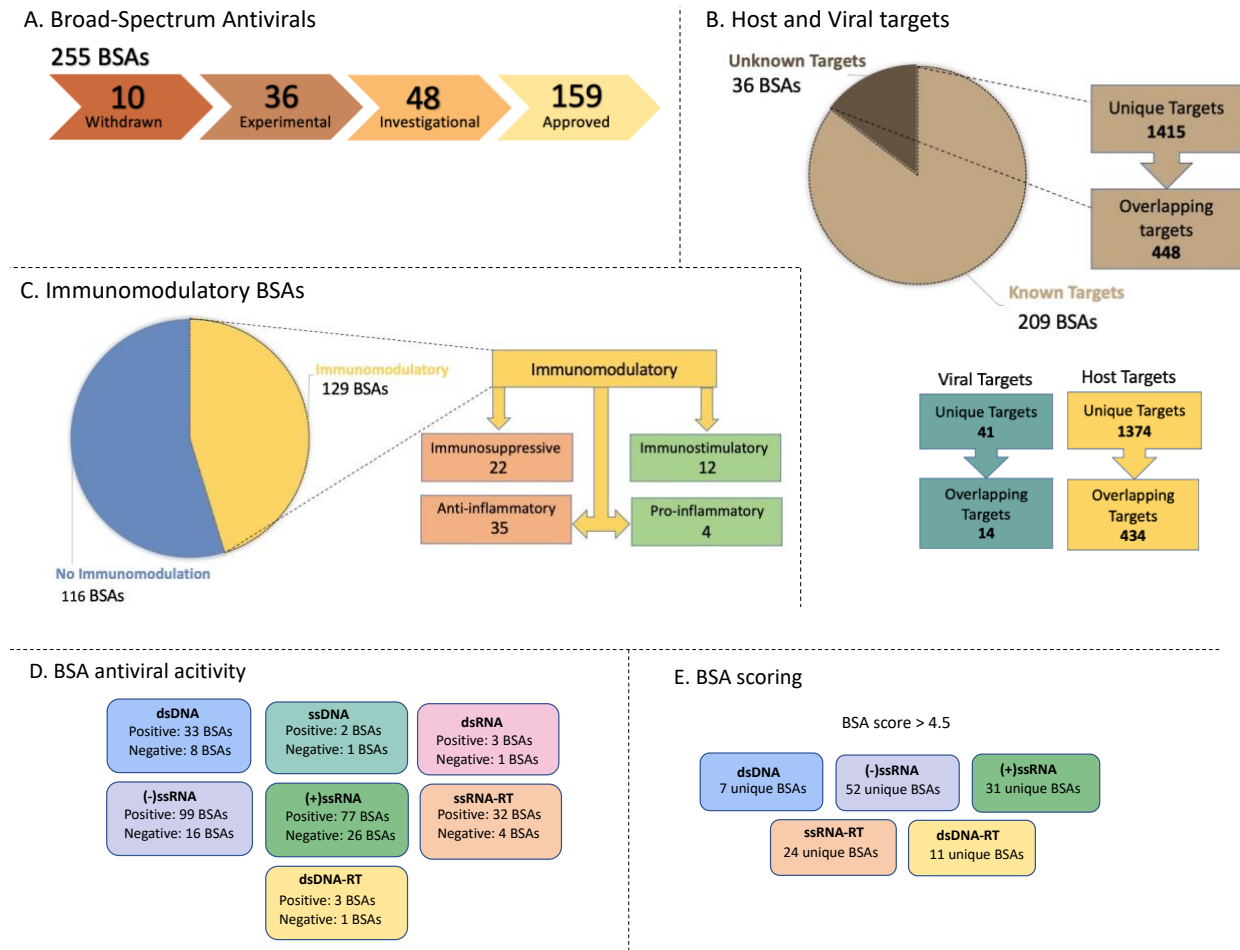
**Equation 2:** BSA score formula.  $BSA\ score = C_{SAR} + C_{DDS} + C_{TR} + C_{IP} + C_{ROA} + C_{Phyl}$

For instance, the activity of Elvucitabine against HBV was scored at 4.5. Elvucitabine showed structural similarities to Lamivudine, which is currently approved for treating HBV, and therefore  $C_{SAR}$  were scored to 0.5. Since  $C_{SAR}$  were less than 1,  $C_{DDS}$  equals 0. Further, elvucitabine blocks reverse transcriptase by inhibiting the viral enzyme reverse transcriptase, and thus  $C_{TR}$  were scored 1. The BSA was not apparent with any immunomodulatory activities, and therefore  $C_{IP}$  were also scored 1. Furthermore, Elvucitabine is orally developed, which fits HBV diseased system, which gives  $C_{ROA}$  that equals 1. The BSA was initially developed for treating HIV, but are also indicated in the treatment of HBV, and therefore were  $C_{Phyl}$  scored 1.

The most promising BSA monotherapies were further evaluated in combinations by developing a four-coefficient BCC scoring system, to identify the most promising combinational therapies. This BCC scoring system were generated by coefficients for drug interaction, drug-target interaction, drug-target stage of replication and drug RoA.

## 4 Results

As for methods, results are divided into two parts: Generation of the DrugVirus.info 2.0 database and a BSA-scoring system. Certain figures are retrieved from the published article, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022, for supportive means (46).

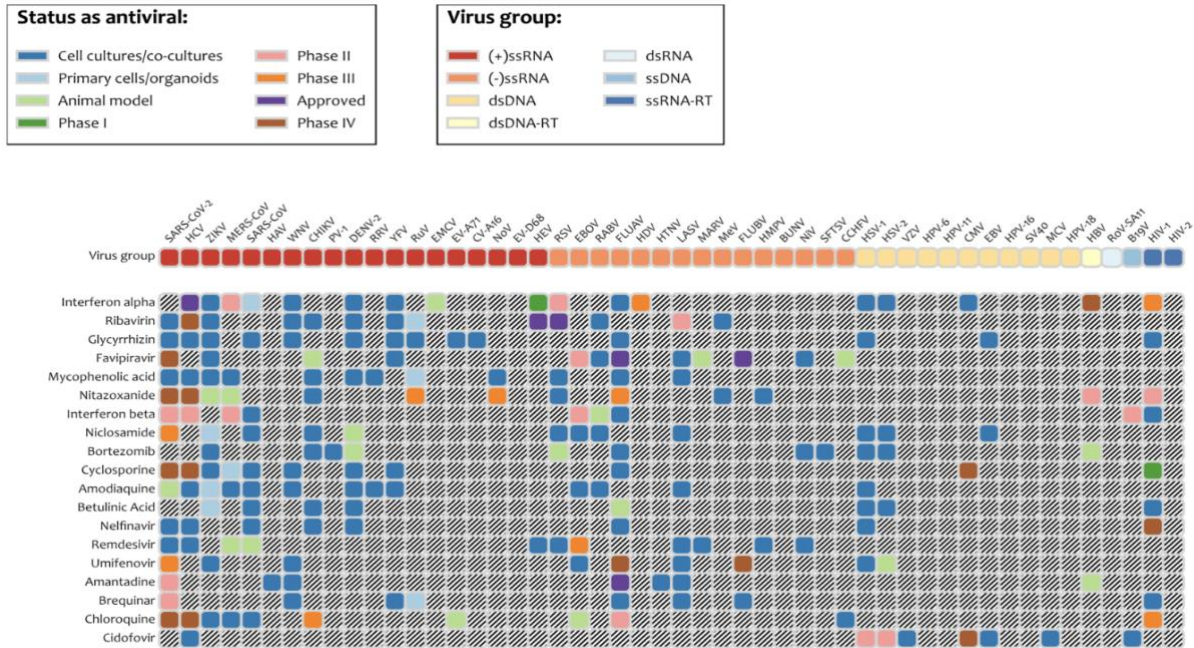


**Figure 7: Summary of results.** A. Our database contains approved, investigational, experimental, or withdrawn BSAs. In total, the database consists of 255 BSAs, whereas 159 are approved for pharmaceutical use in humans. B. Out of the 255 BSAs, 209 had known targets. Together, 1415 unique targets were identified. Interestingly 448 of these targets are commonly seen in two or more BSAs. C. 129 BSAs were identified with immunomodulatory properties. 22 BSAs were evaluated as suppressive of our immune system, meanwhile 12 BSAs were indicated with stimulatory effects. The majority, 35 BSAs, were indicated as anti-inflammatory, meanwhile 4 were indicated pro-inflammatory. D. Positive ( $SI > 1$ ) and negative ( $SI \leq 1$ ) antiviral activity within each BC group. E. From our scoring system, illustrated is the amount of unique BSAs which scored above 4.5 within each BC group.

## Part 1: DrugVirus.info 2.0 database

### 4.1 BSA database expansion

Our database expanded from 116 BSAs to 255 BSAs. These can be reviewed in the Drugvirus.info 2.0 BSA database. This is shown as an integrative heat-map of BSAs, which enables the visualization and exploration of BSA-virus interactions (Figure 8).



**Figure 8: DrugVirus.info 2.0 BSA heat-map.** Figure illustrates a section of the BSA Heat-map within DrugVirus.info 2.0 database. Shown is the BSAs on the vertical axis, and the virus targets on the horizontal axis. The viruses are categorized into its Baltimore class (virus group) in colors. Also indicated is the developmental status (status as antiviral) for each BSA, where grey shading designates BSA-virus interactions not studied or reported. BSAs are also ranged from the ones targeting the most viruses (upper), to the fewest (bottom).

### 4.2 *In silico* assembly of antiviral activity

The manual curation of >2000 PubMed articles allowed the assembly of  $CC_{50}$  and  $EC_{50}$  from published papers. SI could be calculated from these measurements, reflecting each unique BSA activity (Supplementary Table S.2.1). The SIs revealed several BSAs with positive and negative antiviral activities (Figure 7E). BSAs considered with positive antiviral activity were those gaining a  $SI > 1$ . BSAs with negative antiviral activity were predicated when  $SI \leq 1$ .

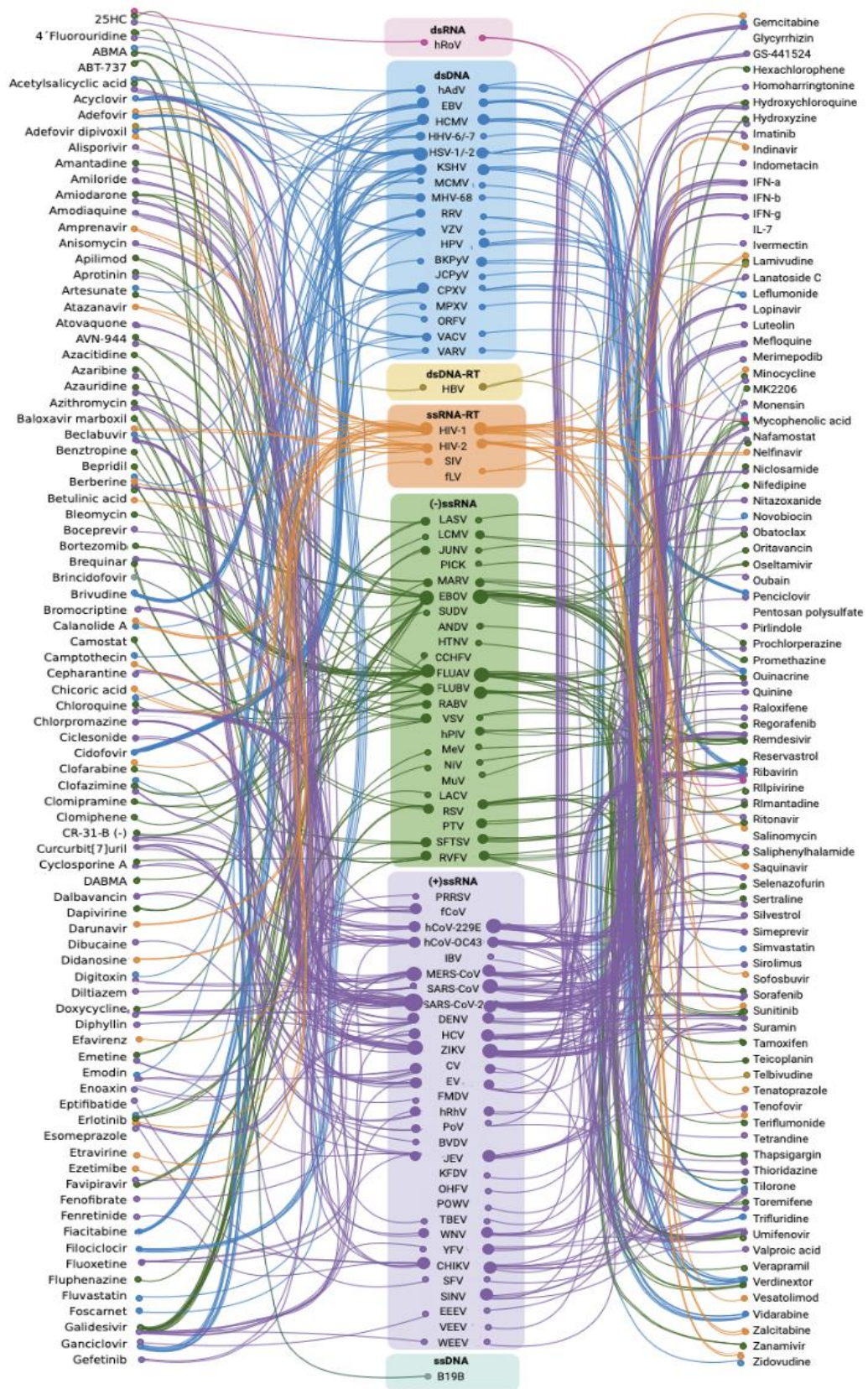
Many already approved BSAs, with known antiviral activity against a particular virus, were indicated with high SI. Interestingly, several not-yet-approved BSAs were reported with

high SI against certain viruses. The majority of BSA antiviral activity was specified against ssRNA viruses. Especially *Filoviridae* and *Orthomyxoviridae* family of (-)ssRNA and *Flaviviridae* and *Coronaviridae* family of (+)ssRNA was most tested *in vitro*. Also, several BSA has been tested against *Retroviridae* family of the ssRNA-RT group. Within the dsDNA group, BSAs are mostly tested against the *Herpesviridae* family of viruses (Figure 9).

Adefovir dipivoxil is approved for the treatment of HBV from the dsDNA-RT BC group. This BSA gained SI > 1 for dsDNA CPXV, VARV, and VACV and the ssRNA-RT HIV-1. Further, brivudine is approved for the treatment of the dsDNA BC group members HSV-1 and VZV. In searches, this BSA gained SI > 1 for other dsDNA viruses (CPXV, EBV, KSHV, HSV-2, MHV-68, RRV, and VACV). This was also the case for ganciclovir, which is approved in the treatment of HCMV (EBV, HHV-6, HHV-7, KSHV, HSV-1, HSV-2, MCMV, MHV-68, and RRV). Favipiravir is approved in Japan for treating influenza strains, and were found with SI > 1 for (-)ssRNA EBOV and SFTSV, and (+)ssRNA SARS-CoV-2.

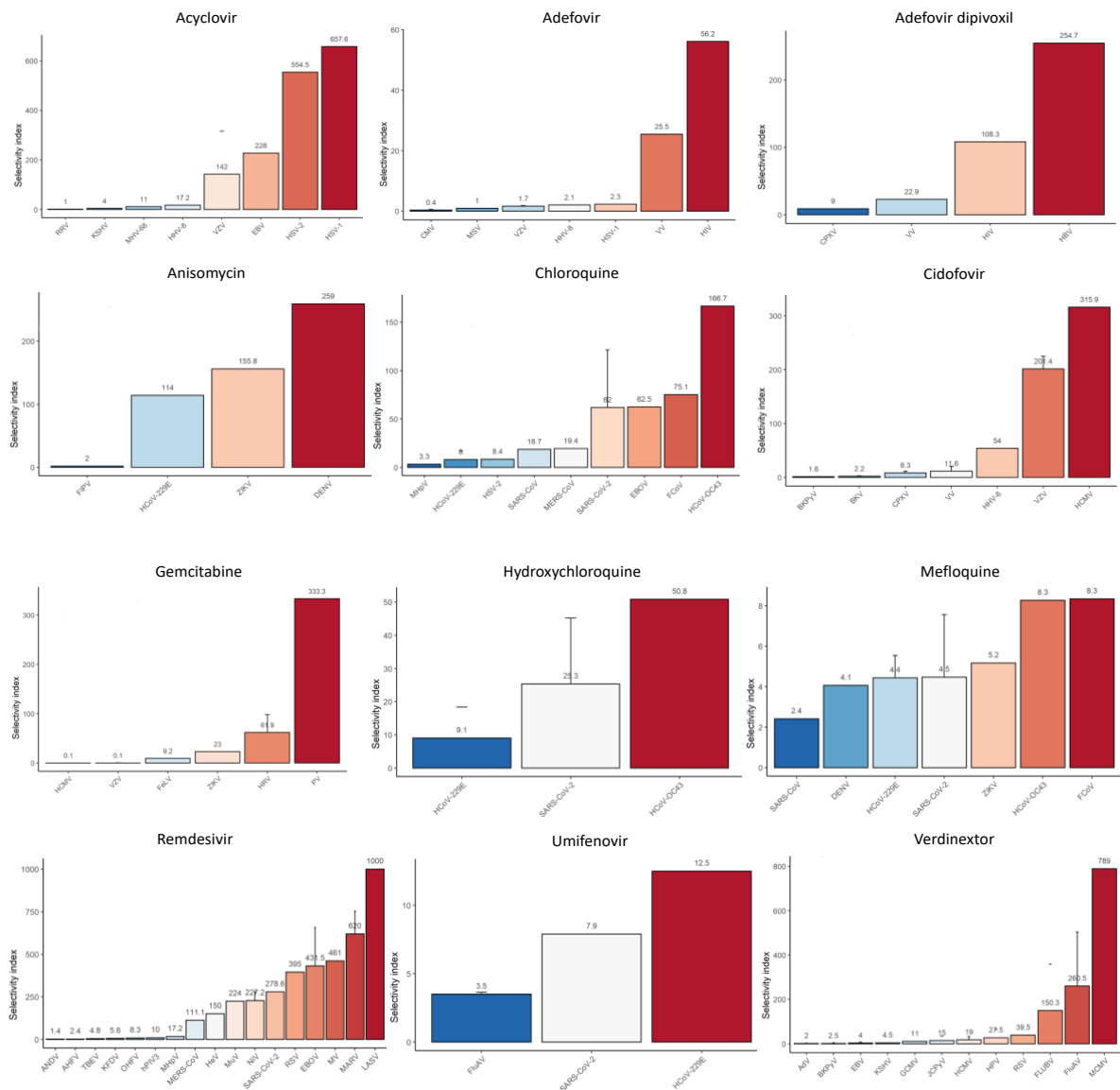
Also, some BSAs showed positive results across a broad range of BC groups. This includes 25HC, chloroquine, clofazimine, quinacrine, and tilorone with antiviral activity against dsRNA, (+)ssRNA and (-)ssRNA BC group; beclabuvir, berberine, erlotinib, and gemcitabine with antiviral activity against dsDNA, (+)ssRNA, (-)ssRNA, and ssRNA-RT BC group; lamivudine with antiviral activity against (-)ssRNA, ssRNA-RT, and dsDNA-RT BC group; minocycline, ritonavir, and sunitinib with antiviral activity against (+)ssRNA, (-)ssRNA and ssRNA-RT BC group; mycophenolic acid and ribavirin with antiviral activity against dsDNA, (+)ssRNA, (-)ssRNA and dsRNA BC group; and adefovir dipivoxil with antiviral activity against dsDNA, ssRNA-RT and dsDNA-RT BC group.

Furthermore, some discontinued BSAs (Table 1, ^) were suggested with positive antiviral activity against other viruses than their primary indication, within the same BC group: boceprevir, formerly against (+)ssRNA HCV, had positive antiviral activity against SARS-CoV-2; vidarabine formerly against dsDNA HSV and VZV, with antiviral activity against CPXV, EBV, KSHV, MHV-68, and RRV; simeprevir formerly against (+)ssRNA HCV, with antiviral activity against SARS-CoV-2 and ZIKV; cidofovir formerly against dsDNA HCMV with antiviral activity against hAdV, BKPyV, CPXV, EBV, HHV-6, HHV-7, KSHV, HSV-1, HSV-2, MPXV, ORFV, VARV, VACV, and VZV (See Supplementary Table S.2.3 for BSAs identified with positive and negative antiviral activity).



**Figure 9: BSAs with SI > 1.** The diagram shows the distribution of BSAs (outer lines) with positive antiviral activity against a particular virus within its BC group (mid-line).

*In vitro* tested monotherapies with CC50, EC50, and resulting SI values were included into the DrugVirus.info 2.0 BSA database. Data outputs are given as bar diagrams, which illustrates the respective BSA and target viruses. The bars indicate SI, which illustrates BSA antiviral activity against a particular virus. This enables the comparison of SIs for a broad range of viruses. For instance, remdesivir are approved for treating cases of SARS-COV-2, and were found to have antiviral activity against a variety of RNA viruses. This can for instance endorse testing of remdesivir against other (+)ssRNA viruses (Figure 10).



**Figure 10: DrugVirus.info 2.0 bar-diagrams.** Figure shows selected bar-diagrams presented in DrugVirus.info 2.0 database. SI values were calculated from EC50 and CC50, illustrated in separate diagrams within the database. The bars represent SI against a particular virus.

## Part 2: BSA scoring system

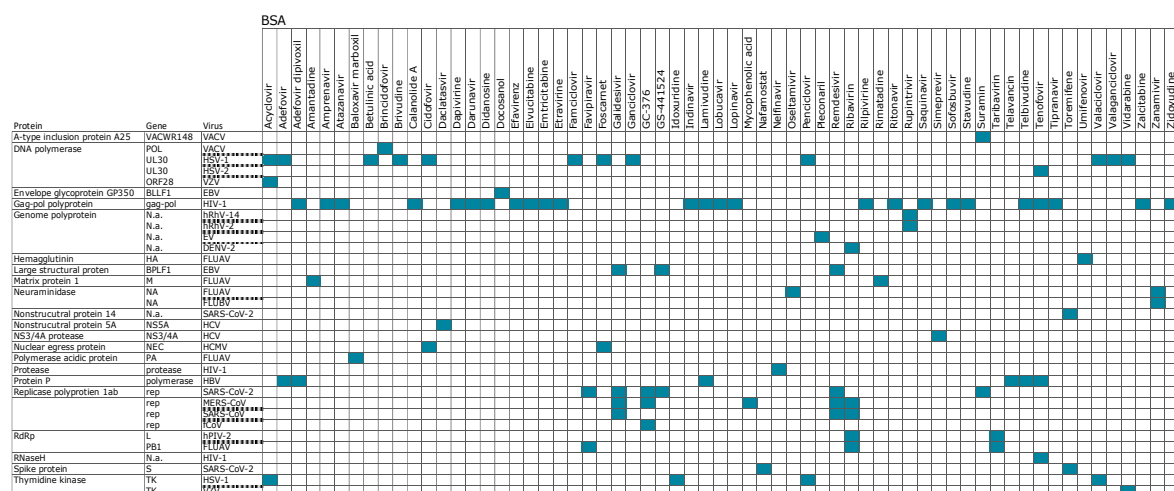
### 4.3 Components of the BSA scoring system

We developed a six-component scoring system for predicting the most promising monotherapies. Components scored were Drug target relevance (DT), Immunomodulatory properties (IP), Route of Administration (RoA), Structure-activity relationships (SAR), phylogeny, and Drug developmental status (DDS). The following sections describe examination of these components.

#### 4.3.1 Drug-target relevance: Host and viral-directed BSA targets

DT component was evaluated by the identification of host and viral-directed BSA targets. From database search, impressive 209 of our BSAs have known targets. Only a minor of our BSAs got no hits when searching for targets in all three databases. 1415 unique targets were identified for 209 of our BSAs, whereas 448 of these showed overlapping targets (Figure 7B).

A cluster of BSAs was identified to target the gag-pol polyprotein of HIV-1, (adefovir dipivoxil; amprenavir; atazanavir; calanolide A; dapivirine; darunavir; didanosine; efavirenz; elvucitabine; emtricitabine; etravirine; indinavir; lamivudine; lobucavir; lopinavir; rilpivirine; ritonavir; saquinavir; sofosbuvir; stavudine; telbivudine; tenofovir; tipranavir; zalcitabine; zidovudine). Also, several BSAs was recognized in interfering with specific proteins of the DNA polymerase (acyclovir, adefovir, betulinic acid, brincidofovir, brivudine, cidofovir, famciclovir, foscarnet, ganciclovir, penciclovir, tenofovir, valaciclovir, valganciclovir and vidarabine). Further, galidesivir, GC-376, remdesivir and rilpivirine was found to target replicase polyproteins of *Coronaviruses* (Figure 11).

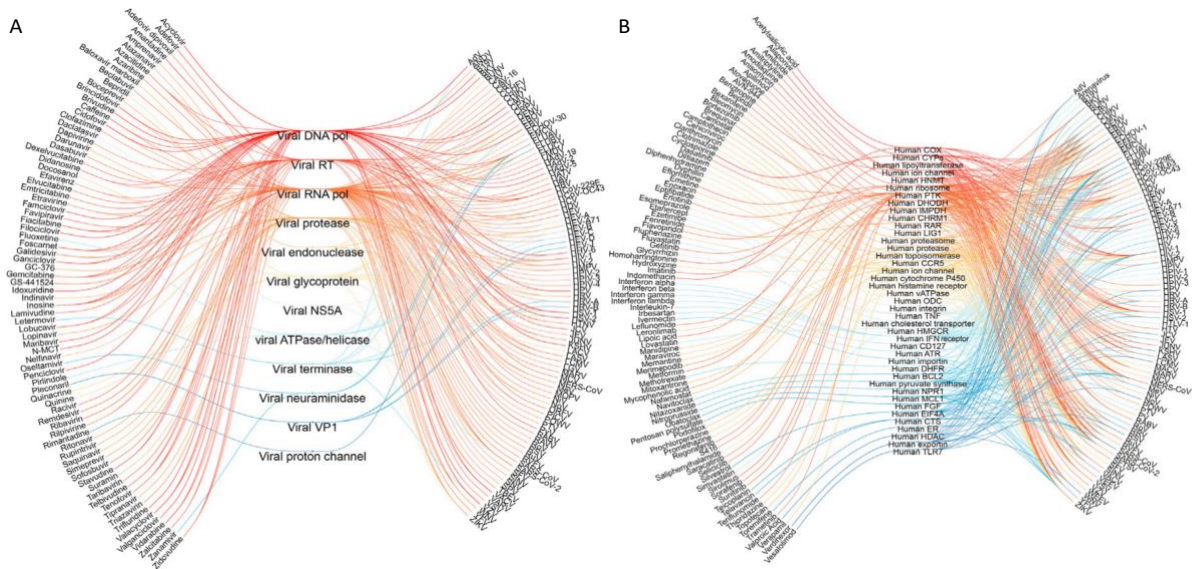


**Figure 11: Virus-directed BSA targets.** Shown are the BSAs (horizontal axis), and virus target protein and gene names (vertical axis). Targets are marked in blue.





BSAs were accordingly identified with several viral and host targets, which are related to different virus strategies. Most virus-directed BSAs work by inhibiting viral nucleic acid synthesis or protein processing (Figure 13A). Host-directed BSAs were identified with more diverse mechanisms, including targeting lipid metabolism, receptor-mediated signaling and protein modification, trafficking, and synthesis (Figure 13B).

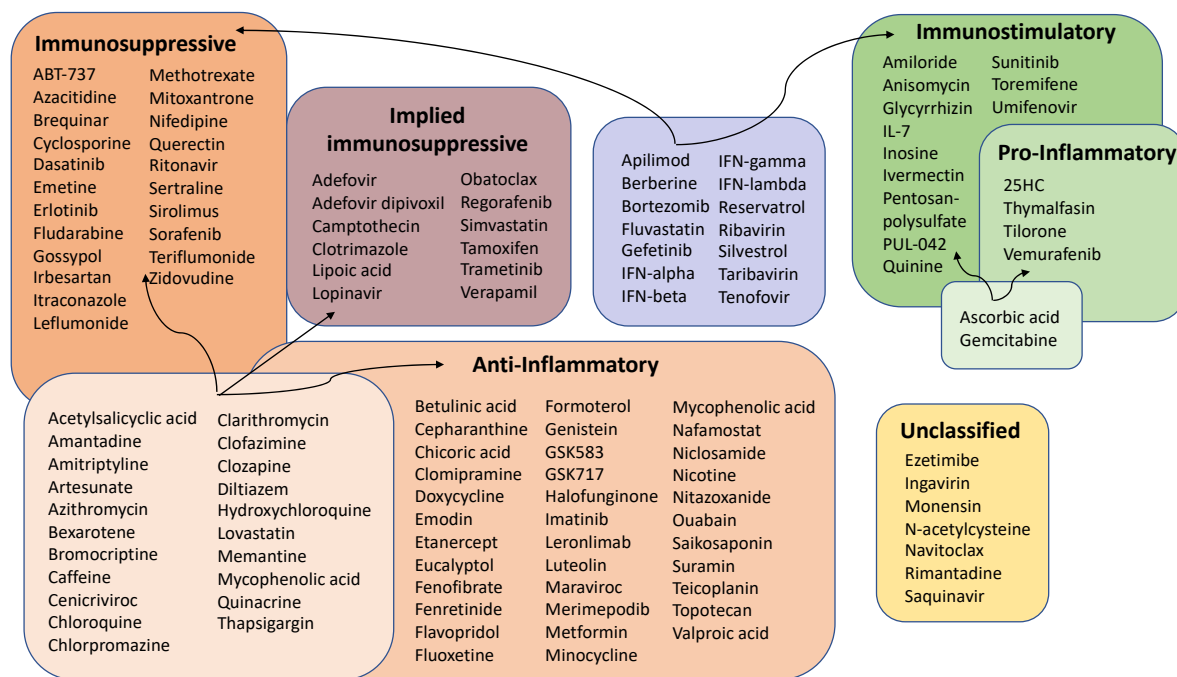


**Figure 13: Eye diagram of primary viral- and host-directed BSA targets.** A. Virus-directed BSAs linked to viruses through targets. B. Host-directed BSAs linked to viruses through targets. The figure are derived from a separate publication within my research group, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022 (46).

#### 4.3.2 Immunomodulatory BSAs

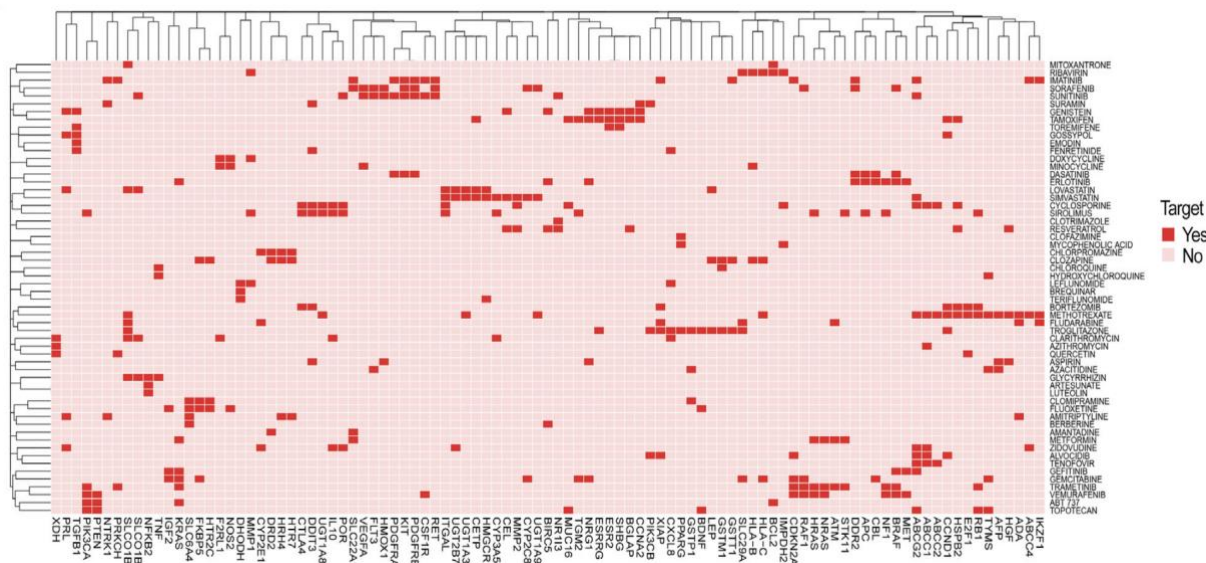
129 out of 245 BSAs showed immunomodulatory properties (IP) (Figure 7C). 22 showed to be immunosuppressive and 12 to be immunostimulatory. Some BSAs was indicated with only minor suppressive activity on the immune system, compared with for instance the potent immunosuppressor sirolimus. Therefore, these BSAs are classified in a side-group named "Implied Immunosuppressive".

Several of the immunomodulatory BSAs showed to have activity on inflammation. There were identified 35 anti-inflammatory BSAs and 4 pro-inflammatory BSAs. Further, Some BSAs were indicated to affect both on immunity and inflammation, where 21 BSAs have both immunosuppressive and anti-inflammatory activity, and 2 BSAs have both immunostimulatory and pro-inflammatory properties. Furthermore, seven of the immunomodulatory BSA were not identified with any distinct activity and are therefore classified as "others". The immunological and inflammatory groups mentioned above can all be shown in Figure 14 (See also the supplementary section S.3.2, Table S.3.2 for explanation of immunomodulatory classification).



**Figure 14: Immunomodulatory BSA and their effect on the immune system and inflammation.** Immunomodulatory BSA were classified into immunosuppressive (orange) and immunostimulatory (green) BSA. Within these groups, many showed to have inflammatory appearances, anti-inflammatory, and pro-inflammatory, respectively. Also, a side group of BSA with reducing activity of immunological functions is shown as “implied immunosuppressive”. The subgroups represent BSA with both immunosuppressive and anti-inflammatory characteristics (orange) and BSA with immunostimulatory and pro-inflammatory characteristics (green). Furthermore, some BSA were identified as both immunostimulatory and immunosuppressive, in different circumstances (purple). Some BSA were unclassified but are implicated as immunomodulatory (yellow).

Several BSA were identified with immunomodulatory targets. For instance, imatinib, tamoxifen, erlotinib, and methotrexate are all BSA identified with several immunomodulatory targets, explaining their immunomodulatory actions. Many BSA target similar clusters of immunomodulatory genes, indicating some functional and structural similarities between the targets (Figure 15).



**Figure 15: BSAs with immunomodulatory targets.** The figure illustrates a selection of 58 BSAs with common immunomodulatory targets. The figure are derived from a separate publication within my research group, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022. (46).

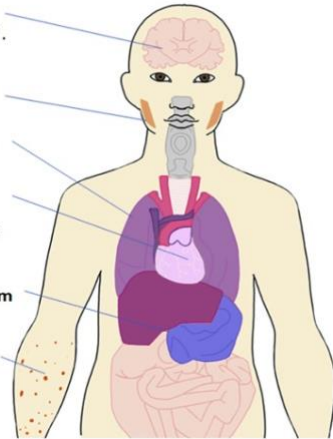
#### 4.3.3 Route of administration and Phylogeny- and Structure-activity relationship

RoA must fit a virus diseased system for achieving maximal antiviral effect and to reduce the potential of adverse effects. Viruses tends to infect diverse diseased systems, such as, nervous, endocrine, respiratory, cardiovascular, immune and lymphatic, digestive and excretory, exocrine, and reproductive systems (Figure 16A). Furthermore, most of the BSAs evaluated were orally developed. Other administration routes identified for the BSAs were intravenous, subcutaneous, ocular, topical, suppository, and inhalation (Figure 16B).

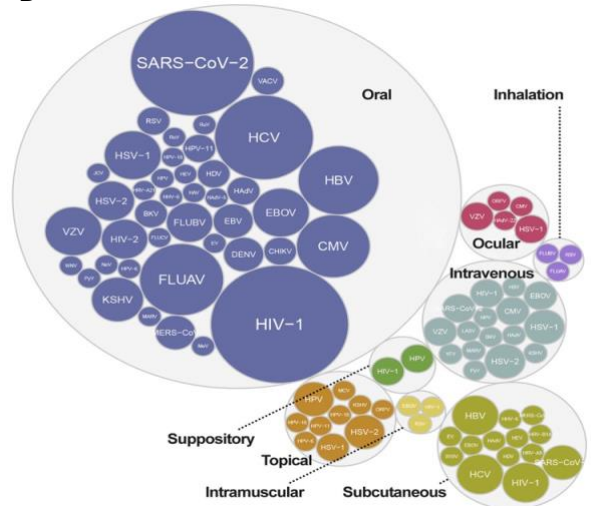
Furthermore, SAR analysis revealed structural similarities between several BSAs. This enabled identification of compounds related to known BSAs. For instance, the non-nucleoside reverse transcriptase inhibitors etravirine, dapivirine and rilpivirine showed structural similarities to alflutinib, melarsoprol and melarsomine (Figure 16C). Also, phylogenetic analysis of drug-virus interaction revealed that most of the BSAs have only been tested against a small subpopulation of related viruses. As phylogenetic similar viruses are more likely to respond to the same drug, this uncovers several BSA treatment options yet not discovered (Figure 17).

A

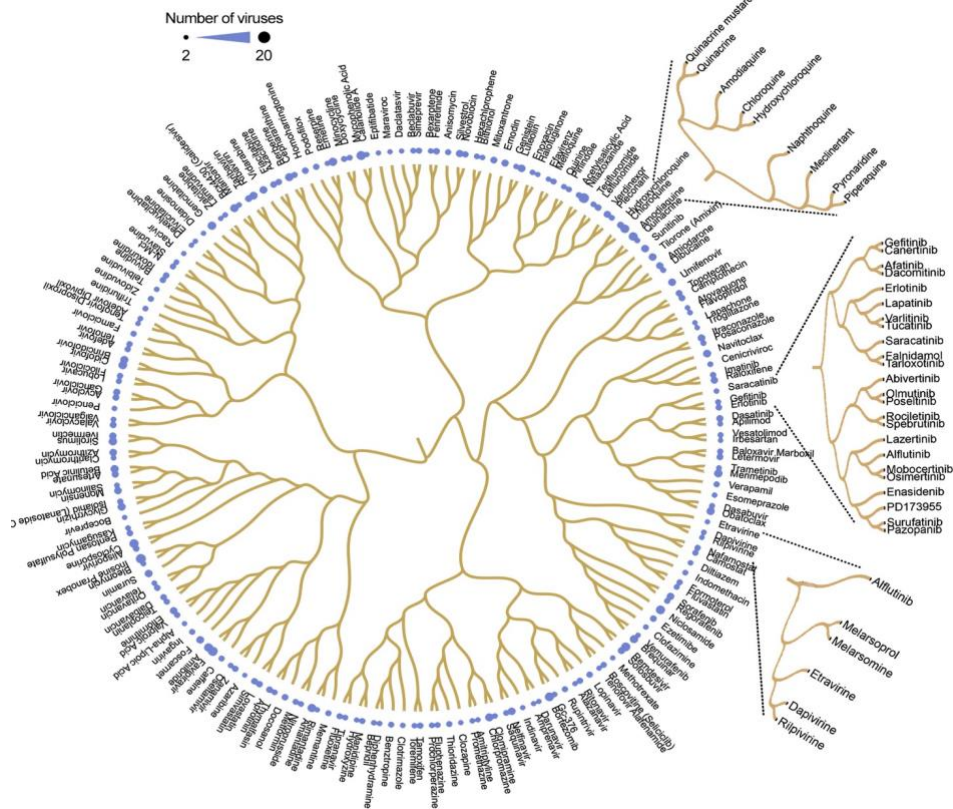
**Nervous system**  
 JCV, MeV, LCMV, LASV, LUJV,  
 EBOV, Polio, HSV-1, AdV, CMV .  
**Endocrine system**  
 MuV, CBV, AdV, FluAV,  
 SARS-CoV-2, ...  
**Respiratory system**  
 FluAV, FluBV, RSV, HPIV, RSV,  
 SARS-CoV-2, AdV, BKV ...  
**Cardiovascular system**  
 CAV, CBV, KSHV, CCHFV, ...  
**Immune and lymphatic system**  
 HIV-1, MARV, EBOV, HSV1,  
 VACV, FluAV, MeV, VZV, ...  
**Digestive and excretory system**  
 HAV, HBV, HCV, HDV, HEV,  
 AdV, RoV, NoV, CBV ..  
**Exocrine system**  
 MuV, VZV, HHV6, HPV, RuV,  
 MeV, CAV ...  
**Reproductive system**  
 HPV, HSV-2, ZIKV, ...



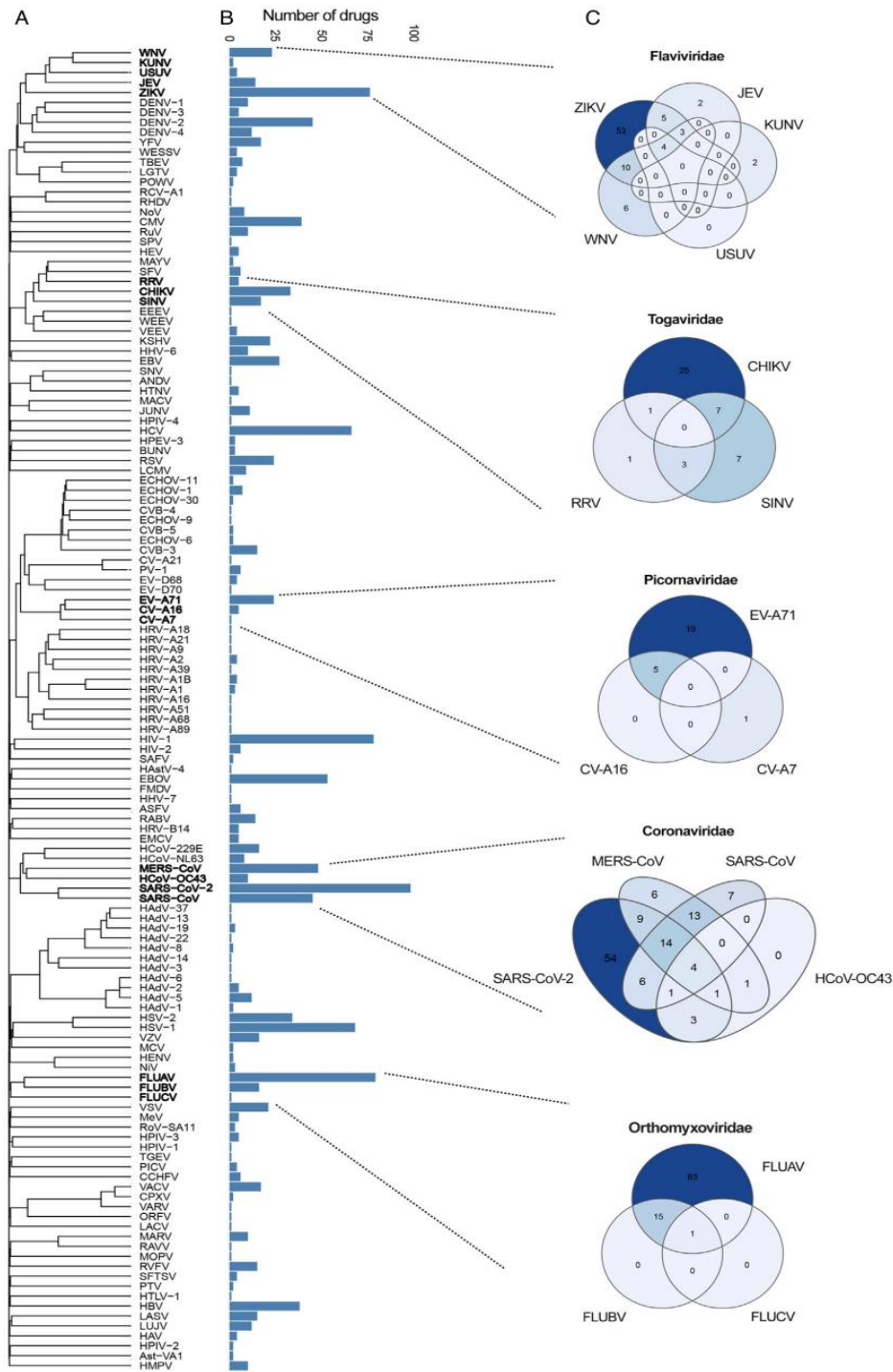
B



C



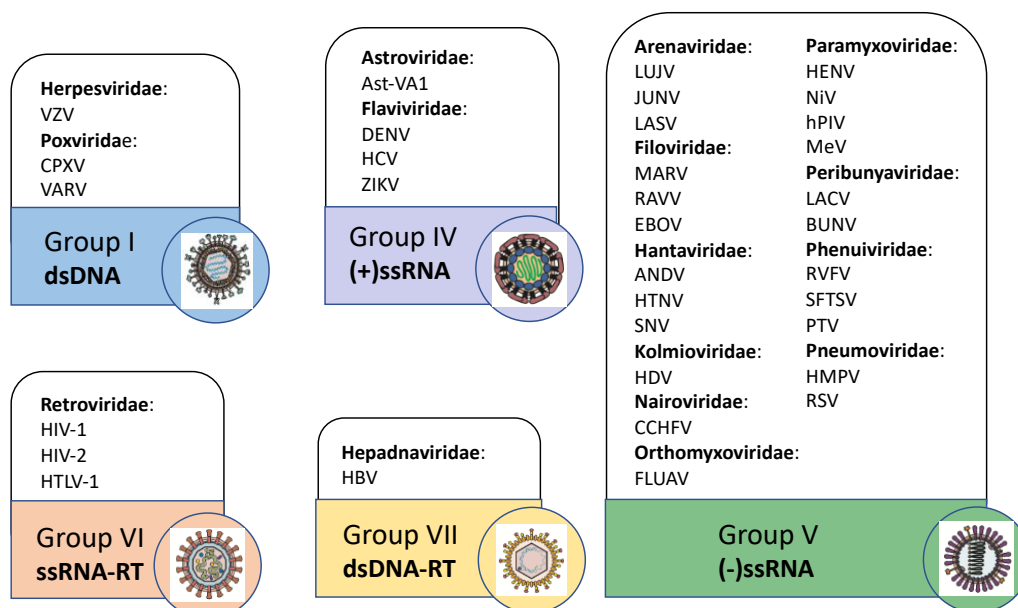
**Figure 16: Route of Administration and Structure-activity relationship.** A. Organ systems where different viruses tend to infect. B. RoA of BSAs, whereas bubbles show the number of BSAs developed against a particular virus. C. Structure-activity relationship (SAR) analysis dendrogram. Clusters include BSAs within our database. Also illustrated are three sub-clusters of BSAs and potential BSA compounds. The figure are derived from a separate publication within my research group, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022 (46).



**Figure 17: Phylogenetic analysis of drug-virus interactions.** A. Phylogenetic tree was generated based on amino acid sequences of viral encoded polymerases and reverse transcriptases. B. The number of BSAs within our database with activity against viruses from the phylogenetic tree. C. Diagram representing the number of BSAs which target closely related viruses. The figure is derived from a separate publication within my research group, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022. (46).

#### 4.4 Generation of BSA Scoring system

In total, 33 viruses were scored against 206 of our BSAs. The viruses cover classes I, IV, V, VI, and VII (Figure 7D). Within the BC groups, the chosen viruses were those which have the highest case fatality or are known to appear at the highest frequencies within populations. From group I, CPXV, VARV and VZV, and Group IV, Ast-VA, DENV, HCV, and ZIKV was scored. Further, from Group V MARV, RAVV, LUJV, JUNV, LASV, EBOV, ANDV, HTNV, SNV, LACV, BUNV, RVFV, SFTSV, PTV, CCHFV, HDV, FLUAV, HENV, NiV, HPIV, MeV, HMPV, and RSV was scored. In the reverse transcriptase groups, Group VI including HIV-1, HIV-2 and HTLV-1, and group VII including HBV was scored (Figure 18).



**Figure 18: Baltimore classification of scored viruses.** All viruses studied can be found within their respective Baltimore group and virus family. See supplementary section, Table S.1 for virus abbreviations.

Table 3A-D and 3 shows result from the six-component scoring system. For the dsDNA group, the highest BSA score was with brivudine, famciclovir, and vidarabine against VZV (6.00), following brincidofovir against CPXV and VARV (4.75) (Table 3A). Likewise, for the (+)ssRNA group, favipiravir gained the highest score against Ast-VA1 (5.25) and ivermectin against DENV (5.75). Boceprevir, beclabuvir, sofosbuvir, and simeprevir gained full score against HCV (6.00). For ZIKV, rilpivirine and sofosbuvir gained the greatest BSA score (5.5) (Table 3B). Further, for ssRNA-RT group, several BSA gained full score against HIV-1, including emtricitabine, zalcitabine, and lamivudine. These BSAs also gained high score against HIV-2 (lamivudine = 6.00, emtricitabine and zalcitabine = 5.50). A large group of BSAs share the highest score against HTLV-1 (3.50) (Table 3C). Furthermore, for dsDNA-RT, lamivudine, telbivudine, and valacyclovir gained full score against HBV (6.00) (Table 3D).

Lastly, the majority of virus species scored was from the (-)ssRNA group, presented in Table 4. Favipiravir gained high score for several of the viruses within this group, including for FLUAV (6.00), LUJV (5.25), JUNV, LASV, MARV, CCHFV, NiV, and RVFV, (5.50), EBOV and SFTSV (5.75), ANDV, HTNV, and SNV (5.25). Other BSAs which gained high scores where as follows: AVN-944, Benzotropine, Raloxifene and Amiodarone against LUJV (5.25); galidesivir against MARV (5.75) and RAVV (5.25); amodiaquine, amiodarone, galidesivir and remdesivir against EBOV (5.75); vandetanib against ANDV (5.25); baloxavir marboxil against HTNV (5.25); bulevirtide against HDV (6.00); baloxavir marboxil, oseltamivir, triazavirin and zanamivir against FLUAV (6.00); gossypol and ivermectin against HENV (4.25); remdesivir against NiV (5.5); GS-441524 against hPIV (5.5); inosine against MeV (4.75); baloxavir against LACV (5.25); saliphenylhalamide against BUNV (5.25); taribavirin against PTV (4.25); oritavancin and remdesivir against HMPV (5.25); and 4'-fluorouridine against RSV (5.5). See also supplementary Table S.3.3, which specify each BSA component score.

*In vitro* tested monotherapies (Supplementary Table S.2.1 and S.2.3) could be evaluated together with results from the BSA-scoring system (Table 3 and 4), to further confirm promising BSA activities for already approved BSAs (Table 1). Favipiravir are currently approved for treatment of Influenza. Favipiravir gained high scores for SFTSV in our BSA scoring system and are estimated with a SI = 4 in Vero cells (117). Trifluridine, brivudine and acyclovir are approved for treatment of herpesviruses. Trifluridine gained decent scores for CPXV, calculated with a SI > 180 in Vero cells. Furthermore, both brivudine and acyclovir gained high scores for CPXV and are indicated with a SI > 3 in Vero cells (118).

Ritonavir is approved for treatment of HIV. Ritonavir gained high scores for RVFV, estimated with a SI > 4 in A549 cells (18). Ribavirin is approved for HCV, FLUV and RSV. Ribavirin gained high scores for DENV, with a SI ranging from 4-9 in different cell lines (18, 119). Furthermore, IFN- $\alpha$  is approved in treatment of HCV, HBV and HPV. From our scoring system, IFN- $\alpha$  gained high scores for ZIKV and are calculated with a SI >7 in Vero cells (120).

Some of the approved BSAs have been discontinued for original purpose. However, these BSAs cut-off effect could potential be beneficial in treating other viruses. Vidarabine have been canceled for treatment for HSV and VZV. Vidarabine gained decent scores for CPXV, estimated with a SI > 110 in Vero cells (118). Similar, simeprevir are canceled for treatment of HCV. Simeprevir gained high scores of ZIKV and indicated with SI > 25 in Vero and U87 cells (121).







## 5 Discussion

Effective BSA therapy elaboration, ready for clinical trials, is an essential step in preparedness once a new emergent strain is introduced. However, the path from discovery to approval is often time-consuming and costly. An attractive solution is drug repositioning, which offers a low-cost and rapid approach to combat emergent viruses. The initial phase, explorative discovery studies, allows the identification of promising antivirals with broad activity against several viruses. For drug repositioning steps to be reachable, accurate and readily available data are crucial.

The BSA landscape and scientific data on antiviral activity have expanded markedly during the past years. A major provocation of this growth is the recent SARS-CoV-2 pandemic. Tools available for summarizing and organizing such viral research are currently underprovided. Therefore, integrative, explorative, and user-friendly bioinformatic tools are urgently needed to handle all this available material. For these reasons, my research group developed the DrugVirus.info database. The database was intended to combine BSA activity to promote discovery and development of novel BSAs.

This initial database was restricted to only a few safe-in-man BSAs. Expansion of the novel Drugvirus.info database allowed the exploration of both BSAs and BSA-containing combinations (BCC). The database further permits analysis of user-provided antivirals, allowing researchers to calculate BSA efficacy and toxicity from raw data. From these measurements, the database calculates the SI and DSS, which is excellent methods for illustrating antiviral activity. These amendments would further provoke the discovery and development of novel BSAs and revealing new insights into BSA-virus interactions and underlying mechanisms that determine the pan-and cross family activities.

There are some limitations associated with the information curated within the database. Both BCCs and BSA database are manually curated by two master students, leading to low coverage of the existing data. The BSA database included manual curation of published scientific papers. A major hurdle when collecting antiviral efficacy and cytotoxicity studies were the lack of available parameters. For instance, some papers did not include cytotoxicity measurements and SI could therefore not be calculated.

EC<sub>50</sub> measurements alone cannot explain the extent of antiviral activity. Several parameters affect EC<sub>50</sub> values, such as assay method, number of replicates and the cell line used. Also, papers use different terminologies of cytotoxicity measurements, as for instance, cytotoxicity of cell morphology (MCC) (122), median cytotoxic, lethal or toxic dose (CD<sub>50</sub>, LD<sub>50</sub>, TC<sub>50</sub>) (123, 124). For curation, all relevant cytotoxicity and antiviral efficacy measurements were used to calculate the SI, independent of terminology used to denote the measures. Thus, the correlation might be inconsistently represented for a BSA

against the same virus and cell line. For these reasons, the database is highly reliant on other researchers' contributions, which would together strengthen the database output and reliability.

Both positive and negative monotherapy results were gathered. However, a relatively low SI was used as cut-off values. Indeed, a higher SI reflect the approaching drug as more accurate and effective in treatment. For instance, a SI on more than 10 have been recommended when evaluating the therapeutic value of medications. If the SI are between 1 and 10, a re-evaluation of the activity is suggested for validation (113, 114). Therefore, several BSAs regarded with positive activities in this thesis would need further confirmations. Also, several papers had contradicting measurements, where the same BSA against a certain virus were reported with both positive and negative antiviral activity. Therefore, new tests should be applied to reconsider the extent of BSA activity (106).

This initial collection of BSA activity was intended to act as a starting point to invite other researchers' contributions. Researchers are encouraged to report new safe-in-man BSAs or novel activity of existing BSAs, which will be updated on request by the website. A suggesting approach would be to invite researchers to incorporate their raw data into the database by request. This would further expand the BSA database, but also increase the reliability from already available information.

Drug repositioning aims to search for BSAs with new indications. Therefore, methods for identifying the most promising BSAs out of thousands is crucial in viral pandemic preparedness. For these reasons, my research group developed a new method for selecting the most promising BSAs within our database. Based on BSA-target relevance, routes of administration, phylogeny- and structure-activity relationship (SAR), and immunomodulatory property evaluation, promising broadly effective antiviral therapies were enlightened.

BSA host and viral targets were evaluated as additional information of BSA-target relevance. A large pool of BSA targets were identified, which could potentially lead to the discovery of new BSA activities. By comparing BSA targets with common virus strategies, new therapeutic alternatives can be applied to a broader range of viruses.

Database searches revealed that most of the BSAs within our database have some specified targets, whereas many showed to be important for viral pathogenesis. This included both host-and viral directed BSAs. Results showed that the pool of host-directed BSAs is remarkably larger than BSAs with viral-directed activity. Thus, underlying larger opportunities for host-directed BSA drug repositioning. Indeed, host-directed BSA repositioning has gained increasing attention following the SARS-CoV-2 pandemic (59, 125). Even though host-directed BSAs are indicated with less appearance of drug

resistance, they generate a higher risk of toxicity. Illustrating this example, most of the approved antivirals' primary targets are viral factors (Table 1).

Interestingly, the identified overlapping host and viral targets would also be valuable when evaluating BCCs. Drugs with the same mode of action, such as nucleoside or nucleotide analogs, cannot be taken together due to the generation of toxicity. Therefore, BSAs with unique mode of action, which targets same replication strategy, is often given in BCCs. BCC target interactions and mode of action are evaluated in Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022.

However, many BSAs within our database do not have any defined targets. Several BSAs also appeared with only minor or uncertain target information. Therefore, further research is needed on BSA-directed activities and their targets.

BSAs targeting host-directed factors were commonly associated with immunomodulatory activities of those targets. Examination of immunomodulatory properties revealed several immunostimulatory and immunosuppressive BSAs. Also, many BSAs have major roles in the inflammatory pathways. There is a narrow definition of immunomodulators. Weakly stimulatory or suppressive medications of the immune system are all defined as immunomodulatory. These BSAs can be expected with less severe effects than potent immunomodulators. Also, medications that act directly on the inflammatory pathway (anti- or pro-inflammatory BSAs) and immunomodulators are in some cases used incomprehensibly. Accordingly, further evaluation of immunomodulatory properties is required.

SAR and phylogeny analysis were used as a component within our scoring system. SAR analysis revealed several new BSA candidates with structural similarities to BSAs within our database (Figure 16C). These are compounds yet not explored as BSAs. To exemplify this, the HIV-1 approved BSA, etravirine, where found to be structural similar to alflutinib. Alflutinib are therefore anticipated with antiviral activity against HIV. Furthermore, phylogenetic analysis of drug-virus interactions revealed that several BSAs target viruses within same viral families (Figure 17). Interestingly, several BSAs within our database were only tested against a few viruses from these families. HIV and HTLV-1 are both within *Retroviridae* family of viruses, which both encode reverse transcriptase. Etravirine can therefore be expected with activity against HTLV-1. Accordingly, SAR and phylogenetic analysis exemplify approaches for expanding the BSA activity landscape and would be valuable in further exploration of potential novel BSA activities.

BSA components were used to generate a scoring system, which made it possible to give each inspected BSA activity an individual score. This score reflects BSA potential, whereas a high score mirrors promising BSA candidates. Interestingly, favipiravir has recently been

approved for treating Influenza A, B, and C (Table 1). Favipiravir gained the highest score for (-)ssRNA viruses, including for treating FLUAV (Table 4). Thus, the BSA scoring system illustrates clinical applicability. Similar, baloxavir marboxil is approved for treating FLUAV. Baloxavir Marboxil also gained high scores for several (-)ssRNA viruses, including FLUAV. Furthermore, rilpivirine is currently approved for treating HIV-1 (Table 1). In our scoring system, rilpivirine gained high scores for ZIKV in (+)ssRNA BC group and HIV-1 (Table 3). Indeed, this designate that BSAs with high scores from our scoring system can be interesting treatment strategies.

However, many of the scored BSAs have only been tested *in vitro*, which lowered the overall BSA score. This scoring restriction, together with limited information on immunomodulators and route of administration, has influenced the scoring system's prediction capacity. For example, most of the BSAs gained full scores for RoA component. This is because many viruses have a complex diseased system, and thus, a variety of RoA could be applied. Further, both the lack of information and the conflicting info on immunomodulators had an impact on the final score.

The most promising BSAs from our six-component BSA scoring system was further investigated in combinations. This resulted in investigation of several promising BSA combinations, which can be retrieved within our first publication, Table 1, Ianevski et al., Mono- and combinational drug therapies for global viral pandemic preparedness, 2022 (46). The proposed BSAs and BCCs would further need to be evaluated *in vitro* and *in vivo* as preparation for entering clinical trials.

*In vitro* tested monotherapies (Supplementary Table S.2.1 and S.2.3) together with promising BSAs from the scoring system (Table 3 and 4) of already approved BSAs (Table 1) were evaluated for further prediction of promising BSA activities. However, only some BSAs had a SI > 10. This includes, trifluridine and vidarabine against CPXV and simeprevir against ZIKV. BSAs with a SI between one and ten would need further evaluation and testing for justification of BSA activities.

BSA activities stand as a baseline for the development of BCCs. BCCs would increase the overall treatment effectiveness by the generation of synergistic effects, enabling maximal efficacy of the treatment. Also, BCCs reduce the individual drug dosage, which would lower potential toxicity and the likelihood of adverse effects. Therefore, immunomodulatory or host-directed BSAs in BCCs could reduce common adverse effects associated with these BSA features. Further, monotherapies are not always effective against poorly characterized viruses or re-emergent viral strains. For these reasons, BCCs are more frequently observed as a successful treatment strategy.

## 6 Further perspectives and Conclusions

Drug repositioning remains an efficient and realistic way of developing antivirals. Within my research group, we have developed a scoring system and expanded the available Drugvirus.info database (Drugvirus.info 2.0). The BSA scoring system prioritizes the development of promising BSAs, out of thousands of present BSAs. It familiarizes central BSA activity components, such as drug targets, immunomodulatory properties, route of administration, Phylogeny and structure-activity relationship, and developmental status. The Drugvirus.info 2.0 database provides available BSA and BCC activities and allows interactive analysis of a user own's measures, for comparison with available published mono- and combinational- therapies. Both projects would assist drug repositioning steps, as preparation for new emergent viral strains by the identification of novel treatment strategies.

Although BCCs have a higher frequency of success due to reduced toxicity and broader antiviral activity, BSA discovery and exploration are crucial for revealing effective BCCs.

Further work includes *in vitro* and *in vivo* examination of high-hits BSAs from the scoring system. Also, regular updates and annotations of the drugvirus.info database are required to remain a comprehensive and up-to-date BSA and BCC database.

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# Supplementary

## S.1 Virus abbreviations

**Table S.1: Virus abbreviations.** Table shows virus abbreviations and complete virus name for all viruses mentioned in this master's thesis.

AHFV	Alkhurma Hemorrhagic Fever virus	HHV	Human herpesvirus
ANDV	Andes virus	HIV	Human immunodeficiency virus
Ast-VA1	Astrovirus VA1	hPiV	Human parainfluenza virus
B19B	Parvovirus B19	HPV	Human papillomavirus
BKPyV	BK polyoma virus	hRhV	Human rhinoviruses
BUNV	Bunyamwera virus	hRoV	Human rotavirus
BVDV	Bovine viral diarrhea virus	HSV	Herpes simplex virus
CCHFV	Crimean-Congo hemorrhagic fever virus	HTLV	Human T-lymphotropic virus
cPIV	Canine parainfluenza virus	HTNV	Hantaan virus
CPXV	Cowpox virus	IBV	Infectious bronchitis virus
CV	Coxsackie virus	JCPyV	JC polyoma virus
DENV	Dengue virus	JEV	Japanese encephalitis virus
EBOV	Ebola virus	JUNV	Junín virus
EBV	Epstein-Barr virus	KFDV	Kyasanur Forest Disease virus
EV	Human enterovirus	KSHV	Kaposi's sarcoma-associated herpesvirus
fCoV	Feline coronavirus	LACV	La Crosse encephalitis virus
FLUAV	Influenza A	LASV	Lassa mammarenavirus
FLUBV	Influenza B	LCMV	Lymphocytic choriomeningitis virus
fLV	Feline leukemia virus	MARV	Marburg virus
FMDV	Foot-and-mouth disease virus	MCMV	Mouse cytomegalovirus
hAdV	Human adenovirus	MERS-CoV	Middle-east respiratory syndrome coronavirus
HBV	Hepatitis B virus	MeV	Measles morbillivirus
HCMV	Human cytomegalovirus	MHV	Murine coronavirus
hCoV-229E	Human coronavirus 229E	MHV-68	Murine gamma herpesvirus-68



hCoV-OC43	Human coronavirus OC43	MPXV	Monkeypox virus
HCV	Hepatitis C virus	MSV	Maize Steak virus
HDV	Hepatitis D virus	MuV	Mumps virus
HeV	Hendra virus	NiV	Nipah virus
OHFV	Omsk Hemorrhagic Fever virus	SARS-CoV	Severe-acute respiratory syndrome coronavirus
ORFV	Orf virus	SFTSV	Severe fever with thrombocytopenia syndrome virus
pCoV	Pangolin coronavirus	SFV	Semliki Forest virus
PICV	Pichinde virus	SINV	Sindbis virus
PoV	Poliovirus	SIV	Simian immunodeficiency virus
POWV	Powassan virus	SNV	Sin Nombre virus
PRRSV	Porcine reproductive and respiratory syndrome virus	SUDV	Sudan ebolavirus
RABV	Rabies virus	TBEV	Tick born encephalitis virus
RAVV	Ravn virus	VEEV	Venezuelan equine encephalitis virus
RRV	Rhadinovirus	WEEV	Wester equine encephalitis virus
RSV	Respiratory syncytial virus	WNV	West Nile virus
RVFV	Rift-valley fever virus	YFV	Yellow fever virus

















Rilpivirine	FLUAV	MDCK	>30uM	300uM	10.	28778830
	FLUAV	MDCK	20uM	336uM	16.8.	25600073
Rimantadine	FLUAV	MDCK	7.3uM	336uM	46.	25600073
	FLUAV	MDCK	>500uM	336uM	<1	25600073
	FLUAV	MDCK	>500uM	336uM	<1	25600073
	FLUAV	MDCK	0.062uM	336uM	5,419.	25600073
	FLUAV	MDCK	0.057uM	336uM	5,894.	25600073
	FLUAV	MDCK	>400uM	336uM	>1	28477572
	FLUAV	MDCK	>400uM	>400uM	>1	28477572
	FLUAV	MDCK	0.32uM	>400uM	1,250.	28477572
	FLUAV	MDCK	0.050uM	>400uM	8,000.	28477572
	FLUAV	MDCK	32.5uM	258uM	7.9.	22870806
	FLUAV	MDCK	33.6uM	258uM	7.7.	22870806
	FLUAV	MDCK	0.15uM	258uM	1,720.	22870806
	FLUAV	MDCK	0.05uM	258uM	5,160.	22870806
	FLUAV	MDCK	0.2uM	165uM (+/-15.825)	12367731	
	FLUAV	MDCK	2.0uM	165uM (+/-15.25)	12367731	
	FLUAV	MDCK	0.16uM	165uM (+/-15.1031)	12367731	
	FLUAV	MDCK	0.4uM	165uM (+/-15.412)	12367731	
	FLUAV	MDCK	0.18uM	165uM (+/-15.916)	12367731	
	FLUAV	MDCK	0.15uM	165uM (+/-15.1,100)	12367731	
FLUAV	MDCK	0.6uM	165uM (+/-15.275)	12367731		
FLUAV	MDCK	0.1uM	175uM (+/-15.1,750)	12367731		
FLUAV	MDCK	1.1uM	185uM (+/-10.168)	12367731		
FLUAV	MDCK	0.15uM	145uM (+/-35.966)	12367731		
FLUAV	MDCK	0.7uM	135uM (+/-25.192)	12367731		
FLUAV	MDCK	0.20uM	130uM (+/-55.650)	12367731		
FLUAV	MDCK	0.15uM	145uM (+/-25.966)	12367731		
FLUAV	MDCK	0.9uM	160uM (+/-20.177)	12367731		
FLUAV	MDCK	0.82uM	165uM (+/-15.201)	12367731		
FLUAV	MDCK	0.63uM	165uM (+/-15.261)	12367731		
FLUAV	MDCK	0.38uM	165uM (+/-15.434)	12367731		
FLUAV	MDCK	0.70uM	165uM (+/-15.235)	12367731		
FLUAV	MDCK	0.54uM	165uM (+/-15.289)	12367731		
FLUAV	MDCK	0.45uM	165uM (+/-15.366)	12367731		
FLUAV	MDCK	0.83uM	165uM (+/-15.198)	12367731		
FLUAV	MDCK	0.27uM	175uM (+/-15.648)	12367731		
FLUAV	MDCK	0.48uM	185uM (+/-10.385)	12367731		
FLUAV	MDCK	0.37uM	145uM (+/-35.391)	12367731		
FLUAV	MDCK	0.76uM	135uM (+/-25.177)	12367731		
FLUAV	MDCK	0.49uM	130uM (+/-55.265)	12367731		
FLUAV	MDCK	0.58uM	145uM (+/-25.250)	12367731		
FLUAV	MDCK	0.78uM	160uM (+/-20.205)	12367731		
FLUAV	MDCK	7.6uM	230uM	30.3.	24941437	
FLUAV	MDCK	5.1uM	230uM	45.1.	24941437	
FLUAV	MDCK	0.81uM	230uM	283.9.	24941437	
FLUAV	MDCK	0.15uM	230uM	450.	24941437	
FLUAV	MDCK	29uM (+/-18)	>100 (MCC)	3.5.	18954995	
FLUAV	MDCK	0.85uM (+/-1.1)	>100 (MCC)	117.6.	18954995	
FLUAV	MDCK	34uM	>500uM	14.7.	24237039	
FLUAV	MDCK	38uM	>500uM	13.2.	24237039	
FLUAV	MDCK	0.84uM	>500uM	595.	24237039	
FLUAV	MDCK	0.82uM	>500uM	609.	24237039	
FLUBV	MDCK	>500uM	336uM	<1	25600073	
FLUBV	MDCK	>500uM	336uM	<1	25600073	
FLUBV	MDCK	>400uM	>400uM	>1	28477572	
FLUBV	MDCK	>400uM	>400uM	>1	28477572	
FLUBV	MDCK	>500uM	258uM	<1	22870806	
FLUBV	MDCK	>500uM	258uM	<1	22870806	
FLUBV	MDCK	>500uM	>500uM	>1	24237039	
FLUBV	MDCK	>500uM	>500uM	>1	24237039	
SARS-CoV	rRnK4	89.2uM	356.9uM	4.	15288617	
Ritonavir	HIV-1	MT-2	0.038uM (+0.00 21.3uM (+/-0.560)		18955518	
	HIV-1	MT-2	0.054uM (+0.00 31.1uM	580	17371811	
	HIV-2	MT-2	0.26uM (+/-0.01) 31.1uM	119.6.	17371811	
	HIV-2	MT-2	0.21uM (+/-0.05) 31.1uM	148.1.	17371811	
	MERS-CoV	Calu-3	24.9uM	>50uM	>2.	31924756
	RVFV	A549	26.8uM	>100uM	>4	29689664
	fCoV	Fcfw-4	0.70uM (+/-0.13)	0.34uM (+/-0.1)		32563698
hCoV-OC43	HCT-8	5.78uM (+/-2.17)	>50uM	>8.7.	32563698	
Saliphenylhalamide	FLUAV	RPE	0.254uM (+/-0.05 7.547uM (+/-29		22910914	
	JEV	Vero76	1.94uM	25.1uM	12.9.	27919709
	WNV	Vero76	2.19uM	25.1uM	11.5.	27919709
	ZIKV	RPE	0.05uM (+/-0.02) > 10.0uM	> 200	28049006	
	ZIKV	Vero76	0.62uM	25.1uM	40.5.	27919709
	ZIKV	Vero76	0.49uM	25.1uM	51.2.	27919709
	HIV-1	MT-2	0.026uM (+/-0.00 19.8uM (+/-2.773)		23403426	
	HIV-1	MT-2	0.014uM (+/-0.00 9.9uM (+/-3.6.710)		18955518	
	HIV-1	MT-2	0.017uM (+/-0.00 11.3uM (+/-2.660)		14506019	
	HIV-1	MT-2	0.008uM (+/-0.00 16.4uM	2,050.	17371811	
	HIV-2	MT-2	0.003uM (+/-0.00 19.8uM (+/-2.6,600)		23403426	
	HIV-2	MT-2	0.0043uM (+/-0.00 16.4uM	38.129.	17371811	
HIV-2	MT-2	0.003uM (+/-0.00 11.3uM (+/-2.3,766)		14506019		
HIV-2	MT-2	0.006uM (+/-0.00 11.3uM (+/-2.1,883)		14506019		
HIV-2	MT-2	0.0030uM (+/-0.00 16.4uM	5,466.	17371811		
Selenazofurin	JEV	Vero76	9.8uM	3,255uM	322.	6151377
	HTNV	VeroE6	4.2uM	3,255uM	775.	6151377
	PICV	Vero76	13uM	3,255uM	250.	6151377
	RVFV	Vero76	9.12uM	3,255uM	356.	6151377
	VEEV	Vero76	1.63uM	3,255uM	1,996.	6151377
	YFV	LLC-MK2	0.26uM	3,255uM	12,519.	6151377
	EBOV	Huh7	3.79uM	22.61uM	5.97.	29939303
	EBOV	293T/17	6.1uM	>10uM	>1.6.	29939303
	hCoV-OC43	LLC-MK2	3.49uM	>10uM	>2.87	33324406
SARS-CoV-2	Vero	9.34uM	27.84uM	2.98.	33324406	
Silvestrol	CCHFV	Murine hep2	0.0285uM	>5uM	>175.	31931103
	hCoV-229E	MRC-5	0.003uM	>1uM	>3300	31931103
	LASV	Murine hep2	0.05073uM	>5uM	>99.	31931103
	MERS-CoV	MRC-5	0.0013uM	>1uM	>7690	31931103
	ZIKV	A549	0.00108uM	0.00942uM	8.8.	31931103
	HCV	Huh7-Luc	0.0081uM	47uM	5,802.	19171797
	HCV	Huh7-Luc	0.013uM	47uM	3,615.	19171797
SARS-CoV-2	VeroE6	1.41uM (+/-0.12)	32.71uM (+/-23.		34929295	
SARS-CoV-2	VeroE6	15uM	59uM	3.9.	34097489	
SARS-CoV-2	Huh7.5	14uM	33uM	2.4.	34097489	
SARS-CoV-2	A549-HACE9	9uM	56uM	6.2.	34097489	
SARS-CoV-2	VeroE6	4.25uM	2.1uM	<1	33984267	
SARS-CoV-2	HEK293T	2.3uM	>50uM	21.7.	33984267	
ZIKV	U-87MG	0.4uM	10.1uM	25.25.	32488021	
Simvastatin	HCMV	HAEC	0.003uM (+/-0.00 1uM (+/-0.01	333.	24976258	
	HCMV	MRC-5	1.57uM (+/-1.04)	3.5uM (+/-0.12.3.	24976258	
Sirolimus	HIV-1	TZM-bl	18.81uM	>30uM	>1	29698664
	hCoV-229E	MRC-5	2.28uM	2.5uM	1.096491	33672333
Sofosbuvir	EBOV	Huh7	>20uM	>20uM	>1.	29939303
	EBOV	293T/17	>20uM	>20uM	>1.	29939303
Sorafenib	CHIKV	Vero	0.16uM	>80uM	>500.	29981794
	EEEV	Vero	6.7uM	>80uM	>11.9.	29981794
	RVFV	Vero	6.4uM, 3.9uM	>160uM	>31.74.	26217313
	SINV	Vero	1.3uM	>80uM	>61.5.	29981794
	VEEV	Vero	4.2uM	>80uM	>19.	29981794
	VEEV	Vero	6.2uM	>80uM	>12.9.	29981794
Sunitinib	CHIKV	Vero	4.67uM	11.9uM	2.6.	28240606
	DENV	MDDC	1.962uM	>20uM	>10	29753658
	DENV-1	BHK-21	0.6uM	>10uM	>16.	28240606
	DENV-2	Huh7, BHK	0.51uM	11.5uM	22.5.	28240606
	DENV-3	BHK-21	0.3uM	>10uM	>33.	28240606
	DENV-4	BHK-21	0.23uM	>10uM	>43.	28240606
	EBOV	Huh7	0.47uM	>10uM	>21	28240606
	EBOV	Vero	0.47uM	>10uM	>21	28240606
	EBOV	Huh7	4.11uM	18.12uM	4.41.	29939303
	EBOV	293T/17	8.2uM	61.7uM	7.5.	29939303
	HCV	Huh7.5	1.2uM	>10uM	>8.3.	28240606
HIV-1	HeLa/TZM-	0.8uM	>20uM	>25.	28240606	
JUNV	Vero	4.8uM	10.4uM	2.2.	28240606	
RSV	Hep2	>0.12uM	12.5uM	<104.2.	28240606	
WNV	MER/Vero	0.55uM	>20uM	>36.4.	28240606	
ZIKV	Huh7	0.51uM	14.1uM	27.6.	28240606	
Suramin	CHIKV	VeroE6	79uM (+/-11.6)	>1000uM	>12.7	26112648
	CHIKV	VeroE6	76uM (+7)	>1000uM	>13.2	26112648
	CHIKV	VeroE6	79uM (+/-12.9)	>1000uM	>12.7	26112648
	CHIKV	BHK-21	21.5uM (+/-7.1)	>700uM	>32.6	26208101
	CHIKV	U2OS	17.9uM (+/-9.5)	>700uM	>39.1	26208101
	CHIKV	MRC-5	18.1uM (+4)	>300uM	>19.3	26208101
	CHIKV	BHK-21	28.9uM (+/-6.8)	>700uM	>24.2	26208101
	CHIKV	U2OS	59.6uM (+/-11.9)	>700uM	>11.7	26208101
	CHIKV	MRC-5	62.1uM (+/-2.7)	>300uM	>4.8.	26208101
	CHIKV	BHK-21	8.8uM (+/-0.5)	>700uM	>79.5.	26208101
	CHIKV	U2OS	43.8uM (+/-6.1)	>700uM	>16.	26208101
	CHIKV	MRC-5	54.1uM (+/-11.8)	>300uM	>5.5.	26208101
	CHIKV	BHK-21	21.9uM (+/-4.8)	>700uM	>31.9.	26208101
	CHIKV	U2OS	36uM (+/-9.6)	>700uM	>19.	26208101
	CHIKV	MRC-5	54.3uM (+/-4.7)	>300uM	>5.5.	26208101
	HCV	Huh7.5	28uM (+/-9.3)	>50uM	>1.8.	27240655
	SARS-CoV-2	VeroE6	20uM (+/-2.7)	>5mM	>250.	32513797
	SFV	VeroE6	40uM (+/-10)	>400uM	>10.	26112648
	SINV	VeroE6	141uM (+/-18.3)	>400uM	>2.8.	26112648
ZIKV	Vero	39.8uM	1900uM	48.	28461070	
Tamoxifen	EBOV	Huh7	0*311uM (+/-0*1	16*29uM (+/-	52	31300330
	EBOV	Huh7	0*108uM (+/-0*0)	>50uM	151	31300330
	EBOV	Vero	3uM	38uM	13.	27622822
	EBOV	Vero	0.75uM	10.09.	13.47.	26585243
	VSV	Vero	4.94uM	10.09.	2.04.	26585243
Teicoplanin	EBOV	HEK293T	0.34uM (+/-0.11)	>500uM	1,470.	26953343
	EBOV	HEK293T	0.39uM (0.12)	>500uM	1,282.	

Valproic Acid	hCoV-229E	MRC5	1,339uM	4000uM	2,987.	33672333	Zalcitabine	HIV-1	MT-4	0.75uM (+-0.55)	>94uM	>127	22870806
	EBOV	Huh7	41.23uM (+-21.6)	>50uM	>1	31300330		HIV-2	MT-4	0.88uM (+-0.53)	>94uM	>108	22870806
Verapamil							Zanamivir	FLUAV	MDCK	0.36uM	>100uM	>277	25600073
	EBOV	Huh7	23.43uM (+-21.3)	>50uM	>2	31300330		FLUAV	MDCK	0.77uM	>100uM	>129	25600073
Verdineoxor	hAdV-5	HeLa	0.18uM	0.18uM	1.	30332435		FLUAV	MDCK	20uM	>100uM	>5	25600073
	hAdV-5	HeLa	0.03uM	0.10uM	3.	30332435		FLUAV	MDCK	5.6uM	>100uM	>17	25600073
	BKPyV	HFF	7.62uM	10.0uM	>1.	30332435		FLUAV	MDCK	5.8uM	>100uM	>17	25600073
	BKPyV	HFF	2.29uM	9.38uM	4.	30332435		FLUAV	MDCK	2.8uM	>100uM	>35	25600073
	EBV	Akata cells	0.48uM	0.68uM	>1.	30332435		FLUAV	MDCK	2.3uM	>100uM	>43	28477572
	EBV	Akata cells	0.05uM	0.34uM	7.	30332435		FLUAV	MDCK	6.8uM	>100uM	>14	28477572
	FLUAV	MDCK	0.20uM	26.8uM	134	24965445		FLUAV	MDCK	0.80uM	>100uM	>125	28477572
	FLUAV	MDCK	0.04uM	26.8uM	670	24965445		FLUAV	MDCK	0.20uM	>100uM	>500	28477572
	FLUAV	MDCK	0.27uM	26.8uM	99	24965445		FLUAV	MDCK	0.018uM	>1000uM	>55,555	12367731
	FLUAV	MDCK	0.18uM	26.8uM	149	24965445		FLUAV	MDCK	0.017uM	>1000uM	>58,823	12367731
	FLUAV	MDCK	0.06uM	26.8uM	447	24965445		FLUAV	MDCK	0.013uM	>1000uM	>76,923	12367731
	FLUAV	MDCK	0.42uM	26.8uM	64	24965445		FLUAV	MDCK	0.008uM	>1000uM	>125,000	12367731
	FLUBV	MDCK	0.09uM	26.8uM	298	24965445		FLUAV	MDCK	0.019uM	>1000uM	>52,631	12367731
	FLUBV	MDCK	0.01uM	26.8uM	2,68	24965445		FLUAV	MDCK	0.03uM	>1000uM	>33,333	12367731
	HCMV	GPL	0.19uM	2.0uM	11.	30332435		FLUAV	MDCK	0.014uM	>1000uM	>71,428	12367731
	HCMV	HFF	0.19uM	1.76uM	9.	30332435		FLUAV	MDCK	0.005uM	>1000uM	>200,000	12367731
	HCMV	HFF	2.5uM	73.3uM	29.	30332435		FLUAV	MDCK	0.012uM	>1000uM	>83,333	12367731
	HCMV	HFF	2.5uM	73.3uM	29.	30332435		FLUAV	MDCK	0.008uM	>1000uM	>125,000	12367731
	HPV-11	HEK293	1.65uM	89.55uM	54.	30332435		FLUAV	MDCK	0.008uM	>1000uM	>125,000	12367731
	HPV-18	PHK	8.30uM	8.30uM	1.	30332435		FLUAV	MDCK	0.016uM	>1000uM	>62,500	12367731
	JCPyV	COS7	7.45uM	10uM	>1.	30332435		FLUAV	MDCK	0.018uM	>1000uM	>55,555	12367731
	JCPyV	COS7	3.14uM	73.3uM	29.	30332435		FLUAV	MDCK	0.016uM	>1000uM	>62,500.	12367731
	KSHV	BCBL-1	0.8uM	2.76uM	4.	30332435		FLUAV	MDCK	0.133uM	>1000uM	>7,518	12367731
	KSHV	BCBL-1	0.27uM	1.40uM	5.	30332435		FLUAV	MDCK	0.123uM	>1000uM	>8,130	12367731
	MCMV	MEF	0.19uM	150uM	789.	30332435		FLUAV	MDCK	0.085uM	>1000uM	>11,764	12367731
	RSV	A549	0.96uM	37.93uM	39.5.	30541831		FLUAV	MDCK	0.073uM	>1000uM	>13,698	12367731
Vesatolimod	HIV-1	PBMC	0.536uM (+-0.83)	22uM (+-5.2)	41.	27799219		FLUAV	MDCK	0.073uM	>1000uM	>13,698	12367731
	HIV-1	PBMC	0.953uM (+-1.11)	22uM (+-5.2)	23.1.	27799219		FLUAV	MDCK	0.033uM	>1000uM	>30,303	12367731
	HIV-1	PBMC	0.0272uM (+-0.0)	22uM (+-5.2)	808.8.	27799219		FLUAV	MDCK	0.075uM	>1000uM	>13,333	12367731
	HIV-1	CD4+ T cell	>10uM	>10uM	1.	27799219		FLUAV	MDCK	0.095uM	>1000uM	>10,526	12367731
	HIV-1	CD4+ T cell	>10uM	>10uM	1.	27799219		FLUAV	MDCK	0.086uM	>1000uM	>11.627	12367731
	HIV-1	CD4+ T cell	>2uM	>10uM	5.	27799219		FLUAV	MDCK	0.162uM	>1000uM	>6,172	12367731
	HIV-1	Isolated mc	>10uM	>10uM	1.	27799219		FLUAV	MDCK	0.113uM	>1000uM	>8,849	12367731
	HIV-1	Isolated mc	>7.3uM	>10uM	1.4.	27799219		FLUAV	MDCK	0.059uM	>1000uM	>16,949	12367731
	HIV-1	Isolated mc	>1.6uM	>10uM	6.25.	27799219		FLUAV	MDCK	0.078uM	>1000uM	>12,820	12367731
Vidarabine	CPXV	Vero	3.4uM	>374uM	>110.	16530858		FLUBV	MDCK	45uM	>100uM	>2.2.	25600073
	CPXV	Vero	2.92uM	>374uM	>128.	16530858		FLUBV	MDCK	26uM	>100uM	>3.9.	25600073
	EBV	P3HR-1	18uM (+-17)	38uM (+-1)	2	25267682		FLUBV	MDCK	0.060uM	>100uM	>1,666	28477572
	HSV	OMK	29uM (+-15)	115uM (+-24)	3	25267682	Zidovudine	EBOV	Huh7	>50uM	>50uM	>1.	29939303
	HSV-1	Vero	6.19uM	117.64uM	19.00.	10967475		EBOV	293T/17	>50uM	>50uM	>1.	29939303
	HSV-1	MRC-5	16.4uM	1020uM	62.2.	7822458		EBV	P3HR-1	37.4uM	198uM	5.3.	9875407
	HSV-1	MRC-5	4.63uM	1020uM	220.3.	7822458		EBV	P3HR-1	<37.4uM	198uM	5.3.	9875407
	HSV-1	HFF	23.95uM	>374uM	15.6.	16530858		HIV-1	MT-4	0.0076uM (+-0.0)	>88.26uM	>11,587	22870806
	HSV-1	HFF	18.33uM	>374uM	20.4.	16530858		HIV-1	MT-4	0.02uM (+-4.42)	>88.26uM	>4,413	22870806
	HSV-2	Vero	5.49uM	117.64uM	21.42.	10967475		HIV-1	MT-4	0.011uM (+-0.00)	>88.26uM	>8,023	22870806
	HSV-2	MRC-5	23.9uM	1020uM	42.7.	7822458		HIV-1	MT-4	0.0049uM (+-0.0)	>88.26uM	>18,012	22870806
	HSV-2	MRC-5	9.11uM	1020uM	111.9.	7822458		HIV-1	P4/R5	0.19uM (+-0.11)	>270uM	>1,421	19596885
	KSHV	BCBL-1	99uM (+-43)	233uM (+-4)	2	25267682		HIV-1	P4/R5	0.21uM (+-0.15)	>270uM	>1,285	19596885
	MHV-68	NIH3T3	2.0uM (+-1.2)	21uM (+-21)	1	25267682		HIV-1	P4/R5	0.21uM (+-0.008)	>270uM	>1,285	19596885
	RRV	RF	118uM (+-16)	> 233uM	> 1	25267682		HIV-1	P4/R5	0.18uM (+-0.16)	>270uM	>1,500	19596885
								HIV-1	P4/R5	213.7uM (+-12.3)	>270uM	>1.3.	19596885
								HIV-1	MT-4	0.005uM (+-0.00)	100uM (+-25)	20,000.	10212126
								HIV-2	MT-4	0.0033uM (+-0.0)	>88.26uM	>28,348	22870806
								HIV-2	MT-4	0.005uM (+-0.00)	100uM (+-25)	20,000.	10212126

**Table S.2.2: BSA and their molecular weight.** Molecular weight in g/mol for some of the BSAs. Used to determine  $\mu\text{M}$ .

BSA	MW (g/mol)	PubChem CID
Acyclovir	225.21	135398513
Adefovir	273.186	60172
Adefovir dipivoxil	501.5	60871
Amantadine	151.25	2130
Amiodarone	645.3	2157
Amprenavir	505.6	65016
Azauridine	245.19	5901
Berberine	336.4	2353
Betulinic acid	456.7	64971
Brivudine	333.13	446727
Camostat	398.4	2536
Camptothecin	348.4	24360
Cidofovir	279.19	60613
Diphenhydramine	255.35	3100
Doxycycline	444.4	54671203
Favipiravir	157.10	492405
Fiacitabine	371.10	50312
Ganciclovir	255.23	135398740
Glycyrrhizin	822.9	128229
Indinavir	613.8	5362440
Lobucavir	265.27	135413519
Minocycline	493.9	54675783
Mycophenolic acid	320.3	446541
Nafamostat	347.4	4413
Nelfinavir	567.8	64143
Oseltamivir	312.40	65028
Penciclovir	253.26	135398748
Pentosan polysulfate	602.5	37720
Ribavirin	244.20	37542
Rimantadine	179.3	5071
Ritonavir	720.9	392622
Saquinavir	670.8	441243
Selenazofurin	307.17	100665
Simprevir	749.9	24873435
Trifluridine	296.20	6256
Umifenovir	477.4	131411
Vidarabine	267.24	21704
Zidovudine	267.24	35370

**Table S.2.3: Positive and negative antiviral activities of BSAs.** Shown in the table are BSAs with positive ( $SI > 1$ ) and negative ( $SI \leq 1$ ) antiviral activities.

A

BC	Virus	SI > 1	SI ≤ 1
I	BKPyV	Cidofovir; Leflunomide; Verdinextor	
	CPXV	Acyclovir; Adefovir; Adefovir dipivoxil; Brivudine; Cidofovir; Erlotinib; Flacitabine; Ribavirin; Trifluridine; Vidarabine	
	EBV	Acyclovir; Adefovir; Brivudine; Cidofovir; Fiacitabine; Ganciclovir; Penciclovir; Ribavirin; Verdinextor; Vidarabine; Zidovudine	
	hAdV	Acetylsalicylic acid; Cidofovir; Filiciclovir; Quinacrine; Tilorone; Verdinextor	Verdinextor
	HCMV	Artesunate; Berberine; Calanolide A; Cidofovir; Emotion; Filiciclovir; Fluvastatin; Ganciclovir; Penciclovir; Quinacrine; Simvastatin; Tilorone	Adefovir; Gemcitabine
	HHV-6	Acyclovir; Cidofovir; Ganciclovir; Penciclovir	
	HHV-7	Acyclovir; Cidofovir; Ganciclovir; Penciclovir	
	HPV	Quinacrine; Tilorone	Verdinextor
	HSV-1	Acetylsalicylic acid; Acyclovir; Beclabuvir; Brivudine; Cidofovir; Fiacitabine; Filiciclovir; Ganciclovir; Gemcitabine; Penciclovir; Trifluridine; Vidarabine	Acyclovir
	HSV-2	ABMA; Acyclovir; Beclabuvir; Brivudine; Chloroquine; Cidofovir; Ganciclovir; Penciclovir; Vidarabine	Adefovir; Brivudine
	KSHV	Acyclovir; Adefovir; Brivudine; Camptothecin; Cidofovir; Fiacitabine; Foscarnet; Ganciclovir; Novobiocin; Penciclovir; Verdinextor; Vidarabine	Penciclovir
	MCMV	Filiciclovir; Ganciclovir	
	MHV-68	Acyclovir; Brivudine; Fiacitabine; Ganciclovir; Verdinextor; Vidarabine	Panciclovir
	MPXV	Cidofovir; Ribavirin	
	ORFV	Cidofovir	
	RRV	Brivudine; Ganciclovir; Mycophenolic acid; Verdinextor; Vidarabine	Acyclovir; Penciclovir
	VACV	Adefovir; Adefovir dipivoxil; Brivudine; Cidofovir; Ribavirin	Acyclovir; Ganciclovir
	VARV	Adefovir dipivoxil; Cidofovir; Ribavirin	
	VZV	Acyclovir; Adefovir; Brivudine; Cidofovir; Clofazimine; Fiacitabine; Filiciclovir; Penciclovir	Gemcitabine

B

BC	Virus	SI > 1	SI ≤ 1
	B19B	Brincidofovir	
II	MSV	N.a.	Adefovir

C

BC	Virus	SI > 1	SI ≤ 1
III	hRoV	25HC; Ribavirin; Mycophenolic acid	Ribavirin

D

BC	Virus	SI > 1	SI ≤ 1
VI	fLV	Gemcitabine; Tenofovir	
	HIV-1	Adefovir; Adefovir dipivoxil; Amprenavir; Atazanavir; Beclabuvir; Berberine; Betulinic acid; Calanolide A; Camptothecin; Chicoric acid; Clofarabine; Darunavir; Efavirenz; Erlotinib; Etravirine; Ezetimibe; Indinavir; Lamivudine; Minocycline; Nelfinavir; Ritonavir; Saquinavir; Sirolimus; Sunitinib; Tenatoprazole; Vesatolimod; Zalcitabine; Zidovudine	Esomeprazole; Vesatolimod
	HIV-2	Adefovir; Amprenavir; Atazanavir; Beclabuvir; Calanolide A; Camptothecin; Chicoric acid; Darunavir; Indinavir; Lamivudine; Nelfinavir; Ritonavir; Saquinavir; Zalcitabine; Zidovudine	Calanolide A; Etravirine
	SIV	Calanolide A	Calanolide A

E

BC	Virus	SI > 1	SI ≤ 1
VII	HBV	Adefovir dipivoxil; Lamivudine; Telbivudine	Adefovir dipivoxil

-

F

BC	Virus	SI > 1	SI ≤ 1
IV	AHFV	Remdesivir	
	BVDB	Beclabuvir	
	CHIKV	Berberine; Bromocriptine; Chloroquine; Eptifibatide; Erlotinib; Fenretinide; Ivermectin; Mycophenolic acid; Sorafenib; Sunitinib; Suramin; Tilorone; Umifenovir	Galidesivir; Quinacrine
	CV	Acetylsalicylic acid; Beclabuvir; Berberine; Curcubit[7]uril; Emodin; Ribavirin; Umifenovir	Mycophenolic acid; Ribavirin
	DENV	Amodiaquine; Anisomycin; Azithromycin; Bromocriptine; Curcubit[7]uril; Doxycycline; Erlotinib; Galidesivir; Mefloquine; Quinacrine; Ribavirin; Sunitinib	Quinacrine; Tilorone
	EEEV	Galidesivir; Sorafenib	
	EV	Curcubit[7]uril; Dalbavancin; Dibucaine; Fluoxetine; Gemcitabine; Pirlindole; Ribavirin	
	tCoV	Amiloride; Anisomycin; Atovaquone; Chloroquine; Doxycycline; Emetine; GS-441524; Homoharringtonine; Mefloquine; Tilorone	Niclosamide; Salinomycin
	FMDV	Amiloride	
	hCoV-229E	Alisporivir; Amodiaquine; Chloroquine Chlorpromazine; CR-31B (-); GS-441524; Hydroxychloroquine; Lopinavir; Mefloquine; Remdesivir; Reservastrol; Silvestrol; Sirolimus; Tetrandine; Valproic acid	Amodiaquine; Quinine
	hCoV-OC43	Anisomycin; Atovaquone; Beclabuvir; Cepharanthine; Chloroquine; Chlorpromazine; Clofazimine; Cyclosporine A; Emetine; Fluoxetine; Gefetinib; GS-441524; Homoharringtonine; Hydroxychloroquine; Imatinib; Luteolin; Mefloquine; Monensin; Niclosamide; Nitazoxanide; Raloxifene; Remdesivir; Salinomycin; Sertraline; Thapsigargin; Thioridazine; Tilorone; Umifenovir	
	HCV	Beclabuvir; Erlotinib; Fluoxetine; Hydroxyzine; IFN-a; IFN-b; IFN-g; Ribavirin; Simprevir; Sunitinib; Suramin	Benzotropine; IFN-a; IL-7; Ribavirin
	hRhV	Acetylsalicylic acid; Beclabuvir; Galidesivir; Gemcitabine; Umifenovir	
	IBV	Umifenovir	
	JEV	Brequinar; Chloroquine; Doxycycline; Emodin; Galidesivir; IFN-a; IFN-b; Minocycline; Ribavirin; Saliphenylthalamide; Selenazofurin	Chloroquine; Monensin; Ribavirin
	KFDV	Remdesivir	
	MERS-CoV	Amiodarone; Chloroquine; Chlorpromazine; Ciclesonide; CR-31B (-); Digitoxin; Enoxacin; Galidesivir; IFN-b; Lanatoside C; Lopinavir; Mycophenolic acid; Niclosamide; Regorafenib; Remdesivir; Ribavirin; Ritonavir; Silvestrol; Toremifene	
	MHV	Chloroquine; Doxycycline; Ivermectin; Remdesivir	
	OHFV	Remdesivir	
	pCoV	Cepharanthine	
	PoV	Beclabuvir; Gemcitabine; Remdesivir; Umifenovir	
	POWV	Quinacrine	Tilorone
	PRRSV	Doxycycline	
	SARS-CoV	Amiodarone; Amodiaquine; Azauridine; Chloroquine; Chlorpromazine; Ciclesonide; Galidesivir; Glycyrrhizin; GS-441524; Hydroxychloroquine; IFN-a; IFN-b; Lopinavir; Mefloquine; Quinine; Remdesivir; Ribavirin; Rimantadine; Sertraline; Toremifene	Glycyrrhizin; Mycophenolic acid; Ribavirin
	SARS-CoV-2	25HC; 4'-fluorouridine; Acetylsalicylic acid; Alisporivir; Amiloride; Amiodarone; Amodiaquine; Aprotinin; Azithromycin; Berberine; Boceprevir; Cepharanthine; Chloroquine; Clofazimine; CR-31B (-); Cyclosporine A; Dalbavancin; Digitoxin; Diltiazem; Doxycycline; Enoxacin; Favipiravir; Fenofibrate; Gefetinib; Gemcitabine; GS-441524; Hydroxychloroquine; Imatinib; Indometacin; IFN-a; IFN-g; Lanatoside C; Lopinavir; Mefloquine; Monensin; Nafamostat; Niclosamide; Nitazoxanide; Obatoclax; Oubain; Penciclovir; Promethazine; Quinine; Raloxifene; Ribavirin; Simeprevir; Suramin; Tenofovir; Thioridazine; Tilorone; Tormeifene; Umifenovir	Quinacrine; Quinine; Simeprevir
	SFV	Curcubit[7]uril; Suramin	
	SINV	Mycophenolic acid; Ribavirin; Sorafenib; Suramin	
	TBEV	Bromocriptine; Remdesivir	
	VEEV	Selenazofurin; Sorafenib	Galidesivir
	WEEV	Galidesivir	
	WNV	Brequinar; Chloroquine; IFN-a; IFN-b; Saliphenylthalamide; Sunitinib	Chloroquine; Monensin; Ribavirin
	YFV	Galidesivir; Mycophenolic acid; Quinacrine; Selenazofurin; Tilorone	Ribavirin
	ZIKV	Anisomycin; AVN-944; Azaribine; Azauridine; Azithromycin; Brequinar; Bromocriptine; Chloroquine; CR-31B (-); Curcubit[7]uril; Diphyltin; Erlotinib; Ezetimibe; Gemcitabine; Hydroxychloroquine; IFN-a; IFN-b; IFN-g; Lopinavir; Mefloquine; Merimepodib; Mycophenolic acid; Obatoclax; Quinacrine; Saliphenylthalamide; Silvestrol; Simeprevir; Sunitinib; Suramin	Monensin; Ribavirin

G

BC	Virus	SI > 1	SI ≤ 1
V	ANDV	Remdesivir	
	CCHFV	CR-31-B (-); Silvestrol	Remdesivir
	EBOV	ABMA; Amoidarone; Amoidaquine; Apilmod; Artesunate; Azauridine; Azithromycin; Benzotropine; Bepidil; Chloroquine; Clomipramine; Clomiphene; Emetine; Erlotinib; Favipiravir; Fluphenazine; Galidesivir; Hydroxychloroquine; Hydroxyzine; Lamivudine; Mycophenolic acid; Niclosamide; Promethazine; Quinacrine; Remdesivir; Ribavirin; Sertraline; Sunitinib; Tamoxifen; Teicoplanin; Teriflumonide; Tilorone; Toremfene; Verapamil	Azauridine; Azithromycin; Bepidil; Chloroquine; Erlotinib; Favipiravir; Lamivudine; Sofosbuvir; Tenofovir; Zidovudine
	FLUAV	ABT-737; Acetylsalicylic acid; Amantadine; Aprotinin; AVN-944; Azaribine; Azithromycin; Baloxavir marboxil; Beclabuvir; Berberine; Bortezomib; Brequinar; Camostat; Dapivirine; Emetine; Favipiravir; Galidesivir; Gemcitabine; MK2206; Mycophenolic acid; Nafamostat; Obatoclax; Oseltamivir; Ribavirin; Rilpivirine; Rimantadine; Saliphenylhalamide; Thapsigargin; Umifenovir; Verdinextor; Zanamivir	Pentosan polysulfate; Ribavirin; Rimantadine
	FLUBV	AVN-944; Azaribine; Baloxavir marboxil; Berberine; Brequinar; Camostat; Dapivirine; Nafamostat; Oseltamivir; Ribavirin; Rimantadine; Umifenovir; Verdinextor; Zanamivir	Amantadine; Oseltamivir; Pentosan polysulfate; Rimantadine
	HDV	Beclabuvir	
	HeV	Remdesivir	
	hPIV	Mycophenolic acid; Remdesivir; Ribavirin; Umifenovir	Camostat; Nafamostat
	HTNV	Selenazofurin; Umifenovir	
	JUNV	Erlotinib ; Galidesivir; Sunitinib	
	LACV	Galidesivir	
	LASV	CR-31-B (-); Galidesivir; Remdesivir; Silvestrol	
	LCMV	ABT-737; Clofazimine; Mycophenolic acid; Obatoclax	
	MARV	Amoidarone; Apilmod; Galidesivir; Hydroxyzine; Promethazine; Remdesivir	Benzotropine
	MeV	Galidesivir; Remdesivir	Camostat; Nafamostat
	MuV	Remdesivir	
	NiV	Galidesivir; Remdesivir	
	PICV	Selenazofurin	
	PTV	Mycophenolic acid; Ribavirin	
	RABV	ABMA; Clofazimine; DABMA	
	RSV	4'-fluorouridine; Acetylsalicylic acid; Erlotinib; Galidesivir; Remdesivir; Ribavirin; Sunitinib; Thapsigargin; Umifenovir; Verdinextor	Camostat; Nafamostat
	RVFV	Azacididine; Bortezomib; Cyclosporine A; Galidesivir; Minocycline; Oritavancin; Quinacrine; Ritonavir; Selenazofurin; Sorafenib	Remdesivir; Tilorone
	SFTSV	Bleomycin; Clofarabine; Favipiravir; Hexachlorophene; Nifedipine; Regorafenib; Ribavirin	
	SUDV	Galidesivir	
	VSV	25HC	
	VSV	Amoidarone; Clomipramine; Doxycycline; Tamoxifen; Toremfene	Amiodarone; Gefetinib; Promethazine; Remdesivir; Teicoplanin; Toremfene







**Figure S.3.1: BSAs with overlapping host target genes.** The colors imply effects the BSA has on the corresponding target: Yellow for BSA acting inhibitory (inhibitor, antagonist, blocker, negative modulator, or inverse agonist), blue for BSA acting stimulatory (Agonist, partial agonist, activator, or inducer), purple for BSA acting modulatory (modulator or allosteric modulator) and green for BSA acting both inhibitory and stimulatory. Note: The two Figures include different targets, but same BSAs. Further, it includes only targets which are aimed by more than two BSAs. \* Targets that are clustered together (e.g STAT\* covers STAT3, STAT4, STAT5 and STAT6). Table S.3.1 shows clustered target gene names.

**Table S.3.1: Host target clusters and its gene members.** The table shows clustered targets (\*), protein name, the gene names included in clusters, and UniProtKB reference for each respective gene.

Target gene	Target protein name	Genes included in *	UniProtKB ID
ABC*	ATP-binding cassette transporters	ABCA1; ABCB1; ABCB4; ABCC1; ABCC10; ABCC2; ABCC3; ABCC4; ABCC5; ABCG2	O05477; P0185; O65342; P21439; P33827; Q07835; Q08387; O15438; O15440; Q9UNQ0
ABL*	Tyrosine-protein kinase ABL	ABL1; ABL2	P00519; P42684
ACE*	Angiotensin converting enzyme	ACE; ACE2	P12821; Q9BYF1
ADA	Adenosine deaminase		P00813
ADORA*	Adenosine receptor A	ADORA1; ADORA2A; ADORA2B; ADORA3	P30542; P29274; P29275; P0DMS8
ADRA*	Adrenergic receptor	ADRA1A; ADRA1B; ADRA1D; ADRA2A; ADRA2B; ADRA2C	P35348; P35368; P25100; P08913; P18089; P18825
AHR	Aryl hydrocarbon receptor		P35869
AKT*	Protein kinase B	AKT1; AKT2; AKT3	P31749; P31751; Q9Y243
ANKK1	Ankyrin repeat and protein kinase domain-containing protein 1		Q8NFD2
APC	Adenomatous polyposis coli protein		P25054
APO*	Apolipoprotein	APOA1; APOA5; APOB; APOC3; APOE	P02647; Q9Q786; P04114; Q02656; P02649
ARAF	Serine/threonine-protein kinase A-Raf		P10388
ARID*	AT-rich interactive domain-containing protein	ARID1A; ARID5B	O14497; Q14865
ASIC*	Acid-sensing ion channel	ASIC1; ASIC2; ASIC3	P78348; Q16515; Q9UHC3
ATPases*	Sodium/potassium-transporting ATPase.	ATP1A1; ATP1A2; ATP1A3; ATP1A4; ATP1B1; ATP1B2; ATP1B3;	P05023; P50993; P13637; Q13733; P05026; P14415; P54709
	Sarcoplasmic/endoplasmic reticulum calcium ATPases	ATP2A1	Q14983
	Potassium-transporting ATPase	ATP4A; ATP4B	P20648; P51164
	ATP synthase	ATP5F1A; ATP5B; ATP5C1; ATP5F1E	P25705; Q0Q0EN7; P36542; P56381
BAX	Apoptosis regulator Bax		Q07612
BCL2	Apoptosis regulator Bcl-2		P10415
BCL2L*	Bcl-2 like protein	BCL2L1; BCL2L2	Q07617; Q92843
BCR	Breakpoint cluster region protein		P11274
BIRC5	Baculoviral IAP repeat-containing protein 5		O15392
BRAF	Serine/threonine-protein kinase B-raf		P15056
CACNA*	Voltage-dependent P/Q-type calcium channel	CACNA1A	O00555
	Voltage-dependent N-type calcium channel	CACNA1B	Q00975
	Voltage-dependent L-type calcium channel	CACNA1D; CACNA1F; CACNA1S; CACNB1; CACNB2; CACNB3; CACNB4	Q01668; Q60840; Q13698; Q02641; Q08289; P54284; O00305
	Voltage-dependent T-type calcium channel	CACNA1G; CACNA1H; CACNA1I	O43497; Q95180; Q9P0X4
	Voltage-dependent calcium channel	CACNA2D1; CACNG1	P54289; Q06432
CALM1	Calmodulin-1		P0DP23
CASP*	Caspase	CASP1; CASP3	P29466; P42574
UBL	E2 ubiquitin-protein ligase		P22681
CCN*	Cyclin	CCNA1; CCNA2; CCNB1; CCND1	P78396; P20248; P14635; P24385
CCR*	C-C chemokine receptor	CCR2; CCR5	P41597; P51681
CD40LG	CD40 ligand		P29965
CDK*	Cyclin-dependent kinase	CDK1; CDK10; CDK2; CDK3; CDK4; CDK5; CDK6; CDK7; CDK8; CDK9	P66493; Q15131; P24941; Q00526; P11802; Q00535; Q00534; P50613; P49339; P50750
CDKN*	Cyclin-dependent kinase inhibitor	CDKN1A; CDKN1B; CDKN2A;	P38936; P46527; P42771
CETP	Cholesteryl ester transfer protein		P11597
CFL1	Cofilin-1		P23528
CHRM*	Muscarinic acetylcholine receptor	CHRM1; CHRM2; CHRMB; CHRM5	P11229; P08172; P20309; P08912
CHRNA*	Neuronal acetylcholine receptor	CHRNA10; CHRNA2; CHRNA3; CHRNA4; CHRNA5; CHRNA6; CHRNA7; CHRNA9	Q9GZ26; Q15822; P32297; P43681; P30532; Q15825; P36544; Q8UGM1
COL*	Collagen alpha-1 chain	COL1A1; COL1A1; COL26A1	P39060; P02452; Q96A83
CSF2	Granulocyte-macrophage colony-stimulating factor (GM-CSF)		P04141
CSNK*	Casein kinase	CSNK1E; CSNK2A1; CSNK2B	P49674; P68400; P67870
CXCL10	C-X-C motif chemokine 10		P02778
CXCL8	Interleukin 8		P10145
CXCR2	IL-8 receptor type 2		P25025
CYP*	Cytochrome P450	CYP1A1; CYP1B1; CYP2A14; CYP2A6; CYP2B6; CYP2C8; CYP2E1; CYP2F1; CYP2J2; CYP3A4; CYP3A5; CYP3A7; CYP4A11; CYP4F2; CYP51A1; CYP7B1	P04798; Q16678; Q9Z1H8; P11509; P20813; P10632; P05181; P24903; P51589; P08684; P20815; P24462; Q02929; P78329; Q16850; Q75081
	25-hydroxyvitamin D-1 alpha hydroxylase, mitochondrial	CYP27B1	O15528
	Vitamin D 25-hydroxylase	CYP2R1	Q6QX0
DCK	Deoxycytidine kinase		P27707
DDIT3	DNA damage-inducible transcript 3 protein		P35638
DDR*	Discoidin domain-containing receptor	DDR1; DDR2	Q08345; Q16832
DHODH	Dihydroorotate dehydrogenase		Q02127
DRD*	Dopamine receptor	DRD1; DRD2; DRD3; DRD4; DRD5	P21728; P14416; P35462; P21917; P21918
E2F1	Transcription factor E2F1		Q01094
ENO*	Enolase	ENO3; ENOSF1	P13929; Q7L5Y1
EPH-R*s*	Ephrin receptor	EPHA1; EPHA10; EPHA2; EPHA3; EPHA4; EPHA5; EPHA6; EPHA7; EPHA8; EPHB1; EPHB2; EPHB3; EPHB4; EPHB6	P21709; Q6J2Y3; P29317; P29320; P54764; P54756; Q9JF33; Q15375; P29322; P54762; P29323; P54753; P54760; O15197
ERBB*	Receptor tyrosine-protein kinase ERBB	EGFR; ERBB2; ERBB3; ERBB4	P00533; P04626; P21860; Q15303
ER*s*	Estrogen receptor	ESR1; ESR2	P03372; Q92731
	Estrogen-related receptor	ESRRA; ESRRB; ESRRG	P11474; Q95718; P62508
CF*s*	Coagulation factor	F12; F13; F2	P00748; P00488; P00734
F2RL1	Coagulation factor II receptor like 1		P55085
FCGR*s*	Fc receptor (high affinity)	FCER1G; FCGR1A	P30273; P12314
	Fc receptor (low affinity)	FCGR2A; FCGR2C; FCGR3A; FCGR3B	P12318; P31995; P08637; Q75015
FGF*	Fibroblast growth factor	FGF1; FGF2; FGF3; FGF4;	P05230; P09038; P11487; P08620
FKBP*	Peptidyl-prolyl cis-trans isomerase	FKBP1A; FKBP4; FKBP5	P82942; Q02790; Q13451
FLT*s*	Vascular endothelial growth factor receptor	FLT1; FLT4	P17948; P35916
	Fms-like tyrosine kinase	FLT3	P36888
FMO*s*	Dimethylamine monoxygenase [N-oxide-forming]	FMO1; FMO3; FMO5	Q01740; P31513; P49326
G6PD	Glucose-6-phosphate 1 dehydrogenase		P11413
GGT1	Glutathione hydrolase 1 proenzyme		P19440
GNRH1	Progonadotropin-releasing hormone 1		P01148
GP1B*	G-protein coupled estrogen receptor 1		Q99527
NMDA-R*s*	Glutamate receptor ionotropic	GRIN1; GRIN2A; GRIN2B; GRIN2C; GRIN2D; GRIN3A; GRIN3B	Q05586; Q12879; Q13224; Q14957; Q15399; Q8TUC5; Q60391
GST*s*	Glutathione S-transferase	GSTP1; GSTT1	P09211; P30711
HDAC*	Histone deacetylase	HDAC10; HDAC11; HDAC2; HDAC3; HDAC4; HDAC5; HDAC7; HDAC8; HDAC9	Q06958; Q96DB2; Q92769; Q15379; P56524; Q9UQL6; Q8WUJ4; Q9BY41; Q8UKV0
HGF	Hepatocyte growth factor		P14210
MHC I*	HLA class I histocompatibility antigen	HLA-A; HLA-B; HLA-C	P04439; P01889; P10321
MHC II*	HLA class II histocompatibility antigen	HLA-DPB1; HLA-DPB2; HLA-DQB1	P04440; N.A.; P01920
HMGCR	HMG-CoA reductase		P04035
HMOX1	Heme oxygenase 1		P09601
HNMT	Histamine N-methyltransferase		P50135
HRAS	GTPase Hras		P01112
HR*s*	Histamine receptor	HRH1; HRH2; HRH4	P35367; P25021; Q9H3N8
HSP*s*	Heat shock protein	HSP90AB1; HSP90AA1; HSPA2; HSPA4; HSPA5; HSPA8; HSPB2	P08238; P07900; P54652; P34932; P11021; P11142; Q16082
5-HT-R*s*	5-hydroxytryptamine receptor	HTR1A; HTR1B; HTR1D; HTR1E; HTR2A; HTR2B; HTR2C; HTR3A; HTR3B; HTR4; HTR6; HTR7	P08908; P28222; P28221; P28566; P28223; P41535; P28335; P46098; Q95264; Q13639; P50406; P34969
ICAM*	Intracellular adhesion molecule	ICAM1; ICAM3	P05362; P32942
IFNL*	Interferon lambda	IFNL3; IFNL4	Q8IZI9; K9M1U5
IGF2	Insulin-like growth factor II		P01344
IKBK*	Inhibitor of nuclear factor kappa-B kinase subunits	IKBK1; IKBKE; IKBK3	O14920; Q14164; Q9Y6K9
IKZF1	DNA-binding protein Ikaros		Q13422
IL10	Interleukin-10		P22301
IL2	Interleukin-2		P60568
IL2RA	Interleukin-2 receptor subunit alpha		P01589
IL6	Interleukin-6		P05231
IMPDH*	Inosine-5'-monophosphate dehydrogenase	IMPDH1; IMPDH2	P20809; P12268
ITG*	Integrin alpha	ITGA2; ITGA2B; ITGA5; ITGAL; ITGAM	P17301; P08514; P08648; P20701; P11215
	Integrin beta	ITGB1; ITGB2; ITGB3	P05556; P05107; P05106
JUN+	Transcription factor Jun		P05412

KCN*	Potassium voltage-gated channel	KCNA1; KCNA10; KCNA3; KCNA4; KCNA5; KCNA6; KCNA7; KCNB1; KCNB2; KCNC1; KCNC2; KCNC3; KCNC4; KCND1; KCND2; KCNE1; KCNE2; KCNE3; KCNE4; KCNE5; KCNF1; KCNG1; KCNG2; KCNG3; KCNG4; KCNH1; KCNH2; KCNH3; KCNH4; KCNH5; KCNH6; KCNH7; KCNH8; KCN11; KCN2; KCN2B; KCN2C; KCNQ4; KCNQ5; KCSN1; KCSN3; KCN11; KCN2; KCNAB1; KCNAB2	Q09470; Q16322; P22001; P22459; P22460; P17658; Q96RP8; Q14721; Q29253; P48547; Q96PR1; Q14003; Q03721; Q9NSA2; Q9NZV8; P15382; Q8YJ6; Q8Y6H6; Q8HW09; Q8LI40; Q9H3M0; Q8UIK4; Q8LU86; Q8TAE7; Q8TDN1; Q92529; Q12809; Q9ULDE; Q9JUC05; Q8NCM2; Q9H252; Q9NS40; Q96142; P51787; Q43526; Q43525; P56996; Q96KK3; Q9BQ31; Q9NR82; Q9PLU1; Q8TDN2; Q14722; Q13303	PTGER*	Prostaglandin E2 receptor	PTGER1; PTGER2; PTGER3	P34995; P43116; P43115
				PTGS*	Prostaglandin G/H synthase	PTGS1; PTGS2	P23219; P35354
				PTH	Parathyroid hormone		P01270
				PTK s*	Protein-tyrosine kinase	PTK2B; PTK6	Q14289; Q13882
				PTP s*	Protein tyrosine phosphatase IVA	PTP4A1; PTP4A3	Q93096; Q75365
	Kv channel-interacting protein	KCNIP1	Q9NZI2		Protein tyrosine phosphatase non-receptor	PTPN12; PTPN6	Q05209; P29350
	Inward rectifier potassium channel	KCNJ11; KCNJ3	Q14654; P48549		Receptor-type tyrosine protein phosphatase	PTPRB; PTPRC; PTPRD; PTPRM	P23467; P08575; P23468; P28827
	Calcium-activated potassium channel	KCNMB1	Q16558	RAF1	Proto-oncogene serine/threonine-protein kinase Raf		P04049
	Intermediate conductance calcium-activated potassium channel protein	KCNN4	Q15554	RB1	Retinoblastoma-associated protein		P06400
	Outward rectifier potassium channel	KCNT1	Q5JUK3	RET	Proto-oncogene tyrosine protein kinase receptor Ret		P07949
KDR	Vascular endothelial growth factor receptor 2		P35988	RRM*	Ribonucleoside-diphosphate reductase	RRM1; RMM2; RRM2B	P23921; P31350; Q7LG56
KIT	Mast/stem cell growth factor receptor Kit		P10721	RYR*	Ryanodine receptor	RYR1; RYR2; RYR3	P21817; Q92736; Q15413
KLK*	Kallikrein	KLK1; KLK3; KLK4	P06870; P07288; Q9Y9K2	SAG	S-arrestin		P10523
KRAS	GTPase KRas		P01116	SCN*	Voltage-gated sodium channel	SCN10A; SCN11A; SCN1A; SCN2A; SCN3A; SCN4A; SCN5A; SCN7A; SCN8A; SCN9A	Q9Y5Y9; Q9LIU3; P35498; Q99250; Q9NY46; P35499; Q14524; Q01178; Q9JUDO; Q15858
LDLR	Low-density lipoprotein receptor		P01130		Sodium channel beta	SCN1B; SCN2B; SCN3B; SCN4B;	Q07699; Q60939; Q9NY72; Q8WT1
LEP	Leptin		P41159		Amloridine-sensitive sodium channel	SCNN1A; SCNN1B; SCNN1D; SCNN1G	P37088; P51168; P51172; P51170
LIPC	Hepatic triacylglycerol lipase		P11150	SIRT*	NAD-dependent protein deacetylase sirtuin	SIRT1; SIRT2; SIRT3	Q96E86; Q8XJ16; Q9NTG7
LPL	Lipoprotein lipase		P06858		NAD-dependent protein deacetylase sirtuin	SIRT5	Q9NXA8
MAP3K*	Mitogen-activated protein kinase kinase kinase	MAP3K1; MAP3K10; MAP3K20	Q13233; Q02779; Q9NVL2	SLC*	Solute carrier family	SLC10A1; SLC14A2; SLC15A1; SLC15A2; SLC16A7; SLC18A2; SLC19A1; SLC19A3; SLC1A1; SLC22A1; SLC22A11; SLC22A12; SLC22A2; SLC22A3; SLC22A4; SLC22A5; SLC22A6; SLC22A7; SLC22A8; SLC23A1; SLC23A2; SLC23A8; SLC28A1; SLC28A2; SLC29A3; SLC29A4; SLC19A2; SLC29A3; SLC29A4; SLC2A1; SLC2A2; SLC2A3; SLC2A4; SLC30A9; SLC46A1; SLC47A1; SLC47A2; SLC5A6; SLC6A12; SLC6A2; SLC6A3; SLC6A4; SLC7A11; SLC8A1; SLC9A1; SLC9A5	Q14973; Q15849; P46059; Q16348; Q90669; Q05940; P41440; Q95ZV2; P43005; Q15245; Q9NSA0; Q98537; Q15244; Q75751; Q9H105; Q76082; Q4U2F8; Q9Y694; Q8TC07; Q9UHI7; Q9UJH3; Q9BRN1; Q00337; Q43868; Q9H4S3; Q99808; Q90779; Q96ZD2; Q7RTT3; P11166; P11168; P11169; P14672; Q9PML9; Q9GNT5; Q96FL8; Q86VL8; Q9Y289; P48095; P32418; Q01859; P1645; Q9JYI5; P32418; P19634; Q14940
MAPK*	Mitogen-activated protein kinase	MAPK1; MAPK10; MAPK11; MAPK12; MAPK13; MAPK14; MAPK15; MAPK3; MAPK4; MAPK6; MAPK7; MAPK8; MAPK9	P28482; P53779; Q15759; P53778; Q15264; Q16539; Q8TD08; P27361; P31152; Q16659; Q13184; P45993; P45994	SLC0*	Solute carrier organic anion transporter	SLC01A2; SLC01B1; SLC01B3; SLC01C1; SLC02B1	P46721; Q9Y6L6; Q9NPD5; Q9NYB5; Q94956;
MMP*	Matrix metalloproteinase	MMP1; MMP2; MMP25; MMP9	P03956; P08253; Q9NPA2; P14780	SOAT1	Sterol O-acetyltransferase 1		P35610
MTOR	Serine/threonine-protein kinase mTOR		P42345	STAG*	Cohesin subunit SA	STAG2; STAG3	Q8N3U4; Q9UJ98
MUC*	Mucin	MUC16; MUC13	Q8WXI7; Q9H3R2	STAT*	Signal transducer and activator of transcription	STAT3; STAT4; STATS5B; STAT6	P40763; Q14765; P51892; P42226
MYC	Myc proto-oncogene protein		P01106	STK11	Serine/threonine-protein kinase STK11		Q15831
MYO9B	Unconventional myosin-IxB		Q13459	TAT	Tyrosine aminotransferase		P17735
NEU*	Sialidase	NEU1; NEU2; NEU3	Q99519; Q9Y3R4; Q9JUQ9	TERT	Telomerase reverse transcriptase		Q14746
NF1	Neurofibromin		P21359	TFAP2A	Transcription factor AP-2-alpha		P05549
NFKB*	Nuclear factor NF-kappa-B subunits	NFKB1; NFKB2	P19838; Q00653	TFP*	Trefoil factor	TFF1; TFF2; TFF3	P04155; Q03403; Q07654
NME*	Nucleoside diphosphate kinase	NME1; NME2	P22392; P15531	TFPI	Tissue factor pathway inhibitor		P10646
NOS*	Nitric oxide synthase	NOS1; NOS2; NOS3	P29475; P35228; P29474	TG	Thyroglobulin		P01266
	Nitric oxide synthase 1 adaptor protein	NOS1AP	Q75052	TGFBI	Transforming growth factor beta-1 proprotein		P01137
NQO2	Quinone reductase 2		P16083	TGM2	Protein-glutamine gamma-glutamyltransferase 2		P21980
NR s*	Nuclear receptor	NR1H2; NR1H3; NR1I2; NR1I3; NR2E3; NR3C1; NR4A1; NR4A3	P55055; Q13133; Q75469; Q14994; Q9Y5X4; P04150; P22736; Q92570	THBS1	Thrombospondin-1		P07996
NRAS	GTPase NRas		P01111	TK*	Thymidine kinase	TK1; TK2	P04183; Q00142
NRG1	Pro-neuregulin-1		Q02297	TLR*	Toll-like receptor	TLR3; TLR4; TLR7; TLR9	Q15455; Q00206; Q9NYK1; Q9NR96
NT5*	Cytosolic 5'-nucleotidase	NT5C1A; NT5C2; NT5C3A;	Q9BXI3; P49902; Q9H0P0	TNF*	Tumor necrosis factor	TNF	P01375
	5'-nucleotidase	NT5E	P21589		Tumor necrosis factor induced protein	TNFAIP3; TNFAIP6	P21580; P98066
NTRK*	Nerve growth factor receptor	NTRK1; NTRK2	P04629; Q16620	TNFRSF*	Tumor necrosis factor receptor	TNFRSF10B; TNFRSF11A; TNFRSF1A; TNFRSF1B	Q14763; Q9Y6Q6; P19438; P20333
P2RY*	P2X purinoceptor	P2RX1; P2RX2; P2RX3; P2RX4; P2RX5; P2RX6; P2RX7	P51575; Q9JUBL9; P56373; Q99571; Q93086; Q15547; Q99572	TOP*	DNA topoisomerase	TOP1; TOP1MT; TOP2A; TOP2B	P11387; Q969P6; P11388; Q02880
	P2Y purinoceptor	P2RY1; P2RY10; P2RY11; P2RY12; P2RY13; P2RY14; P2RY2; P2RY4; P2RY6; P2RY8	P47900; Q00398; Q96G91; Q9H244; Q9BPU6; Q15391; P41231; P51582; Q15077; Q86VZ1;	TP53	Cellular tumor antigen p53		P04837
PDGFR*	Platelet-derived growth factor receptor	PDGFA; PDGFRB	P16234; P09619	TRP*	Transient receptor potential cation channel	TRPA1; TRPM2; TRPM3; TRPM4; TRPM7; TRMP6; TRPV1; TRPV2	Q75762; Q84759; Q9HCF6; Q8TD43; Q96QT4; Q72ZV7; Q9NER1; Q9Y5S1
PK3C s*	PI4,5-bisphosphate 3-kinase subunit	PIK3CA; PIK3CB; PIK3CD; PIK3CG;	P42336; P42338; Q00329; P48736		Short transient receptor potential channel	TRPC1; TRPC5; TRPC7	P48995; Q9UL62; Q9HCX4
	PI 3-kinase regulatory subunit	PIK3R2	Q00459	TYMS	Thymidylate synthase		P04818
PLA2G*	Phospholipase	PLA2G1B; PLA2G2A; PLA2G4A PLA2G6	P04054; P41555; P47712; Q60733	UGT s*	UDP-glucuronosyltransferase	UGT1A1; UGT2A10; UGT1A3; UGT1A4; UGT1A5; UGT1A7; UGT1A8; UGT1A9; UGT2A1; UGT2B10; UGT2B7; UGT3A1	P22308; Q9HAW8; P35503; P22310; P35504; Q9HAW7; Q9HAW9; Q60656; P001E4; P36637; P16662; Q6NUS8
POR	NADPH-cytochrome P450 reductase		P16435	VEGF*	Vascular endothelial growth factor	VEGFA; VEGFC	P15692; P49767
PPAR*	Peroxisome proliferator-activated receptor	PPARA; PPARB; PPARC; PPARC1B	Q07869; Q03181; P37231; Q86YN6	VHL	Von Hippel-Lindau disease tumor suppressor		P40337
PRKC*	Protein kinase C	PRKCA; PRKCB; PRKCD; PRKCE; PRKCG; PRKCH; PRKI; PRKQ; PRKC2; PRKD1	P17252; P05771; Q05655; Q02158; P05129; P24729; P41143; Q47459; Q05513; Q15159	XDH	Xanthine dehydrogenase/oxidase		P47989
	DNA-dependent protein kinase	PRKDC	P78527	XIAP	E3 ubiquitin-protein ligase XIAP		P98170
PRL	Prolactin		P01236				
PRSS*	Trypsin	PRSS1; PRSS2; PRSS3	P07477; P07478; P35030				
PTEN	PI3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN		P60484				

### S.3.2 Immunomodulatory BSA

**Table S.3.2: BSAs with immunomodulatory properties.** The table shows BSAs identified with Immunomodulatory activities, and explanation behind this reasoning. Specified are BSA name and its effect on the immune system and/or inflammation.

BSA	Effect on Immune system	Activity
25HC	Amplifies inflammatory signaling	Pro
ABT-737	Indirectly initiates apoptotic cascade of immune cells	Suppressive
Acetylsalicylic acid	Modulate innate and adaptive immune responses; apoptosis of immune cells; regulate cytokine production of immune cells.	Suppressive; Anti
Adefovir	Inhibitory effect on cell mediated immunity	Implied suppressive
Adefovir Dipivoxil	Inhibitory effect on cell mediated immunity	Implied suppressive
Amantadine	Inhibits T lymphocytes; reduce production of pro-inflammatory cytokines	Implied suppressive; Anti
Amiloride	DNA-adjuvant; promote humoral immune responses	Stimulatory
Amitriptyline	Inhibits TNF-alpha and IL-12 production	Suppression; Anti
Anisomycin	Induce expression of immune-regulation associated genes; Indirectly stimulates NK cells	Stimulatory
Apilimod	Enhance IL-10 production; Suppress synthesis of IL-12 and IL-23; Reduced Th1 and Th17 cytokines and chemokines	Suppressive; Stimulatory; Anti
Artesunate	Anti-complement activity, inhibiting C4 and C3 activation and assembly of MAC.	Suppressive; Anti
Ascorbic acid	Stimulate DC to produce more IL-12; activation of T and B cell functions	Stimulatory; Pro
Azacitidine	Proapoptotic; inhibition of T cell activation; impairs DNA methylation	Suppressive
Azithromycin	Inhibition of pro-inflammatory cytokine production; inhibition of neutrophil influx	Implied suppressive; Anti
Berberine	Inhibition of pro-inflammatory cytokine production, TNF-alpha, IFN-gamma and IL-17; Increase in expression of IL-10 and IL-4	Suppressive; Stimulatory; Anti
Betulinic acid	Decrease in IL-6 production; Enhance TNF-alpha and IL-1beta production	Anti
Bexarotene	Downregulate IL-6 and IL-8 and monocyte chemoattractant protein-1.	Implied suppressive; Anti
Bortezomib	Decrease T cell count; enhanced B cell and DC apoptosis; loss of antigen presentation; reduce inflammatory cytokines IL-10, IL-6, IL-12, IFN-gamma and IFN-alpha; stimulation of NK cell actions.	Suppressive; Stimulatory; Anti
Brequinar	Inhibition of T cell proliferation and antibody production	Suppressive
Bromocriptine	Suppress cell-mediated, humoral and autoimmune reactions. Reduced level of extracellular TNF-alpha	Suppressive; Anti
Caffeine	Suppress NEU and MO chemotaxis; suppress production of TNF-alpha; reduce T cell proliferation and impair production of Th1, Th2 and Th3 cytokines.	Implied suppressive; Anti
Camptothecin	Increase expression of PD-L1; Suppression of adaptive immune system	Implied suppressive
Cenicriviroc	Inhibits monocyte chemotaxis	Implied suppressive; Anti
Cepharanthine	Suppress pro-inflammatory molecules	Anti
Chichoric acid	Pro-apoptotic activities	Anti
Chloroquine	Reduce cytokine production, IL-1 and IL-6; Inhibits TLR signaling	Suppressive; Anti
Chlorpromazine	Downregulate IL-2, IFN-gamma, IL-4, TNF and GM-CSF; upregulates secretion of IL-10; enhance humoral autoimmune reactions; block cellular immune responses	Suppressive; Anti
Clarithromycin	Reduction in MF, NEU, EOS counts; Reduction in IFN-gamma and TNF-alpha	Suppressive; Anti
Clofazimine	Inhibition of MF, NEU and lymphocyte transformation	Suppressive; Anti
Clomipramine	Decrease in TNF-alpha; Increase TGF-beta and IL-10	Anti
Clotrimazole	Inhibits IKCa1 channels in activated lymphocytes	Implied suppressive
Clozapine	Increased IL-1RA production; dampened NF-kB activation and TNF-alpha production; decrease in TLR expression levels	Suppressive; Anti
Cyclosporine	Blocking transcription of cytokine genes of IL-4 and IL-2, thus inhibiting T cell activation	Suppressive
Dasatanib	Inhibits proliferation and activation of T lymphocytes; suppress cytotoxic activity of NK cells	Suppressive
Diltiazem	Decreased production of inflammatory cytokines; Inhibits Kv1.3 channels expressed on lymphocytes	Suppressive; Anti
Doxycycline	Modulate NF-kB, p38 and ERK1/2/MAPK pathways; Reduction in IL-6, IL-1beta and TNF-alpha levels	Anti
Emetine	Suppress maturation of T cells in thymus	Suppressive
Emodin	Anti-proliferative effect on lymphocytes; Reduce formation and release of Th1 and Th17; Induced Th2 and Treg.	Anti
Eptifibatide	Reduce levels of IL-8, IL-6, MCP-1, IL-1beta and TNF-alpha	Anti
Erlotinib	Inhibition of T cell activation and proliferation; Inhibits secretion of pro-inflammatory cytokines	Suppressive
Etanercept	Inhibits production of TNF-alpha, IL-6 and IL-1	Anti
Eucalyptol	Inhibits NLRP2 inflammasome activation and pro inflammatory cytokine production; Reduce inflammatory cell infiltration	Anti
Ezetimibe	Modulate CD4+ T helper cells and memory T cells	N.a.
Fenofibrate	Inhibits T helper cell differentiation; Suppress production of pro-inflammatory cytokines; Upregulation of IL-10; Suppress plasma levels of IgG	Anti
Fenretinide	Decrease expression of inflammatory cytokines; Inhibits phosphorylation of ERK1/2	Anti
Flavopridol	Activates STAT1 in IFN-gamma signalling; Inhibits IFN-gamma induced NO production	Anti

Fludarabine	Depletion of lymphocytes; Induction of prolonged immunosuppression; inhibits cytokine induced activation of STAT1	Suppressive
Fluoxetine	Decrease in TNF-alpha and INF-gamma; increase of IL-10	Anti
Fluvastatin	Induce IL-1beta release; trigger inflammasome activation; reduced leukocyte adherence responses to platelet activation factor; reduction in NF-kB	Anti; Pro
Formoterol	Inhibitory effect on granulocyte adhesion to epithelium; inhibition of inflammatory cells	Anti
Gefetinib	Increase NK cells and IFN-gamma; decrease IL-6; inhibition of TNF-alpha and IL-1	Anti; Pro
Gemcitabine	Promote naive T cell activation; enhance responses to vaccines	Stimulatory; Pro
Genistein	Reduction in pro-inflammatory processes; increased activity of CTLs and NK cells	Anti
Glycyrrhizin	Activation of CD4+ and CD8+ immune cells; Increasing IL-2, IL-6, IL-7 levels; Decrease in TNF-alpha levels	Stimulatory
Gossypol	Pro-apoptotic activities	Suppressive
GSK583	Blocks NOD2 signaling	Anti
GSK717	Blocks NOD2 signalling	Anti
Halofunginone	Inhibition of T cell functions and pro-inflammatory cytokines; Inhibits NF-kB and p38 MAPK phosphorylation	Anti
Hydroxychloroquine	Reduction in cytokine production, IL-1 and IL-6; Inhibits TLR signalling	Suppressive; Anti
IFN-alpha	Inducing antiviral immune response by innate immune system; Increased expression of MHC antigen; Increased NK and CTL activity; Induction of cytokines; Production of endogenous interferons	Stimulatory; Suppressive
IFN-beta	Modulate function of APCs to down regulate antigen presentation; promote Treg promoting cytokines, IL-4, IL-5 and IL-13; increase in B cell activity	Stimulatory; Suppressive
IFN-gamma	Regulator of antigen presentation; regulates proliferation and differentiation of lymphocytes	Stimulatory; Suppressive
IFN-lambda	Promote Th1 response; stimulate NK activity; enhance NEU activity	Stimulatory; Suppressive
IL-7	T cell development within thymus and survival in periphery; B cell maturation	Stimulatory
Imatinib	Inhibits T cell proliferation; Attenuation of pro-inflammatory cytokine release, IL-6 and TNF-alpha	Anti
Ingavirin	Activation of TLR/RLR signaling of innate and adaptive immunity; differentiation of hematopoietic cell precursors	N.a.
Inosine	Enhances production of cytokines; differentiation of T lymphocytes	Stimulatory
Irbersartan	Downregulation of activator protein-1; inhibiting T lymphocytes	Suppressive
Itraconazole	Suppressive activity on alloreactivity	Suppressive
Ivermectin	Stimulate functions of T helper lymphocytes	Stimulatory
Leflunomide	Inhibition of DHODH; inhibit signaling of T and B cell proliferation	Suppressive
Leronlimab	Reduction of cytokine storm, IL-6	Anti
Lipoic acid	Decrease expression of IL-2 and IL-2Ralpha	Implied suppressive
Lopinavir	Decrease in activated CD4+ cells and memory cells	Implied suppressive
Lovastatin	Inhibits Kv1.3 channels expressed on lymphocytes; inhibits MHC class II expression	Implied suppressive; Anti
Luteolin	Inhibits recreation of pro-inflammatory cytokine TNF-alpha	Anti
Maraviroc	Decrease inflammation	Anti
Memantine	Inhibits Kv1.3 channels expressed on lymphocytes; inhibition of T cell responsiveness	Suppressive; Anti
Merimepodib	Suppress lymphocyte development	Anti
Metformin	Reduced production of pro-inflammatory cytokines; enhance formation of NETs	Anti
Methotrexate	Inhibition of NF-kB activation; inhibition of T cells, MF and endothelial cells	Suppressive
Minocycline	Anti-apoptotic; inhibition of MMPs, COX iNOS and PLA2	Anti
Mitoxantrone	Inhibition of proliferation of MF and T and B lymphocytes; Lowering secretion of IFN-gamma, TNF-alpha and IL-2; Apoptosis of T and B lymphocytes	Suppressive
Monensin	Reduced IL-1beta secretion; inhibits phagocytosis and reducing lysosomal activity	N.a.
Mycophenolic acid	Blocking lymphocyte proliferation	Suppressive; Anti
N-acetylcysteine	Modulate oxidative stress and inflammation of small intestine	N.a.
Nafamostat	Suppression of NF-kB activation	Anti
Navitoclax	Pro-apoptotic	N.a.
Niclosamide	Suppress expansion of follicular helper T cells	Anti
Nicotine	Limits production of pro-inflammatory cytokines, IL-6, IL-1beta and TNF-alpha	Anti
Nifedipine	Calcium channel blocker; dampen T cell immune responses	Suppressive
Nitazoxanide	Inhibits proliferation of T lymphocytes; Decrease of IL-1beta, IL-2, IL-6, IL-10 and IL-12	Anti
Obatoclax	Prevent development of immune responses	Implied suppressive
Ouabain	Inhibits NEU migration; reduced TNF-alpha and IFN-gamma levels	Anti
Pentosan polysulfate	Induce immune responses	Stimulatory
PUL-042	Stimulate lung innate immune system	Stimulatory
Quercetin	Reduce expression of pro-inflammatory cytokines and chemokine; reduce expression of MHC class II; Blocks endocytosis of DCs.	Suppressive

Quinacrine	Inhibiting phospholipase A2, modulating Th1/Th2 response; inhibit recreation of pro-inflammatory cytokines and TLR7 and TLR9	Implied suppressive; Anti
Quinine	Stimulate innate immune defences	Stimulatory
Regorafenib	Dampen IFN-gamma induced PD-L1 expression; inhibits JAK1/2 STAT1 signaling	Implied suppressive
Reservastrol	Promote release of pro-inflammatory cytokines from immune cells, IL-10; Suppress production of TNF-alpha; Inhibition of COX-2; Suppression of NF-kB	Anti; Pro
Ribavirin	Shift from Th2 to Th1 immune response; Increase in Th1 cytokine production; Reduction in MF activation	Anti; Pro
Rimantadine	Diminished local immune responses	N.a.
Ritonavir	Decrease in memory and CD8+ T cells	Suppressive
Saikosaponin	Enhanced production of immunosuppressive mediators, Th1/Th2 cells, IL-4 and IL-10; Suppression of pro-immune mediators, TNF-alpha	Anti
Saquinavir	Inhibition of cytokine production	N.a.
Sertraline	Inhibits components of innate signaling pathway	Suppressive
Silvestrol	Start of infection, suppress generation of anti-inflammatory MF and DC phenotypes. In inflammation, accelerate transition from pro to anti-inflammatory status	Anti; Pro
Simvastatin	Reduce cytokine production and NF-kB activation; Inhibits MHC-II mediated T cell activation	Implied suppressive
Sirolimus	Inhibits mTOR; Prevents IL-2 induced T cell proliferation	Suppressive
Sorafenib	Inhibition of T cell proliferation; increase in PD-1	Suppressive
Sunitinib	Reduce expression of immunosuppressive cytokines and co-stimulatory molecules as IL-1, foxp3, PD-1, CTLA-4	Stimulatory
Suramin	Attenuate pro-inflammatory cytokines	Anti
Tamoxifen	Inhibits P-glycoprotein, regulate immunity; modulate NF-kB	Implied suppressive
Taribavirin	Shift from Th2 to Th1 immune response; Increase in Th1 cytokine production; Reduction in MF activation	Anti; Pro
Teicoplanin	Decrease chemotaxis; lowering pro-inflammatory markers as CRP and IL-6	Anti
Tenofovir	Stimulate secretion of IL-1beta, IL-10 and TNF-alpha from MF; activation of MIP-1alpha in MF and lymphocytes	Anti; Pro
Teriflunomide	Inhibits DHODH, reduced lymphocyte proliferation	Suppressive
Thapsigargin	Suppress T cell proliferation; Suppress Th1 and Th17 differentiation	Implied suppressive; Anti
Thymalfasin	Promote T cell differentiation and maturation; increased CD4+ and CD8+ T cells	Pro
Tilorone	Induce interferon production; activate NK cells and T lymphocytes	Pro
Topotecan	Anti-TNF activity	Anti
Toremifene	Increased proliferation and cytotoxicity of CD8+ T cells; Increased Treg polarization	Stimulatory
Trametinib	Transient inhibition T cell proliferation of cytokine and immunomodulatory gene	Implied suppressive
Umifenovir	Inducing interferon and MF activation; stimulate phagocytosis	Stimulatory
Valproic acid	Inhibits production of pro-inflammatory cytokines as TNF-alpha and IL-6; inhibits NF-kB; Blocks migration of MF; triggers apoptosis in CD8+ T lymphocytes	Anti
Vemurafenib	Increase in immune stimulatory cytokine levels; decrease in immunosuppressive cytokine levels	Pro
Verapamil	Inhibits lymphocyte responses, generation of cytotoxic T cells and NK cell activity	Implied suppressive
Zidovudine	Suppression of antigen derived T cell proliferation	Suppressive

### S.3.3 BSA scoring system

**Table S.3.3: Results from the six-component BSA-scoring system.** Designated are the virus abbreviation, virus family, BC group, diseased system, and case fatality rate in %. Furthermore, BSA name, BSA target, developmental status, route of administration and immunomodulatory properties are specified, together with the BSA scores.

															BSA Scores							
Virus	Family	Group	Diseased system	CFR %	Name	Drug target	Target virus	Dev. status	RoA	Immunomod	SAR	Phyl	TR	DDS	RoA	IP	Total					
<b>MARV</b>	Filoviridae	(-)ssRNA	Multiple	50	Galidesivir	Viral RNA pol	MARV	Clinical trials	Intravenous	N.a.	1	1	1	0,75	1	1	5,75					
					Favipiravir	Viral RNA pol	MARV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5					
					Remdesivir	Viral RNA pol	MARV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25					
					Tilorone	Human (multip)	MARV	Approved	Peroral	Yes	1	1	1	1	1	0	5					
					Amiloride	Human ion cha	MARV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Apilimod	Human PTK	MARV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Amodiaquine	Human HNMT	EBOV	Clinical trials	Peroral	No	0	0,5	0	0	1	1	2,5					
					Amiodarone	Human (multip)	EBOV	In vitro studies	Intravenous	N.a.	0	0,5	0	0	1	1	2,5					
					Sunitinib	Human PTK	EBOV	Clinical trials	Peroral	Yes	0	0,5	1	0	1	0	2,5					
					IFN-b	Human IFNAR	EBOV	Clinical trials	Subcutaneous	Yes	0	0,5	1	0	0	0	1,5					
					IFN-g	Human IFNGR	EBOV	In vitro studies	Subcutaneous	Yes	0	0,5	1	0	0	0	1,5					
					ABMA	Human GTPase	EBOV	In vitro studies	Subcutaneous	N.a.	0	0,5	0	0	0	1	1,5					
					Artesunate	Human (multip)	EBOV	Clinical trials	Intravenous	Yes	0	0,5	0	0	1	0	1,5					
					Azithromycin	Human (multip)	EBOV	Clinical trials	Peroral	Yes	0	0,5	0	0	1	0	1,5					
					Lovastatin	Human HMGCo	EBOV	In vitro studies	Peroral	Yes	0	0,5	0	0	1	0	1,5					
					Merimepodib	Human IMPDH	EBOV	In vitro studies	Peroral	Yes	0	0,5	0	0	1	0	1,5					
					<b>RAVV</b>	Filoviridae	(-)ssRNA	Multiple	24	Galidesivir	Viral RNA pol	RAVV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
										Favipiravir	Viral RNA pol	MARV	Animal studies	Peroral	N.a.	0,5	0,5	1	0	1	1	4
										Remdesivir	Viral RNA pol	MARV	In vitro studies	Intravenous	N.a.	0,5	0,5	1	0	1	1	4
										Tilorone	Human (multip)	MARV	Approved	Peroral	Yes	0	0,5	1	0	1	0	2,5
										Amiloride	Human ion cha	MARV	In vitro studies	Peroral	Yes	0	0,5	1	0	1	0	2,5
										Apilimod	Human PTK	MARV	In vitro studies	Peroral	Yes	0	0,5	1	0	1	0	2,5
										Amodiaquine	Human HNMT	EBOV	Clinical trials	Peroral	No	0	0,5	0	0	1	1	2,5
										IFN-b	Human IFNAR	EBOV	Clinical trials	Subcutaneous	Yes	0	0,5	1	0	0	0	1,5
IFN-g	Human IFNGR	EBOV	In vitro studies	Subcutaneous						Yes	0	0,5	1	0	0	0	1,5					
ABMA	Human GTPase	EBOV	In vitro studies	Subcutaneous						N.a.	0	0,5	0	0	0	1	1,5					
Amiodarone	Human (multip)	EBOV	In vitro studies	Intravenous						N.a.	0	0,5	0	0	1	1	2,5					
Sunitinib	Human PTK	EBOV	Clinical trials	Peroral						Yes	0	0,5	0	0	1	0	1,5					
Artesunate	Human (multip)	EBOV	Clinical trials	Intravenous						Yes	0	0,5	0	0	1	0	1,5					
Azithromycin	Human (multip)	EBOV	Clinical trials	Peroral						Yes	0	0,5	0	0	1	0	1,5					
Lovastatin	Human HMGCo	EBOV	In vitro studies	Peroral						Yes	0	0,5	0	0	1	0	1,5					
Merimepodib	Human IMPDH	EBOV	In vitro studies	Peroral						Yes	0	0,5	0	0	1	0	1,5					
<b>LUJV</b>	Arenaviridae	(-)ssRNA	Respiratory, digestive and excretory	80						AVN-944	Human IMPDH	LUJV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
										Benztriopine	Human CHRMs	LUJV	In vitro studies	Peroral, Intra	N.a.	1	1	1	0,25	1	1	5,25
										Favipiravir	Viral RNA pol	LUJV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
										Raloxifene	Human (multip)	LUJV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
										Amiodarone	Human (multip)	LUJV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
										Ribavirin	Viral RNA pol	LUJV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
										Brequinar	Human DHODH	LUJV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Mycophenolic acid	Human IMPDH	LUJV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Nicosamide	Human (multip)	LUJV	In vitro studies	Peroral, Inhal	Yes	1	1	1	0,25	1	0	4,25					
					Obatoclox	Human MCL1	LUJV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25					
					Tamoxifen	Human (multip)	LUJV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Apilimod	Human PTK	LUJV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Toremifene	Human ER	LUJV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Merimepodib	Human IMPDH	LASV	In vitro studies	Peroral	Yes	0,5	0,75	1	0	1	0	3,25					
					<b>JUNV</b>	Arenaviridae	(-)ssRNA	Vascular, neurological and immune system	25	Favipiravir	Viral RNA pol	JUNV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
										Remdesivir	Viral RNA pol	JUNV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
										Ribavirin	Viral RNA pol	JUNV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
										Caffeine	Viral RNA pol	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Merimepodib	Human IMPDH	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Sunitinib	Human PTK	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Teriflunomide	Human DHODH	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Umifenovir	Human (multip)	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Sertraline	Human seroto	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
										Amantadine	Viral ion chann	JUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
Leflunomide	Human DHODH	JUNV	In vitro studies	Peroral						Yes	1	1	1	0,25	1	0	4,25					
Mycophenolic acid	Human IMPDH	JUNV	In vitro studies	Peroral						Yes	1	1	1	0,25	1	0	4,25					
Obatoclox	Human MCL1	JUNV	In vitro studies	Intravenous						Yes	1	1	1	0,25	1	0	4,25					
Amiloride	Human ion cha	JUNV	In vitro studies	Peroral						Yes	1	1	1	0,25	1	0	4,25					
Brequinar	Human DHODH	JUNV	In vitro studies	Peroral						Yes	1	1	1	0,25	1	0	4,25					
IFN-a	Human IFNAR	JUNV	In vitro studies	Subcutaneous						Yes	1	1	1	0,25	1	0	4,25					
IFN-b	Human IFNAR	JUNV	In vitro studies	Subcutaneous						Yes	1	1	1	0,25	1	0	4,25					
IFN-g	Human IFNGR	JUNV	In vitro studies	Subcutaneous						Yes	1	1	1	0,25	1	0	4,25					
<b>LASV</b>	Arenaviridae	(-)ssRNA	Respiratory, digestive and excretory	13						Favipiravir	Viral RNA pol	LASV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
										Amodiaquine	Human HNMT	LASV	In vitro studies	Peroral	No	1	1	1	0,25	1	1	5,25
										Tyrphostin AG1472	Human PTK	LASV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
										Ribavirin	Viral RNA pol	LASV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
										Silvestrol	Human EIF4A	LASV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
										Amiloride	Human ion cha	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Sertraline	Human seroto	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Umifenovir	Human (multip)	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					CR-31-B (-)	Human EIF4A	LASV	In vitro studies	Intraperitone	No	1	1	1	0,25	0	1	4,25					
					Merimepodib	Human IMPDH	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Mycophenolic acid	Human IMPDH	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Remdesivir	Viral RNA pol	LASV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	0	1	4,25					
					Umifenovir	Human (multip)	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Amantadine	Viral ion chann	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Apilimod	Human PTK	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Genistein	Human PTK	LASV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25					
					Nicosamide	Human (multip)	LASV	In vitro studies	Peroral, Inhal	Yes	1	1	1	0,25	1	0	4,25					
					Obatoclox	Human MCL1	LASV	In vitro studies	Intravenous	Yes	1	1	1	0,25	0	0	3,25					

EBOV	Filoviridae	(-)ssRNA	Multiple	66	Amodiaquine	Human HNMT	EBOV	Clinical trials	Peroral	N.a.	1	1	1	0,75	1	1	5,75
					Favipiravir	Viral RNA pol	EBOV	Clinical trials	Peroral	N.a.	1	1	1	0,75	1	1	5,75
					Amiodarone	Human (multi)	EBOV	Clinical trials	Intravenous	N.a.	1	1	1	0,75	1	1	5,75
					Galidesivir	Viral RNA pol	EBOV	Clinical trials	Intravenous	N.a.	1	1	1	0,75	1	1	5,75
					Remdesivir	Viral RNA pol	EBOV	Clinical trials	Intravenous	N.a.	1	1	1	0,75	1	1	5,75
					N4-Hydroxycytidin	Viral RNA pol	EBOV	Animal studies	Subcutaneous	N.a.	1	1	1	0,5	1	1	5,5
					Clomiphene	Human ER	EBOV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Digitoxin	Human ion tra	EBOV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Tyrphostin AG1478	Human PTK	EBOV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					ABMA	Human GTPase	EBOV	In vitro studies	Subcutaneous	N.a.	1	1	1	0,25	1	1	5,25
					DABMA	Human GTPase	EBOV	In vitro studies	N.a.	N.a.	1	1	1	0,25	1	1	5,25
					S416	Human DHODI	EBOV	In vitro studies	Intraperitone	N.a.	1	1	1	0,25	1	1	5,25
					Tilorone	Human (multi)	EBOV	Approved	Peroral	Yes	1	1	1	1	1	0	5
					Artesunate	Human (multi)	EBOV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					IFN-b	Human IFNAR	EBOV	In vitro studies	Subcutaneous	Yes	1	1	1	0,75	1	0	4,75
					Azithromycin	Human (multi)	EBOV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Erlotinib	Human PTK	EBOV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Sunitinib	Human PTK	EBOV	Clinical trials	Intravenous	Yes	1	1	1	0,75	1	0	4,75
					Tamoxifen	Human (multi)	EBOV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Chloroquine	Human (multi)	EBOV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Toremifene	Human ER	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Sertraline	Human serotr	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Merimepodib	Human IMPDH	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Fluvastatin	Human HMGCo	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					25HC	Human membi	EBOV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Genistein	Human PTK	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Lamivudine	Viral RNA pol	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Tetrandrine	Human ion cha	EBOV	Animal studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Umifenovir	Viral RNA pol	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Verapamil	Human ion cha	EBOV	Animal studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Zidovudine	Viral RNA pol	EBOV	In vitro studies	Peroral, Intrav	Yes	1	1	1	0,25	1	0	4,25
					Amiloride	Human ion cha	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Apilimod	Human PTK	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Clomipramine	Viral glycoprot	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					IFN-g	Human IFNGR	EBOV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					Nafamostat	Human protea	EBOV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Quinacrine	Viral glycoprot	EBOV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ribavirin	Viral RNA pol	LASV	Clinical trials	Peroral	Yes	0,5	0,25	1	0	1	0	2,75
ANDV	Hantaviridae	(-)ssRNA	Respiratory and cardiovascular	23	Favipiravir	Viral RNA pol	ANDV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Vandetanib	Human PTK	ANDV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Baloxavir	Viral endonuck	HTNV	In vitro studies	Peroral	N.a.	0	0,75	1	0	1	1	3,75
HTNV	Hantaviridae	(-)ssRNA	Multiple	7	Baloxavir	Viral endonuck	HTNV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Favipiravir	Viral RNA pol	HTNV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Zidovudine	Viral RNA pol	HTNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Amantadine	Viral ion chann	HTNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Regorafenib	Human PTK	HTNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Sorafenib	Human PTK	HTNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ribavirin	Viral RNA pol	HTNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
SNV	Hantaviridae	(-)ssRNA	Respiratory and cardiovascular	50	Favipiravir	Viral RNA pol	SNV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Ribavirin	Viral RNA pol	SNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	1	5,25
					Baloxavir	Viral endonuck	HTNV	In vitro studies	Peroral	N.a.	0	1	1	0	1	1	4,25
LACV	Peribunyviridae	(-)ssRNA	Multiple	1	Baloxavir	Viral endonuck	LACV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Favipiravir	Viral RNA pol	SNV	In vitro studies	Peroral	N.a.	0	0,25	1	0	1	1	3,25
BUNV	Peribunyviridae	(-)ssRNA	Multiple	0	Saliphenylhalamid	Human vATPas	BUNV	In vitro studies	Intraperitone	N.a.	1	1	1	0,25	1	1	5,25
					Navitoclax	Human BCLXL	BUNV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Favipiravir	Viral RNA pol	SNV	In vitro studies	Peroral	N.a.	0	0,25	1	0	1	1	3,25
RVFV	Phenuiviridae	(-)ssRNA	Multiple	1	Favipiravir	Viral RNA pol	RVFV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
					Selenazofurin	Viral RNA pol	RVFV	In vitro studies	Intraperitone	N.a.	1	1	1	0,25	1	1	5,25
					Oritavancin	Human catheti	RVFV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
					Galidesivir	Viral RNA pol	RVFV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
					Ribavirin	Viral RNA pol	RVFV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Siroлимus	Human PTK	RVFV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Monensin	Unknown	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Bortezomib	Human protea	RVFV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Emetine	Human ribosom	RVFV	In vitro studies	Intramuscular	Yes	1	1	1	0,25	1	0	4,25
					Cyclosporine	Human CYPs	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Minocycline	Human MIF	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ritonavir	Unknown	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Suramin	Human (multi)	RVFV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Azaciđidine	Viral RNA pol	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ezetimibe	Human cholest	RVFV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
SFTSV	Phenuiviridae	(-)ssRNA	Multiple	21	Favipiravir	Viral RNA pol	SFTSV	Animal studies	Peroral	N.a.	1	1	1	0,75	1	1	5,75
					Hexachlorophene	Unknown	SFTSV	In vitro studies	Skin, Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Baloxavir	Viral endonuck	SFTSV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Nifedipine	Human ion cha	SFTSV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Regorafenib	Human PTK	SFTSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Bortezomib	Human protea	SFTSV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Fludarabine	Viral RNA pol	SFTSV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					IFN-a	Human IFNAR	SFTSV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					IFN-b	Human IFNAR	SFTSV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					IFN-g	Human IFNGR	SFTSV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					Ribavirin	Viral RNA pol	SFTSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
PTV	Phenuiviridae	(-)ssRNA	Multiple	n.a.	Taribavirin	Viral RNA pol	PTV	Animal studies	Peroral	Yes	1	1	1	0,25	1	1	4,25
					IFN-a	Human IFNAR	PTV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					Favipiravir	Viral RNA pol	RVFV	Animal studies	Peroral	N.a.	0	1	1	0	1	1	4
					Baloxavir	Viral endonuck	SFTSV	In vitro studies	Peroral	N.a.	0	1	1	0	1	1	4
CCHFV	Nairoviridae	(-)ssRNA	Multiple	25	Favipiravir	Viral RNA pol	CCHFV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
					CR-31-B (-)	Human EIF4A	CCHFV	In vitro studies	Intraperitone	N.a.	1	1	1	0,25	1	1	5,25
					Ribavirin	Viral RNA pol	CCHFV	Clinical trials	Peroral	Yes	1	1	1</				



HDV	Kolmiiviridae (-)ssRNA	Digestive and excretor	11	Bulevirtide	Human NTCP	HDV	Approved	Subcutaneous	N.a.	1	1	1	1	1	1	6				
				Adefovir	HBV DNA pol	HDV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
				Ezetimibe	Human cholest	HDV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
				IFN-a	Human IFNAR	HDV	Clinical trials	Subcutaneous	Yes	1	1	1	0,75	1	0	4,75				
				Lamivudine	Human RNA pol	HDV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
				Ritonavir	Unknown	HDV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
				Ribavirin	Human RNA pol	HDV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
				Taribavirin	Viral RNA pol	HDV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
				Etanercept	Human TNF	HDV	Animal studies	Subcutaneous	Yes	1	1	1	0,5	1	0	4,5				
				Irbesartan	Human ATR	HDV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
				Sirolimus	Human PTK	HDV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
				Suramin	Human (multit)	HDV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25				
				FLUAV	Orthomyxoviridae (-)ssRNA	Respiratory system	0,003	Baloxavir	Viral endonucle	FLUAV	Approved	Peroral	N.a.	1	1	1	1	1	1	6
								Favipiravir	Viral RNA pol	FLUAV	Approved	Peroral	N.a.	1	1	1	1	1	1	6
								Oseltamivir	Viral neuramin	FLUAV	Approved	Peroral	N.a.	1	1	1	1	1	1	6
Triazavirin	Viral RNA pol	FLUAV	Approved					Peroral	N.a.	1	1	1	1	1	1	6				
Zanamivir	Unknown	FLUAV	Approved					Inhalation	N.a.	1	1	1	1	1	1	6				
Dyphyllin	Human vATPas	FLUAV	Animal studies					Intravenous	N.a.	1	1	1	0,5	1	1	5,5				
Kasugamycin	Unknown	FLUAV	Animal studies					Peroral	N.a.	1	1	1	0,5	1	1	5,5				
Molnupiravir	Viral RNA pol	FLUAV	Animal studies					Peroral	N.a.	1	1	1	0,5	1	1	5,5				
Saliphenylalamid	Human vATPas	FLUAV	Animal studies					Intraperitone	N.a.	1	1	1	0,5	1	1	5,5				
Camostat	Human protease	FLUAV	In vitro studies					Peroral	N.a.	1	1	1	0,25	1	1	5,25				
Dapivirine	Unknown	FLUAV	In vitro studies					Vaginal	N.a.	1	1	1	0,25	1	1	5,25				
Esomeprazole	Human vATPas	FLUAV	In vitro studies					Peroral	N.a.	1	1	1	0,25	1	1	5,25				
Foscarnet	Viral RNA pol	FLUAV	In vitro studies					Intravenous	N.a.	1	1	1	0,25	1	1	5,25				
S416	Human DHODP	FLUAV	In vitro studies					Intraperitone	N.a.	1	1	1	0,25	1	1	5,25				
Selenazofurin	Viral RNA pol	FLUAV	Animal studies					Intraperitone	N.a.	1	1	1	0,25	1	1	5,25				
Amantadine	Viral ion chann	FLUAV	Approved					Peroral, inhala	Yes	1	1	1	1	1	0	5				
Umifenovir	Human (multit)	FLUAV	Approved					Peroral	Yes	1	1	1	1	1	0	5				
Acetylsalicylic acid	Human COX	FLUAV	Approved					Peroral	Yes	1	1	1	1	1	0	5				
Azithromycin	Unknown	FLUAV	Clinical trials					Peroral	Yes	1	1	1	1	1	0	5				
Ingavirin	Unknown	FLUAV	Approved					Peroral	Yes	1	1	1	1	1	0	5				
Rimantadine	Viral ion chann	FLUAV	Approved					Peroral	Yes	1	1	1	1	1	0	5				
Chloroquine	Human (multit)	FLUAV	Clinical trials					Peroral	Yes	1	1	1	0,75	1	0	4,75				
Clarithromycin	Human ion cha	FLUAV	Clinical trials					Peroral	Yes	1	1	1	0,75	1	0	4,75				
Inosine	Viral RNA pol	FLUAV	Clinical trials					Peroral	Yes	1	1	1	0,75	1	0	4,75				
IFN-a	Human IFNAR	FLUAV	Clinical trials					Peroral, Intra	Yes	1	1	1	0,75	1	0	4,75				
IFN-b	Human IFNAR	FLUAV	Clinical trials					Subcutaneous	Yes	1	1	1	0,75	1	0	4,75				
Ribavirin	Viral RNA pol	FLUAV	Clinical trials					Peroral, inhala	Yes	1	1	1	0,75	1	0	4,75				
Sirolimus	Human PTK	FLUAV	Clinical trials					Peroral	Yes	1	1	1	0,75	1	0	4,75				
Adefovir	Viral RNA pol	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Amtriptyline	Human ion cha	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Diltiazem	Human ion cha	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Epiftbatide	Human integrin	FLUAV	Animal studies					Intravenous	Yes	1	1	1	0,5	1	0	4,5				
Etanercept	Human TNF	FLUAV	Animal studies					Subcutaneous	Yes	1	1	1	0,5	1	0	4,5				
Flavopiridol	Human PTK	FLUAV	Animal studies					Intravenous	Yes	1	1	1	0,5	1	0	4,5				
Genistein	Human PTK	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Itraconazole	Unknown	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Metformin	Human PTK	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Monensin	Unknown	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Navitoclax	Human BCLXL	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Resveratrol	Human multipl	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Salinomycin	Viral ion chann	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Verdinexor	Human export	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Eucalyptol	Unknown	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
Fenofibrate	Human PPAR	FLUAV	Animal studies					Peroral	Yes	1	1	1	0,5	1	0	4,5				
PUL-042	Human TLR	FLUAV	Animal studies					Inhalation	Yes	1	1	1	0,5	1	0	4,5				
Caffeine	Viral RNA pol	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Nafamostat	Human protease	FLUAV	In vitro studies					Intravenous	Yes	1	1	1	0,25	1	0	4,25				
Obatoclox	Human MCL1	FLUAV	In vitro studies					Intravenous	Yes	1	1	1	0,25	1	0	4,25				
Saquinavir	Unknown	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Azacitidine	Viral RNA pol	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Berberine	Unknown	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Betulinic Acid	Unknown	FLUAV	In vitro studies					Intraperitone	Yes	1	1	1	0,25	1	0	4,25				
Bortezomib	Human protease	FLUAV	In vitro studies					Intravenous	Yes	1	1	1	0,25	1	0	4,25				
Brequinar	Human DHODP	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Campthothecin	Human topois	FLUAV	In vitro studies					Intravenous	Yes	1	1	1	0,25	1	0	4,25				
Cyclosporine	Human CYPs	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Emodin	Human (multit)	FLUAV	In vitro studies					Peroral, Intra	Yes	1	1	1	0,25	1	0	4,25				
Fluvastatin	Human HMGCoA	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Gemcitabine	Viral RNA pol	FLUAV	In vitro studies					Intravenous, i	Yes	1	1	1	0,25	1	0	4,25				
Glycyrrhizin	Human TNF	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
IFN-I	Human IFNLR	FLUAV	In vitro studies					Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
Luteolin	Human COPI	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Memantine	Human ion cha	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Mycophenolic acid	Human IMPDH	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Nelfinavir	Unknown	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Nitazoxanide	Human pyruvat	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Niclosamide	Human (multit)	FLUAV	In vitro studies					Peroral, inhala	Yes	1	1	1	0,25	1	0	4,25				
Pentosan polysulfate	Human FGF	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Podoflox	Human topois	FLUAV	In vitro studies					Topical	N.a.	1	1	1	0,25	1	0	4,25				
Quercetin	Unknown	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Quinine	Viral glycoprote	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Regorafenib	Human PTK	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Silvestrol	Human EIF4A	FLUAV	In vitro studies					Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
Simvastatin	Human HMGCoA	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Sorafenib	Human PTK	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Taribavirin	Viral RNA pol	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Teicoplanin	Human CTS	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Teriflunomide	Human DHODP	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Thapsigargin	Human ion cha	FLUAV	In vitro studies					Intraperitone	Yes	1	1	1	0,25	1	0	4,25				
Topotecan	Human topois	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Trametinib	Human ER	FLUAV	In vitro studies					Peroral, Intra	Yes	1	1	1	0,25	1	0	4,25				
Vemurafenib	Human (multit)	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Verapamil	Human ion cha	FLUAV	In vitro studies					Peroral	Yes	1	1	1	0,25	1	0	4,25				
Emetine	Human ribosom	FLUAV	In vitro studies					Intramuscular	Yes	1	1	1	0,25	1	0	4,25				
Lovastatin	Human HMGCoA	RSV	In vitro studies					Peroral	Yes	0,5	0,25	0	0	1	0	1,75				

<b>HENV</b>	<b>Paramyxoviridae</b>	<b>(-)ssRNA</b>	<b>Multiple</b>	<b>60</b>	Gossypol	Human import	HENV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ivermectin	Human import	HENV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
<b>NIV</b>	<b>Paramyxoviridae</b>	<b>(-)ssRNA</b>	<b>Multiple</b>	<b>61</b>	Remdesivir	Viral RNA pol	NIV	Animal studies	Intravenous	N.a.	1	1	1	0,5	1	1	5,5
					Favipiravir	Viral RNA pol	NIV	In vitro studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
					25HC	Human membr	NIV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Bortezomib	Human proteas	NIV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
<b>HPV</b>	<b>Paramyxoviridae</b>	<b>(-)ssRNA</b>	<b>Respiratory system</b>	<b>1</b>	GS-441524	Viral RNA pol	HPV	In vitro studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
					Zanamivir	Unknown	HPV	In vitro studies	Inhalation	N.a.	1	1	1	0,25	1	1	5,25
					AVN-944	Human IMPDH	HPV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Ingavirin	Unknown	HPV	In vitro studies	Peroral	Yes	1	1	1	1	1	0	5
					Inosine	Viral RNA pol	HPV	In vitro studies	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Suramin	Human (multipl	HPV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					Glycyrrhizin	Human TNF	HPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					IFN-b	Human IFNAR	HPV	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25
					Lovastatin	Human HMGC	HPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Merimepodib	Human IMPDH	HPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Quercetin	Unknown	HPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ribavirin	Viral RNA pol	HPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
<b>MeV</b>	<b>Paramyxoviridae</b>	<b>(-)ssRNA</b>	<b>Respiratory system</b>	<b>1</b>	Inosine	Viral RNA pol	MeV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Amiloride	Human ion cha	MeV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Navitoclax	Human BCLXL	MeV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Nitazoxanide	Human pyruva	MeV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Ribavirin	Viral RNA pol	MeV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
<b>HMPV</b>	<b>Pneumoviridae</b>	<b>(-)ssRNA</b>	<b>Respiratory system</b>	<b>n.a.</b>	Oritavancin	Unknown	HMPV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
					Remdesivir	Viral RNA pol	HMPV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
					Ribavirin	Viral RNA pol	HMPV	Animal studies	Intravenous	Yes	1	1	1	0,5	1	0	4,5
					Itraconazole	Unknown	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Lopinavir	Unknown	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Monensin	Unknown	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Azacitidine	Viral RNA pol	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Emetine	Human ribosom	HMPV	In vitro studies	Intramuscular	Yes	1	1	1	0,25	1	0	4,25
					Ingavirin	Unknown	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Nitazoxanide	Human pyruva	HMPV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Obatoclox	Human MCL1	HMPV	In vitro studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
<b>RSV</b>	<b>Pneumoviridae</b>	<b>(-)ssRNA</b>	<b>Respiratory system</b>	<b>n.a.</b>	4'-Fluorouridine	Viral RNA pol	RSV	Animal studies	Peroral	N.a.	1	1	1	0,5	1	1	5,5
					AVN-944	Human IMPDH	RSV	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25
					Docosanol	Viral glycoprote	RSV	In vitro studies	Topical	N.a.	1	1	1	0,25	1	1	5,25
					Remdesivir	Viral RNA pol	RSV	In vitro studies	Intravenous	N.a.	1	1	1	0,25	1	1	5,25
					Ribavirin	Viral RNA pol	RSV	Approved	Intravenous	Yes	1	1	1	1	1	0	5
					Azithromycin	Unknown	RSV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Clarithromycin	Human ion cha	RSV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75
					Resveratrol	Human multipl	RSV	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5
					Fenretinide	Human RAR	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Monensin	Unknown	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Salinomycin	Unknown	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Sunitinib	Human PTK	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Thapsigargin	Human ion cha	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Verdinexor	Human export	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Berberine	Unknown	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Bortezomib	Human proteas	RSV	Animal studies	Intravenous	Yes	1	1	1	0,25	1	0	4,25
					IFN-a	Human IFNAR	RSV	Clinical trials	Peroral, Intrav	Yes	1	1	1	0,25	1	0	4,25
					Lovastatin	Human HMGC	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Merimepodib	Human IMPDH	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Mycophenolic acid	Human IMPDH	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Niclosamide	Human (multipl	RSV	In vitro studies	Peroral, Inhal	Yes	1	1	1	0,25	1	0	4,25
					Nitazoxanide	Human pyruva	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
					Quercetin	Unknown	RSV	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25
<b>CPXV</b>	<b>Poxviridae</b>	<b>dsDNA</b>	<b>Skin, mucosal and systemic</b>	<b>1</b>	Brincidofovir	Viral DNA pol	VVARV	Clinical trials	Peroral	No	1	0	1	0,75	1	1	4,75
					Acyclovir	Viral DNA pol	HSV-2	n.a.	Peroral; Intrav	No	0	0	1	0	1	1	3
					Brivudine	Viral DNA pol	VZV	n.a.	Peroral; Ocula	No	0	0	1	0	1	1	3
					Cidofovir	Viral DNA pol	CMV	n.a.	Intravenous	No	0	0	1	0	1	1	3
					Didanosine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Efavirenz	Viral RNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Famciclovir	Viral DNA pol	VZV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Favipiravir	Viral RNA pol	FLUAV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Foscarnet	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Ganciclovir	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Idoxuridine	Viral DNA pol	HSV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Remdesivir	Viral RNA pol	SARS-CoV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Sofosbuvir	Viral RNA pol	HCV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Stavudine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Telbivudine	Viral DNA pol	HCV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Trifluridine	Viral DNA pol	HSV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Vidarabine	Viral DNA pol	VZV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Valacyclovir	Viral DNA pol	HSV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Valganciclovir	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Zalcitabine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Taribavirin	Viral RNA pol	HCV	n.a.	Peroral	Yes	0	0	1	0	1	0	2
					Dapivirine	Unknown;Viral	HIV-1	n.a.	Suppository	No	0	0	1	0	0	1	2
					Peniclovir	Viral DNA pol	HSV-2	n.a.	Peroral	No	0	0	1	0	0	1	2
					Ribavirin	Viral RNA pol	HCV	n.a.	Peroral	Yes	0	0	1	0	0	1	2
					Rilpivirine	Viral RNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	0	1	2
					Tenofovir	Viral DNA pol	HSV-2	n.a.	Peroral	Yes	0	0	1	0	0	1	2
					Zidovudine	Viral DNA pol	HIV-1	n.a.	Peroral	Yes	0	0	1	0	0	1	2
<b>VARV</b>	<b>Poxviridae</b>	<b>dsDNA</b>	<b>Skin, mucosal and systemic</b>	<b>30</b>	Brincidofovir	Viral DNA pol	VVARV	Clinical trials	Peroral	No	1	0	1	0,75	1	1	4,75
					Acyclovir	Viral DNA pol	HSV-2	n.a.	Peroral; Intrav	No	0	0	1	0	1	1	3
					Brivudine	Viral DNA pol	VZV	n.a.	Peroral; Ocula	No	0	0	1	0	1	1	3
					Cidofovir	Viral DNA pol	CMV	n.a.	Intravenous	No	0	0	1	0	1	1	3
					Didanosine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Efavirenz	Viral RNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Famciclovir	Viral DNA pol	VZV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Favipiravir	Viral RNA pol	FLUAV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Foscarnet	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Ganciclovir	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Idoxuridine	Viral DNA pol	HSV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Remdesivir	Viral RNA pol	SARS-CoV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Sofosbuvir	Viral RNA pol	HCV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Stavudine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Telbivudine	Viral DNA pol	HCV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Trifluridine	Viral DNA pol	HSV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Valacyclovir	Viral DNA pol	HSV-2	n.a.	Peroral	No	0	0	1	0	1	1	3
					Valganciclovir	Viral DNA pol	CMV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Vidarabine	Viral DNA pol	VZV	n.a.	Peroral	No	0	0	1	0	1	1	3
					Zalcitabine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	0	1	1	3
					Taribavirin	Viral RNA pol	HCV	n.a.	Peroral	Yes	0	0	1	0	1	0	2
					D												

VZV	Herpesviridae	dsDNA	Skin and systemic	0.1	Brivudine	Viral DNA pol	VZV	Approved	Peroral; Ocular	No	1	1	1	1	1	1	6
					Famciclovir	Viral DNA pol	VZV	n.a.	Peroral	No	1	1	1	1	1	1	6
					Vidarabine	Viral DNA pol	VZV	Approved	Peroral	No	1	1	1	1	1	1	6
					Acyclovir	Viral DNA pol	HSV-2	Approved	Peroral; Intra	No	0.5	1	1	1	1	1	4,5
					Foscarnet	Viral DNA pol	CMV	Approved	Peroral	No	0.5	1	1	1	1	1	4,5
					Valacyclovir	Viral DNA pol	HSV-2	Approved	Peroral	No	0.5	1	1	1	1	1	4,5
					Cidofovir	Viral DNA pol	CMV	Approved	Intravenous	No	0.5	0.5	1	1	1	1	4
					Ganciclovir	Viral DNA pol	CMV	Approved	Peroral	No	0.5	0.5	1	1	1	1	4
					Idoxuridine	Viral DNA pol	HSV-1	Approved	Peroral	No	0.5	0.5	1	1	1	1	4
					Trifluridine	Viral DNA pol	HSV-2	Approved	Peroral	No	0.5	0.5	1	1	1	1	4
					Valganciclovir	Viral DNA pol	CMV	Approved	Peroral	No	0.5	0.5	1	1	1	1	4
					Penciclovir	Viral DNA pol	HSV-2	Approved	Peroral	No	0.5	0.5	1	1	1	1	3
					Brincidofovir	Viral DNA pol	VVARV	n.a.	Peroral	No	0	0	1	1	1	1	3
					Didanosine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	1	1	1	3
					Efavirenz	Viral RNA pol	HIV-1	n.a.	Peroral	No	0	0	1	1	1	1	3
					Favipiravir	Viral RNA pol	FLUAV	n.a.	Peroral	No	0	0	1	1	1	1	3
					Remdesivir	Viral RNA pol	SARS-CoV-2	n.a.	Peroral	No	0	0	1	1	1	1	3
					Sofosbuvir	Viral RNA pol	HCV	n.a.	Peroral	No	0	0	1	1	1	1	3
					Stavudine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	1	1	1	3
					Telbivudine	Viral DNA pol	HBV	n.a.	Peroral	No	0	0	1	1	1	1	3
					Zalcitabine	Viral DNA pol	HIV-1	n.a.	Peroral	No	0	0	1	1	1	1	3
					Tenofovir	Viral DNA pol	HSV-2	Approved	Peroral	Yes	0.5	0	1	1	1	1	2,5
					Taribavirin	Viral RNA pol	HCV	n.a.	Peroral	Yes	0	0	1	1	1	1	2
					Dapivirine	Unknown; Viral	HIV-1	n.a.	Suppository	No	0	0	1	1	1	1	2
					Ribavirin	Viral RNA pol	HCV	n.a.	Peroral	Yes	0	0	1	1	1	1	2
					Rilpivirine	Viral RNA pol	HIV-1	n.a.	Peroral	No	0	0	1	1	1	1	2
					Zidovudine	Viral DNA pol	HIV-1	n.a.	Peroral	Yes	0	0	1	1	1	1	2
HIV-1	Retroviridae	ssRNA-RT	Multiple	47	Amprenavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Atazanavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Darunavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Didanosine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Efavirenz	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Emtricitabine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Etravirine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Indinavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Lamivudine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Rilpivirine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Stavudine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Tipranavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Zalcitabine	Viral RT	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	6
					Dapivirine	Viral RT	HIV-1	Approved	Suppository	No	1	1	1	1	1	1	6
					Telbivudine	Viral RT	HIV-1	Clinical trials	Peroral	No	1	1	1	0,75	1	1	5,75
					Nelfinavir	Viral protease	HIV-1	Approved	Peroral	Yes	1	1	1	1	1	1	5
					Lopinavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	5
					Ritonavir	Viral protease	HIV-1	Approved	Peroral	No	1	1	1	1	1	1	5
					Saquinavir	Viral protease	HIV-1	Approved	Peroral	Yes	1	1	1	1	1	1	5
					Tenofovir	Viral RT	HIV-1	Approved	Peroral	Yes	1	1	1	1	1	1	5
					Zidovudine	Viral RT	HIV-1	Approved	Peroral; Intra	Yes	1	1	1	1	1	1	5
					Maraviroc	Host CXCR4	HIV-1	Approved	Peroral	Yes	1	1	1	1	1	1	5
					Adefovir	Viral RT	HIV-1	Clinical trials	Peroral	Yes	1	1	1	0,75	1	1	4,75
					Racivir	Viral RT	HIV-1	Clinical trials	Peroral	No	0,5	1	1	1	1	1	4,5
					Elvicitabine	Viral RT	HIV-1	Clinical trials	Peroral	No	0,5	1	1	1	1	1	4,5
					Enoxacin	Human topoiso	HIV-1	In vitro studies	Peroral	No	0,5	1	1	1	1	1	4,5
					Raloxifene	Human (Multi)	HIV-1	In vitro studies	Peroral	No	0,5	1	1	1	1	1	4,5
					Lobucavir	Viral RT	HIV-1	Clinical trials	Peroral	No	0	1	1	1	1	1	4
					Docosanol	Viral glycoprote	HIV-1	In vitro studies	Topical	No	0	1	1	1	1	1	4
					Alisporivir	Human CYPs	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	4
					Vesatolimod	Human TLR7	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	4
					Tenatoprazole	Human vesicul	HIV-1	Clinical trials	Peroral	No	0	1	1	1	1	1	4
					Dyphylline	Human vATPas	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	4
					Indomethacin	Human COX	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	4
					Ilaprazole	Human vesicul	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	4
					Calanolide A	Viral RT	HIV-1	Approved	Preoral	No	0	1	1	1	1	1	4
					Lapachone	Viral transcript	HIV-1	In vitro studies	Preoral; Intra	No	0	1	1	1	1	1	4
					Ementine	Human ribosom	HIV-1	In vitro studies	Preoral; Subc	No	0	1	1	1	1	1	4
					Selliciclib	Human PTK	HIV-1	In vitro studies	Preoral	No	0	1	1	1	1	1	4
					Famciclovir	Viral DNA pol	HBV	Clinical trials	Peroral	No	0,5	0,25	1	1	1	1	3,75
					Fiacitabine	Viral RT	HBV	Animal model	Peroral	No	0,5	0,25	1	1	1	1	3,75
					Navitoclax	Human BCL2	HIV-1	In vitro studies	Peroral	Yes	0,5	1	1	1	1	1	3,5
					Gemcitabine	Viral RT	HIV-1	In vitro studies	Intravenous	Yes	0,5	1	1	1	1	1	3,5
					Valacyclovir	Viral RT	HBV	Approved	Peroral	No	0	0,25	1	1	1	1	3,25
					Imbruvic	Viral DNA pol	HBV	In vitro studies	Topical	No	0	0,25	1	1	1	1	3,25
					Irbesartan	Human ATR	HBV	In vitro studies	Peroral	No	0	0,25	1	1	1	1	3,25
					Memantine	Human ion cha	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Nitazoxanide	Human Pyruva	HIV-1	Clinical trials	Peroral	No	0	1	1	1	1	1	3
					Ivermectin	Human import	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	3
					Pentosan polysulfate	Human FGF	HIV-1	In vitro studies	Peroral	No	0	1	1	1	1	1	3
					Leniviroc	Host CCR5	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Inosine	Viral RT	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Topotecan	Human topoiso	HIV-1	Clinical trials	Intravenous	Yes	0	1	1	1	1	1	3
					Azactidine	Viral RT	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Siroliimus	Human PTK	HIV-1	Approved	Peroral	Yes	0	1	1	1	1	1	3
					Azithromycin	Unknown	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Chloroquine	Human (Multi)	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Ezetimibe	Human cholest	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Hydroxychloroquin	Human (Multi)	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Tamoxifen	Human (Multi)	HIV-1	Clinical trials	Peroral	Yes	0	1	1	1	1	1	3
					Brequinar	Human DHODH	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Sunitinib	Human PTK	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Cyclosporine	Human CYPs	HIV-1	Approved	Peroral; Intra	Yes	0	1	1	1	1	1	3
					Clozapine	Unknown	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Dasatinib	Human PTK	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Lipoic acid	Human lipoyltr	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Trametinib	Human PTK	HIV-1	In vitro studies	Peroral	Yes	0	1	1	1	1	1	3
					Leronlimab	Human CCR5	HIV-1	Clinical trials	Subcutaneous	Yes	0	1	1	1	1	1	3
					IFN- $\alpha$	Human IFNAR	HIV-1	Clinical trials	Subcutaneous	Yes	0	1	1	1	1	1	3
					IL7	Human CD127	HIV-1	Clinical trials	Subcutaneous	Yes	0	1	1	1	1	1	3
					Thymalfasin	Human (Unkn	HIV-1	Clinical trials	Subcutaneous	Yes	0	1	1	1	1	1	3
					Minocycline	Human MIF	HIV-1	Animal model	Peroral	Yes	0	1	1	1	1	1	3
					Interferon beta	Human IFNAR	HIV-1	In vitro studies	Subcutaneous	Yes	0	1	1	1	1	1	3
					Suramin	Human (Multi)	HIV-1	In vitro studies	Intravenous	Yes	0	1	1	1	1	1	3
					Camptothecin	Human topoiso	HIV-1	In vitro studies	Intravenous	Yes	0	1	1	1	1	1	3



DENV	Flaviviridae	(+)ssRNA	Multiple	0,37													
	Ivermectin	Human import	DENV-2	Clinical trials	Peroral	N.a.	1	1	1	0,75	1	1	5,75				
	Ivermectin	Human import	DENV-3	Clinical trials	Peroral	N.a.	1	1	1	0,75	1	1	5,75				
	Ivermectin	Human import	DENV-4	Clinical trials	Peroral	N.a.	1	1	1	0,75	1	1	5,75				
	Nitroprusside	Human NPR1	DENV	Animal studies	Injection	N.a.	1	1	1	0,5	1	1	5,5				
	Prochlorperazine	Human clathrin	DENV-2	Animal studies	Injection	N.a.	1	1	1	0,5	1	1	5,5				
	ABMA	Human GTPase	DENV	In vitro studies	Subcutaneous	N.a.	1	1	1	0,25	1	1	5,25				
	Posaconazole	Human OSBP	DENV-1	In vitro studies	Injection	N.a.	1	1	1	0,25	1	1	5,25				
	Azauridine	Viral RNA pol	DENV-1	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Galidesivir	Viral RNA pol	DENV-2	In vitro studies	Injection	N.a.	1	1	1	0,25	1	1	5,25				
	Posaconazole	Human OSBP	DENV-2	In vitro studies	Injection	N.a.	1	1	1	0,25	1	1	5,25				
	Amiodarone	Human (multip)	DENV-2	In vitro studies	Peroral; Inject	N.a.	1	1	1	0,25	1	1	5,25				
	Amodiaquine	Human (Multi)	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Azauridine	Viral RNA pol	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	GS-441524	Viral RNA pol	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Lanatoside C	Unknown	DENV-2	In vitro studies	Peroral, intrav	N.a.	1	1	1	0,25	1	1	5,25				
	Manidipine	Human ion cha	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Nelfinavir	Unknown	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Raloxifene	Human ER	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Saracatinib	Human PTK	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Sofosbuvir	Viral RNA pol	DENV-2	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Posaconazole	Human OSBP	DENV-4	In vitro studies	Injection	N.a.	1	1	1	0,25	1	1	5,25				
	Azauridine	Viral RNA pol	DENV-4	In vitro studies	Peroral	N.a.	1	1	1	0,25	1	1	5,25				
	Ivermectin	Human import	DENV-1	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
	Amantadine	Unknown	DENV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				
	Chloroquine	Human (Multi)	DENV	Clinical trials	Peroral; Inject	Yes	1	1	1	0,75	1	0	4,75				
	Niclosamide	Human (multi)	DENV-2	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Sunitinib	Human PTK	DENV-1	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Bortezomib	Human proteas	DENV-2	Animal studies	Injection	Yes	1	1	1	0,5	1	0	4,5				
	Erlotinib	Human PTK	DENV-2	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Fenretinide	Human RAR	DENV-2	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Lovastatin	Human HMGCF	DENV-2	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Minocycline	Human MIF	DENV-2	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Fenretinide	Human RAR	DENV-3	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Sunitinib	Human AP2	DENV-3	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Fenretinide	Plasma membr	DENV-4	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Sunitinib	Human PTK	DENV-4	Animal studies	Peroral	Yes	1	1	1	0,5	1	0	4,5				
	Quinine	Viral protease	DENV-2	In vitro studies	Injection	Yes	1	1	1	0,25	1	0	4,25				
	Fluvastatin	Human HMGCF	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Itraconazole	Human OSBP	DENV-2	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	Labyrinthopepti	Unknown	DENV	In vitro studies	Intraperitone	N.a.	1	1	1	0,25	0	1	4,25				
	Breguarin	Human DHODI	DENV	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	Anisomycin	Human ribosom	DENV-1	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
	Betulinic Acid	Unknown	DENV-1	In vitro studies	Peroral; Topici	Yes	1	1	1	0,25	1	0	4,25				
	Glycyrrhizin	Human TNF	DENV-1	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	IFN- $\alpha$	Human IFNAR	DENV-1	In vitro studies	Peroral; Intrav	Yes	1	1	1	0,25	1	0	4,25				
	Minocycline	Human MIF	DENV-1	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Ribavirin	Viral RNA pol	DENV-1	In vitro studies	Peroral; Inhal	Yes	1	1	1	0,25	1	0	4,25				
	Cucurbit[7]uril	Human polyam	DENV-2	In vitro studies	N.a.	N.a.	1	1	1	0,25	0	1	4,25				
	IFN- $\gamma$	Human IFNGR	DENV-2	In vitro studies	Injection	Yes	1	1	1	0,25	1	0	4,25				
	Mitoxantrone	Unknown	DENV-2	In vitro studies	Injection	Yes	1	1	1	0,25	1	0	4,25				
	Topotecan	Human topois	DENV-2	In vitro studies	Injection	Yes	1	1	1	0,25	1	0	4,25				
	Anisomycin	Human ribosom	DENV-2	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
	Betulinic Acid	Unknown	DENV-2	In vitro studies	Peroral; Topici	Yes	1	1	1	0,25	1	0	4,25				
	Chlorpromazine	Human AP2	DENV-2	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	Cyclosporine	Human CYPs	DENV-2	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	Fluoxetine	Unknown	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Glycyrrhizin	Human TNF	DENV-2	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	GSK583	Human RIPK2	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Halofuginone	Human tRNA s	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Hydroxychloroqui	Human (Multi)	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	IFN- $\alpha$	Human IFNAR	DENV-2	In vitro studies	Peroral; Intrav	Yes	1	1	1	0,25	1	0	4,25				
	Luteolin	Unknown	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Metformin	Unknown	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Mycophenolic acid	Human IMPDH	DENV-2	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	Quinacrine	Human proteas	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Ribavirin	Viral RNA pol	DENV-2	In vitro studies	Peroral; Inhal	Yes	1	1	1	0,25	1	0	4,25				
	Simvastatin	Human HMGCF	DENV-2	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Anisomycin	Human ribosom	DENV-3	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
	Betulinic Acid	Unknown	DENV-3	In vitro studies	Peroral; Topici	Yes	1	1	1	0,25	1	0	4,25				
	Minocycline	Human MIF	DENV-3	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Suramin	Viral helicase	DENV-4	In vitro studies	Injection	Yes	1	1	1	0,25	1	0	4,25				
	Anisomycin	Human ribosom	DENV-4	In vitro studies	Subcutaneous	Yes	1	1	1	0,25	1	0	4,25				
	Betulinic Acid	Unknown	DENV-4	In vitro studies	Peroral; Topici	Yes	1	1	1	0,25	1	0	4,25				
	Glycyrrhizin	Human TNF	DENV-4	In vitro studies	Peroral; Inject	Yes	1	1	1	0,25	1	0	4,25				
	IFN- $\alpha$	Human IFNAR	DENV-4	In vitro studies	Peroral; Intrav	Yes	1	1	1	0,25	1	0	4,25				
	Metformin	Unknown	DENV-4	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Minocycline	Human MIF	DENV-4	In vitro studies	Peroral	Yes	1	1	1	0,25	1	0	4,25				
	Ribavirin	Viral RNA pol	DENV-4	In vitro studies	Peroral; Inhal	Yes	1	1	1	0,25	1	0	4,25				
	Fenretinide	Human RAR	DENV-1	Animal studies	Peroral	Yes	1	1	1	0,5	0	3,5					
	GSK717	Human NOD2	DENV-2	In vitro studies	N.a.	Yes	1	1	1	0,25	0	3,25					
<b>HCV</b>	<b>Flaviviridae</b>	<b>(+)ssRNA</b>	<b>Digestive and excret</b>	<b>6,3</b>													
	Boceprevir	Viral protease	HCV	Approved	Peroral	No	1	1	1	1	1	1	6				
	Daclatasvir	Viral NS5A	HCV	Approved	Peroral	N.a.	1	1	1	1	1	1	6				
	Sofosbuvir	Viral RNA pol	HCV	Approved	Peroral	N.a.	1	1	1	1	1	1	6				
	Simeprevir	Viral protease	HCV	Approved	Peroral	N.a.	1	1	1	1	1	1	6				
	Alisporivir	Human CYPs	HCV	Clinical trials	Peroral	No	1	1	1	0,75	1	1	5,75				
	IFN- $\alpha$	Human IFNAR	HCV	Approved	Peroral, Intrav	Yes	1	1	1	1	1	0	5				
	Ribavirin	Viral RNA pol	HCV	Approved	Peroral	Yes	1	1	1	1	1	0	5				
	Cyclosporine	Human CYPs	HCV	Clinical trials	Peroral	Yes	1	1	1	0,75	1	0	4,75				

