Table 1.3.4.3. *Protein structures of important human pathogenic protozoa, fungi and helminths*

(*a*) Protozoa

Organism	Disease	Protein structures solved	Reference
Acanthamoeba sp.	Opportunistic meningoencephalitis, corneal ulcers	Actophorin	[1]
		Profilin	[2]
Cryptosporidium parvum	Cryptosporidiosis	None	
Entamoeba histolytica	Amoebic dysentery, liver abscesses	None	
Giardia lamblia	Giardiasis	None	
Leishmania sp.	Leishmaniasis	Adenine phosphoribosyltransferase	[3]
		Dihydrofolate reductase-thymidylate synthase	[4]
		Glyceraldehyde-3-phosphate dehydrogenase	[5]
		Leishmanolysin	[6]
		Nucleoside hydrolase	[7]
		Pyruvate kinase	[8]
		Triosephosphate isomerase	[9]
Plasmodium sp.	Malaria	Fructose-1,6-bisphosphate aldolase	[10]
		Lactate dehydrogenase	[11]
		MSP1	[12]
		Plasmepsin II	[13]
		Purine phosphoribosyltransferase	[14]
		Triosephosphate isomerase	[15]
Pneumocystis carinii	Pneumonia	Dihydrofolate reductase	[16]
Toxoplasma gondii	Toxoplasmosis	HGXPRTase	[17]
		UPRTase	[18]
Trichomonas vaginalis	Trichomoniasis	None	
Trypanosoma brucei	Sleeping sickness	Fructose-1,6-bisphosphate aldolase	[19]
		Glyceraldehyde-3-phosphate dehydrogenase	[20]
		6-Phosphogluconate dehydrogenase	[21]
		Phosphoglycerate kinase	[22]
		Triosephosphate isomerase	[23]
		VSG	[24]
Trypanosoma cruzi	Chagas' disease	Cruzain (cruzipain)	[25]
		Glyceraldehyde-3-phosphate dehydrogenase	[26]
		Hypoxanthine phosphoribosyltransferase	[27]
		Triosephosphate isomerase	[28]
		Trypanothione reductase	[29]
		Tyrosine aminotransferase	[30]

(*b*) Fungi

Organism	Disease	Protein structures solved	Reference
Aspergillus fumigatus	Aspergillosis	Restrictocin	[31]
Blastomyces dermatidis	Blastomycosis	None	
Candida albicans	Candidiasis	Dihydrofolate reductase	[32]
		N-Myristoyl transferase	[33]
		Phosphomannose isomerase	[34]
		Secreted Asp protease	[35]
Coccidiodes immitis	Coccidioidomycosis	None	
Cryptococcus neoformans	Cryptococcosis	None	
Histoplasma capsulatum	Histoplasmosis	None	
Mucor sp.	Mucormycosis	None	
Paracoccidioides brasiliensis	Paracoccidioidomycosis	None	
Rhizopus sp.	Phycomycosis	Lipase II	[36]
		Rhizopuspepsin	[37]
		RNase Rh	[38]

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Table 1.3.4.3. *Protein structures of important human pathogenic protozoa, fungi and helminths* (*cont.*)

(*c*) Helminths

Organism	Disease	Protein structures solved	Reference
Clonorchis sinensis	Clonorchiasis	None	
Fasciola hepatica	Fasciolasis	Glutathione S-transferase	[39]
Fasciolopsis buski	Fasciolopsiasis	None	
Paragominus westermani	Paragonimiasis	None	
Schistosoma sp.	Schistosomiasis	Glutathione S-transferase	[39], [40]
		Hexokinase	[41]
Diphyllobotrium latum	Diphyllobothriasis	None	
Echinococcus granulosus	Unilocular hydatid cyst disease	None	
Taenia saginata	Taeniasis	None	
Taenia solium	Taeniasis	None	
Ancylostoma duodenale	Old World hookworm disease	None	
Anisakis	Anisakiasis	None	
Ascaris lumbricoides	Ascariasis	Haemoglobin	[42]
		Major sperm protein	[43]
		Trypsin inhibitor	[44]
Enterobius vermicularis	Pinworm infection	None	
Necator	New World hookworm disease	None	
Strongyloides stercoralis	Strongyloidiasis	None	
Trichinella spiralis	Trichinosis	None	
Trichuris trichiura	Whipworm infection	None	
Brugia malayi	Filariasis	Peptidylprolyl isomerase	[45], [46]
Dracunculus medinensis	Guinea worm disease	None	
Loa loa	Loiasis	None	
Onchocerca volvulus	River blindness	None	
Toxocara canis	Visceral larva migrans	None	
Wuchereria bancrofti	Lymphatic filariasis (elephantiasis)	None	

References: [1] Leonard *et al.* (1997); [2] Liu *et al.* (1998); [3] Phillips *et al.* (1999); [4] Knighton *et al.* (1994); [5] Kim *et al.* (1995); [6] Schlagenhauf *et al.* (1998); [7] Shi, Schramm & Almo (1999); [8] Rigden *et al.* (1999); [9] Williams *et al.* (1999); [10] Kim *et al.* (1998); [11] Read *et al.* (1999); [12] Chitarra *et al.* (1999); [13] Silva *et al.* (1996); [14] Shi, Li *et al.* (1999); [15] Velanker *et al.* (1997); [16] Champness *et al.* (1994); [17] Schumacher *et al.* (1996); [18] Schumacher *et al.* (1998); [19] Chudzik *et al.* (2000); [20] Vellieux *et al.* (1993); [21] Phillips *et al.* (1998); [22] Bernstein *et al.* (1998); [23] Wierenga *et al.* (1987); [24] Freymann *et al.* (1990); [25] McGrath *et al.* (1995); [26] Souza *et al.* (1998); [27] Focia *et al.* (1998); [28] Maldonado *et al.* (1998); [29] Lantwin *et al.* (1994); [30] Blankenfeldt *et al.* (1999); [31] Yang & Moffat (1995); [32] Whitlow *et al.* (1997); [33] Weston *et al.* (1998); [34] Cleasby *et al.* (1996); [35] Cutfield *et al.* (1995); [36] Kohno *et al.* (1996); [37] Suguna *et al.* (1987); [38] Kurihara *et al.* (1992); [39] Rossjohn, Feil, Wilce *et al.* (1997); [40] McTigue *et al.* (1995); [41] Mulichak *et al.* (1998); [42] Yang *et al.* (1995); [43] Bullock *et al.* (1996); [44] Huang *et al.* (1994); [45] Mikol *et al.* (1998); [46] Taylor *et al.* (1998).

Table 1.3.4.4. *Mechanisms of resistance*

Overexpress target protein
Mutate target protein
Use other protein with same function
Remove target altogether
Overexpress detoxification enzyme
Mutate detoxification enzyme
Create new detoxification enzyme
Mutate membrane porin protein
Remove or underexpress membrane porin protein
Overexpress efflux pumps
Mutate efflux pumps
Create/steal new efflux pumps
Improve DNA repair
Mutate prodrug conversion enzyme

threatens the effective treatment of bacterial infections of essentially every person on this planet. This implies that we will constantly have to be aware of the potential occurrence of mono- and also *multi*-drug resistance, which has profound consequences for drug-design strategies for essentially all infectious diseases. It requires the development of *many* different compounds attacking many different target proteins and nucleic acids in the infectious agent. It appears to be crucial to use, from the very beginning, several new drugs *in combination* so that the chances of the occurrence of resistance are minimal. Multi-drug regimens have been spectacularly successful in the case of leprosy and HIV. Obviously, the development of vaccines is by far the better solution, but it is not always possible. Antigenic variation, see *e.g.* the influenza virus, requires global vigilance and constant re-engineering of certain vaccines every year. Moreover, for higher organisms, and even for many bacterial species like *Shigella* (Levine & Noriega, 1995), with over 50 serotypes per species, the development of successful vaccines has, unfortunately, proved to be very difficult indeed. For sleeping sickness, the development of a vaccine is generally considered to be impossible. It is most likely, therefore, that world health will depend for centuries on a wealth of