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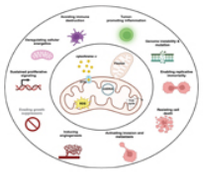

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Therapeutic targeting of HSP90 in herpesvirus infections, past and future challenges

Abir Chakraborty [1,2], Pia Roos-Mattjus [3,2*] & Silvia Gramolelli [1,3,4*]

[1]*Faculty of Science and Engineering, Cell Biology, Åbo Akademi University, Turku, Finland,* [2]*Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku, Finland,* [3]*Faculty of Science and Engineering, Biochemistry, Åbo Akademi University, Turku, Finland,* [4]*InFLAMES Research Flagship, Åbo Akademi University, Turku, Finland*
**Author for correspondence: Email: Pia.Roos-Mattjus@abo.fi; Silvia.Gramolelli@abo.fi*

Eukaryotic cells rely on a highly conserved chaperone machinery to maintain protein homeostasis (proteostasis). The activity of the HSP90 chaperone is critical for the appropriate folding and stability of a wide range of substrate proteins (client proteins) involved in fundamental cellular functions. Despite its abundance, HSP90 levels increase during pathological conditions such as cancer and viral infections, leading to cellular dependence on its activity. Hence, the inhibition of HSP90 has emerged as a potential therapeutic avenue, which has been explored particularly in cancer, antiplasmodial and antiviral treatments. This review provides a general overview of the structure and functions of HSP90, the main inhibitors that have been developed and the outcome, as well as HSP90 involvement in different herpesvirus infections. Compelling evidence identifies HSP90 as a promising pan-herpesviral target. Notably HSP90 inhibitors could outperform other antivirals as they do not promote the insurgence of resistant viral strains. Regardless, there are still great challenges ahead towards the development of safe and efficacious HSP90 inhibitors. New research should still pursue this avenue and aim to develop more selective and less toxic compounds.

Keywords: **HSP90; chaperone; HSP90 inhibitors; herpesviruses**

1. THE MOLECULAR CHAPERONE HSP90: STRUCTURE AND MECHANISM

Heat Shock Protein 90 kDa/HSP90 is a 90 kDa ATP-driven chaperone that plays a key role in the cellular proteostasis network under both stressed and physiological conditions in all eukaryotes (Biebl and Buchner, 2019). Broadly, HSP90 is required for protein folding, conformational regulation and for preventing protein aggregation (Biebl and Buchner, 2019). The pleiotropic functions of this highly abundant and ubiquitous protein include regulation of essential cellular processes such as cell cycle progression, proliferation, migration and invasion (Biebl and Buchner, 2019; Burrows *et al*., 2004). Different HSP90 isoforms are present in the cytoplasm, nucleus, and organelles. HSP90 isoforms include the stress-inducible HSP90α (HSP90AA1) and constitutively expressed HSP90β (HSP90AB1) in the cytosol/nucleus, endoplasmic reticulum (ER)-specific isoform (Grp94/Gp96), and the TNF receptor-associated protein-1 (TRAP1) in mitochondria (Sreedhar *et al*., 2004). HSP90α and HSP90β are 86% identical at the amino acid level, and these two isoforms partly overlap in function but bind distinct substrates (Chang *et al*., 2023). Although the research on HSP90 mainly has focused on their intracellular functions, HSP90α and HSP90β are found also in the extracellular space (W. Li *et al*., 2013). HSP90 participates in modelling the extracellular *milieu* through the activation of extracellular matrix (ECM)-linked cell signalling cascades, changes in morphology and expression of ECM components (Chakraborty and Edkins, 2021).

HSP90 interacts with a plethora of substrate proteins collectively known as 'client proteins' (Picard, 2024; Taipale *et al*., 2012). Client proteins are classified as the set of proteins that depend on chaperone machinery for folding, stability, and function (Taipale *et al*., 2012). It is suggested that HSP90 functions later in the protein folding pathways when most proteins are partially folded and require stabilisation. HSP90 is a functional homodimer. Each monomer consists of an N-terminal ATP binding domain (N domain), the middle (M) client protein binding domain, and a C-terminal dimerisation domain (C domain) (Biebl and Buchner, 2019; Didenko *et al*., 2012). The extreme C-terminus of HSP90 contains the EEVD motif, which is bound by tetratricopeptide repeat (TPR) domains contained in selected HSP90 co-chaperones like Hsp70-Hsp90 organising protein (HOP) (Röhl *et al*., 2015). A charged linker connects the N-terminal domain to the M domain and operates in client activation, and binding of some classes of co-chaperones, including HSP40, cell division cycle 37 homolog (CDC37/p50), an activator of HSP90 ATPase homolog 1(AHA1), and p23 (Chadli *et al*., 2008).

The HSP90 chaperone functions through a process of sophisticated conformational changes fuelled by ATP hydrolysis whereby the stability of client proteins is regulated. The correct assembly and initiation of the chaperone cycle requires a well-orchestrated collaboration of HSP90 with a

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set of co-chaperones. HSP90 is constitutively dimerised at the C-terminus and in an inactive state adopts an open conformation where the N-terminal domains are separated, and the protein resembles a V-shaped structure (J. Li and Buchner, 2013). Following ATP binding to the N-terminal domain, HSP90 undergoes a conformational change and forms the first intermediate state in which the N-terminal domains are dimerised. After that, the N-terminal domain interacts with the M domain and forms a closed compact structure known as the second intermediate structure. In this form, ATP is hydrolysed, releasing ADP and Pi, and HSP90 returns to its open configuration in which the N-terminal domains are separate (J. Li and Buchner, 2013; Whitesell and Lindquist, 2005).

2. LIGHTS AND SHADES OF HSP90 INHIBITION

HSP90 provides conformational stability, especially under diseased conditions, to a variety of clients, such as kinases, transcription factors, and receptors (Picard, 2024; Vartholomaiou *et al*., 2016). HSP90 has been linked to several disorders, including cancer, viral diseases, autoimmune diseases, parasite infections, cystic fibrosis, lung fibrosis, and diabetes (Chiosis *et al*., 2023; Hoter *et al*., 2018). In cancer cells, high expression of mutant proteins establishes an 'addiction for chaperone' and the higher levels of HSP90 are needed to facilitate the folding and maturation of otherwise unstable mutant proteins. Mutated proteins in cancer cells, in turn, support the aberrant signalling network necessary to sustain the oncogenic transformation (Jaeger and Whitesell, 2019). Similarly, in case of viral infections, HSP90 functions become essential. During the viral replication steps viral proteins are produced at a fast pace as they are needed to compose the new viral particles that will then be released out of the cells (Aviner and Frydman, 2020). Since the proteins that compose the viral capsid are often insoluble, an efficient chaperone machinery is essential for folding and assembly, and thus for the completion of the viral life cycle. HSP90 is therefore a promising target in cancer and viral infections where much higher levels of HSP90 have often been reported, thus offering a window for therapeutic intervention.

Over the past few decades, multiple HSP90 inhibitors have been synthesised and evaluated in clinical trials across a wide range of different diseases, particularly in cancer therapy (Rastogi *et al*., 2024). Regrettably, these trials have faced critical challenges, leading to termination due to limited effectiveness or dose-dependent toxicities – such as ocular, hepatic, and neurological adverse effects. However, over the years inhibitors have been, and still are, developed with less toxicities, and second-generation inhibitors are more tolerable (Butler *et al*., 2015; Dernovšek and Tomašič, 2023; Neckers and Workman, 2012). Very recently, one HSP90 inhibitor, pimitespib, received clinical approval, albeit exclusively in Japan. Its indicated use targets gastrointestinal stromal tumours (GISTs) that have progressed following chemotherapy treatment (with kinase inhibitors imatinib, sunitinib and regorafenib) (Doi *et al*., 2024; Hoy, 2022). This approval encourages the exploration of additional HSP90 inhibitors in other specific settings.

All HSP90 inhibitors tested so far in clinical trials bind to the N-terminus of HSP90 (Wang and McAlpine, 2015). A notable limitation of N-terminal HSP90 inhibitors lies in their propensity to induce a heat shock response (HSR) (Wang and McAlpine, 2015). This response leads to the transcriptional upregulation of additional HSP70 and HSP90, effectively counteracting the intended inhibition of HSP90. Heat shock transcription factor 1 (HSF1) is the master regulator of the HSR (Joutsen and Sistonen, 2019). The current model proposes that monomeric HSF1 resides in a complex together with chaperones such as HSP70 and HSP90, and that HSP90 inhibitors disrupt the interaction between HSP90 and HSF1, thus allowing HSF1 to trimerise, localise to the nucleus and activate the HSR (Gomez-Pastor *et al*., 2018). To mitigate this unwanted HSR induction, researchers are now, with promising results, developing C-terminal HSP90 inhibitors that still efficiently inhibit HSP90 without inducing a HSR (Amatya *et al*., 2024; Amatya and Blagg, 2023). Most HSP90 inhibitors tested in clinical trials inhibit all 4 isoforms: HSP90α, HSP90β, TRAP1 and Grp94 (Dernovšek and Tomašič, 2023). However, this approach poses challenges related to toxicity and dosing, as each isoform interacts with specific client proteins crucial for normal cellular functions. Currently, isoform-specific inhibitors are being developed and tested in various conditions (Amatya and Blagg, 2023; Sanchez *et al*., 2020). Pimitespib, the only clinically approved inhibitor so far, is a HSP90α and β specific inhibitor. It has less ocular toxicity than other tested HSP90 inhibitors and the toxicity is reversible if the dosing is changed (Doi *et al*., 2024). Extracellular HSP90 is also a promising target for therapy, due to its role in cell migration. Currently, researchers are developing cell-impermeable inhibitors that target the extracellular HSP90α (Mathenjwa *et al*., 2024; Reynolds and Blagg, 2023; Sager *et al*., 2022).

Beyond cancer treatment, the exploration of HSP90 inhibition extends to viral infections. HSP90 is a crucial host factor required by a wide range of viruses for multiple phases of their life cycle including viral entry, nuclear import, transcription and replication. Therefore, HSP90 emerges as a promising broad-spectrum antiviral target (Aviner and Frydman, 2020; Wang *et al*., 2017). Different HSP90 inhibitors show antiviral activity in tissue cultures or mouse models against multiple viruses (Aviner and Frydman, 2020). One challenge with antiviral drugs is the selection of drug-resistant viral strains. Encouragingly, HSP90 inhibitors do not seem to produce drug resistance in viruses (Geller *et al*., 2007). Unlike cancer treatment, where prolonged drug administration is common, acute viral infections may benefit from shorter treatment courses. HSP90 inhibitors could offer effective antiviral therapy without prolonged exposure, potentially reducing side effects. Further studies are warranted to explore the specific role of HSP90 in the life cycle of individual viruses. Understanding the interplay between HSP90 and viral infection will guide the development of targeted antiviral strategies.

In the following section, we will provide a synthesis of the roles of HSP90 as well as the challenges and hopes of its inhibition in the context of herpesviral infections.

3. THE ROLE OF HSP90 IN HERPESVIRUS LIFE CYCLE AND ITS THERAPEUTIC POTENTIAL

As intracellular parasites that are completely dependent on the cellular machinery for survival, viruses must hijack and manipulate several cellular processes to successfully complete their life cycle, including the protein chaperone machinery (Sullivan and Pipas, 2001). Herpesviruses are a conserved family of large dsDNA viruses that code for more than one hundred open reading frames. The complexity of their

Table 1. Human herpesvirus classification.

Subfamily	Virus	Common sites of productive infection	Common sites of latent infection	Associated diseases
Alpha	HSV-1	Oral mucosa	Trigeminal ganglia	Oro-labial herpes, encephalitis
	HSV-2	Genital mucosa	Sensory neurons	Genital herpes, encephalitis
	VZV	Epithelial cells of the skin	Trigeminal ganglia	Chicken pox and shingles
Beta	HCMV	Fibroblasts	Myeloid cells	Neuropathies
	HHV-6 A, B	$CD4^+$ lymphocytes	—	Sixth disease
	HHV-7	—	Lymphocytes	Chronic disease syndrome
Gamma	EBV	Epithelial cells	Memory B cells	B and T cell lymphomas, gastric cancer, nasopharyngeal carcinoma, multiple sclerosis
	HHV-8, KSHV	Endothelial and epithelial cells, fibroblasts	Memory B cells	Primary effusion lymphoma, multicentric Castleman's disease, Kaposi's sarcoma

Abbreviations: HSV: Herpes simplex virus, VZV: Varicella zoster virus, HCMV: Human cytomegalovirus, HHV: Human herpesvirus, EBV: Epstein-Barr virus, KSHV: Kaposi's sarcoma herpesvirus.

genome mirrors the complexity of the interplay with the cells. Herpesviruses infect a broad range of hosts, including mammals, reptiles, fish and birds; however, a specific herpesvirus usually has a single or a very limited host range. To date, 8 human herpesviruses have been identified and characterised to different extents (reviewed in Jeffery-Smith and Riddell, 2021). Herpesviruses are divided into α, β and γ herpesvirus subfamilies (see Table 1 for a list of human herpesviruses). Although herpesviral infections in immunocompetent individuals do not cause serious pathological states, a weakening of the host's immune system can lead to several, sometimes fatal, herpesvirus-related diseases (reviewed in Šudomová and Hassan, 2023). It has been estimated that each human being is infected with at least one, and more often, with multiple herpesviruses. Herpesviral infections are life long and, to date there is no approved standard treatment able to clear the infection (Jeffery-Smith and Riddell, 2021; Šudomová and Hassan, 2023). The main characteristic of viruses belonging to this family is their biphasic life cycle. All herpesviruses display a lytic, productive replication phase where all lytic genes are expressed according to a well-orchestrated temporal cascade. During this phase, viral genomes are replicated and assembled into newly synthesised viral capsids and the new viral particles are released from the cell. The lytic phase is alternated to a latent phase where the viruses persist in the infected cells. The viral genome is replicated once per cell cycle by the cell DNA replication machinery and the viral genome persists as a non-integrated episome. During this phase, only a restricted pool of viral genes and miRNAs are expressed (reviewed in Jeffery-Smith and Riddell, 2021).

HSP90 protein is involved in several phases of herpesviral life cycle (for a general overview see Figure 1). During the early stages of Herpes simplex virus-1 (HSV-1) lytic replication HSP90 localisation changes from the typical cytoplasmic diffuse pattern and the protein accumulates during the first hours after infection within peculiar nuclear structures called VICE (viral-induced chaperone enriched) domains (Livingston *et al.*, 2009). VICE domains localise in proximity to the viral replication compartments where the viral genome is replicated, and viral capsid proteins are assembled. VICE domains contain, along with HSP90, several other members of the protein control and protein degradation machineries and a viral encoded HSP40-like chaperone is needed for the assembly of these structures (Bastian *et al.*, 2010). Although the function of these structures has not been yet completely demonstrated, a well-accepted hypothesis is that VICE domains, like nuclear inclusion bodies, are protein quality control centres, necessary to assist and ensure successful viral capsid assembly (Livingston *et al.*, 2009). Additionally, in multiple independent studies HSP90 inhibitors have been tested and reported to significantly affect different phases of HSV-1 life cycle, from entry to DNA replication till the egress (Qin *et al.*, 2021, 2022; Wang *et al.*, 2017). Mechanistically, Burch and Weller in 2005 documented a mislocalisation of the viral DNA polymerase UL30 upon HSP90 inhibition (Burch and Weller, 2005). Even though a direct interaction between HSP90 and UL30 has not been demonstrated empirically, a subsequent *in silico* study predicted an interaction between HSP90 and UL30 together with the viral-encoded DNA processivity factor UL42 (Qin *et al.*, 2022). Therefore, it is possible that HSP90 participates not only in ensuring the appropriate folding of the viral structural proteins (as a component of the VICE domains) but also promotes the viral genome replication by ensuring correct folding of the DNA polymerase and processivity factor so that these proteins can localise within the replication compartments. Despite the large genome size (152 Kbp) and the complexity of the viral particle, HSV-1 life cycle can be completed, in permissive cells, in as little as 4–12 h. During this limited time, generous amounts of viral structural proteins are translated and assembled, the viral genome is used as a template for both transcription and viral DNA genome replication. In this very dynamic and chaotic cellular environment, chaperones such as HSP90, are the ideal tools to co-ordinate these processes and ensure the correct folding and appropriate assembly of the viral proteome. Although β human herpesvirus family has not been as extensively explored as the α herpesvirus family, it has been demonstrated that Human cytomegalovirus (HCMV) viral replication is sensitive to HSP90 inhibition (Basha *et al.*, 2005).

On the other side of the spectrum of herpesvirus family lie Epstein–Barr viruses (EBV) and Kaposi's sarcoma-associated herpesviruses (KSHV, HHV-8), the two oncogenic γ-herpesviruses. For these viruses, latency is the default persistence phase, and the lytic reactivation occurs only sporadically in immunocompetent individuals. *In vitro,* the life cycle of

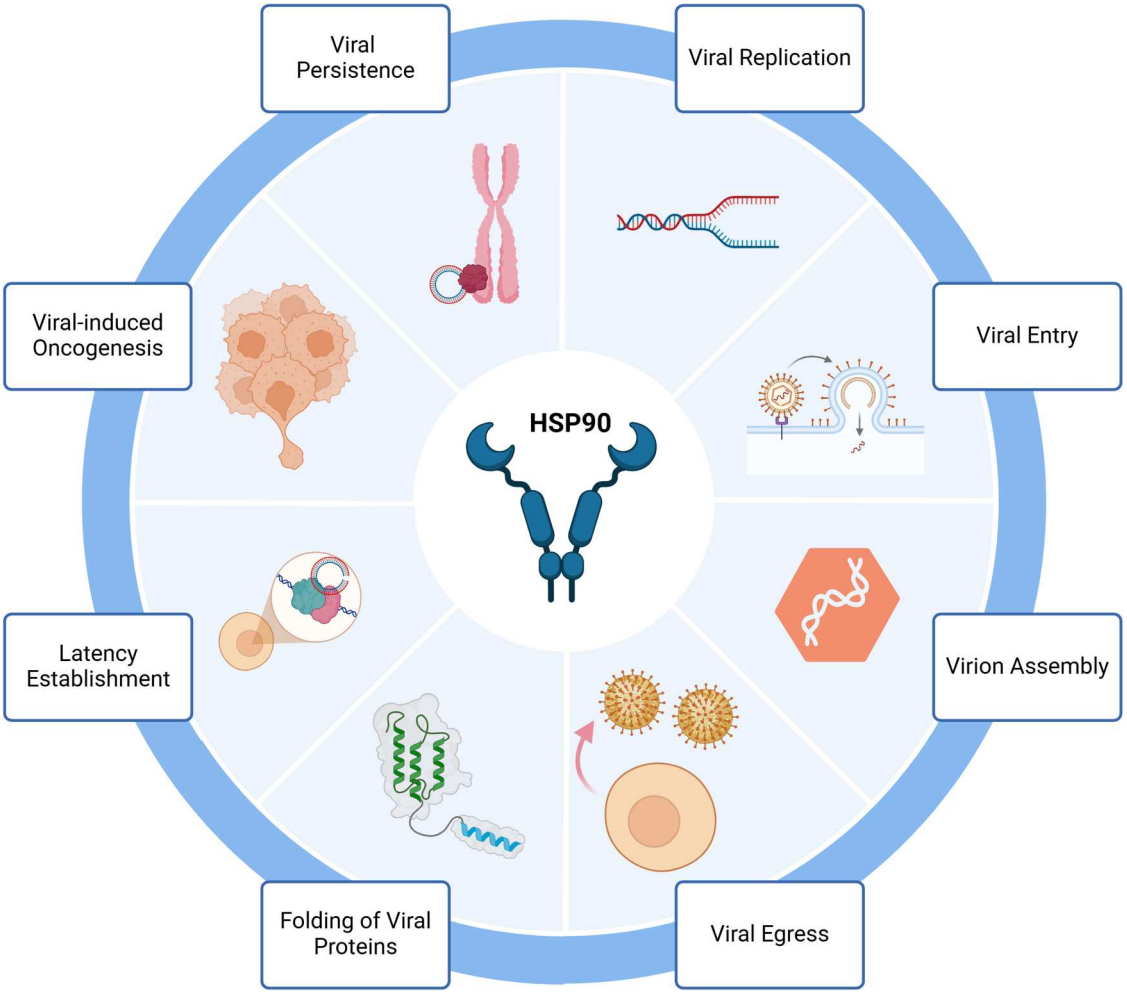

Figure 1. The multifaceted role of HSP90 on herpesviral life cycle. HSP90 has been implicated in various stages of the herpesviral life cycle. HSP90 interacts with viral and host proteins to facilitate viral entry, replication, gene expression, virion assembly and egress. It aids in the proper folding and stability of viral proteins, has pivotal role in latency establishment and ensures the persistence of the herpesviral episome. In oncogenic gamma-herpesviruses HSP90 has also been implicated in tumorigenesis. Made with Biorender.

these viruses can last up to 96 h. Therefore, they proceed at a much slower pace than HSV-1. Regardless, also in this context HSP90 serves an essential role and HSP90 functions are key to viral persistence and replication. Inhibition of HSP90 in KSHV and EBV-infected cells downregulated LANA and EBNA1, respectively. These proteins are the multifunctional master regulators of latency and ensure viral persistence in the latently infected cells (Chen *et al.*, 2012; Sun *et al.*, 2010). Given that latency establishment in B cells is the *conditio sine qua non* for EBV and KSHV lifelong persistence and for B cell tumorigenesis, targeting LANA and EBNA1 has been an attractive therapeutic strategy (Speck and Ganem, 2010). When treated with HSP90 inhibitors, B cells did not undergo transformation upon EBV infection, indicating that HSP90 could indeed be a successful target for viral-induced lymphomas. This was further supported by a study showing that EBV-positive, transformed B cells were killed upon HSP90 inhibition (Shatzer *et al.*, 2017). Furthermore, in a preclinical SCID mouse model of EBV-positive B cell lymphoma, tumour size was significantly reduced and HSP90 inhibition did not cause major side effects (Shatzer *et al.*, 2017). In another study, the HSP90 inhibitor PU-H71 was tested on multiple EBV and/or KSHV-infected B cell lymphomas showing a nanomolar range IC50 *in vitro* and in a xenograft mouse model (Nayar *et al.*, 2013). A proteomic capture approach was undertaken to understand the mechanism of action. Interestingly, it was discovered that PU-H71 caused cell death by inducing the degradation of several components of the NF-κB pathway, autophagy and inhibition of the apoptotic response, all processes known to be key to viral-induced lymphomagenesis (Nayar *et al.*, 2013). Given the encouraging evidence *in vitro* and *in vivo* on the possible efficacy of targeting HSP90 in EBV-induced cancers, a patient with an EBV lymphoproliferative disorder has been treated with Ganetespib. As a result, a 50% reduction in the percentage of EBV-positive B cells in blood was observed (Shatzer *et al.*, 2017). Overall, the dependency on HSP90 is a leitmotif in herpesvirology. Remarkably, viral replication is sensitive to HSP90 inhibition at doses that do not affect the viability of uninfected cells, hence providing hope that newly developed molecules could target HSP90 as a pan anti-herpesviral strategy in the future. This would be a particularly meaningful approach since lifelong herpesvirus infections often cause several and diverse pathological conditions, and to date, no treatments are available to clear infections with these viruses.

4. CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the lack of success so far in the development of HSP90 inhibitors, the knowledge gained from previous trials on their toxicities, along with the development of new molecules and advancements in molecular profiling, suggests that this therapeutic avenue remains promising. The approval of pimitespib in Japan and the ongoing research into other (isoform-specific) HSP90 inhibitors with improved safety profiles highlight the potential for these treatments to be effective in personalised cancer therapies. The ability to tailor treatments based on the molecular characteristics of individual tumours not only enhances efficacy but also reduces unnecessary side effects. Therefore, continued exploration and development of HSP90 inhibitors could lead to success in specific subsets of cancer patients.

Notably, HSP90 inhibitors have also emerged as broad spectrum antiherpesvirals. This is particularly relevant as lifelong herpesvirus infections represent a severe healthcare burden and cause a large range of diseases worldwide. One of the reasons why antivirals lose efficacy is the emergence of resistant viral strains. In these cases, the selective pressure of the antiviral treatment promotes the emergence of viral strains able to use different pathways that are not targeted by the antiviral therapy. Interestingly, HSP90 inhibition in herpesviral infections has not elicited the emergence of resistant viral strains, thus pointing to HSP90 as one of the most fundamental host factors for viruses to complete its life cycle and thus as a very promising therapeutic target.

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ORCID

Abir Chakraborty http://orcid.org/0000-0002-3131-0808
Pia Roos-Mattjus http://orcid.org/0000-0002-7187-2012
Silvia Gramolelli http://orcid.org/0000-0003-0095-6769

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