AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MINIREVIEW

100 Years of Suramin

Natalie Wiedemar,[a,b] Dennis A. Hauser,[a,b] Pascal Mäser[a,b]

[a]Swiss Tropical and Public Health Institute, Department of Medical Parasitology and Infection Biology, Basel, Switzerland
[b]University of Basel, Basel, Switzerland

ABSTRACT Suramin is 100 years old and is still being used to treat the first stage of acute human sleeping sickness, caused by *Trypanosoma brucei rhodesiense*. Suramin is a multifunctional molecule with a wide array of potential applications, from parasitic and viral diseases to cancer, snakebite, and autism. Suramin is also an enigmatic molecule: What are its targets? How does it get into cells in the first place? Here, we provide an overview of the many different candidate targets of suramin and discuss its modes of action and routes of cellular uptake. We reason that, once the polypharmacology of suramin is understood at the molecular level, new, more specific, and less toxic molecules can be identified for the numerous potential applications of suramin.

KEYWORDS *Trypanosoma brucei*, human African trypanosomiasis, polypharmacology, sleeping sickness, suramin

SURAMIN, THE FRUIT OF EARLY MEDICINAL CHEMISTRY

When suramin was introduced for the treatment of African sleeping sickness in 1922, it was one of the first anti-infective agents that had been developed in a medicinal chemistry program. Starting from the antitrypanosomal activity of the dye trypan blue, synthesized in 1904 by Paul Ehrlich, Bayer made a series of colorless and more potent derivatives. Molecule 205 was suramin (Fig. 1), synthesized by Oskar Dressel, Richard Kothe, and Bernhard Heymann in 1916. Sleeping sickness (also known as human African trypanosomiasis [HAT]) was at the forefront of research at that time, not a neglected disease as it is today, and the development of suramin was a breakthrough for the emerging field of chemotherapy. While the history of suramin has been reviewed elsewhere (1), we focus here on the many potential applications of suramin and its enigmatic mode of action.

SURAMIN AS AN ANTIPARASITIC DRUG

Suramin is still being used for the treatment of *Trypanosoma brucei rhodesiense* infections (2). However, it does not cross the blood-brain barrier and therefore is administered only for the first (hemolymphatic) stage of sleeping sickness, when the trypanosomes have not yet invaded the patient's central nervous system (CNS). The standard treatment regimen for suramin is an initial test dose of 4 to 5 mg/kg of body weight followed by five weekly doses of 20 mg/kg (but not more than 1 g) injected intravenously (i.v.) (3). Suramin is also used for surra (mal de caderas), caused by *Trypanosoma evansi*, in particular for the treatment of camels (4). The treatment regimen is a single i.v. injection of 10 mg/kg suramin, i.e., about 6 to 10 g (4). *In vitro*, suramin also has some activity against *Trypanosoma cruzi* (5). However, it is not used for Chagas' disease, and studies in mice have even suggested that suramin would exacerbate the disease (6). *In vitro* activity of suramin against *Leishmania major* and *Leishmania donovani* has recently been described (7). Furthermore, suramin blocks host cell invasion by the malaria parasite *Plasmodium falciparum*. This was observed for both the invasion of erythrocytes by *P. falciparum* merozoites (8) and the invasion of HepG2 hepatoma cells by *P. falciparum* sporozoites (9).

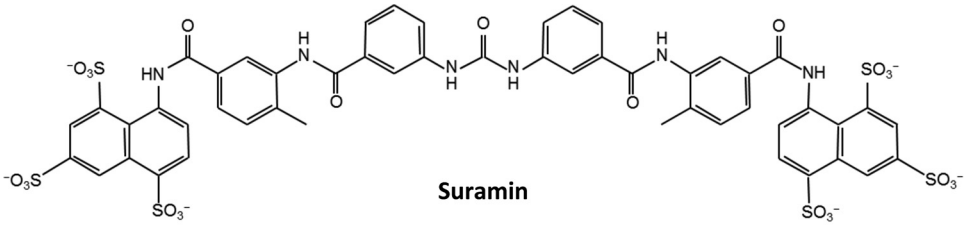
Citation Wiedemar N, Hauser DA, Mäser P. 2020. 100 years of suramin. Antimicrob Agents Chemother 64:e01168-19. https://doi.org/10.1128/AAC.01168-19.

Copyright © 2020 American Society for Microbiology. All Rights Reserved.

Address correspondence to Pascal Mäser, pascal.maeser@unibas.ch.

Accepted manuscript posted online 16 December 2019
Published 21 February 2020

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.



Molecular weight	1297 Da
H-bond donors	12
H-bond acceptors	23
logP	0.00023
Protein binding	99.7%
Metabolites	none
Biological half-life	44-54 days
Metabolites	none
Elimination pathway	urinary

FIG 1 Suramin structure and medicinal chemistry parameters. Except for its good solubility in water, suramin lacks lead-like properties as defined, e.g., by Lipinski's rule of 5 (186).

Suramin had been in use for river blindness, caused by the filarial parasite *Onchocerca volvulus* (10). It acts both on microfilariae and, to a greater extent, on adult worms (11, 12). However, suramin was subsequently replaced by the less toxic, and orally bioavailable, ivermectin (13, 14). The adverse effects of suramin are indeed manifold, including nephrotoxicity, hypersensitivity reactions, dermatitis, anemia, peripheral neuropathy, and bone marrow toxicity (3, 15). However, despite its potential toxicity, the lack of bioavailability, and the absence of lead-like properties (Fig. 1), suramin has found a surprising variety of repurposing applications. Table 1 provides an overview of the biological activities of suramin, and Table 2 lists clinical trials performed with suramin.

SURAMIN AS AN ANTIVIRAL AGENT

The antiviral and antibacteriophage activities of suramin have been known since the mid-20th century (16, 17). Soon after the discovery of retroviruses, suramin was found to inhibit retroviral reverse transcriptase (18), which served as a rationale to test suramin against human immunodeficiency virus (HIV). Suramin protected T cells from HIV infection *in vitro* (19), and in AIDS patients, it reduced the viral burden in some of the study subjects; however, no improvement of the immunological features and clinical symptoms was achieved (20–22). Later, suramin was found to inhibit host cell attachment through binding to the HIV-1 envelope glycoprotein gp120, indicating that the *in vitro* protection against HIV infection is mediated through inhibition of viral entry (23).

Suramin also inhibits the binding of dengue virus to host cells through a direct effect on the viral envelope protein (24). Inhibition of host cell attachment was also found for herpes simplex (25) and hepatitis C (26) viruses, which explained the previously reported protective effects of suramin against *in vitro* herpes simplex virus infections (27) and *in vivo* infections of ducks with duck hepatitis B virus (28). Similar to the experience with HIV, suramin had been initially tested against hepatitis viruses due to its inhibitory effect on the viral DNA polymerase (29, 30). However, in a small clinical trial, suramin was found to be ineffective and toxic in chronic active hepatitis B patients (31). Suramin neutralized enterovirus 71 (EV71) in cell culture and in a mouse model by binding to capsid proteins (32–34).

Suramin also has potential against emerging viruses. It was shown to inhibit both RNA synthesis and replication in chikungunya virus (35). *In vitro*, suramin conferred protection if present at the time of infection, and this was attributed to a reduction of viral host cell binding and uptake (36). In the murine

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

TABLE 1 Diseases and pathogens susceptible to suramin

Disease and/or pathogen	Activity in[a]: Cell culture	Animal model	Patient
Parasitic infections			
T. b. rhodesiense HAT	X	X	X
T. brucei gambiense HAT	X	X	X
Surra, *T. evansi*	X	X	NA
River blindness, *O. volvulus*	X	X	X
T. cruzi	X		
Leishmania spp.	X		
P. falciparum	X		
Viral infections			
Hepatitis virus	X	X	X
AIDS, HIV	X		X
Herpes simplex virus	X	X	
Chikungunya virus	X	X	
Enterovirus 71	X	X	
Dengue virus	X		
Zika virus	X		
Ebola virus	X		
Neoplastic diseases			
Non-small cell lung cancer	X	X	
Breast cancer	X	X	
Bladder cancer	X	X	
Brain tumors	X	X	
Prostate cancer	X	X	X
Other			
Snakebite	X	X	
Arthritis	X	X	
Autism	NA	X	X

[a]X, activity; NA, not applicable.

model, suramin led to a reduction of pathognomonic lesions if injected prior to chikungunya virus infection (37). Suramin also inhibited host cell invasion by Ebola virus (38) and Zika virus, even when added after viral exposure of the cell cultures (39).

TABLE 2 Clinical trials with suramin

Registry ID or reference[a]	Disease	Phase[b]	Yr
NCT02508259	Autism spectrum disorders	I, II	2015
NCT01671332	Non-small cell lung cancer	II	2012
NCT01038752	Non-small cell lung cancer	II	2010
NCT00083109	Recurrent renal cell carcinoma	I, II	2004
NCT00066768	Recurrent non-small cell lung cancer	I	2003
NCT00054028	Recurrent breast cancer	I, II	2002
NCT00006929	Recurrent non-small cell lung cancer	II	2000
NCT00006476	Bladder cancer	I	2000
NCT00004073	Brain and CNS tumors	II	1999
NCT00002921	Adrenocortical carcinoma	II	1997
NCT00003038	Advanced solid tumors	I	1997
NCT00002723	Prostate cancer	III	1996
NCT00002881	Prostate cancer	III	1996
NCT00002652	Multiple myeloma and plasma cell neoplasm	II	1995
NCT00002639	Brain and CNS tumors	II	1995
NCT00001381	Bladder neoplasms, transitional cell carcinoma	I	1994
NCT00001266	Prostatic neoplasm	II	1990
NCT00001230	Filariasis	Obs.	1988
42	Solid tumors	Obs.	1987
20	AIDS	Obs.	1987
31	Hepatitis B	Obs.	1987

[a]Trials with a registered NCT number are from ClinicalTrials.gov; others are from the literature.
[b]Obs., observational study.

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

SURAMIN AGAINST CANCER

The first studies on the effects of suramin on neoplasms in animals were carried out in the 1940s; mice engrafted with lymphosarcoma developed significantly smaller tumors when simultaneously treated with suramin (40). In the 1970s, it was shown that suramin could enhance the actions of cyclophosphamide and adriamycin in mice engrafted with Ehrlich carcinoma (41). The first clinical trial with suramin was carried out in the 1980s in advanced-stage adrenal and renal cancer patients (42). Around half of the patients showed either partial or minimal responses, and none showed complete remission. Nevertheless, a number of subsequent clinical trials with suramin were carried out (Table 2). In particular, suramin was tested against prostate cancer (43–51), non-small cell lung cancer (52), breast cancer (52), bladder cancer (53, 54), and brain tumors (55, 56). Most of the studies were based on the potential of suramin to act as an antagonist of growth factors (57–59), which are often overexpressed by tumors. In addition, suramin directly exhibits cytostatic activity on cultured tumor cells (60–62). However, the initial clinical tests did not warrant the further development of suramin as an anticancer monotherapy.

Subsequent tests focused on suramin as a chemosensitizer, based on the findings that, at subcytotoxic levels (<50 μM), it enhanced the efficacy of anticancer drugs, such as mitomycin C, taxol, or doxorubicin, in *ex vivo* cultures and in animal models (63–65). Suramin combined with taxol inhibited invasiveness and prevented metastasis in a xenograft mouse model (66). Different explanations are conceivable for the chemosensitizing effects of suramin on tumor cells, including inhibition of telomerase (67) or inhibition of fibroblast growth factors and angiogenesis (68). A phase II clinical study was performed in patients with advanced, drug-resistant non-small cell lung cancer treated with taxol or carboplatin; supplementation with nontoxic doses of suramin did not overcome drug resistance (69). Randomized controlled studies to validate the use of suramin as a chemosensitizer in chemotherapy-naive lung cancer patients remain to be performed. A combination of estramustine, docetaxel, and suramin gave promising results in hormone-refractory prostate cancer patients (51).

SURAMIN AS AN ANTIDOTE

Three of the many biological activities of suramin support its potential use as a protective agent: the inhibition of thrombin, the inhibition of phospholipase A2, and the inhibition of purinergic signaling. Several vipers possess toxins that mimic thrombin (70), perfidiously triggering the coagulation cascade in mammalian blood. Suramin not only inhibits thrombin itself (71), but also the thrombin-like proteases of snake venom (72), and was therefore proposed as an antidote for snakebite. Other common constituents of metazoan venoms are phospholipases A2, which convert phospholipids into lysophospholipids. Again, suramin inhibits mammalian phospholipase A2 (73), as well as the orthologues from snake venom (74–76) and bee venom (77), suggesting that it can act as an antidote. A certain degree of protection from venoms by suramin was confirmed in mouse models (77–79). The potential use of suramin as an antidote is attractive, given the high global burden of snakebites (80) and the current shortage of antivenom (81).

Suramin's ability to block P2 purinergic, G protein-coupled receptors (82) may counteract the action of neurotoxins that trigger arachidonic acid signaling, e.g., via phospholipase A2 activity (83). A possible explanation is that suramin prevents the activation of ATP receptors at the motor nerve ending, which otherwise would depress Ca^{2+} currents and reduce acetylcholine release at the presynaptic membrane (84). Suramin was also proposed to serve as a neuroprotective agent (85, 86) and as an antidote for kidney toxicity during cancer chemotherapy (87) and, based on its antiapoptotic effect, to protect against liver failure (88). Suramin also inhibits connexin channels of the tight junction, thereby suppressing ATP release and protecting cells from pore-forming bacterial toxins, such as hemolysin (89). The suramin analogs NF340 and NF546 were cardioprotective in a mouse model for heart graft rejection, presumably via inhibition of the purinergic G protein-coupled receptor P2Y11 (90).

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

FURTHER POTENTIAL USES OF SURAMIN

Suramin was found to have beneficial effects in a rat arthritis model (91) and to suppress fear responses in the rat (92). It also promoted the expansion of T cells during immunization of mice and was therefore considered as a small-molecule adjuvant for vaccination (93). Based on the cell danger hypothesis, suramin has recently been tested for the treatment of autism spectrum disorders (ASD). The cell danger hypothesis suggests that a systemic stress response that involves mitochondria and purinergic signaling contributes to the development of psychopathologies like autism. Suramin had been shown to act as an inhibitor of purinergic signaling (94) and mitochondrial function (95) and was therefore proposed as a potential therapy for ASD (96). First tests in mouse models showed correction of symptoms in juveniles (96), as well as in adults (97). A first small human trial was carried out and, even though difficult to quantify, showed improvement of ASD symptoms (98).

(TOO) MANY TARGETS

Suramin is a large molecule that carries six negative charges at physiological pH (Fig. 1). It is likely to bind to, and thereby inhibit, various proteins (99). Thus, the many and diverse potential applications of suramin reflect its polypharmacology. Indeed, a large number of enzymes have been shown to be inhibited by suramin (Table 3). Suramin inhibits many glycolytic enzymes (100, 101), enzymes involved in galactose catabolism (PubChem BioAssay no. 493189 [187]), and enzymes of the Krebs cycle (102). Suramin further decreases the activities of a large number of enzymes involved in DNA and RNA synthesis and modification: DNA polymerases (103, 104), RNA polymerases (103, 105, 106), reverse transcriptase (18, 103), telomerase (67), and enzymes involved in winding/unwinding of DNA (107, 108) are inhibited by suramin, as well as histone- and chromatin-modifying enzymes like chromobox proteins (109), methyltransferases (110), and sirtuin histone deacetylases (111). Suramin is also an inhibitor of other sirtuins (112) and protein kinases (113, 114), glutaminase (PubChem BioAssay no. 624170), phospholipase A2 (72, 77), protein tyrosine phosphatases (115), lysozyme (116), and different serine and cysteine proteases (117–119). For caspases, cysteine proteases involved in apoptosis, suramin was described as acting as either inhibitor or activator (120, 121). Suramin further inhibits the Na^+,K^+-ATPase and other ATPases (122–124), certain classes of GABA receptors (125, 126), and several G protein-coupled receptors (127), including P2 purinoceptors and follicle-stimulating hormone receptor (128, 129). Suramin also showed inhibitory effects against components of the coagulation cascade (71, 130) and the complement system (131–133) and against deubiquitinating enzymes (PubChem BioAssay no. 504865 and 463106). It also interacts with prion protein, inhibiting conversion into the pathogenic form PrP^{Sc} (134). Besides its many inhibitory activities, suramin also activates certain nuclear receptors that act as transcription factors (135) and intracellular calcium channels (136).

ENIGMATIC MECHANISMS OF ACTION AGAINST AFRICAN TRYPANOSOMES

Somewhat ironically, much less appears to be known about the targets of suramin in African trypanosomes, where it has been in use for a century, than those in tumor cells or viruses. Suramin was shown to inhibit glycolytic enzymes of *T. brucei*, with selectivity over their mammalian orthologues, in particular, hexokinase, aldolase, phosphoglycerate kinase, and glycerol-3-phosphate dehydrogenase (100). Intriguingly, the trypanosomal enzymes have higher isoelectric points (>9), which is due to extra arginines and lysines that are absent in the mammalian orthologues (137). These residues form positively charged surface-exposed "hot spots" that were proposed to be bound by the negatively charged suramin (100). Inhibition of trypanosomal glycolysis by suramin is in agreement with the dose-dependent inhibition of oxygen consumption and ATP production observed in trypanosomes isolated from suramin-treated rats (138). However, the glycolytic enzymes of *T. brucei* are localized inside glycosomes (139), and it is unclear how suramin could penetrate the glycosomal membrane or if suramin could bind to glycolytic enzymes in the cytosol before they were imported into

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

TABLE 3 Putative target proteins of suramin, biological processes, and mechanisms

Putative target[a]	Reference(s)
Metabolism	
6-Phosphofructokinase	100
Fructose-l,6-bisphosphate aldolase	100
Glucose-6-phosphate isomerase	100
Glyceraldehyde-3-phosphate dehydrogenase	100
Glycerol-3-phosphate dehydrogenase	100, 141
Glycerol kinase	100
Hexokinase	100
Phosphoglycerate kinase	100
Pyruvate kinase	101
Triose-phosphate isomerase	100
Succinic dehydrogenase	102
Galactokinase	493189[b]
Glutaminase	624170[b]
Glycerophosphate oxidase	141
Nucleoside triphosphate diphosphohydrolases 1 and 2	123, 124, 157–160
Nucleotide pyrophosphatases/phosphodiesterases 1 and 3	161
Nucleic acids	
DNA polymerase alpha	103, 104
DNA polymerase beta	103, 104
DNA polymerase gamma	103
DNA polymerase delta	104
DNA polymerase I	103, 104
Terminal deoxynucleotidyltransferase	103
DNA primase	103
DNA-dependent RNA polymerase	103, 106
RNA-dependent RNA polymerase	105
Reverse transcriptase	18, 103
Telomerase	67
RNase H	162
Flavivirus RNA helicase	39, 107, 163
DNA topoisomerase II	108
Tyrosyl-DNA phosphodiesterase 1	164
Human antigen R	165
DNA-binding protein MCM10	166
Epigenetics	
Chromobox protein homologue 1 beta	488953[b]
Chromobox protein homologue 7	109
Histone methyltransferases	110, 167
Precorrin-4 C(11)-methyltransferase	168
Sirtuins 1, 2, and 5	111, 112, 169
Protease	
Kallikrein	119
Alpha thrombin	71
Human neutrohphil cathepsin G	118
Human neutrophil elastase	118
Human neutrophil proteinase 3	118
Rhodesain	117
Caspases 1, 2, 8, 9, and 10	120, 121, 170, 171
Falcipain 2	172
Extracellular matrix	
Hyaluronidase	173, 174
Iduronate sulfatase	174
β-Glucuronidase	174
Membrane channels and signaling	
Nonjunctional connexin 43 hemichannels	89
Na^+,K^+ ATPase	122
Cystic fibrosis transmembrane regulator	175
Ryanodine receptor 1	136
$GABA_A$ receptors	125, 126
P2X purinergic receptors	94

(Continued on next page)

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

TABLE 3 (Continued)

Putative target[a]	Reference(s)
P2Y purinergic receptors	94
N-Methyl-D-aspartate receptor	176
DNA-dependent protein kinase	113
Protein kinase C	114
Protein tyrosine phosphatases	115
VIP receptor	127
Follicle-stimulating hormone receptor	129
Pregnane X receptor	135
Diadenosine tetraphosphate hydrolase	177
Other	
Prion (Prp^C)	134
Complement factors	119, 131–133
Phospholipase A_2	72, 178
Lysozyme	116
Antimicrobial peptide CM15	179
Ubiquitin carboxyl-terminal hydrolases 1 and 2	504865; 463106[b]
HSP 60 chaperonin system	180, 181
GroEL chaperonin system	180, 181

[a]Suramin acts as an inhibitor or antagonist in all cases except the pregnane X receptor and the ryanodine receptor. The mode of action against caspase is controversial.
[b]PubChem BioAssay; last retrieved 29 April 2019.

glycosomes (140). Alternative targets proposed for the trypanocidal effect of suramin are glycerophosphate oxidase (141, 142); a serine oligopeptidase termed OP-Tb (143); and REL1 (144), the RNA-editing ligase of the trypanosome's kinetoplast. It is unclear how suramin would pass the inner mitochondrial membrane, but suramin inhibited oxidative phosphorylation in mitochondrial preparations of the trypanosomatid *Crithidia fasciculata* (145). Suramin also appeared to inhibit cytokinesis in *T. brucei*, as indicated by the finding that suramin treatment resulted in an increased number of trypanosomes with two nuclei (146).

UPTAKE ROUTES OF SURAMIN INTO CELLS

The negative charges of suramin (Fig. 1) not only promote binding to various proteins, they also prevent diffusion across biological membranes. However, the majority of targets (Table 3) are intracellular, and radiolabeled suramin was shown to be taken up by human endothelial and carcinoma cells (147, 148) and by *T. brucei* bloodstream forms (138, 149). Suramin is not a substrate of P-glycoprotein (150) or of any other known transporter. Thus, suramin must be imported by endocytosis. Mammalian cells can take up suramin in complex with serum albumin by receptor-mediated endocytosis (148). This had originally also been thought to happen in *T. brucei* (138). However, the trypanosomes do not take up albumin by receptor-mediated endocytosis (151), and LDL (low-density lipoprotein) was proposed to act as the vehicle instead (149). Suramin bound to LDL and inhibited the binding and uptake of LDL, while LDL enhanced the uptake of suramin in bloodstream form *T. brucei* (149). In contrast, overexpression in procyclic *T. b. brucei* of Rab4, a small GTPase involved in the recycling of endosomes, decreased suramin binding and uptake without affecting LDL binding or uptake (152). In the same study, overexpression of a mutant Rab5, which was locked in the active GTP-bound form, increased LDL uptake without affecting suramin uptake (152). These findings indicated that, at least in the procyclic trypanosomes of the tsetse fly midgut, LDL and suramin are imported independently of each other.

The development of genome-wide RNA interference (RNAi) screens in bloodstream form *T. brucei* combined with next-generation sequencing offered new opportunities to address the genetics of drug resistance. This approach identified genes whose silencing reduced sensitivity to suramin (153). They included a number of genes encoding endosomal and lysosomal proteins, in agreement with uptake of suramin through endocytosis. The invariant surface glycoprotein ISG75 was identified as a likely receptor

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

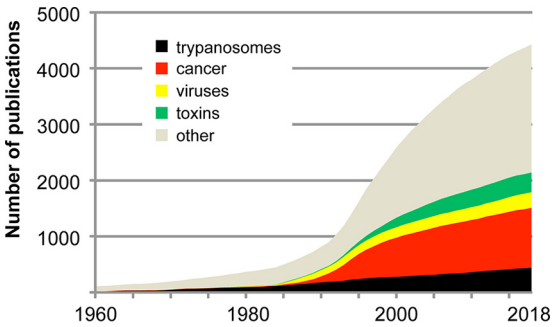


FIG 2 Publications on suramin in PubMed. Cumulative numbers are shown for papers on suramin and trypanosomes or trypanosomiasis (search term "trypanosom*"), cancer ("cancer OR tumor"), viruses ("virus OR viral OR hiv OR aids"), and toxins ("toxin OR venom"). Other papers on suramin are also shown. There is no saturation yet, and it is surprising that only a minority of the publications on suramin actually deal with trypanosomes.

of suramin, since knockdown of ISG75 in bloodstream form *T. brucei* decreased suramin binding and suramin susceptibility (153). ISG75 is a surface protein of unknown function whose abundance is controlled by ubiquitination (154). Thus, there appear to be (at least) two pathways for receptor-mediated endocytosis of suramin in *T. brucei* bloodstream forms: either directly, with ISG75 as the receptor, or after binding of suramin to LDL, together with the LDL receptor.

CONCLUSIONS

Suramin remains controversial. Is its polypharmacology a liability or an asset? Is it toxic or protective? Dated or timeless? Whatever the verdict on suramin, there is hardly another molecule with as many biological activities. The list of potential targets is indeed impressive, and the publication stream on suramin is not stagnating. The large majority of papers are not about trypanosomes or trypanosomiasis (Fig. 2). The list of potential targets has to be taken with a grain of salt, though, since the negative charges of suramin, and its promiscuity in protein binding, can cause all kinds of artifacts. Suramin can dissolve Matrigel (155), resulting in a false-positive signal in cell-based screening campaigns that use Matrigel for support, e.g., for inhibitors of angiogenesis (155). On the other hand, suramin's high affinity for albumin (156) may give false-negative results in cell-based tests that contain mammalian serum. However, in spite of the various confounders, a number of different drug-target interactions for suramin have been experimentally validated and are directly supported by crystal structures (Table 4).

Several routes of investigation of the bioactivities of suramin have culminated in clinical trials with healthy volunteers (i.e., phase I) or patients (i.e., phases II and III)

TABLE 4 Solved structures of suramin complexed to target proteins

PDB ID	Protein	Reference
6CE2	Myotoxin I from *Bothrops moojeni*	75
4YV5	Myotoxin II from *B. moojeni*	74
1Y4L	Myotoxin II from *Bothrops asper*	72
3BJW	Ecarpholin S from *Echis carinatus*	76
1RML	Acid fibroblast growth factor	182
NA[a]	Human epidermal growth factor (hEGF)	183
4X3U	CBX7 chromodomain	109
3BF6, 2H9T	Human thrombin	184
2NYR	Human sirtuin homologue 5	112
3PP7	*Leishmania mexicana* pyruvate kinase	101
3GAN	*Arabidopsis thaliana* At3g22680	NA
3UR0	Murine norovirus RNA-dependent RNA polymerase	105
4J4V	Pentameric bunyavirus nucleocapsid protein	185
4J4R	Hexameric bunyavirus nucleocapsid protein	185

[a]NA, not applicable.

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

(Table 2). However, to our knowledge, none of these trials was a striking success, and it is unclear whether suramin will ever find medical applications outside the field of parasitology. However, molecules that act similarly to suramin may be identified via target-based screening once the mode of action is understood—new molecules that are more specific and less toxic and possess better pharmacological properties than suramin. Thus, it will be important to dissect the polypharmacology of suramin at the molecular level. We hope that the compiled list of targets (Table 3) will serve this purpose.

ACKNOWLEDGMENTS

We are grateful to the Swiss National Science Foundation for financial support and to Alan Fairlamb for sharing insights into the possible molecular interactions of suramin.

REFERENCES

1. Wainwright M. 2010. Dyes, trypanosomiasis and DNA: a historical and critical review. Biotech Histochem 85:341–354. https://doi.org/10.3109/10520290903297528.
2. Brun R, Blum J, Chappuis F, Burri C. 2010. Human African trypanosomiasis. Lancet 375:148–159. https://doi.org/10.1016/S0140-6736(09)60829-1.
3. Burri C, Chappuis F, Brun R. 2014. Human African trypanosomiasis, p 606–691. *In* Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White N (ed), Manson's tropical diseases, 23rd ed. Saunders, Ltd., Philadelphia, PA.
4. Giordani F, Morrison LJ, Rowan TG, DE Koning HP, Barrett MP. 2016. The animal trypanosomiases and their chemotherapy: a review. Parasitology 143:1862–1889. https://doi.org/10.1017/S0031182016001268.
5. Bisaggio DFR, Adade CM, Souto-Padrón T. 2008. In vitro effects of suramin on Trypanosoma cruzi. Int J Antimicrob Agents 31:282–286. https://doi.org/10.1016/j.ijantimicag.2007.11.001.
6. Santos EC, Novaes RD, Cupertino MC, Bastos DSS, Klein RC, Silva EAM, Fietto JLR, Talvani A, Bahia MT, Oliveira LL. 2015. Concomitant benznidazole and suramin chemotherapy in mice infected with a virulent strain of Trypanosoma cruzi. Antimicrob Agents Chemother 59:5999–6006. https://doi.org/10.1128/AAC.00779-15.
7. Khanra S, Kumar YP, Dash J, Banerjee R. 2018. In vitro screening of known drugs identified by scaffold hopping techniques shows promising leishmanicidal activity for suramin and netilmicin. BMC Res Notes 11:319. https://doi.org/10.1186/s13104-018-3446-y.
8. Fleck SL, Birdsall B, Babon J, Dluzewski AR, Martin SR, Morgan WD, Angov E, Kettleborough CA, Feeney J, Blackman MJ, Holder AA. 2003. Suramin and suramin analogues inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite Plasmodium falciparum. J Biol Chem 278:47670–47677. https://doi.org/10.1074/jbc.M306603200.
9. Müller HM, Reckmann I, Hollingdale MR, Bujard H, Robson KJ, Crisanti A. 1993. Thrombospondin related anonymous protein (TRAP) of Plasmodium falciparum binds specifically to sulfated glycoconjugates and to HepG2 hepatoma cells suggesting a role for this molecule in sporozoite invasion of hepatocytes. EMBO J 12:2881–2889. https://doi.org/10.1002/j.1460-2075.1993.tb05950.x.
10. Hawking F. 1958. Chemotherapy of onchocerciasis. Trans R Soc Trop Med Hyg 52:109–111. https://doi.org/10.1016/0035-9203(58)90032-4.
11. Ashburn LL, Burch TA, Brady FJ. 1949. Pathologic effects of suramin, hetrazan and arsenamide on adult Onchocerca volvulus. Boletin Oficina Sanit Panam Pan Am Sanit Bur 28:1107–1117.
12. Burch TA, Ashburn LL. 1951. Experimental therapy of onchocerciasis with suramin and hetrazan; results of a three-year study. Am J Trop Med Hyg 31:617–623. https://doi.org/10.4269/ajtmh.1951.s1-31.617.
13. Babalola OE. 2011. Ocular onchocerciasis: current management and future prospects. Clin Ophthalmol 5:1479–1491. https://doi.org/10.2147/OPTH.S8372.
14. Coyne PE, Maxwell C. 1992. Suramin and therapy of onchocerciasis. Arch Dermatol 128:698. https://doi.org/10.1001/archderm.1992.01680150132023.
15. Voogd TE, Vansterkenburg EL, Wilting J, Janssen LH. 1993. Recent research on the biological activity of suramin. Pharmacol Rev 45:177–203.
16. Reiter B, Oram JD. 1962. Inhibition of streptococcal bacteriophage by suramin. Nature 193:651–652. https://doi.org/10.1038/193651a0.
17. Herrmann-Erlee MP, Wolff L. 1957. Inhibition of mumps virus reproduction by Congo red and suramine. Arch Int Pharmacodyn Ther 110:340–341.
18. De Clercq E. 1979. Suramin: a potent inhibitor of the reverse transcriptase of RNA tumor viruses. Cancer Lett 8:9–22. https://doi.org/10.1016/0304-3835(79)90017-x.
19. Mitsuya H, Popovic M, Yarchoan R, Matsushita S, Gallo RC, Broder S. 1984. Suramin protection of T cells in vitro against infectivity and cytopathic effect of HTLV-III. Science 226:172–174. https://doi.org/10.1126/science.6091268.
20. Kaplan LD, Wolfe PR, Volberding PA, Feorino P, Levy JA, Abrams DI, Kiprov D, Wong R, Kaufman L, Gottlieb MS. 1987. Lack of response to suramin in patients with AIDS and AIDS-related complex. Am J Med 82:615–620. https://doi.org/10.1016/0002-9343(87)90108-2.
21. Broder S, Yarchoan R, Collins JM, Lane HC, Markham PD, Klecker RW, Redfield RR, Mitsuya H, Hoth DF, Gelmann E. 1985. Effects of suramin on HTLV-III/LAV infection presenting as Kaposi's sarcoma or AIDS-related complex: clinical pharmacology and suppression of virus replication in vivo. Lancet ii:627–630. https://doi.org/10.1016/S0140-6736(85)90002-9.
22. Cheson BD, Levine AM, Mildvan D, Kaplan LD, Wolfe P, Rios A, Groopman JE, Gill P, Volberding PA, Poiesz BJ. 1987. Suramin therapy in AIDS and related disorders. Report of the US Suramin Working Group JAMA 258:1347–1351. https://doi.org/10.1001/jama.1987.03400100081025.
23. Yahi N, Sabatier JM, Nickel P, Mabrouk K, Gonzalez-Scarano F, Fantini J. 1994. Suramin inhibits binding of the V3 region of HIV-1 envelope glycoprotein gp120 to galactosylceramide, the receptor for HIV-1 gp120 on human colon epithelial cells. J Biol Chem 269:24349–24353.
24. Chen Y, Maguire T, Hileman RE, Fromm JR, Esko JD, Linhardt RJ, Marks RM. 1997. Dengue virus infectivity depends on envelope protein binding to target cell heparan sulfate. Nat Med 3:866–871. https://doi.org/10.1038/nm0897-866.
25. Aguilar JS, Rice M, Wagner EK. 1999. The polysulfonated compound suramin blocks adsorption and lateral diffusion of herpes simplex virus type-1 in Vero cells. Virology 258:141–151. https://doi.org/10.1006/viro.1999.9723.
26. Garson JA, Lubach D, Passas J, Whitby K, Grant PR. 1999. Suramin blocks hepatitis C binding to human hepatoma cells in vitro. J Med Virol 57:238–242. https://doi.org/10.1002/(SICI)1096-9071(199903)57:3<238::AID-JMV5>3.0.CO;2-G.
27. Alarcón B, Lacal JC, Fernández-Sousa JM, Carrasco L. 1984. Screening for new compounds with antiherpes activity. Antiviral Res 4:231–244. https://doi.org/10.1016/0166-3542(84)90029-9.
28. Offensperger WB, Offensperger S, Walter E, Blum HE, Gerok W. 1993. Suramin prevents duck hepatitis B virus infection in vivo. Antimicrob Agents Chemother 37:1539–1542. https://doi.org/10.1128/aac.37.7.1539.
29. Tsiquaye K, Zuckerman A. 1985. Suramin inhibits duck hepatitis B virus DNA polymerase activity. J Hepatol 1:663–669. https://doi.org/10.1016/s0168-8278(85)80009-x.
30. Tsiquaye KN, Collins P, Zuckerman AJ. 1986. Antiviral activity of the polybasic anion, suramin and acyclovir in Hepadna virus infection. J

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

Antimicrob Chemother 18(Suppl B):223–228. https://doi.org/10.1093/jac/18.supplement_b.223.
31. Loke RH, Anderson MG, Coleman JC, Tsiquaye KN, Zuckerman AJ, Murray-Lyon IM. 1987. Suramin treatment for chronic active hepatitis B—toxic and ineffective. J Med Virol 21:97–99. https://doi.org/10.1002/jmv.1890210113.
32. Wang Y, Qing J, Sun Y, Rao Z. 2014. Suramin inhibits EV71 infection. Antiviral Res 103:1–6. https://doi.org/10.1016/j.antiviral.2013.12.008.
33. Ren P, Zou G, Bailly B, Xu S, Zeng M, Chen X, Shen L, Zhang Y, Guillon P, Arenzana-Seisdedos F, Buchy P, Li J, von Itzstein M, Li Q, Altmeyer R. 2014. The approved pediatric drug suramin identified as a clinical candidate for the treatment of EV71 infection—suramin inhibits EV71 infection in vitro and in vivo. Emerg Microbes Infect 3:e62. https://doi.org/10.1038/emi.2014.60.
34. Ren P, Zheng Y, Wang W, Hong L, Delpeyroux F, Arenzana-Seisdedos F, Altmeyer R. 2017. Suramin interacts with the positively charged region surrounding the 5-fold axis of the EV-A71 capsid and inhibits multiple enterovirus A. Sci Rep 7:42902. https://doi.org/10.1038/srep42902.
35. Albulescu IC, van Hoolwerff M, Wolters LA, Bottaro E, Nastruzzi C, Yang SC, Tsay S-C, Hwu JR, Snijder EJ, van Hemert MJ. 2015. Suramin inhibits chikungunya virus replication through multiple mechanisms. Antiviral Res 121:39–46. https://doi.org/10.1016/j.antiviral.2015.06.013.
36. Ho Y-J, Wang Y-M, Lu J, Wu T-Y, Lin L-I, Kuo S-C, Lin C-C. 2015. Suramin inhibits chikungunya virus entry and transmission. PLoS One 10:e0133511. https://doi.org/10.1371/journal.pone.0133511.
37. Kuo S-C, Wang Y-M, Ho Y-J, Chang T-Y, Lai Z-Z, Tsui P-Y, Wu T-Y, Lin C-C. 2016. Suramin treatment reduces chikungunya pathogenesis in mice. Antiviral Res 134:89–96. https://doi.org/10.1016/j.antiviral.2016.07.025.
38. Henß L, Beck S, Weidner T, Biedenkopf N, Sliva K, Weber C, Becker S, Schnierle BS. 2016. Suramin is a potent inhibitor of Chikungunya and Ebola virus cell entry. Virol J 13:149. https://doi.org/10.1186/s12985-016-0607-2.
39. Tan CW, Sam I-C, Chong WL, Lee VS, Chan YF. 2017. Polysulfonate suramin inhibits Zika virus infection. Antiviral Res 143:186–194. https://doi.org/10.1016/j.antiviral.2017.04.017.
40. Williams WL. 1946. The effects of suramin (germanin), azo dyes, and vasodilators on mice with transplanted lymphosarcomas. AACR 6:344–353.
41. Osswald H, Youssef M. 1979. Suramin enhancement of the chemotherapeutic actions of cyclophosphamide or adriamycin of intramuscularly-implanted Ehrlich carcinoma. Cancer Lett 6:337–343. https://doi.org/10.1016/s0304-3835(79)80091-9.
42. Stein CA, LaRocca RV, Thomas R, McAtee N, Myers CE. 1989. Suramin: an anticancer drug with a unique mechanism of action. J Clin Oncol 7:499–508. https://doi.org/10.1200/JCO.1989.7.4.499.
43. Bowden CJ, Figg WD, Dawson NA, Sartor O, Bitton RJ, Weinberger MS, Headlee D, Reed E, Myers CE, Cooper MR. 1996. A phase I/II study of continuous infusion suramin in patients with hormone-refractory prostate cancer: toxicity and response. Cancer Chemother Pharmacol 39:1–8. https://doi.org/10.1007/s002800050531.
44. Rosen PJ, Mendoza EF, Landaw EM, Mondino B, Graves MC, McBride JH, Turcillo P, deKernion J, Belldegrun A. 1996. Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. J Clin Oncol 14:1626–1636. https://doi.org/10.1200/JCO.1996.14.5.1626.
45. Dawson NA, Figg WD, Cooper MR, Sartor O, Bergan RC, Senderowicz AM, Steinberg SM, Tompkins A, Weinberger B, Sausville EA, Reed E, Myers CE. 1997. Phase II trial of suramin, leuprolide, and flutamide in previously untreated metastatic prostate cancer. J Clin Oncol 15:1470–1477. https://doi.org/10.1200/JCO.1997.15.4.1470.
46. Hussain M, Fisher EI, Petrylak DP, O'Connor J, Wood DP, Small EJ, Eisenberger MA, Crawford ED. 2000. Androgen deprivation and four courses of fixed-schedule suramin treatment in patients with newly diagnosed metastatic prostate cancer: a Southwest Oncology Group study. J Clin Oncol 18:1043–1049. https://doi.org/10.1200/JCO.2000.18.5.1043.
47. Small EJ, Meyer M, Marshall ME, Reyno LM, Meyers FJ, Natale RB, Lenehan PF, Chen L, Slichenmyer WJ, Eisenberger M. 2000. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 18:1440–1450. https://doi.org/10.1200/JCO.2000.18.7.1440.
48. Calvo E, Cortés J, Rodríguez J, Sureda M, Beltrán C, Rebollo J, Martínez-Monge R, Berián JM, de Irala J, Brugarolas A. 2001. Fixed higher dose schedule of suramin plus hydrocortisone in patients with hormone refractory prostate carcinoma: a multicenter phase II study. Cancer 92:2435–2443. https://doi.org/10.1002/1097-0142(20011101)92:9<2435::aid-cncr1593>3.0.co;2-o.
49. Small EJ, Halabi S, Ratain MJ, Rosner G, Stadler W, Palchak D, Marshall E, Rago R, Hars V, Wilding G, Petrylak D, Vogelzang NJ. 2002. Randomized study of three different doses of suramin administered with a fixed dosing schedule in patients with advanced prostate cancer: results of intergroup 0159, cancer and leukemia group B 9480. J Clin Oncol 20:3369–3375. https://doi.org/10.1200/JCO.2002.10.022.
50. Vogelzang NJ, Karrison T, Stadler WM, Garcia J, Cohn H, Kugler J, Troeger T, Giannone L, Arrieta R, Ratain MJ, Vokes EE. 2004. A phase II trial of suramin monthly x 3 for hormone-refractory prostate carcinoma. Cancer 100:65–71. https://doi.org/10.1002/cncr.11867.
51. Safarinejad MR. 2005. Combination chemotherapy with docetaxel, estramustine and suramin for hormone refractory prostate cancer. Urol Oncol 23:93–101. https://doi.org/10.1016/j.urolonc.2004.10.003.
52. Mirza MR, Jakobsen E, Pfeiffer P, Lindebjerg-Clasen B, Bergh J, Rose C. 1997. Suramin in non-small cell lung cancer and advanced breast cancer. Two parallel phase II studies. Acta Oncol 36:171–174. https://doi.org/10.3109/02841869709109226.
53. Ord JJ, Streeter E, Jones A, Le Monnier K, Cranston D, Crew J, Joel SP, Rogers MA, Banks RE, Roberts ISD, Harris AL. 2005. Phase I trial of intravesical suramin in recurrent superficial transitional cell bladder carcinoma. Br J Cancer 92:2140–2147. https://doi.org/10.1038/sj.bjc.6602650.
54. Uchio EM, Linehan WM, Figg WD, Walther MM. 2003. A phase I study of intravesical suramin for the treatment of superficial transitional cell carcinoma of the bladder. J Urol 169:357–360. https://doi.org/10.1097/01.ju.0000032745.90528.dc.
55. Grossman SA, Phuphanich S, Lesser G, Rozental J, Grochow LB, Fisher J, Piantadosi S, New Approaches to Brain Tumor Therapy CNS Consortium. 2001. Toxicity, efficacy, and pharmacology of suramin in adults with recurrent high-grade gliomas. J Clin Oncol 19:3260–3266. https://doi.org/10.1200/JCO.2001.19.13.3260.
56. Laterra JJ, Grossman SA, Carson KA, Lesser GJ, Hochberg FH, Gilbert MR, NABTT CNS Consortium Study. 2004. Suramin and radiotherapy in newly diagnosed glioblastoma: phase 2 NABTT CNS Consortium study. Neuro Oncol 6:15–20. https://doi.org/10.1215/S1152851703000127.
57. Hosang M. 1985. Suramin binds to platelet-derived growth factor and inhibits its biological activity. J Cell Biochem 29:265–273. https://doi.org/10.1002/jcb.240290310.
58. Coffey RJ, Leof EB, Shipley GD, Moses HL. 1987. Suramin inhibition of growth factor receptor binding and mitogenicity in AKR-2B cells. J Cell Physiol 132:143–148. https://doi.org/10.1002/jcp.1041320120.
59. Pollak M, Richard M. 1990. Suramin blockade of insulinlike growth factor I-stimulated proliferation of human osteosarcoma cells. J Natl Cancer Inst 82:1349–1352. https://doi.org/10.1093/jnci/82.16.1349.
60. Spigelman Z, Dowers A, Kennedy S, DiSorbo D, O'Brien M, Barr R, McCaffrey R. 1987. Antiproliferative effects of suramin on lymphoid cells. Cancer Res 47:4694–4698.
61. Takano S, Gately S, Engelhard H, Tsanaclis AM, Brem S. 1994. Suramin inhibits glioma cell proliferation in vitro and in the brain. J Neurooncol 21:189–201. https://doi.org/10.1007/bf01063768.
62. Guo XJ, Fantini J, Roubin R, Marvaldi J, Rougon G. 1990. Evaluation of the effect of suramin on neural cell growth and N-CAM expression. Cancer Res 50:5164–5170.
63. Song S, Yu B, Wei Y, Wientjes MG, Au J-S. 2004. Low-dose suramin enhanced paclitaxel activity in chemotherapy-naive and paclitaxel-pretreated human breast xenograft tumors. Clin Cancer Res 10:6058–6065. https://doi.org/10.1158/1078-0432.CCR-04-0595.
64. Xin Y, Lyness G, Chen D, Song S, Wientjes MG, Au J-S. 2005. Low dose suramin as a chemosensitizer of bladder cancer to mitomycin C. J Urol 174:322–327. https://doi.org/10.1097/01.ju.0000161594.86931.ea.
65. Kosarek CE, Hu X, Couto CG, Kisseberth WC, Green EM, Au JLS, Wientjes MG. 2006. Phase I evaluation of low-dose suramin as chemosensitizer of doxorubicin in dogs with naturally occurring cancers. J Vet Intern Med 20:1172–1177. https://doi.org/10.1892/0891-6640(2006)20[1172:pieols]2.0.co;2.
66. Singla AK, Bondareva A, Jirik FR. 2014. Combined treatment with paclitaxel and suramin prevents the development of metastasis by inhibiting metastatic colonization of circulating tumor cells. Clin Exp Metastasis 31:705–714. https://doi.org/10.1007/s10585-014-9661-6.
67. Gan Y, Lu J, Yeung BZ, Cottage CT, Wientjes MG, Au J-S. 2015. Pharmacodynamics of telomerase inhibition and telomere shortening by

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

noncytotoxic suramin. AAPS J 17:268–276. https://doi.org/10.1208/s12248-014-9703-7.
68. Villalona-Calero MA, Wientjes MG, Otterson GA, Kanter S, Young D, Murgo AJ, Fischer B, DeHoff C, Chen D, Yeh T-K, Song S, Grever M, Au J-S. 2003. Phase I study of low-dose suramin as a chemosensitizer in patients with advanced non-small cell lung cancer. Clin Cancer Res 9:3303–3311. https://doi.org/10.1016/S0169-5002(03)92198-2.
69. Villalona-Calero MA, Otterson GA, Wientjes MG, Weber F, Bekaii-Saab T, Young D, Murgo AJ, Jensen R, Yeh T-K, Wei Y, Zhang Y, Eng C, Grever M, Au J-S. 2008. Noncytotoxic suramin as a chemosensitizer in patients with advanced non-small-cell lung cancer: a phase II study. Ann Oncol 19:1903–1909. https://doi.org/10.1093/annonc/mdn412.
70. Stocker K, Fischer H, Meier J. 1982. Thrombin-like snake venom proteinases. Toxicon 20:265–273. https://doi.org/10.1016/0041-0101(82)90225-2.
71. Monteiro RQ, Campana PT, Melo PA, Bianconi ML. 2004. Suramin interaction with human alpha-thrombin: inhibitory effects and binding studies. Int J Biochem Cell Biol 36:2077–2085. https://doi.org/10.1016/j.biocel.2004.03.007.
72. Murakami MT, Arruda EZ, Melo PA, Martinez AB, Calil-Eliás S, Tomaz MA, Lomonte B, Gutiérrez JM, Arni RK. 2005. Inhibition of myotoxic activity of Bothrops asper myotoxin II by the anti-trypanosomal drug suramin. J Mol Biol 350:416–426. https://doi.org/10.1016/j.jmb.2005.04.072.
73. Aragão EA, Vieira DS, Chioato L, Ferreira TL, Lourenzoni MR, Silva SR, Ward RJ. 2012. Characterization of suramin binding sites on the human group IIA secreted phospholipase A2 by site-directed mutagenesis and molecular dynamics simulation. Arch Biochem Biophys 519:17–22. https://doi.org/10.1016/j.abb.2012.01.002.
74. Salvador GHM, Dreyer TR, Cavalcante WLG, Matioli FF, Dos Santos JI, Velazquez-Campoy A, Gallacci M, Fontes M. 2015. Structural and functional evidence for membrane docking and disruption sites on phospholipase A2-like proteins revealed by complexation with the inhibitor suramin. Acta Crystallogr D Biol Crystallogr 71:2066–2078. https://doi.org/10.1107/S1399004715014443.
75. Salvador GHM, Dreyer TR, Gomes AAS, Cavalcante WLG, Dos Santos JI, Gandin CA, de Oliveira Neto M, Gallacci M, Fontes M. 2018. Structural and functional characterization of suramin-bound MjTX-I from Bothrops moojeni suggests a particular myotoxic mechanism. Sci Rep 8:10317. https://doi.org/10.1038/s41598-018-28584-7.
76. Zhou X, Tan T-C, Valiyaveettil S, Go ML, Kini RM, Velazquez-Campoy A, Sivaraman J. 2008. Structural characterization of myotoxic ecarpholin S from Echis carinatus venom. Biophys J 95:3366–3380. https://doi.org/10.1529/biophysj.107.117747.
77. El-Kik CZ, Fernandes FFA, Tomaz MA, Gaban GA, Fonseca TF, Calil-Elias S, Oliveira SDS, Silva CLM, Martinez AMB, Melo PA. 2013. Neutralization of Apis mellifera bee venom activities by suramin. Toxicon 67:55–62. https://doi.org/10.1016/j.toxicon.2013.02.007.
78. Arruda EZ, Silva NMV, Moraes RAM, Melo PA. 2002. Effect of suramin on myotoxicity of some crotalid snake venoms. Braz J Med Biol Res 35:723–726. https://doi.org/10.1590/s0100-879x2002000600013.
79. Fathi B, Amani F, Jami-Al-Ahmadi A, Zare A. 2010. Antagonistc effect of suramin against the venom of the Iranian snake Echis carinatus in mice. Iranian J Vet Sci Technol 2:19–15.
80. Anonymous. 2017. Snake-bite envenoming: a priority neglected tropical disease. Lancet 390:2.
81. Arnold C. 2016. Vipers, mambas and taipans: the escalating health crisis over snakebites. Nature 537:26–28. https://doi.org/10.1038/537026a.
82. den Hertog A, Nelemans A, Van den Akker J. 1989. The inhibitory action of suramin on the P2-purinoceptor response in smooth muscle cells of guinea-pig taenia caeci. Eur J Pharmacol 166:531–534. https://doi.org/10.1016/0014-2999(89)90370-1.
83. Kuruppu S, Chaisakul J, Smith AI, Hodgson WC. 2014. Inhibition of presynaptic neurotoxins in taipan venom by suramin. Neurotox Res 25:305–310. https://doi.org/10.1007/s12640-013-9426-z.
84. Grishin S, Shakirzyanova A, Giniatullin A, Afzalov R, Giniatullin R. 2005. Mechanisms of ATP action on motor nerve terminals at the frog neuromuscular junction. Eur J Neurosci 21:1271–1279. https://doi.org/10.1111/j.1460-9568.2005.03976.x.
85. Ong WY, Motin LG, Hansen MA, Dias LS, Ayrout C, Bennett MR, Balcar VJ. 1997. P2 purinoceptor blocker suramin antagonises NMDA receptors and protects against excitatory behaviour caused by NMDA receptor agonist (RS)-(tetrazol-5-yl)-glycine in rats. J Neurosci Res 49:627–638. https://doi.org/10.1002/(SICI)1097-4547(19970901)49:5<627::AID-JNR13>3.0.CO;2-S.
86. Kharlamov A, Jones SC, Kim DK. 2002. Suramin reduces infarct volume in a model of focal brain ischemia in rats. Exp Brain Res 147:353–359. https://doi.org/10.1007/s00221-002-1251-1.
87. Dupre TV, Doll MA, Shah PP, Sharp CN, Kiefer A, Scherzer MT, Saurabh K, Saforo D, Siow D, Casson L, Arteel GE, Jenson AB, Megyesi J, Schnellmann RG, Beverly LJ, Siskind LJ. 2016. Suramin protects from cisplatin-induced acute kidney injury. Am J Physiol Renal Physiol 310:F248–F258. https://doi.org/10.1152/ajprenal.00433.2015.
88. Doggrell SA. 2004. Suramin: potential in acute liver failure. Expert Opin Invest Drugs 13:1361–1363. https://doi.org/10.1517/13543784.13.10.1361.
89. Chi Y, Gao K, Zhang H, Takeda M, Yao J. 2014. Suppression of cell membrane permeability by suramin: involvement of its inhibitory actions on connexin 43 hemichannels. Br J Pharmacol 171:3448–3462. https://doi.org/10.1111/bph.12693.
90. Bourguignon T, Benoist L, Chadet S, Miquelestorena-Standley E, Fromont G, Ivanes F, Angoulvant D. 2019. Stimulation of murine P2Y11-like purinoreceptor protects against hypoxia/reoxygenation injury and decreases heart graft rejection lesions. J Thorac Cardiovasc Surg 158:780–790.e1. https://doi.org/10.1016/j.jtcvs.2018.12.014.
91. Sahu D, Saroha A, Roy S, Das S, Srivastava PS, Das HR. 2012. Suramin ameliorates collagen induced arthritis. Int Immunopharmacol 12:288–293. https://doi.org/10.1016/j.intimp.2011.12.003.
92. Zou CJ, Onaka TO, Yagi K. 1998. Effects of suramin on neuroendocrine and behavioural responses to conditioned fear stimuli. Neuroreport 9:997–999. https://doi.org/10.1097/00001756-199804200-00008.
93. Denkinger M, Shive CL, Pantenburg B, Forsthuber TG. 2004. Suramin has adjuvant properties and promotes expansion of antigen-specific Th1 and Th2 cells in vivo. Int Immunopharmacol 4:15–24. https://doi.org/10.1016/j.intimp.2003.09.004.
94. Dunn PM, Blakeley AG. 1988. Suramin: a reversible P2-purinoceptor antagonist in the mouse vas deferens. Br J Pharmacol 93:243–245. https://doi.org/10.1111/j.1476-5381.1988.tb11427.x.
95. Bernardes CF, Fagian MM, Meyer-Fernandes JR, Castilho RF, Vercesi AE. 2001. Suramin inhibits respiration and induces membrane permeability transition in isolated rat liver mitochondria. Toxicology 169:17–23. https://doi.org/10.1016/s0300-483x(01)00477-2.
96. Naviaux RK, Zolkipli Z, Wang L, Nakayama T, Naviaux JC, Le TP, Schuchbauer MA, Rogac M, Tang Q, Dugan LL, Powell SB. 2013. Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model. PLoS One 8:e57380. https://doi.org/10.1371/journal.pone.0057380.
97. Naviaux JC, Schuchbauer MA, Li K, Wang L, Risbrough VB, Powell SB, Naviaux RK. 2014. Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy. Transl Psychiatry 4:e400. https://doi.org/10.1038/tp.2014.33.
98. Naviaux RK, Curtis B, Li K, Naviaux JC, Bright AT, Reiner GE, Westerfield M, Goh S, Alaynick WA, Wang L, Capparelli EV, Adams C, Sun J, Jain S, He F, Arellano DA, Mash LE, Chukoskie L, Lincoln A, Townsend J. 2017. Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial. Ann Clin Transl Neurol 4:491–505. https://doi.org/10.1002/acn3.424.
99. Town BW, Wills ED, Wilson EJ, Wormall A. 1950. Studies on suramin; the action of the drug on enzymes and some other proteins. General considerations. Biochem J 47:149–158. https://doi.org/10.1042/bj0470149.
100. Willson M, Callens M, Kuntz DA, Perié J, Opperdoes FR. 1993. Synthesis and activity of inhibitors highly specific for the glycolytic enzymes from Trypanosoma brucei. Mol Biochem Parasitol 59:201–210. https://doi.org/10.1016/0166-6851(93)90218-m.
101. Morgan HP, McNae IW, Nowicki MW, Zhong W, Michels PAM, Auld DS, Fothergill-Gilmore LA, Walkinshaw MD. 2011. The trypanocidal drug suramin and other trypan blue mimetics are inhibitors of pyruvate kinases and bind to the adenosine site. J Biol Chem 286:31232–31240. https://doi.org/10.1074/jbc.M110.212613.
102. Stoppani AO, Brignone JA. 1957. Inhibition of succinic dehydrogenase by polysulfonated compounds. Arch Biochem Biophys 68:432–451. https://doi.org/10.1016/0003-9861(57)90375-2.
103. Ono K, Nakane H, Fukushima M. 1988. Differential inhibition of various deoxyribonucleic and ribonucleic acid polymerases by suramin. Eur J Biochem 172:349–353. https://doi.org/10.1111/j.1432-1033.1988.tb13893.x.
104. Jindal HK, Anderson CW, Davis RG, Vishwanatha JK. 1990. Suramin affects DNA synthesis in HeLa cells by inhibition of DNA polymerases. Cancer Res 50:7754–7757.
105. Mastrangelo E, Pezzullo M, Tarantino D, Petazzi R, Germani F, Kramer D, Robel I, Rohayem J, Bolognesi M, Milani M. 2012. Structure-based

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

inhibition of norovirus RNA-dependent RNA polymerases. J Mol Biol 419:198–210. https://doi.org/10.1016/j.jmb.2012.03.008.
106. Waring MJ. 1965. The effects of antimicrobial agents on ribonucleic acid polymerase. Mol Pharmacol 1:1–13.
107. Basavannacharya C, Vasudevan SG. 2014. Suramin inhibits helicase activity of NS3 protein of dengue virus in a fluorescence-based high throughput assay format. Biochem Biophys Res Commun 453:539–544. https://doi.org/10.1016/j.bbrc.2014.09.113.
108. Bojanowski K, Lelievre S, Markovits J, Couprie J, Jacquemin-Sablon A, Larsen AK. 1992. Suramin is an inhibitor of DNA topoisomerase II in vitro and in Chinese hamster fibrosarcoma cells. Proc Natl Acad Sci U S A 89:3025–3029. https://doi.org/10.1073/pnas.89.7.3025.
109. Ren C, Morohashi K, Plotnikov AN, Jakoncic J, Smith SG, Li J, Zeng L, Rodriguez Y, Stojanoff V, Walsh M, Zhou M-M. 2015. Small-molecule modulators of methyl-lysine binding for the CBX7 chromodomain. Chem Biol 22:161–168. https://doi.org/10.1016/j.chembiol.2014.11.021.
110. Feng Y, Li M, Wang B, Zheng YG. 2010. Discovery and mechanistic study of a class of protein arginine methylation inhibitors. J Med Chem 53:6028–6039. https://doi.org/10.1021/jm100416n.
111. Trapp J, Meier R, Hongwiset D, Kassack MU, Sippl W, Jung M. 2007. Structure-activity studies on suramin analogues as inhibitors of NAD+-dependent histone deacetylases (sirtuins). ChemMedChem 2:1419–1431. https://doi.org/10.1002/cmdc.200700003.
112. Schuetz A, Min J, Antoshenko T, Wang C-L, Allali-Hassani A, Dong A, Loppnau P, Vedadi M, Bochkarev A, Sternglanz R, Plotnikov AN. 2007. Structural basis of inhibition of the human NAD+-dependent deacetylase SIRT5 by suramin. Structure 15:377–389. https://doi.org/10.1016/j.str.2007.02.002.
113. Hosoi Y, Matsumoto Y, Tomita M, Enomoto A, Morita A, Sakai K, Umeda N, Zhao H-J, Nakagawa K, Ono T, Suzuki N. 2002. Phosphorothioate oligonucleotides, suramin and heparin inhibit DNA-dependent protein kinase activity. Br J Cancer 86:1143–1149. https://doi.org/10.1038/sj.bjc.6600191.
114. Hensey CE, Boscoboinik D, Azzi A. 1989. Suramin, an anti-cancer drug, inhibits protein kinase C and induces differentiation in neuroblastoma cell clone NB2A. FEBS Lett 258:156–158. https://doi.org/10.1016/0014-5793(89)81639-4.
115. Zhang YL, Keng YF, Zhao Y, Wu L, Zhang ZY. 1998. Suramin is an active site-directed, reversible, and tight-binding inhibitor of protein-tyrosine phosphatases. J Biol Chem 273:12281–12287. https://doi.org/10.1074/jbc.273.20.12281.
116. Lominski I, Gray S. 1961. Inhibition of lysozyme by Suramin. Nature 192:683. https://doi.org/10.1038/192683a0.
117. Vicik R, Hoerr V, Glaser M, Schultheis M, Hansell E, McKerrow JH, Holzgrabe U, Caffrey CR, Ponte-Sucre A, Moll H, Stich A, Schirmeister T. 2006. Aziridine-2,3-dicarboxylate inhibitors targeting the major cysteine protease of Trypanosoma brucei as lead trypanocidal agents. Bioorg Med Chem Lett 16:2753–2757. https://doi.org/10.1016/j.bmcl.2006.02.026.
118. Cadène M, Duranton J, North A, Si-Tahar M, Chignard M, Bieth JG. 1997. Inhibition of neutrophil serine proteinases by suramin. J Biol Chem 272:9950–9955. https://doi.org/10.1074/jbc.272.15.9950.
119. Eisen V, Loveday C. 1973. Effects of suramin on complement, blood clotting, fibrinolysis and kinin formation. Br J Pharmacol 49:678–687. https://doi.org/10.1111/j.1476-5381.1973.tb08544.x.
120. Eichhorst ST, Krueger A, Müerköster S, Fas SC, Golks A, Gruetzner U, Schubert L, Opelz C, Bilzer M, Gerbes AL, Krammer PH. 2004. Suramin inhibits death receptor-induced apoptosis in vitro and fulminant apoptotic liver damage in mice. Nat Med 10:602–609. https://doi.org/10.1038/nm1049.
121. Tayel A, Ebrahim MA, Ibrahim AS, El-Gayar AM, Al-Gayyar MM. 2014. Cytotoxic effects of suramin against HepG2 cells through activation of intrinsic apoptotic pathway. J BUON 19:1048–1054.
122. Fortes PA, Ellory JC, Lew VL. 1973. Suramin: a potent ATPase inhibitor which acts on the inside surface of the sodium pump. Biochim Biophys Acta 318:262–272. https://doi.org/10.1016/0005-2736(73)90119-3.
123. Demenis MA, Furriel RPM, Leone FA. 2003. Characterization of an ectonucleoside triphosphate diphosphohydrolase 1 activity in alkaline phosphatase-depleted rat osseous plate membranes: possible functional involvement in the calcification process. Biochim Biophys Acta 1646:216–225. https://doi.org/10.1016/S1570-9639(03)00021-9.
124. Magalhães L, de Oliveira AHC, de Souza Vasconcellos R, Mariotini-Moura C, de Cássia Firmino R, Fietto JLR, Cardoso CL. 2016. Label-free assay based on immobilized capillary enzyme reactor of Leishmania infantum nucleoside triphosphate diphosphohydrolase (LicNTPDase-2-ICER-LC/UV). J Chromatogr B Analyt Technol Biomed Life Sci 1008:98–107. https://doi.org/10.1016/j.jchromb.2015.11.028.
125. Luo H, Wood K, Shi F-D, Gao F, Chang Y. 2018. Suramin is a novel competitive antagonist selective to $\alpha1\beta2\gamma2$ GABAA over $\rho1$ GABAC receptors. Neuropharmacology 141:148–157. https://doi.org/10.1016/j.neuropharm.2018.08.036.
126. Nakazawa K, Inoue K, Ito K, Koizumi S, Inoue K. 1995. Inhibition by suramin and reactive blue 2 of GABA and glutamate receptor channels in rat hippocampal neurons. Naunyn Schmiedebergs Arch Pharmacol 351:202–208. https://doi.org/10.1007/bf00169334.
127. Chung W-C, Kermode JC. 2005. Suramin disrupts receptor-G protein coupling by blocking association of G protein alpha and betagamma subunits. J Pharmacol Exp Ther 313:191–198. https://doi.org/10.1124/jpet.104.078311.
128. El-Ajouz S, Ray D, Allsopp RC, Evans RJ. 2012. Molecular basis of selective antagonism of the P2X1 receptor for ATP by NF449 and suramin: contribution of basic amino acids in the cysteine-rich loop. Br J Pharmacol 165:390–400. https://doi.org/10.1111/j.1476-5381.2011.01534.x.
129. Stevis PE, Deecher DC, Lopez FJ, Frail DE. 1999. Pharmacological characterization of soluble human FSH receptor extracellular domain: facilitated secretion by coexpression with FSH. Endocrine 10:153–160. https://doi.org/10.1385/ENDO:10:2:153.
130. La Rocca RV, Stein CA, Danesi R, Cooper MR, Uhrich M, Myers CE. 1991. A pilot study of suramin in the treatment of metastatic renal cell carcinoma. Cancer 67:1509–1513. https://doi.org/10.1002/1097-0142(19910315)67:6<1509::aid-cncr2820670608>3.0.co;2-f.
131. Fong JS, Good RA. 1972. Suramin—a potent reversible and competitive inhibitor of complement systems. Clin Exp Immunol 10:127–138.
132. Tsiftsoglou SA, Sim RB. 2004. Human complement factor I does not require cofactors for cleavage of synthetic substrates. J Immunol 173:367–375. https://doi.org/10.4049/jimmunol.173.1.367.
133. Tsiftsoglou SA, Willis AC, Li P, Chen X, Mitchell DA, Rao Z, Sim RB. 2005. The catalytically active serine protease domain of human complement factor I. Biochemistry 44:6239–6249. https://doi.org/10.1021/bi047680t.
134. Nunziante M, Kehler C, Maas E, Kassack MU, Groschup M, Schätzl HM. 2005. Charged bipolar suramin derivatives induce aggregation of the prion protein at the cell surface and inhibit PrPSc replication. J Cell Sci 118:4959–4973. https://doi.org/10.1242/jcs.02609.
135. Shukla SJ, Sakamuru S, Huang R, Moeller TA, Shinn P, Vanleer D, Auld DS, Austin CP, Xia M. 2011. Identification of clinically used drugs that activate pregnane X receptors. Drug Metab Dispos 39:151–159. https://doi.org/10.1124/dmd.110.035105.
136. Klinger M, Freissmuth M, Nickel P, Stäbler-Schwarzbart M, Kassack M, Suko J, Hohenegger M. 1999. Suramin and suramin analogs activate skeletal muscle ryanodine receptor via a calmodulin binding site. Mol Pharmacol 55:462–472.
137. Wierenga RK, Swinkels B, Michels PA, Osinga K, Misset O, Van Beeumen J, Gibson WC, Postma JP, Borst P, Opperdoes FR. 1987. Common elements on the surface of glycolytic enzymes from Trypanosoma brucei may serve as topogenic signals for import into glycosomes. EMBO J 6:215–221. https://doi.org/10.1002/j.1460-2075.1987.tb04741.x.
138. Fairlamb AH, Bowman IB. 1980. Uptake of the trypanocidal drug suramin by bloodstream forms of Trypanosoma brucei and its effect on respiration and growth rate in vivo. Mol Biochem Parasitol 1:315–333. https://doi.org/10.1016/0166-6851(80)90050-x.
139. Opperdoes FR, Borst P. 1977. Localization of nine glycolytic enzymes in a microbody-like organelle in Trypanosoma brucei: the glycosome. FEBS Lett 80:360–364. https://doi.org/10.1016/0014-5793(77)80476-6.
140. Wang CC. 1995. Molecular mechanisms and therapeutic approaches to the treatment of African trypanosomiasis. Annu Rev Pharmacol Toxicol 35:93–127. https://doi.org/10.1146/annurev.pa.35.040195.000521.
141. Fairlamb AH, Bowman IB. 1977. Trypanosoma brucei: suramin and other trypanocidal compounds' effects on sn-glycerol-3-phosphate oxidase. Exp Parasitol 43:353–361. https://doi.org/10.1016/0014-4894(77)90040-6.
142. Fairlamb A. 1975. A study of glycerophosphate oxidase in Trypanosoma brucei. PhD thesis. University of Edinburgh, Edinburgh, United Kingdom.
143. Morty RE, Troeberg L, Pike RN, Jones R, Nickel P, Lonsdale-Eccles JD, Coetzer TH. 1998. A trypanosome oligopeptidase as a target for the trypanocidal agents pentamidine, diminazene and suramin. FEBS Lett 433:251–256. https://doi.org/10.1016/s0014-5793(98)00914-4.
144. Zimmermann S, Hall L, Riley S, Sørensen J, Amaro RE, Schnaufer A.

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

2016. A novel high-throughput activity assay for the Trypanosoma brucei editosome enzyme REL1 and other RNA ligases. Nucleic Acids Res 44:e24. https://doi.org/10.1093/nar/gkv938.
145. Roveri OA, Franke de Cazzulo BM, Cazzulo JJ. 1982. Inhibition by suramin of oxidative phosphorylation in Crithidia fasciculata. Comp Biochem Physiol B 71:611–616. https://doi.org/10.1016/0305-0491(82)90470-9.
146. Thomas JA, Baker N, Hutchinson S, Dominicus C, Trenaman A, Glover L, Alsford S, Horn D. 2018. Insights into antitrypanosomal drug mode-of-action from cytology-based profiling. PLoS Negl Trop Dis 12:e0006980. https://doi.org/10.1371/journal.pntd.0006980.
147. Gagliardi AR, Taylor MF, Collins DC. 1998. Uptake of suramin by human microvascular endothelial cells. Cancer Lett 125:97–102. https://doi.org/10.1016/s0304-3835(97)00496-5.
148. Baghdiguian S, Boudier JL, Boudier JA, Fantini J. 1996. Intracellular localisation of suramin, an anticancer drug, in human colon adenocarcinoma cells: a study by quantitative autoradiography. Eur J Cancer 32A:525–532. https://doi.org/10.1016/0959-8049(95)00588-9.
149. Vansterkenburg EL, Coppens I, Wilting J, Bos OJ, Fischer MJ, Janssen LH, Opperdoes FR. 1993. The uptake of the trypanocidal drug suramin in combination with low-density lipoproteins by Trypanosoma brucei and its possible mode of action. Acta Trop 54:237–250. https://doi.org/10.1016/0001-706x(93)90096-t.
150. Sanderson L, Khan A, Thomas S. 2007. Distribution of suramin, an antitrypanosomal drug, across the blood-brain and blood-cerebrospinal fluid interfaces in wild-type and P-glycoprotein transporter-deficient mice. Antimicrob Agents Chemother 51:3136–3146. https://doi.org/10.1128/AAC.00372-07.
151. Coppens I, Opperdoes FR, Courtoy PJ, Baudhuin P. 1987. Receptor-mediated endocytosis in the bloodstream form of Trypanosoma brucei. J Protozool 34:465–473. https://doi.org/10.1111/j.1550-7408.1987.tb03216.x.
152. Pal A, Hall BS, Field MC. 2002. Evidence for a non-LDL-mediated entry route for the trypanocidal drug suramin in Trypanosoma brucei. Mol Biochem Parasitol 122:217–221. https://doi.org/10.1016/s0166-6851(02)00096-8.
153. Alsford S, Eckert S, Baker N, Glover L, Sanchez-Flores A, Leung KF, Turner DJ, Field MC, Berriman M, Horn D. 2012. High-throughput decoding of antitrypanosomal drug efficacy and resistance. Nature 482:232–236. https://doi.org/10.1038/nature10771.
154. Zoltner M, Leung KF, Alsford S, Horn D, Field MC. 2015. Modulation of the surface proteome through multiple ubiquitylation pathways in African trypanosomes. PLoS Pathog 11:e1005236. https://doi.org/10.1371/journal.ppat.1005236.
155. Prigozhina NL, Heisel AJ, Seldeen JR, Cosford NDP, Price JH. 2013. Amphiphilic suramin dissolves matrigel, causing an "inhibition" artefact within in vitro angiogenesis assays. Int J Exp Pathol 94:412–417. https://doi.org/10.1111/iep.12043.
156. Vansterkenburg EL, Wilting J, Janssen LH. 1989. Influence of pH on the binding of suramin to human serum albumin. Biochem Pharmacol 38:3029–3035. https://doi.org/10.1016/0006-2952(89)90011-7.
157. Dias DA, de Barros Penteado B, Dos Santos LD, Dos Santos PM, Arruda CCP, Schetinger MRC, Leal DBR, Dos Santos Jaques JA. 2017. Characterization of ectonucleoside triphosphate diphosphohydrolase (E-NTPDase; EC 3.6.1.5) activity in mouse peritoneal cavity cells. Cell Biochem Funct 35:358–363. https://doi.org/10.1002/cbf.3281.
158. Oses JP, Cardoso CM, Germano RA, Kirst IB, Rücker B, Fürstenau CR, Wink MR, Bonan CD, Battastini AMO, Sarkis J. 2004. Soluble NTPDase: an additional system of nucleotide hydrolysis in rat blood serum. Life Sci 74:3275–3284. https://doi.org/10.1016/j.lfs.2003.11.020.
159. Vasconcellos RDS, Mariotini-Moura C, Gomes RS, Serafim TD, Firmino RDC, Silva E, Bastos M, de Castro FF, de Oliveira CM, Borges-Pereira L, de Souza ACA, de Souza RF, Gómez GAT, Pinheiro ADC, Maciel TEF, Silva-Júnior A, Bressan GC, Almeida MR, Baqui MMA, Afonso LCC, Fietto J. 2014. Leishmania infantum ecto-nucleoside triphosphate diphosphohydrolase-2 is an apyrase involved in macrophage infection and expressed in infected dogs. PLoS Negl Trop Dis 8:e3309. https://doi.org/10.1371/journal.pntd.0003309.
160. Santos RF, Pôssa MAS, Bastos MS, Guedes PMM, Almeida MR, Demarco R, Verjovski-Almeida S, Bahia MT, Fietto J. 2009. Influence of ecto-nucleoside triphosphate diphosphohydrolase activity on Trypanosoma cruzi infectivity and virulence. PLoS Negl Trop Dis 3:e387. https://doi.org/10.1371/journal.pntd.0000387.
161. Iqbal J, Lévesque SA, Sévigny J, Müller CE. 2008. A highly sensitive CE-UV method with dynamic coating of silica-fused capillaries for monitoring of nucleotide pyrophosphatase/phosphodiesterase reactions. Electrophoresis 29:3685–3693. https://doi.org/10.1002/elps.200800013.
162. Andréola ML, Tharaud D, Litvak S, Tarrago-Litvak L. 1993. The ribonuclease H activity of HIV-1 reverse transcriptase: further biochemical characterization and search of inhibitors. Biochimie 75:127–134. https://doi.org/10.1016/0300-9084(93)90034-p.
163. Mukherjee S, Hanson AM, Shadrick WR, Ndjomou J, Sweeney NL, Hernandez JJ, Bartczak D, Li K, Frankowski KJ, Heck JA, Arnold LA, Schoenen FJ, Frick DN. 2012. Identification and analysis of hepatitis C virus NS3 helicase inhibitors using nucleic acid binding assays. Nucleic Acids Res 40:8607–8621. https://doi.org/10.1093/nar/gks623.
164. Marchand C, Lea WA, Jadhav A, Dexheimer TS, Austin CP, Inglese J, Pommier Y, Simeonov A. 2009. Identification of phosphotyrosine mimetic inhibitors of human tyrosyl-DNA phosphodiesterase I by a novel AlphaScreen high-throughput assay. Mol Cancer Ther 8:240–248. https://doi.org/10.1158/1535-7163.MCT-08-0878.
165. Kakuguchi W, Nomura T, Kitamura T, Otsuguro S, Matsushita K, Sakaitani M, Maenaka K, Tei K. 2018. Suramin, screened from an approved drug library, inhibits HuR functions and attenuates malignant phenotype of oral cancer cells. Cancer Med 7:6269–6280. https://doi.org/10.1002/cam4.1877.
166. Paulson CN, John K, Baxley RM, Kurniawan F, Orellana K, Francis R, Sobeck A, Eichman BF, Chazin WJ, Aihara H, Georg GI, Hawkinson JE, Bielinsky A-K. 2019. The anti-parasitic agent suramin and several of its analogues are inhibitors of the DNA binding protein Mcm10. Open Biol 9:190117. https://doi.org/10.1098/rsob.190117.
167. Horiuchi KY, Eason MM, Ferry JJ, Planck JL, Walsh CP, Smith RF, Howitz KT, Ma H. 2013. Assay development for histone methyltransferases. Assay Drug Dev Technol 11:227–236. https://doi.org/10.1089/adt.2012.480.
168. Peinado RDS, Olivier DS, Eberle RJ, de Moraes FR, Amaral MS, Arni RK, Coronado MA. 2019. Binding studies of a putative C. pseudotuberculosis target protein from vitamin B12 metabolism. Sci Rep 9:6350. https://doi.org/10.1038/s41598-019-42935-y.
169. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang L-L, Scherer B, Sinclair DA. 2003. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature 425:191–196. https://doi.org/10.1038/nature01960.
170. Trueblood KE, Mohr S, Dubyak GR. 2011. Purinergic regulation of high-glucose-induced caspase-1 activation in the rat retinal Müller cell line rMC-1. Am J Physiol Cell Physiol 301:C1213–C1223. https://doi.org/10.1152/ajpcell.00265.2011.
171. Stark S, Schuller A, Sifringer M, Gerstner B, Brehmer F, Weber S, Altmann R, Obladen M, Buhrer C, Felderhoff-Mueser U. 2008. Suramin induces and enhances apoptosis in a model of hyperoxia-induced oligodendrocyte injury. Neurotox Res 13:197–207. https://doi.org/10.1007/bf03033503.
172. Marques AF, Esser D, Rosenthal PJ, Kassack MU, Lima L. 2013. Falcipain-2 inhibition by suramin and suramin analogues. Bioorg Med Chem 21:3667–3673. https://doi.org/10.1016/j.bmc.2013.04.047.
173. Beiler JM, Martin GJ. 1948. Inhibition of hyaluronidase action by derivatives of hesperidin. J Biol Chem 174:31–35.
174. Constantopoulos G, Rees S, Cragg BG, Barranger JA, Brady RO. 1980. Experimental animal model for mucopolysaccharidosis: suramin-induced glycosaminoglycan and sphingolipid accumulation in the rat. Proc Natl Acad Sci U S A 77:3700–3704. https://doi.org/10.1073/pnas.77.6.3700.
175. Bachmann A, Russ U, Quast U. 1999. Potent inhibition of the CFTR chloride channel by suramin. Naunyn Schmiedebergs Arch Pharmacol 360:473–476. https://doi.org/10.1007/s002109900096.
176. Peoples RW, Li C. 1998. Inhibition of NMDA-gated ion channels by the P2 purinoceptor antagonists suramin and reactive blue 2 in mouse hippocampal neurones. Br J Pharmacol 124:400–408. https://doi.org/10.1038/sj.bjp.0701842.
177. Sharma A, Yogavel M, Sharma A. 2016. Structural and functional attributes of malaria parasite diadenosine tetraphosphate hydrolase. Sci Rep 6:19981. https://doi.org/10.1038/srep19981.
178. Vieira DS, Aragão EA, Lourenzoni MR, Ward RJ. 2009. Mapping of suramin binding sites on the group IIA human secreted phospholipase A2. Bioorg Chem 37:41–45. https://doi.org/10.1016/j.bioorg.2009.01.002.
179. Quemé-Peña M, Juhász T, Mihály J, Cs Szigyártó I, Horváti K, Bősze S,

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.

Henczkó J, Pályi B, Németh C, Varga Z, Zsila F, Beke-Somfai T. 2019. Manipulating active structure and function of cationic antimicrobial peptide CM15 with the polysulfonated drug suramin: a step closer to in vivo complexity. Chembiochem 20:1578–1590. https://doi.org/10.1002/cbic.201800801.

180. Abdeen S, Salim N, Mammadova N, Summers CM, Goldsmith-Pestana K, McMahon-Pratt D, Schultz PG, Horwich AL, Chapman E, Johnson SM. 2016. Targeting the HSP60/10 chaperonin systems of Trypanosoma brucei as a strategy for treating African sleeping sickness. Bioorg Med Chem Lett 26:5247–5253. https://doi.org/10.1016/j.bmcl.2016.09.051.
181. Stevens M, Abdeen S, Salim N, Ray A-M, Washburn A, Chitre S, Sivinski J, Park Y, Hoang QQ, Chapman E, Johnson SM. 2019. HSP60/10 chaperonin systems are inhibited by a variety of approved drugs, natural products, and known bioactive molecules. Bioorg Med Chem Lett 29:1106–1112. https://doi.org/10.1016/j.bmcl.2019.02.028.
182. Lozano RM, Jiménez M, Santoro J, Rico M, Giménez-Gallego G. 1998. Solution structure of acidic fibroblast growth factor bound to 1,3,6-naphthalenetrisulfonate: a minimal model for the anti-tumoral action of suramins and suradistas. J Mol Biol 281:899–915. https://doi.org/10.1006/jmbi.1998.1977.
183. Huang H-W, Mohan SK, Yu C. 2010. The NMR solution structure of human epidermal growth factor (hEGF) at physiological pH and its interactions with suramin. Biochem Biophys Res Commun 402:705–710. https://doi.org/10.1016/j.bbrc.2010.10.089.
184. Lima L, Becker CF, Giesel GM, Marques AF, Cargnelutti MT, de Oliveira Neto M, Monteiro RQ, Verli H, Polikarpov I. 2009. Structural and thermodynamic analysis of thrombin:suramin interaction in solution and crystal phases. Biochim Biophys Acta 1794:873–881. https://doi.org/10.1016/j.bbapap.2009.03.011.
185. Jiao L, Ouyang S, Liang M, Niu F, Shaw N, Wu W, Ding W, Jin C, Peng Y, Zhu Y, Zhang F, Wang T, Li C, Zuo X, Luan C-H, Li D, Liu Z-J. 2013. Structure of severe fever with thrombocytopenia syndrome virus nucleocapsid protein in complex with suramin reveals therapeutic potential. J Virol 87:6829–6839. https://doi.org/10.1128/JVI.00672-13.
186. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 46:3–26.
187. Wang Y, Cheng T, Bryant SH. 2017. PubChem BioAssay: a decade's development toward open high-throughput screening data sharing. SLAS Discov 22:655–666. https://doi.org/10.1177/2472555216685069.

Downloaded from https://journals.asm.org/journal/aac on 05 July 2021 by 23.168.144.163.