

# Protein network analysis indicates that Ebola virus, *Neisseria meningitidis* and *Trypanosoma brucei* trigger common host defense response pathways

Shishir K Gupta

Julius-Maximilians-Universität Würzburg

Alicia Ponte-Sucre

Universidad Central de Venezuela Instituto de Biomedicina

Elena Bencurova

Julius-Maximilians-Universität Würzburg

Thomas Dandekar (✉ [dandekar@biozentrum.uni-wuerzburg.de](mailto:dandekar@biozentrum.uni-wuerzburg.de))

University of Würzburg <https://orcid.org/0000-0003-1886-7625>

---

## Research article

**Keywords:** blood-borne pathogen; interactome; protein-protein interaction; life cycle; hub proteins; antibiotic targeting; pathway analysis; Ebola virus; *Neisseria meningitidis*; Human African Trypanosomiasis

**Posted Date:** October 21st, 2019

**DOI:** <https://doi.org/10.21203/rs.2.16270/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

**Version of Record:** A version of this preprint was published at Computational and Structural Biotechnology Journal on September 16th, 2021. See the published version at <https://doi.org/10.1016/j.csbj.2021.09.017>.

# Abstract

**Background:** Sepsis is the most severe final state of infection. Might pathogens belonging to different kingdoms of life and pathogen classes trigger analogous responses pathways in the host? Is there a common denominator or strategy to prevent it? Here we use interactomics and comparative evolutionary analysis of three serious infectious pathogens, spanning viruses, bacteria and parasites: *Filovirus ebolavirus* (ZE; *Zaire ebolavirus*, *Bundibugyo ebolavirus*), *Neisseria meningitidis* (NM), and *Trypanosoma brucei* (Tb) that target the blood during their infectious life cycle. **Results:** We analyze 2797 unique human proteins targeted by the pathogens. The comparison resulted in specific and shared protein-protein interactions (PPIs) with each pathogen, derived from orthology searches of experimentally validated PPIs. Furthermore, we narrow down the data set of effected genes of the human (defense) immune response and describe human proteins predicted to participate in at least two of the compared host-pathogen networks. Only four proteins were common to all three host-pathogen interactomes. This interaction clade of four proteins, common to all three host-pathogen networks, suggests a central cluster of host response formed by elongation factor 1-alpha 1 (EF-1-alpha-1), the SWI/SNF complex subunit SMARCC2 (matrix-associated actin-dependent regulator of chromatin subfamily C), the dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit 1, and the tubulin beta-5 chain. These hub proteins are functionally connected, suggesting according to the collected data including experimental information on VP24 from Ebola virus that these, as well as some joined interaction partners, may orchestrate a common host response to infection.

## Background

About  $10^{13}$  human cells coexist with  $10^{14}$  bacterial, fungal, and protozoan cells, i.e. thousands of microbial species. Microbes create the human flora, limited to areas of the body such as skin, mouth, large intestine, and vagina. We live in close intimacy with microbes. However, only some pathogens (including microbes, fungi or viruses) may cause symptomatic infections -or death- in humans, one example being meningococcal bacteria (Rouphael and Stephens 2012; van Deuren, et al. 2000). How can this happen? When is the eco-system broken? Often immunocompromised individuals get infected, highlighting the fundamental role of the immune system (Alberts 2002).

In contrast, dedicated pathogens (including virus, bacteria or even eukaryotic organisms) do not require an immunocompromised or injured host. Pathogen physiology allows them to cross cellular barriers and trigger specific responses in the invaded organism that may contribute to pathogen survival and multiplication, as happens for *Ebolavirus* and *Trypanosoma sp* (Goeijenbier, et al. 2014; Moole, et al. 2015; Ponte-Sucre 2016; Rewar and Mirdha 2014; Stijlemans, et al. 2016). Thus, healthy people are “invaded” by dedicated pathogens (Alberts 2002). Cohabitation between populations at risk and their animals - as pathogen reservoirs -, is common in disease transmission (Welburn, et al. 2015).

Ecological and evolutionary hints, together with the disease dynamics, are fundamental for understanding and analysing the temporal, organizational and spatial interactions, even within a single pathogen. That is, hours to months, cellular to ecosystem levels, and local to pandemic spread of diseases (Welburn, et al. 2015). Additionally, some pathogens circulate between individuals of a single species, while others flow among multiple hosts, need arthropod vectors, or subsist in reservoirs. May pathogens belonging to different kingdoms of life and pathogen classes trigger analogous responses pathways in the host?

Appreciating that protein-protein interactions and conservation testify these different levels and scales of interactions paving the route to infection for the pathogen, as well as providing the backbone of defenses for the host, we herein compare for the first time the conserved and specific protein interactions of three serious pathogens [*Filovirus ebolavirus* (ZE for *Zaire ebolavirus*, *Bundibugyo ebolavirus*), *Neisseria meningitidis* (NM for *N. meningitidis*) and *Trypanosoma brucei* (Tb for *T. gambiense* and *rhodesiense*, *T. brucei sp.*)], all sharing a blood-stage. The following detailed bioinformatics analysis of all available data highlights specific and conserved interactions and discusses implications for conserved immune mechanisms activation, and infection biology.

## Results

Conserved host and pathogen-specific pathways

Binding of pathogen proteins to specific host targets may affect specific host functions, including defense mechanisms. However, in general, they do not disrupt completely host networks, as the interactions mainly occur due to biophysical properties of the involved proteins. Herein we analyzed host-pathogen interactions comparing a virus (*Zaire ebolavirus*, Bundibugyo ebolavirus, **ZE**), a prokaryotic bacterium (*Neisseria meningitidis*, **NM**) and an eukaryotic parasite (*Trypanosoma brucei gambiense* and *rhodesiense*, **Tb**) that all three can cause severe infection including sepsis. By predicting physical protein-protein interactions (PPIs) between host and each pathogen proteins, we described common pathways existing on the three host-pathogen interaction networks.

Detailed information on disease characteristics for ZE, NM and Tb are listed and explained in Additional file 1 and Additional file 2. The focus on this information is on general responses occurring during the infection processes comparing all three pathogens. Thorough analysis of the summarized data points out functional similarities and differences occurring during infection processes. Therefore, individual host-pathogen PPIs could be established based on these functional similarities and differences. This information -and a literature-driven pathway analysis-, was a key step to address the next step of our investigation based on interactome data and comparisons between the three host-pathogen interactions.

Thus, to translate the observed characteristics into interactome data and describe the differences between **ZE**, **NM** and **Tb**, we performed a systematic analysis using bioinformatical techniques. We mapped physical protein-protein interactions (**PPIs**) between host and each pathogen, using orthology relations and host-pathogen interaction databases. Additionally, a stringent mapping pipeline, that refines interaction predictions by considering known domain-domain interactions (see material and methods) was used. This approach produces high-quality interactome data with a low false-discovery rate (Itzhaki, et al. 2006; Zhou, et al. 2013).

To characterize the function of proteins in the above mentioned interactions we used the GO annotation. Results are depicted in Fig. 1 and 2. Fig. 1 displays the number of genes involved in the interactome for each pathogen and its counterpart in humans. Although each protein-protein interaction networks express unique characteristics, the overall profile of gene type involved in the interaction is similar not depending on to which animal kingdom the pathogen belongs. That is, most host proteins involved in the interaction are expressed either in the plasma membrane, or relate to DNA or RNA functions, or are mitochondrial proteins. Furthermore, with increasing complexity of the invading pathogen, an increasing number of proteins seem to be involved in all compartments or functions. On the other hand, most pathogen proteins participating in the interaction are unknown proteins.

Fig. 2A compares the percentage of human genes related to each category participating in the interactome for each disease, while Fig. 2B illustrates the percentage of pathogen genes related to each category involved in the interactome for each disease, excluding **ZE**. The results indicate that the overall profile of protein type contributing to the interaction is similar and does not depend to which kingdom the pathogen belongs thus suggesting a “meta language” involved in host-pathogen interaction.

Due to this overlapping network of interacting proteins, belonging to pathogen and host that participate in the interactome for each pathogen and its human counterpart, we analyzed (see Additional file 3) the role of the described **PPIs** in host defense. The resulting subnetwork suggests the presence of common mechanisms to fight these three pathogens as depicted in Fig. 3 and summarized in Table 1 (details in Additional file 4).

In this figure, the conserved **PPIs** are clearly indicated. The color of the nodes indicates the different organisms (blue = *Trypanosoma brucei*; red = *Neisseria meningitidis*; yellow = *Zaire ebolavirus*; and green = human). The complex blue/red nodes represent the *Trypanosoma*/*Neisseria* orthologs. Different human compartments are indicated including the confidence of their assignment, and human proteins may reappear in several subcellular localizations. The border thickness around green human nodes indicates the confidence of localization in the cellular compartments. Pathogen proteins which are also membrane proteins are given in italics and exclusive membrane proteins are underlined. Redundancy in **PPIs** is permeating and fundamental for survival during such host-pathogen battles (Phizicky and Fields 1995): either to impair or to promote host protection, relying on innate and cellular defense mechanisms (Dyer, et al. 2007).

Domain analysis reveals that exposed protein domains with high structural and physical-chemical interaction affinity are central, conserved (Rual, et al. 2005) and selected by evolution in this long term battle (Aloy, et al. 2003; Littler and Hubbard 2005; Panchenko, et al. 2005; Teichmann 2002; Valdar and Thornton 2001). Host-pathogen interaction details and individual protein function including host defense-related signaling pathways and compartments are given in Table 1. This table categorizes unique (U) and conserved (C) interactions. Specific host defenses elicited by shared protection mechanism against all three pathogens

include interferon, antigen-antibody interaction, the HLA system, shared cytokines and chemokines and proteasome associated proteins. Regulation of this shared host defense network is achieved by transcription factors via cell recognition associated proteins. Moreover, the **ZE** host defense interaction system centers on two human proteins, one at the nuclear level (related to proliferation) and one with multiple locations at the cytoplasm, Golgi apparatus, and plasma membrane: the CD antigen CD317, or stromal bone marrow antigen-2, a lipid raft associated protein (see also Additional file 5).

Pathogen interacting proteins re-occur in all three host-pathogen networks

In the next step of analysis, all proteins that participate in the interactome, represented in all three pathogen-human interaction networks were analyzed. A total of 2797 unique human proteins were targeted by the pathogens. Interesting, data related to shared interaction nodes are detailed in Additional file 6 and summarized in Table 1, stressing again host-defense-activation-system-related proteins. Fig. 4 summarizes unique, shared, and common interactions for all three pathogen-human **PPIs**.

Pathogens tend to interact with hubs in the host network, in order to hijack them for their own profit (Yang, et al. 2011). However, the host network remains/stays robust, as a catastrophic failure of host cell metabolism would hinder pathogen survival and proliferation as well as kill the host (Crua Asensio, et al. 2017). The eukaryotic cells herein represented by trypanosomes achieve the highest number of specific interactions (1414), followed by *Neisseria* (753) and only then by 57 ZE-specific interactions.

Pathway classifications were collected by different methods using Netpath (Kandasamy, et al. 2010), BioCarta (Nishimura 2001), KEGG (Kanehisa, et al. 2008) and Reactome (Vastrik, et al. 2007) database classification. The obtained results contributed to further dissect pathways involved in host-pathogen interaction:

For example and regarding the trypanosome interactome, the Netpath database perceives EGFR, TSLP and androgen receptor pathways, while the databank reactome recognizes host defense mechanisms, immune signalling, cell senescence, and response to stress as top categories involved in the host-pathogen interaction. According to the BioCarta database, further signalling relies mainly on Thrombospondin-1 (TSp-1) induced apoptosis, Extracellular-signal regulated kinases/FYN proto-oncogene, src family tyrosine kinase/Tyrosine kinase (Erk/Fyn/Tyr) activation and EGF signalling. These results are further supported by KEGG which identifies NOD-like receptor signalling, antigen processing, and trypanosomal defense pathways, as central for the host-pathogen interactome. In fact, the innate DB (database) classifies the innate response against trypanosomes as relying on IL2 and IL12 as well as osteopontin and atypical NF-kB mediated processes (Additional file 7).

Although this is a common network for all three pathogens, the host defense details of course vary for each disease. Thus, interactions of host proteins specifically shared only between the smallest pathogens **NM** and **ZE** include mRNA stability, gene expression control, and mRNA splicing (reactome classification). Interestingly Netpath reveals again androgen receptor pathways as important, and that the TNFalpha response pathway is involved in the host response to these two pathogens.

Interestingly, and according to the reactome database, **ZE** and **Tb**, pathogens at the two ends of complexity and size, share specific defense systems centering on pathways for eukaryotic translation, elongation, life cycle, and infection. This involves ribosomes and PID-Bard1 signalling, and is modulated by Rb and p53 proteins according to KEGG. Netpath on the other hand shows a shared TSLP pathway response and again the TNFalpha response.

In conclusion, our data suggest that conserved host-pathogen interactions always include host defense and differentiation/maturation pathways. Additionally, the two bigger interactomes (**NM**, **Tb**) also involve reprogramming of host-cell senescence and apoptosis; the two smaller pathogens both influence mRNA, and **Tb** and **ZE** impact protein translation in their favor and induce specific host defense pathways.

Central interactome proteins shared by all pathogens and humans, implications

The previous results illustrate that out of the 2797 unique targeted proteins, only four [the elongation factor 1-alpha 1 (EF1a), the SWI/SNF complex subunit SMARCC2, the dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit 1, and the tubulin beta-5 chain] were common to all three host-pathogen interactomes. These top four hub proteins share a common trait: they are exploited by pathogens to gain entry to the host and survive inside it. As illustrated in Fig. 5, (colour codes differentiating all three

pathogens), these four central proteins are strongly and well connected proteins. It is known that such hub proteins are often well conserved (Brown and Jurisica 2007; Fraser, et al. 2002) and hence present good pathogen targets (Durmus Tekir, et al. 2012).

Based on the results presented herein we would like to suggest that these host proteins may represent potential targets for the design of infection disruption tools, as due to their central role, their manipulation would probably stop all three infections. For example, EF1a activity is related to functional changes in the host cell so that infection can better exploit cell ongoing protein synthesis. The SWI/SNF-related matrix-associated actin-dependent regulator and the tubulin beta-5 chain may target hubs of the cytoskeleton related to infection and their modulation may block all three infections. The Dolichyl-diphosphooligosaccharide–protein glycosyltransferase subunit 1 might provide an Achilles-heel on glycosyl and lipid metabolism, which any of the three infective agents exploits. Recent data for NM underline that tubulin interactions influence tubulin polymerization, an essential step for pathogen phagosome engulfment or escape (Tala, et al. 2014). Moreover, **Table 2** examines in detail the conserved four human proteins and their interactions. It gives some more detail about the function and processes they are involved in as well as available direct evidence that these proteins are interacting with any of the pathogens. For Ebola virus this has been verified regarding VP24 and all four human interactions (Garcia-Dorival et al., 2014; Pichlmair et al., 2012).

## Discussion

Proteins often interact with other protein molecules either from the same organism or bridging host organism and an invading microbe. The latter interaction has direct implications for host and pathogen, as it may either impair defenses (pathogens) or help to defend the microbe (host) by activating innate or cellular or systemic defense (immune) mechanisms. This all highlights the importance to understand the human-pathogen interactome, to provide insights into the pathophysiological mechanisms of infection potentially common to many infectious diseases. Herein we analyzed the interactome between the human host and a eukaryote, a bacterium, and a virus. The integrated results are interpreted around two key questions: are there conserved host and pathogen-specific pathways fundamental for defense (immune system) activation? if so, which interactive pathways are shared between all three or just two kingdoms of life? For the discussion we focus on host-defense responses unique to a particular pathogen and those shared by the different pathogens.

### A common defense network for blood borne pathogens

To analyze if there is a common defense-mechanism against bloodborne pathogens, starting from conserved pathways and PPIs, we will elaborate on the herein obtained results.

### ZE interacts with the complement cascade

Cell entry mechanisms for **ZE** have not been well defined (Falasca, et al. 2015). However, cholesterol-enriched lipid raft microdomains, or plasma membrane microdomains, seem to represent the main gateway used by this virus (entry and exit) (Bavari, et al. 2002; Falasca, et al. 2015). On the other hand, by stimulating antibody production and promoting the appearance of virus-antibody complexes, that bind to monocytes and macrophage Fc-receptors, **ZE** enhance its infectivity (Furuyama, et al. 2016; Takada, et al. 2007; Takada, et al. 2003a). Virus-antibody complexes also activate the complement cascade and facilitate virus entry into cells. Still, neither mechanism completely explains the non mediated Fc-receptors or complement cascade promoted increased infectivity described in **ZE** infected primate kidney cells (Ito, et al. 2001; Takada, et al. 2003b; Watanabe, et al. 2000). **ZE** stimulated antibody production may enhance infectivity due to its binding to specific antigen epitopes located at two or more molecules of monomeric IgG antibodies. This process permits complement cascade component C1 to bind to the antibodies Fc portion. The complex constituted by virus, antibodies, and C1, then binds C1q ligands at the immune cell surface, promoting either virus binding to **ZE**-specific receptors or endocytosis into target cells by intracellular signaling via C1q ligands (Takada, et al. 2003a).

Once internalized, a cytopathogenic effect of **ZE** causes annihilation of infected cells. Monocytes/macrophages and dendritic cells (DCs) are **ZE** early replication sites and exert key roles in the dissemination of the virus from the spleen and lymph nodes to other tissues; and fibroblasts, hepatocytes, adrenal cells and epithelial cells can be infected by the virus (Falasca, et al. 2015). Further amplifying mechanisms of the initial cytopathogenic effect result in the destruction/impairment of vital body functions. Two proteins are involved in the **ZE**-human host defense interactome as herein described.

PCNA (see Table 1), a proliferating cell nuclear antigen (Cyclin), essential for replication and involved in DNA repair, epigenetics and chromatin remodeling (Moldovan, et al. 2007). **ZE** evades Type-I IFNs response (IFN- $\alpha$  and IFN- $\beta$ ), thus eliminating the protective role of IFN- $\alpha$ . Additionally, multifunctional molecules like VP35 and VP24 -associated with viral particle maturation and immune activity suppression-, as well as inhibition of the tetherin activity seem to participate in the evasion process mechanisms.

Interestingly, the bone marrow stromal antigen 2 of the human-**ZE** interactome (see Table 1), belongs to the IFN-dependent antiviral response path. Its expression restricts viral factors once the virus or its viral components are detected by immune host cells.

Thus, upon virus recognition, a cascade of controlled interactions occur between signaling molecules, up to the upregulation of interferon-stimulated genes expression that further activate neighbor cells, and increase the expression of viral restriction factors, among them tetherin (Douglas, et al. 2010; Kuhl and Pohlmann 2012; Le Tortorec, et al. 2011). In conclusion, one of the two **ZE** proteins involved in host defense interaction mechanisms guarantees proliferation, while the second one restricts viral spreading. The implications of this balance should be further analyzed.

Additionally, **ZE** infection induces a massive cytokine/chemokine production by peripheral blood mononuclear cells (PBMC) or monocytes/macrophages. This occurs even after the first hour of **ZE** exposure, prior to virus gene expression. Shed glycoprotein molecules activate non-infected DCs and macrophages, inducing the secretion of pro- and anti-inflammatory cytokines via TLR4 stimulation.

Furthermore, downstream effects of antigen-presenting cell dysfunction affect adaptive immunity. A massive natural killer (NK) cell loss in the peripheral blood impact the capacity of infected cell clearance and may be partially responsible for the unbalanced maturation signals for DCs. Thus, lymphoid depletion and necrosis occur in spleen, thymus and lymph nodes of dying patients, with a drastic decrease in the number of circulating T lymphocytes in succumbing people but not in survivors. Interestingly, despite the large loss of lymphocytes at work, no signs of lymphocyte virus infection is detected, suggesting a bystander mechanism of apoptosis, probably a non-apoptotic form of cell death or necrotic cell death (Douglas, et al. 2010). At the end, the overwhelming immune response disturbs the balance and promotes the precipitation of the survival of both, the host and the pathogen.

#### NM and Tb activate common pathways in the host

Diseases caused by both NM and Tb have a blood stage and both, accidentally or not, may end invading the brain and causing either meningitis, in the case of NM, or a second stage disease in the case of Tb. Interestingly, the respective interactome, between each pathogen and the human defense mechanisms, overlap in high proportion (see Table 1). A plethora of molecules related to antigen presentation, as well as to cytokine and chemokine secretion and antibody production are involved in the respective interactome, suggesting that both pathogens activate in a similar way host defense and consequently, the immune system. In fact, conserved inflammatory molecules: Interleukin-2 receptor subunit beta, TNF receptor-associated factor 6 and Interleukin-18-binding protein, participate in the interactome, trigger processes such as thrombo-inflammation in different human host areas in a pathogen-specific way (Table 1).

LTBP4, the latent-transforming growth factor beta (TGF- $\beta$ )-binding-protein-4, participate in the human-NM interactome, but not in the human-Tb interactome. LTBP4 is an extracellular matrix (ECM) structural component and TGF- $\beta$  signaling regulator (Robertson, et al. 2015). Herein we comment on two different host-pathogen interacting mechanisms, present in both host-pathogen networks, fundamental for disease blood stage before invading the central nervous system: antigenic variation and complement activation.

Variations in blood parasitemia in cases of Tb are linked to host immune responses, but also to variation on the surface antigenic molecules expressed by the parasites (Stijlemans, et al. 2016). The glycoprotein coat of bloodstream parasites or Variant Surface Glycoprotein -VSG- is crucial for evading host antibody activity, and the complement cascade (Donelson, et al. 1998; Horn and McCulloch 2010; Pays 2006; Vanhamme, et al. 2004). Thus, to avoid these defense mechanisms, a high-frequency antigenic variation of the surface VSG occurs. Parasites are "hidden" from the immune system and therefore survive while in the bloodstream. Upon invading mammalian host bloodstream, the surface VSG triggers a humoral immune response. To cope with it, a small proportion of trypanosomes express a "new VSG", survive, and impair the "effective" immune response (Ponte-Sucre 2016).

Similarly, high-frequency antigenic variation on surface antigens, like lipo-oligosaccharide (LOS), opacity-associated proteins (Opa) and type IV pili, means poor immune control of infections caused by pathogenic species of *Neisseria*, including NM. Random

switching in nucleotide repeat numbers during DNA replication, -on and off- of accessory LOS glycosyltransferases, or complete *Opa* genes mediate LOS and *Opa* variation. Additionally, type IV pilin changes by gene conversion between silent storage copies of variant pilin and the single expressed pilin gene (*pilE*), and through changes in nucleotide repeat number in *pilC* genes (van der Woude and Baumler 2004).

Common to **NM** and **Tb** diseases is also the depletion of the complement cascade function. In trypanosoma infections by *Tb gambiense* and *Tb rhodesiense*, reduction in complement activity is caused, at least partially, by massive activation triggered by the parasites themselves (Vincendeau and Bouteille 2006). This happens also in the cattle disease produced by *T. congolense*, where both the classical (Nielsen and Sheppard 1977) and alternative pathways (Tabel 1982) are activated, and by *Tb brucei*, where the classical pathway activation by VSG occurs in an antibody-independent fashion (Musoke and Barbet 1977). The complement cascade seems thus to be unable to prevent the establishment of parasites in the bloodstream (Devine, et al. 1986; Namangala 2011). Of note, Devine et al. (Devine, et al. 1986), described that *Tb gambiense* activates the alternative complement pathway in human serum, without activating a lytic activity. The cascade does not continue beyond the establishment of complement receptor 3 (C3) convertase on trypanosome surface.

On the other hand, human infection by **NM** begins by the colonization of the mucosal epithelium by the bacteria. **NM** adhere to the apical surface of mucosal epithelial cells in the cervix, conjunctiva, fallopian tubes, nasopharynx, rectum and urethra, by means of type IV pilin. The *Opa* proteins mediate intimate adherence and internalization, and adhesins and invasins, like LOS, mediate the infection of epithelial cell subgroups; the pilus and the porins interact cooperatively with CR3 on cervical epithelium (Coureuil, et al. 2013). Each mucosa might have special adhesins and molecules involved in adhesion and internalization that will not be described herein.

#### Conserved host and pathogen-specific pathways

Next we searched for a common denominator that could lead us through the results depicted in Fig. 3, to accomplish the potential existence of common, as well as pathogen-specific -unique- interaction mechanisms to guide the host-pathogen communication. Detailed conserved and unique PPIs occurring in different compartments are listed in Table 1.

In Fig. 3 host proteins that interact with proteins from the three pathogens are organized according to their location (green nodes), in six different cellular compartments.

Common (and conserved) extracellular proteins are used to build up the interactome from the NM and Tb pathogen side: immunoglobulin heavy constant gamma-1 (IGHG1) chain, tubulointerstitial nephritis antigen-like protein (TINAGL1), latent-transforming growth factor beta-binding protein-4 (LTBP4) and interleukin-18-binding protein (IL18BP).

Host plasma membrane proteins include HLAs (human leukocyte antigen; HLA-B, HLA-DRA, HLA-DRB1 and HLA-DRB5), CD surface protein (CD74), Macrophage-expressed gene 1 protein (MPEG1), immunoglobulin superfamily member-6 (IGSF6) and sialic acid-binding Ig-like lectin-11 (SIGLEC11). All these are conserved human proteins used to build up the interactome for both NM and Tb diseases.

Cytoplasmic proteins include the host factor p53 (Tp53, to modulate apoptosis and inflammation for a suitable infection environment) and transforming growth factor beta-1-induced transcript 1 protein (TGFB1i1) that regulates integrin, Wnt and TGFB signaling pathways. Of note the multiple subcellular localization of host key proteins, potentially increase probability interaction. This redundant localization includes HLA molecules (HLA-DRB1 and HLA-DRB5) in Golgi apparatus and in endoplasmic reticulum. Key interactions produced in the cytoplasm reoccur at the nucleus; for instance p53 or TGFB1i1 (also in the cytoskeleton).

Cyto-nuclear interactions include proteasome related proteins (PSME2 and PSMD3), Transforming growth factor beta regulator 1 (TBRG1) and Pre-B-cell leukemia transcription factor 2 (PBX2); finally, in the lysosomal compartment, interaction with HLA molecules (HLA-DRB1 and HLA-DRB5) is common for NM and Tb pathogens.

#### Host-pathogen interactions conserved in the three networks

The triple comparison highlights conserved host protein interactions with proteins from all three pathogens, as well as the interactions of core four conserved proteins present in all three interactomes as detailed in Fig. 5. Of note, kingdom-typical

interactions are evident: trypanosomes are eukaryotes and potentially can interact with proteins located either at the nucleus or the mitochondria, while bacteria and viruses are prokaryotic and the potential interactions include metabolic enzymes.

Typical virus-interactions switch off the host translation or transcription machinery as is the case for the herein described protein PCNA (cyclin), a proliferating nuclear antigen essential for replication and involved in DNA repair, epigenetics and chromatin remodeling. Examples of this type of interaction exist in the literature. The Myxovirus Resistance Protein (MX1) interacts with tubulin. MX1 is upregulated during virus infection and has been involved in the inhibition of virus replication in many species like Influenza A virus in rodents (Haller, et al. 2007), or binding to the nucleocapsid viral protein in humans, inhibiting replication, or nucleocapsid transport to the nucleus -where they replicate- (Martens and Howard 2006). Alternatively, the cell function of MX1 may relate to protein transport through the microtubules network (Racicot and Ott 2011).

The roles of pathogen vs. host-cell cytoskeletal proteins during invasion, interaction and successful establishment of infection are challenging to dissect in eukaryotic pathogens. For example, *Leishmania donovani* parasite cyclophilin 40 (LdCyP40) mutants express similar properties for living as promastigotes (viability, axenic amastigote differentiation, and resistance to environmental stress), as wild type parasites. However, stationary growth phase –infective- parasites, that interact with the mammalian host cell, express defects in cell shape, subpellicular tubulin network organization and motility. Mutant parasites do not establish intracellular infection in murine macrophages and are easily eliminated at first 24 h post infection; complemented parasites express restored infectivity. This result suggests a crucial role for CyP40 on development of infecting parasites and of phosphorylation as a crucial regulator of protein-protein interaction during infection (Yau, et al. 2014).

When talking about the EF1a, an essential component of the translation machinery that delivers aminoacyl-tRNA to ribosomes, illustrative examples exist: Human immunodeficiency virus type 1 (HIV-1) gag-encoded proteins are fundamental for almost all stages of the viral life cycle. One of them, HIV-1 matrix protein (MA), interacts with EF1a. By this interaction EF1a is incorporated in HIV-1 virion membranes, and cleaved by the viral protease. This interaction impairs translation in vitro, a result consistent with a previously proposed model in which inhibition of translation by accumulation of Gag serves to release viral RNA from polysomes, permitting the RNA to be packaged into nascent virions (Cimarelli and Luban 1999; Ejiri 2002). Additionally, excretory–secretory products fundamental for the pathogenesis of *Giardia intestinalis* seem to be relevant for host parasite interactions, among them, EF1a and a 58 kDa protein, identified as arginine deiminase. EF1a localizes to the nuclear region in trophozoites but relocalizes to the cytoplasm during host cell interaction. Recombinant EF1a is recognized by giardiasis patients serum suggesting the importance of the released EF-1a during *Giardia* infection (Skarin, et al. 2011).

### Implications for Infection Biology

The results highlight the fundamental role of “recognition” as an initial step and “effector” activation as a final step within the chain of events that would eventually lead to the specific immune (defense) system activation. In fact, the Venn Diagram describes that trypanosomes, being eukaryotes, have the highest number of specific interactions with the host, followed by **NM** and being the **ZE**-specific interactions very low. A high proportion of overlap exist between *Neisseria*- and trypanosome- human interactions, and these conserved **PPIs** focus on host proteins related to the: immune system signaling, response to stress and reprogramming of host cell senescence. On the contrary, overlapping interactions between **ZE** and **NM** focus on mRNA stability and splicing while interaction overlap between **ZE** and **Tb** concerns translation and elongation, ribosome function and life cycle, meaning focus on protein translation.

Most interestingly, the interactome analysis singles out the clade of only four interacting proteins present in the host and interacting with all three pathogens. The aforementioned clade seems to participate in assuring the proper decoding of the genomic message to produce cellular proteins and relocate them at the appropriate place. Three of these four central fundamental hub proteins clearly relate with cytoskeleton organization and remodeling, being EF1a undoubtedly related to protein translation. However, EF1a proteins, also modulate cytoskeleton activities, exhibit chaperone-like activity, and are key proteins for cell proliferation and cell death in human tumors (Abbas, et al. 2015). In fact, EF1a assists replication of many RNA viruses, such as the respiratory syncytialvirus (RSV). In this case, down-regulation of EF1a restricts the expression of viral genomic RNA and the release of infectious virus (Wei, et al. 2014); in parasites, EF1a has also been implicated in pathogenesis (Nandan and Reiner 2005) and host cell invasion (Matsubayashi, et al. 2013).



This theme suggests organizational complexity along the evolution from virus, to bacteria, to metazoans, and offers multiple avenues for regulatory control, all with the aim of producing the appropriate cellular response to external stimuli. The pathogens activate a highly conserved, concerted immune (defense) response to preserve the integrity of the host. Whether or not this is the case for the herein analyzed pathogens has to be demonstrated.

### Probing the revealed protein-protein interactions of the central backbone of host defense

To validate these findings, potential experiments may be suggested with focus on the viral pathogen EBOV: In HIV viruses, the SWI/SNF complex subunit SMARCC2 (matrix-associated actin-dependent regulator of chromatin subfamily C) is a key factor in chromatin remodeling, being its innate function to suppress transcription. Thus, knocking down the HIV-1 associated SMARCC2 (Baf53) gene, increase viral gene expression from transiently and chronically infected cells (Van Duyne, et al. 2011). A similar experimental approach, and the potential functional regulation exerted by phosphorylation would shed light in EBOV infections.

On the other hand, oligosaccharyltransferase complexes seem to be fundamental host factors for the propagation and replication of dengue virus. By the use of a genome-wide clustered, regularly interspaced, short palindromic repeat (CRISPR) screen, (Lin, et al. 2017) it has been demonstrated that the oligosaccharyltransferase complexes may be functioning as scaffolds, but also may act on nonstructural dengue virus proteins to mediate efficient synthesis, folding, and/or recruitment of nonstructural proteins to specific sites in the endoplasmic reticulum (Lin, et al. 2017). Similar experiments would share light to the mechanisms involved in the conserved host-pathogen **PPIs** herein described.

In addition to the central interaction clade, most host cell compartments are targeted by the pathogens, the overlap between host-pathogen interactions exposed best when comparing **NM** and **Tb**. Shared interacting host genes relate to antigen-presenting and proteasome processing of antigens, as well as tissue antigens, immunoglobulins and cytokines (IL2, IL18, TNF, TGF), and their receptors. Additionally, **NM** plasma membrane proteins have multiple localization niches indicating the reuse of function in these niches. This data highlights potential therapeutic targets for the design of agents to impair the infection produced by these pathogens.

What is clear is that as the sculptor of organisms is evolution, phenotypes favoring survival retain and contain information useful for this aim and permit evolution and survival to continue, and be preserved. We have defined for three pathogens, belonging to three kingdoms of life basic **PPIs** that seem to be central for pathogen interactions with the human host in general. The network may orchestrate an ancient common host response to infection, is validated for all four human interactions with Ebola virus protein VP24 (Garcia-Dorival et al., 2014; Pichlmair et al., 2012) and should guide infection therapy design in a more rational and efficient way.

## Conclusions

We compared human host-pathogen interactions from three kingdoms of life and described conserved host responses triggered independently of the kingdom of life origin of the pathogen, virus, prokaryotic or eukaryotic pathogens. Though we span a huge evolutionary distance between the three pathogens studied regarding protein-interaction networks with the host, our results suggest and confirm by all available protein-protein interaction data and analysis of conservation and orthology an unexpected interaction clade of cytoskeletal and ribosomal proteins common to all three networks.

All three pathogens attack a similar (or the same) host mechanism that we may call a “non-identified Achilles heel of the host”, central to the affected response. In combination with some joined interaction partners this mechanism may orchestrate a common defense response to all three diseases, a fundamental but general response, validated interactions are available for VP24 from ZE for all four conserved human proteins.

These findings should prompt a number of further studies to show further conservation of this host defense backbone for other pathogens by bioinformatical analysis as well as direct experimental tests of the predicted general and specific protein interactions.

## Methods

### Proteomes and amino acid sequences

The reference proteomes of human (reference proteome accession: UP000005640) and *Bundibugyo ebolavirus* (reference proteome accession: UP000143891) were retrieved from Uniprot database (The UniProt 2017). Furthermore, the reference proteomes of *Trypanosoma brucei brucei* TREU927 (genome assembly ASM244v1, RefSeq assembly accession: GCF\_000002445.1) and *Neisseria meningitidis* MC58 (genome assembly ASM880v1, RefSeq assembly accession: GCF\_000008805.1) were retrieved from RefSeq database (O'Leary, et al. 2016).

### **Inferring protein-protein interactions based on interologs**

The aim, design and setting of the study was hence to seek direct information on the proteins and protein interactions in three pathogens from different kingdoms to reveal potential conserved host interactions as well as specific or only partly shared protein interactions. The key method to obtain for such comparisons sufficient data is the inference of protein-protein interactions based on interologs. Our specific approach is given in the following.

The experimentally determined host-pathogen PPIs from PHISTO database (Durmus Tekir, et al. 2013) and PPIs present in the DIP (Database of Interacting Proteins) database (Salwinski, et al. 2004) were used as a template to reconstruct interologs (Yu, et al. 2004) based PPIs networks of human-ZE, human-Tb and human-NM. The stand-alone InParanoid program version 4.1 was used to assign proteins from the three pathogens to orthology groups. It uses the reciprocal best blast hit strategy to identify the clusters of orthologs and paralogs (Sonnhammer and Ostlund 2015). Only the seed ortholog pair whose Bootstrap values was 100% were considered to increase prediction confidence.

### **Pruning PPIs with domain-domain interactions**

The amino acid sequences of identified non-redundant DIP based interologs host-pathogen PPIs were extracted and domains were assigned to the sequences using Pfam version 29.0 (Finn, et al. 2016). The information of interacting protein domains was prepared using the three databases Domine (Yellaboina, et al. 2011), DIMA 3.0 (Luo, et al. 2011) and IDDI database (Kim, et al. 2012). They consider the information of the Pfam families suggested to interact based on structural information present in the protein complexes available in Protein Data Bank (PDB) (Berman, et al. 2002). This list was used to parse the DIP based interologs PPIs using customized Perl scripts and only those interolog interactions were retained that consist of at least one true domain-domain interaction pair as mentioned in the used databases.

### **Host-pathogen PPI networks**

The host-pathogen PPIs predicted from both the PHISO and domain-domain interactions supported DIP based interactions were merged and redundancies were removed. Cytoscape version 2.8.1 (Shannon, et al. 2003) was used to visualize the all three host-pathogen PPI networks. The network hubs were determined using the cyto-Hubba plugin (Chin, et al. 2014). The networks were further curated by extensive manual effort and the connectors of proteins related to human immune system were retrieved to generate three subnetworks.

### **Gene-Ontology (GO) annotation**

The protein sequences of pathogen interacting host proteins were extracted from all three-established host-pathogen PPIs and resulting proteins were functionally annotated by the BLAST2GO software suite version 2.4.1 (Conesa, et al. 2005). Fisher's exact test was used to identify significantly over-represented GO terms.

### **Pathway over-representation analysis**

The pathway over-representation analysis of conserved human proteins that were targeted by at least two pathogens was performed using the pathway analysis tool at InnateDB database (Breuer, et al. 2013). The p-value was calculated using hypergeometric tests, and Benjamini-Hochberg adjustment was used for multiple test correction.

### **Subcellular localization**

The subcellular localization of immune related human proteins was determined with extended version of KnowPredsite (Lin, et al. 2009) available at UniLoc server (bioapp.iis.sinica.edu.tw/UniLoc/), a knowledge-based classifier for protein subcellular

localization. The prediction server KnowPredsite II is capable of predicting single and multiple localization sites for both the eukaryotic and prokaryotic proteins.

## Abbreviations

PPI, protein-protein interaction; PPIs, protein-protein interactions; DIP, database of interacting proteins; HLA, human leucocyte antigen; **ZE** for *Zaire ebolavirus*, Bundibugyo ebolavirus; **NM**, *Neisseria meningitidis*; **Tb** for *Trypanosoma brucei*; individual protein abbreviations see Additional file 3;

## Declarations

### Ethics approval and consent to participate or to publish:

Not applicable, this manuscript does not include human participants, human data or human tissue.

### Availability of data and material:

The datasets generated and analysed during the current study are all available in the manuscript and its supplementary materials

### Competing interests:

The authors declare that they have no competing interests neither financial nor non-financial.

### Funding:

This work was supported by the Deutsche Forschungsgemeinschaft (GRK 2157 3D tissue infect; project number **270563345**) for funding. APS acknowledges the support of the Alexander von Humboldt Foundation for return visits to Würzburg University and Missionärztliches Institut, Würzburg.

### Author contributions:

TD was responsible for project design, data analysis, manuscript writing and correction; SG was responsible for data collection, bioinformatic data analysis, manuscript writing and correction; EB was responsible for data collection and manuscript correction; APS was responsible for literature collection, data analysis, manuscript writing and correction.

### Acknowledgements:

We thank Dr. Rapp-Galmiche for stylistic and language corrections.

## References

- Abbas W, Kumar A, Herbein G 2015. The eEF1A Proteins: At the Crossroads of Oncogenesis, Apoptosis, and Viral Infections. *Front Oncol* 5: 75. doi: 10.3389/fonc.2015.00075
- Alberts B, Johnson, A., Lewis, J., Raff, M., Roberts, K. X., Walter P. . 2002. *Molecular Biology of the Cell*, 4th edition. New York: Garland Science.
- Aloy P, Ceulemans H, Stark A, Russell RB 2003. The relationship between sequence and interaction divergence in proteins. *J Mol Biol* 332: 989-998.
- Bavari S, et al. 2002. Lipid raft microdomains: a gateway for compartmentalized trafficking of Ebola and Marburg viruses. *J Exp Med* 195: 593-602.
- Berman HM, et al. 2002. The Protein Data Bank. *Acta Crystallogr D Biol Crystallogr* 58: 899-907.

- Breuer K, et al. 2013. InnateDB: systems biology of innate immunity and beyond—recent updates and continuing curation. *Nucleic Acids Res* 41: D1228-1233. doi: 10.1093/nar/gks1147
- Brown KR, Jurisica I 2007. Unequal evolutionary conservation of human protein interactions in interologous networks. *Genome Biol* 8: R95. doi: 10.1186/gb-2007-8-5-r95
- Chin CH, et al. 2014. cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC Syst Biol* 8 Suppl 4: S11. doi: 10.1186/1752-0509-8-S4-S11
- Cimarelli A, Luban J 1999. Translation elongation factor 1-alpha interacts specifically with the human immunodeficiency virus type 1 Gag polyprotein. *J Virol* 73: 5388-5401.
- Conesa A, et al. 2005. Blast2GO: a universal tool for annotation, visualization and analysis in functional genomics research. *Bioinformatics* 21: 3674-3676. doi: 10.1093/bioinformatics/bti610
- Coureur M, et al. 2013. Pathogenesis of meningococemia. *Cold Spring Harb Perspect Med* 3. doi: 10.1101/cshperspect.a012393
- Crua Asensio N, Munoz Giner E, de Groot NS, Torrent Burgas M 2017. Centrality in the host-pathogen interactome is associated with pathogen fitness during infection. *Nat Commun* 8: 14092. doi: 10.1038/ncomms14092
- Devine DV, Falk RJ, Balber AE 1986. Restriction of the alternative pathway of human complement by intact *Trypanosoma brucei* subsp. *gambiense*. *Infect Immun* 52: 223-229.
- Donelson JE, Hill KL, El-Sayed NM 1998. Multiple mechanisms of immune evasion by African trypanosomes. *Mol Biochem Parasitol* 91: 51-66.
- Douglas JL, et al. 2010. The great escape: viral strategies to counter BST-2/tetherin. *PLoS Pathog* 6: e1000913. doi: 10.1371/journal.ppat.1000913
- Durmus Tekir S, et al. 2013. PHISTO: pathogen-host interaction search tool. *Bioinformatics* 29: 1357-1358. doi: 10.1093/bioinformatics/btt137
- Durmus Tekir S, Cakir T, Ulgen KO 2012. Infection Strategies of Bacterial and Viral Pathogens through Pathogen-Human Protein-Protein Interactions. *Front Microbiol* 3: 46. doi: 10.3389/fmicb.2012.00046
- Dyer MD, Murali TM, Sobral BW 2007. Computational prediction of host-pathogen protein-protein interactions. *Bioinformatics* 23: i159-166. doi: 10.1093/bioinformatics/btm208
- Ejiri S 2002. Moonlighting functions of polypeptide elongation factor 1: from actin bundling to zinc finger protein R1-associated nuclear localization. *Biosci Biotechnol Biochem* 66: 1-21. doi: 10.1271/bbb.66.1
- Falasca L, et al. 2015. Molecular mechanisms of Ebola virus pathogenesis: focus on cell death. *Cell Death Differ* 22: 1250-1259. doi: 10.1038/cdd.2015.67
- Finn RD, et al. 2016. The Pfam protein families database: towards a more sustainable future. *Nucleic Acids Res* 44: D279-285. doi: 10.1093/nar/gkv1344
- Fraser HB, Hirsh AE, Steinmetz LM, Scharfe C, Feldman MW 2002. Evolutionary rate in the protein interaction network. *Science* 296: 750-752. doi: 10.1126/science.1068696
- Furuyama W, et al. 2016. Fcγ-receptor 1a-mediated Src Signaling Pathway Is Essential for the Antibody-Dependent Enhancement of Ebola Virus Infection. *PLoS Pathog* 12: e1006139. doi: 10.1371/journal.ppat.1006139
- García-Dorival, I, et al. 2014. Elucidation of the Ebola virus VP24 cellular interactome and disruption of virus biology through targeted inhibition of host-cell protein function. *Journal of proteome research* 13.11 (2014): 5120-5135. doi: 10.1021/pr500556d

- Goeijenbier M, van Kampen JJ, Reusken CB, Koopmans MP, van Gorp EC 2014. Ebola virus disease: a review on epidemiology, symptoms, treatment and pathogenesis. *Neth J Med* 72: 442-448.
- Haller O, Stertz S, Kochs G 2007. The Mx GTPase family of interferon-induced antiviral proteins. *Microbes Infect* 9: 1636-1643. doi: 10.1016/j.micinf.2007.09.010
- Horn D, McCulloch R 2010. Molecular mechanisms underlying the control of antigenic variation in African trypanosomes. *Curr Opin Microbiol* 13: 700-705. doi: 10.1016/j.mib.2010.08.009
- Ito H, Watanabe S, Takada A, Kawaoka Y 2001. Ebola virus glycoprotein: proteolytic processing, acylation, cell tropism, and detection of neutralizing antibodies. *J Virol* 75: 1576-1580. doi: 10.1128/JVI.75.3.1576-1580.2001
- Itzhaki Z, Akiva E, Altuvia Y, Margalit H 2006. Evolutionary conservation of domain-domain interactions. *Genome Biol* 7: R125. doi: 10.1186/gb-2006-7-12-r125
- Kandasamy K, et al. 2010. NetPath: a public resource of curated signal transduction pathways. *Genome Biol* 11: R3. doi: 10.1186/gb-2010-11-1-r3
- Kanehisa M, et al. 2008. KEGG for linking genomes to life and the environment. *Nucleic Acids Res* 36: D480-484. doi: 10.1093/nar/gkm882
- Kim Y, Min B, Yi GS 2012. IDDI: integrated domain-domain interaction and protein interaction analysis system. *Proteome Sci* 10 Suppl 1: S9. doi: 10.1186/1477-5956-10-S1-S9
- Kuhl A, Pohlmann S 2012. How Ebola virus counters the interferon system. *Zoonoses Public Health* 59 Suppl 2: 116-131. doi: 10.1111/j.1863-2378.2012.01454.x
- Le Tortorec A, Willey S, Neil SJ 2011. Antiviral inhibition of enveloped virus release by tetherin/BST-2: action and counteraction. *Viruses* 3: 520-540. doi: 10.3390/v3050520
- Lin DL, et al. 2017. Dengue Virus Hijacks a Noncanonical Oxidoreductase Function of a Cellular Oligosaccharyltransferase Complex. *MBio* 8. doi: 10.1128/mBio.00939-17
- Lin HN, Chen CT, Sung TY, Ho SY, Hsu WL 2009. Protein subcellular localization prediction of eukaryotes using a knowledge-based approach. *BMC Bioinformatics* 10 Suppl 15: S8. doi: 10.1186/1471-2105-10-S15-S8
- Littler SJ, Hubbard SJ 2005. Conservation of orientation and sequence in protein domain-domain interactions. *J Mol Biol* 345: 1265-1279. doi: 10.1016/j.jmb.2004.11.011
- Luo Q, Pagel P, Vilne B, Frishman D 2011. DIMA 3.0: Domain Interaction Map. *Nucleic Acids Res* 39: D724-729. doi: 10.1093/nar/gkq1200
- Martens S, Howard J 2006. The interferon-inducible GTPases. *Annu Rev Cell Dev Biol* 22: 559-589. doi: 10.1146/annurev.cellbio.22.010305.104619
- Matsubayashi M, et al. 2013. Elongation factor-1 $\alpha$  is a novel protein associated with host cell invasion and a potential protective antigen of *Cryptosporidium parvum*. *J Biol Chem* 288: 34111-34120. doi: 10.1074/jbc.M113.515544
- Moldovan GL, Pfander B, Jentsch S 2007. PCNA, the maestro of the replication fork. *Cell* 129: 665-679. doi: 10.1016/j.cell.2007.05.003
- Moole H, et al. 2015. Association of clinical signs and symptoms of Ebola viral disease with case fatality: a systematic review and meta-analysis. *J Community Hosp Intern Med Perspect* 5: 28406. doi: 10.3402/jchimp.v5.28406
- Musoke AJ, Barbet AF 1977. Activation of complement by variant-specific surface antigen of trypanosoma brucei. *Nature* 270: 438-440.

- Namangala B 2011. How the African trypanosomes evade host immune killing. *Parasite Immunol* 33: 430-437. doi: 10.1111/j.1365-3024.2011.01280.x
- Nandan D, Reiner NE 2005. Leishmania donovani engages in regulatory interference by targeting macrophage protein tyrosine phosphatase SHP-1. *Clin Immunol* 114: 266-277. doi: 10.1016/j.clim.2004.07.017
- Nielsen K, Sheppard J 1977. Activation of complement by trypanosomes. *Experientia* 33: 769-771.
- Nishimura D 2001. BioCarta. Biotech Software & Internet Report: The Computer Software Journal for Scientist 2: 117-120.
- O'Leary NA, et al. 2016. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res* 44: D733-745. doi: 10.1093/nar/gkv1189
- Panchenko AR, Wolf YI, Panchenko LA, Madej T 2005. Evolutionary plasticity of protein families: coupling between sequence and structure variation. *Proteins* 61: 535-544. doi: 10.1002/prot.20644
- Pays E 2006. The variant surface glycoprotein as a tool for adaptation in African trypanosomes. *Microbes Infect* 8: 930-937. doi: 10.1016/j.micinf.2005.10.002
- Phizicky EM, Fields S 1995. Protein-protein interactions: methods for detection and analysis. *Microbiol Rev* 59: 94-123.
- Pichlmair A, et al. 2012. Viral immune modulators perturb the human molecular network by common and unique strategies. *Nature* 487.7408 (2012): 486. doi: 10.1038/nature11289
- Ponte-Sucre A 2016. An Overview of Trypanosoma brucei Infections: An Intense Host-Parasite Interaction. *Front Microbiol* 7: 2126. doi: 10.3389/fmicb.2016.02126
- Racicot K, Ott T 2011. The myxovirus resistance protein, MX1, interacts with tubulin beta in uterine glandular epithelial cells. *Am J Reprod Immunol* 65: 44-53. doi: 10.1111/j.1600-0897.2010.00885.x
- Rewar S, Mirdha D 2014. Transmission of ebola virus disease: an overview. *Ann Glob Health* 80: 444-451. doi: 10.1016/j.aogh.2015.02.005
- Robertson IB, et al. 2015. Latent TGF-beta-binding proteins. *Matrix Biol* 47: 44-53. doi: 10.1016/j.matbio.2015.05.005
- Rouphael NG, Stephens DS 2012. Neisseria meningitidis: biology, microbiology, and epidemiology. *Methods Mol Biol* 799: 1-20. doi: 10.1007/978-1-61779-346-2\_1
- Rual JF, et al. 2005. Towards a proteome-scale map of the human protein-protein interaction network. *Nature* 437: 1173-1178. doi: 10.1038/nature04209
- Salwinski L, et al. 2004. The Database of Interacting Proteins: 2004 update. *Nucleic Acids Res* 32: D449-451. doi: 10.1093/nar/gkh086
- Shannon P, et al. 2003. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 13: 2498-2504. doi: 10.1101/gr.1239303
- Skarin H, Ringqvist E, Hellman U, Svard SG 2011. Elongation factor 1-alpha is released into the culture medium during growth of Giardia intestinalis trophozoites. *Exp Parasitol* 127: 804-810. doi: 10.1016/j.exppara.2011.01.006
- Sonnhammer EL, Ostlund G 2015. InParanoid 8: orthology analysis between 273 proteomes, mostly eukaryotic. *Nucleic Acids Res* 43: D234-239. doi: 10.1093/nar/gku1203
- Stijlemans B, et al. 2016. Immune Evasion Strategies of Trypanosoma brucei within the Mammalian Host: Progression to Pathogenicity. *Front Immunol* 7: 233. doi: 10.3389/fimmu.2016.00233

Tabel H 1982. Activation of the alternative pathway of bovine complement by *Trypanosoma congolense*. *Parasite Immunol* 4: 329-335.

Takada A, Ebihara H, Feldmann H, Geisbert TW, Kawaoka Y 2007. Epitopes required for antibody-dependent enhancement of Ebola virus infection. *J Infect Dis* 196 Suppl 2: S347-356. doi: 10.1086/520581

Takada A, Feldmann H, Ksiazek TG, Kawaoka Y 2003a. Antibody-dependent enhancement of Ebola virus infection. *J Virol* 77: 7539-7544.

Takada A, et al. 2003b. Identification of protective epitopes on ebola virus glycoprotein at the single amino acid level by using recombinant vesicular stomatitis viruses. *J Virol* 77: 1069-1074.

Tala A, et al. 2014. Serogroup-specific interaction of *Neisseria meningitidis* capsular polysaccharide with host cell microtubules and effects on tubulin polymerization. *Infect Immun* 82: 265-274. doi: 10.1128/IAI.00501-13

Teichmann SA 2002. The constraints protein-protein interactions place on sequence divergence. *J Mol Biol* 324: 399-407.

The UniProt C 2017. UniProt: the universal protein knowledgebase. *Nucleic Acids Res* 45: D158-D169. doi: 10.1093/nar/gkw1099

Valdar WS, Thornton JM 2001. Protein-protein interfaces: analysis of amino acid conservation in homodimers. *Proteins* 42: 108-124.

van der Woude MW, Baumlér AJ 2004. Phase and antigenic variation in bacteria. *Clin Microbiol Rev* 17: 581-611, table of contents. doi: 10.1128/CMR.17.3.581-611.2004

van Deuren M, Brandtzaeg P, van der Meer JW 2000. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev* 13: 144-166, table of contents.

Van Duyne R, et al. 2011. Varying modulation of HIV-1 LTR activity by Baf complexes. *J Mol Biol* 411: 581-596. doi: 10.1016/j.jmb.2011.06.001

Vanhamme L, et al. 2004. The *Trypanosoma brucei* reference strain TREU927/4 contains *T. brucei* rhodesiense-specific SRA sequences, but displays a distinct phenotype of relative resistance to human serum. *Mol Biochem Parasitol* 135: 39-47.

Vastrik I, et al. 2007. Reactome: a knowledge base of biologic pathways and processes. *Genome Biol* 8: R39. doi: 10.1186/gb-2007-8-3-r39

Vincendeau P, Bouteille B 2006. Immunology and immunopathology of African trypanosomiasis. *An Acad Bras Cienc* 78: 645-665.

Watanabe S, et al. 2000. Functional importance of the coiled-coil of the Ebola virus glycoprotein. *J Virol* 74: 10194-10201.

Wei T, et al. 2014. The eukaryotic elongation factor 1A is critical for genome replication of the paramyxovirus respiratory syncytial virus. *PLoS One* 9: e114447. doi: 10.1371/journal.pone.0114447

Welburn SC, Beange I, Ducrotoy MJ, Okello AL 2015. The neglected zoonoses—the case for integrated control and advocacy. *Clin Microbiol Infect* 21: 433-443. doi: 10.1016/j.cmi.2015.04.011

Yang H, et al. 2011. Insight into bacterial virulence mechanisms against host immune response via the *Yersinia pestis*-human protein-protein interaction network. *Infect Immun* 79: 4413-4424. doi: 10.1128/IAI.05622-11

Yau WL, et al. 2014. The *Leishmania donovani* chaperone cyclophilin 40 is essential for intracellular infection independent of its stage-specific phosphorylation status. *Mol Microbiol* 93: 80-97. doi: 10.1111/mmi.12639

Yellaboina S, Tasneem A, Zaykin DV, Raghavachari B, Jothi R 2011. DOMINE: a comprehensive collection of known and predicted domain-domain interactions. *Nucleic Acids Res* 39: D730-735. doi: 10.1093/nar/gkq1229

Zhou H, et al. 2013. Stringent DDI-based prediction of *H. sapiens*-*M. tuberculosis* H37Rv protein-protein interactions. BMC Syst Biol 7 Suppl 6: S6. doi: 10.1186/1752-0509-7-S6-S6



|                 | ZE                 | NM                         | TB                         | Full name / description of the protein   |
|-----------------|--------------------|----------------------------|----------------------------|--|
| Extracellular   |                    | IGHA2 <sup>5U</sup>        | IGHA2 <sup>3U</sup>        | Ig alpha-2 chain C region  |
|                 |                    | LTBP4 <sup>3U, 1C</sup>    | LTBP4 <sup>3U, 1C</sup>    | Latent-transforming growth factor beta-binding protein 4   |
|                 |                    | TINAGL1 <sup>11U, 2C</sup> | TINAGL1 <sup>3U, 2C</sup>  | Tubulointerstitial nephritis antigen-like (Glucocorticoid-inducible protein 5, (Oxidized LDL-responsive gene 2 protein) (Tubulointerstitial nephritis antigen-related protein, TIN Ag-related protein, TIN-Ag-RP)          |
|                 |                    | IL18BP <sup>1C</sup>       | IL18BP <sup>2U, 1C</sup>   | Interleukin-18-binding protein (IL-18BP, Tadekinig-alfa)   |
|                 |                    | IGKC <sup>10U</sup>        | IGKC <sup>2U</sup>         | Ig kappa chain C region (Fragment)   |
|                 |                    | IGHG1 <sup>2U, 1C</sup>    | IGHG1 <sup>1C</sup>        | Ig gamma-1 chain C region  |
|                 |                    | CD74 <sup>7U, 2C</sup>     | CD74 <sup>5U, 2C</sup>     | HLA class II histocompatibility antigen gamma chain (HLA-DR antigens-associated invariant chain, Ia antigen-associated invariant chain, Ii, p33)   |
| Plasma membrane | BST2 <sup>1U</sup> |                            |                            | Bone marrow stromal antigen 2 (HM1.24 antigen, Tetherin, CD antigen CD317)   |
|                 |                    | MPEG1 <sup>1C</sup>        | MPEG1 <sup>1C</sup>        | Macrophage-expressed gene 1 protein (Macrophage gene 1 protein, Mpg-1)   |
|                 |                    | IGHA2 <sup>5U</sup>        | IGHA2 <sup>3U</sup>        | Ig alpha-2 chain C region  |
|                 |                    | IL2RB <sup>1U</sup>        | IL2RB <sup>1U</sup>        | Interleukin-2 receptor subunit beta (IL-2 receptor subunit beta, IL-2R subunit beta, IL-2RB, High affinity IL-2 receptor subunit beta, p70-75, p75, CD antigen CD122)  |
|                 |                    | BCAP31 <sup>1U</sup>       | BCAP31 <sup>1U</sup>       | B-cell receptor-associated protein 31 (BCR-associated protein 31, Bap31, 6C6-AG tumor-associated antigen, Protein CDM, p28)  |
|                 |                    | IFI27 <sup>1U</sup>        | IFI27 <sup>1U</sup>        | Interferon alpha-inducible protein 27, mitochondrial (p27, Interferon alpha-induced 11.5 kDa protein, Interferon-stimulated gene 12a protein, ISG12(a))  |
|                 |                    | NKTR <sup>1U</sup>         | NKTR <sup>1U</sup>         | NK-tumor recognition protein (NK-TR protein) (Natural-killer cells cyclophilin-related protein, [Includes: Putative peptidyl-prolyl cis-trans isomerase (PPIase, EC 5.2.1.8, Rotamase)])                                   |
|                 |                    | SIGLEC11 <sup>1U, 1C</sup> | SIGLEC11 <sup>1U, 1C</sup> | Sialic acid-binding Ig-like lectin 11 (Sialic acid-binding lectin 11, Siglec-11)   |
|                 |                    | MCEMP1 <sup>1U</sup>       | MCEMP1 <sup>2U</sup>       | Mast cell-expressed membrane protein 1   |
|                 |                    | MS4A1 <sup>2U</sup>        | MS4A1 <sup>1U</sup>        | B-lymphocyte antigen CD20 (B-lymphocyte surface antigen B1, Bp35, Leukocyte surface antigen Leu-16, Membrane-spanning 4-domains subfamily A member 1, CD antigen CD20)   |
|                 |                    | CD74 <sup>7U, 2C</sup>     | CD74 <sup>5U, 2C</sup>     | HLA class II histocompatibility antigen gamma chain (HLA-DR antigens-associated invariant chain, Ia antigen-associated invariant chain, Ii, p33)   |
|                 |                    | TINAGL1 <sup>11U, 2C</sup> | TINAGL1 <sup>3U, 2C</sup>  | Tubulointerstitial nephritis antigen-like (Glucocorticoid-inducible protein 5, Oxidized LDL-responsive gene 2 protein, OLRG-2) (Tubulointerstitial nephritis antigen-related protein) (TIN Ag-related protein) (TIN-Ag-RP) |
|                 |                    | HLA-A <sup>1U</sup>        | HLA-A <sup>2U</sup>        | HLA class I histocompatibility antigen, A-29 alpha chain (Aw-19, MHC class I antigen A*29)   |
|                 |                    | HLA-B <sup>3U, 1C</sup>    | HLA-B <sup>1C</sup>        | HLA class I histocompatibility antigen, B-42 alpha chain (MHC class I antigen B*42)  |
|                 |                    | HLA-E <sup>3U</sup>        | HLA-E <sup>1U</sup>        | HLA class I histocompatibility antigen, alpha chain E (MHC class I antigen E)  |
|                 |                    | HLA-DRA <sup>1U, 1C</sup>  | HLA-DRA <sup>1U, 1C</sup>  | HLA class II histocompatibility antigen, DR alpha chain (MHC class II antigen DRA)   |
|                 |                    | HLA-DRB1 <sup>2U, 2C</sup> | HLA-DRB1 <sup>2C</sup>     | HLA class II histocompatibility antigen, DRB1-3 chain (Clone P2-beta-3, MHC class II antigen DRB1*3)   |
|                 |                    | HLA-DRB5 <sup>1U, 1C</sup> | HLA-DRB5 <sup>1C</sup>     | HLA class II histocompatibility antigen, DRB1-3 chain (Clone P2-beta-3, MHC class II antigen DRB1*3)   |
|                 |                    | IGSF6 <sup>1C</sup>        | IGSF6 <sup>1C</sup>        | Immunoglobulin superfamily member 6 (IgSF6) (Protein DORA)   |
| Cytoplasm       | BST2 <sup>1U</sup> |                            |                            | Bone marrow stromal antigen 2 (HM1.24 antigen, Tetherin, CD antigen CD317)   |
|                 |                    | PSME2 <sup>2C</sup>        | PSME2 <sup>2U, 2C</sup>    | Proteasome activator complex subunit 2 (11S regulator complex subunit beta) (REG-beta) (Activator of multicatalytic protease subunit 2, Proteasome activator 28 subunit beta, PA28b, PA28beta)                             |
|                 |                    | TRAF6 <sup>1U</sup>        | TRAF6 <sup>6U</sup>        | TNF receptor-associated factor 6 (EC 6.3.2.-) (E3 ubiquitin-protein ligase TRAF6, Interleukin-1 signal transducer, RING finger protein 85)   |
|                 |                    | TP53 <sup>2U, 1C</sup>     | TP53 <sup>5U, 1C</sup>     | Cellular tumor antigen p53 (Antigen NY-CO-13, Phosphoprotein p53, Tumor suppressor p53)  |

|                       |                    |                           |                        |   |
|-----------------------|--------------------|---------------------------|------------------------|---|
|                       |                    | PSMA7 <sup>1U</sup>       | PSMA7 <sup>1U</sup>    | Proteasome subunit alpha type-7 (EC 3.4.25.1) (Proteasome subunit RC6-1, Proteasome subunit XAPC7)  |
|                       |                    | TGFB1i1 <sup>1C</sup>     | TGFB1i1 <sup>1C</sup>  | Transforming growth factor beta-1-induced transcript 1 protein (Androgen receptor coactivator 55 kDa protein, Androgen receptor-associated protein of 55 kDa, Hydrogen peroxide-inducible clone 5 protein, Hic-5) |
|                       |                    | PSMD3 <sup>2C</sup>       | PSMD3 <sup>2C</sup>    | 26S proteasome non-ATPase regulatory subunit 3 (26S proteasome regulatory subunit RPN3, 26S proteasome regulatory subunit S3, Proteasome subunit p58)   |
|                       |                    | PAAF1 <sup>1U</sup>       | PAAF1 <sup>3U</sup>    | Proteasomal ATPase-associated factor 1 (Protein G-16, WD repeat-containing protein 71)  |
| Cytoskeleton          |                    | TGFB1i1 <sup>1C</sup>     | TGFB1i1 <sup>1C</sup>  | Transforming growth factor beta-1-induced transcript 1 protein (Androgen receptor coactivator 55 kDa protein, Androgen receptor-associated protein of 55 kDa, Hydrogen peroxide-inducible clone 5 protein, Hic-5) |
|                       |                    | PAAF1 <sup>1U</sup>       |                        | Proteasomal ATPase-associated factor 1 (Protein G-16, WD repeat-containing protein 71)  |
| Lysosome              |                    | HLA-DRB1 <sup>2U,2C</sup> | HLA-DRB1 <sup>2C</sup> | HLA class II histocompatibility antigen, DRB1-3 chain (Clone P2-beta-3, MHC class II antigen DRB1*3)  |
|                       |                    | HLA-DRB5 <sup>1U,1C</sup> | HLA-DRB5 <sup>1C</sup> | HLA class II histocompatibility antigen, DR beta 5 chain (DR beta-5) (DR2-beta-2, (Dw2, MHC class II antigen DRB5)  |
| Nucleus               | PCNA <sup>1U</sup> |                           | PCNA <sup>3U</sup>     | Proliferating cell nuclear antigen (Cyclin)   |
|                       |                    | TRAF6 <sup>1U</sup>       | TRAF6 <sup>6U</sup>    | TNF receptor-associated factor 6 (EC 6.3.2.-) (E3 ubiquitin-protein ligase TRAF6, Interleukin-1 signal transducer, RING finger protein 85)  |
|                       |                    | PSME2 <sup>2C</sup>       | PSME2 <sup>2U,2C</sup> | Proteasome activator complex subunit 2 (11S regulator complex subunit beta) (REG-beta) (Activator of multicatalytic protease subunit 2, Proteasome activator 28 subunit beta, PA28b, PA28beta)                    |
|                       |                    | PAAF1 <sup>1U</sup>       | PAAF1 <sup>3U</sup>    | Proteasomal ATPase-associated factor 1 (Protein G-16, WD repeat-containing protein 71)  |
|                       |                    | TBRG1 <sup>1U,1C</sup>    | TBRG1 <sup>1U,1C</sup> | Transforming growth factor beta regulator 1 (Nuclear interactor of ARF and Mdm2)  |
|                       |                    | PBX2 <sup>1C</sup>        | PBX2 <sup>1U,1C</sup>  | Pre-B-cell leukemia transcription factor 2 (Homeobox protein PBX2) (Protein G17)  |
|                       |                    | PSMD3 <sup>2C</sup>       | PSMD3 <sup>2C</sup>    | 26S proteasome non-ATPase regulatory subunit 3 (26S proteasome regulatory subunit RPN3, 26S proteasome regulatory subunit S3, Proteasome subunit p58)   |
|                       |                    | PSMA7 <sup>1U</sup>       | PSMA7 <sup>1U</sup>    | Proteasome subunit alpha type-7 (EC 3.4.25.1) (Proteasome subunit RC6-1, Proteasome subunit XAPC7)  |
|                       |                    | TGFB1i1 <sup>1C</sup>     | TGFB1i1 <sup>1C</sup>  | Transforming growth factor beta-1-induced transcript 1 protein (Androgen receptor coactivator 55 kDa protein, Androgen receptor-associated protein of 55 kDa, Hydrogen peroxide-inducible clone 5 protein, Hic-5) |
| Endoplasmic reticulum |                    | TP53 <sup>2U,1C</sup>     | TP53 <sup>5U,1C</sup>  | Cellular tumor antigen p53 (Antigen NY-CO-13, Phosphoprotein p53, Tumor suppressor p53)   |
|                       |                    | HLA-DRB1 <sup>2U,2C</sup> | HLA-DRB1 <sup>2C</sup> | HLA class II histocompatibility antigen, DRB1-3 chain (Clone P2-beta-3, MHC class II antigen DRB1*3)  |
|                       |                    | HLA-DRB5 <sup>1U,1C</sup> | HLA-DRB5 <sup>1C</sup> | HLA class II histocompatibility antigen, DR beta 5 chain (DR beta-5) (DR2-beta-2, (Dw2, MHC class II antigen DRB5)  |
|                       |                    | BCAP31 <sup>1U</sup>      | BCAP31 <sup>1U</sup>   | B-cell receptor-associated protein 31 (BCR-associated protein 31) (Bap31, 6C6-AG tumor-associated antigen, Protein CDM, p28)  |
| Golgi apparatus       | BST2 <sup>1U</sup> |                           |                        | Bone marrow stromal antigen 2 (HM1.24 antigen, Tetherin, CD antigen CD317)  |
|                       |                    | HLA-DRB1 <sup>2U,2C</sup> | HLA-DRB1 <sup>2C</sup> | HLA class II histocompatibility antigen, DRB1-3 chain (Clone P2-beta-3, MHC class II antigen DRB1*3)  |
|                       |                    | HLA-DRB5 <sup>1U,1C</sup> | HLA-DRB5 <sup>1C</sup> | HLA class II histocompatibility antigen, DR beta 5 chain (DR beta-5) (DR2-beta-2, (Dw2, MHC class II antigen DRB5)  |
|                       |                    | BCAP31 <sup>1U</sup>      | BCAP31 <sup>1U</sup>   | B-cell receptor-associated protein 31 (BCR-associated protein 31) (Bap31, 6C6-AG tumor-associated antigen, Protein CDM, p28)  |
| Centriole             |                    | PAAF1 <sup>1U</sup>       | PAAF1 <sup>3U</sup>    | Proteasomal ATPase-associated factor 1 (Protein G-16, WD repeat-containing protein 71)  |

Color code: **Inteferon associated proteins**, **Antigen, antibody and HLA associated proteins**, **Cytokine and chemokine associated proteins**, **Proteasome associated proteins**, **Transcription factors associated proteins**, **Cell recognition associated proteins**. Note that EBOV-human immune system interaction concentrates in two proteins, one at the nuclear level (proliferation) and one that can be found in the cytoplasm,

Golgi apparatus and plasma membrane. On the other hand, human -immune related- proteins involved in the interaction with *T. brucei* and *N. meningitidis* overlap in high proportion. In the table the following codes are used: U for unique, and C for conserved interactions; the numbers correspond to the number of pathogenic proteins in corresponding category interacting with them. Information about the function of these proteins can be found in the Additional file 3.

\

**Table 2: List of proteins identified as shared hubs among the human interactome and ZE, TB and NM proteins**

| Human protein  | UniProt ID | Human protein function                                       | Pathogen                         | Protein from pathogen   | Uniprot ID | Pathogen protein function                                | Reported experimental validation   | Reference                   |
|--|------------|--|----------------------------------|---|------------|--|------------------------------------|-----------------------------|
| Nucleoside diphosphate-4-epimerase<br>in<br>Nucleoside transferase<br>it 1 | P04843     | Post-translational protein modification                      | <i>Trypanosoma brucei brucei</i> | DNA polymerase kappa  | Q384G6     | Error-prone translesion synthesis                        | N/A                                |                             |
|  |            |  | <i>Trypanosoma brucei brucei</i> | Endoplasmic reticulum oxidoreductin                                 | Q57UW3     | Protein folding  | N/A                                |                             |
|  |            |  | <i>Trypanosoma brucei brucei</i> | Protein transport protein Sec13                                     | Q388I4     | Protein transport from endoplasmic reticulum             | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | DNA polymerase IV   | Q9JYS8     | DNA replication, Error-prone translesion synthesis       | N/A                                |                             |
|  |            |  | Ebola virus                      | Membrane-associated protein VP24                                    | Q05322     | Host-virus interaction, influencing host immune response | affinity chromatography technology | García-Dorival, et al. 2014 |
| Interferon complex subunit<br>ICC2   | Q8TAQ2     | Chromatin remodeling   | <i>Trypanosoma brucei brucei</i> | Aldehyde dehydrogenase  | Q38AY7     | Catalysis aldehyde oxidation                             | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | Succinate-semialdehyde dehydrogenase                                | Q9JYP4     | Cell grown in presence of Mn                             | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | Ferrochelatase  | Q9K097     | Porphyrin biosynthesis                                   | N/A                                |                             |
|  |            |  | Ebola virus                      | Membrane-associated protein VP24                                    | Q05322     | Host-virus interaction, influencing host immune response | tandem affinity purification       | Pichlmair, et al. 2012      |
| Transcription factor 1-alpha   | P68104     | Transcription regulation                                     | <i>Trypanosoma brucei brucei</i> | Elongation factor 1 gamma   | Q382L7     | Transcription regulation                                 | N/A                                |                             |
|  |            |  | <i>Trypanosoma brucei brucei</i> | ATP-dependent Clp protease subunit, heat shock protein 100 (HSP100) | Q586B8     | Regulating mitochondrial DNA replication                 | N/A                                |                             |
|  |            |  | <i>Trypanosoma brucei brucei</i> | Mitogen-activated protein kinase                                    | Q26802     | Intracellular survival of <i>Trypanosoma</i>             | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | Cytidylate kinase   | P57065     | Nucleic acid biosynthesis                                | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | Uncharacterized protein   | Q9JYB3     | N/A  | N/A                                |                             |
|  |            |  | Ebola virus                      | Membrane-associated protein VP24                                    | Q05322     | Host-virus interaction, influencing host immune response | tandem affinity purification       | Pichlmair, et al. 2012      |
| in beta-5 chain  | P07437     | The major component of microtubules (cytoskeleton formation) | <i>Trypanosoma brucei brucei</i> | Mitogen-activated protein kinase                                    | Q26802     | Intracellular survival of <i>Trypanosoma</i>             | N/A                                |                             |
|  |            |  | <i>Neisseria meningitidis</i>    | Biosynthetic arginine decarboxylase                                 | Q9K0U3     | Agmatine biosynthesis                                    | N/A                                |                             |
|  |            |  |                                  |   |            |  |                                    |                             |

|  |  |  |             |                                  |        |  |                              |                        |
|--|--|--|-------------|----------------------------------|--------|--|------------------------------|------------------------|
|  |  |  | Ebola virus | Membrane-associated protein VP24 | Q05322 | Host-virus interaction, influencing host immune response | tandem affinity purification | Pichlmair, et al. 2012 |
|--|--|--|-------------|----------------------------------|--------|--|------------------------------|------------------------|

N/A - not available

Figures

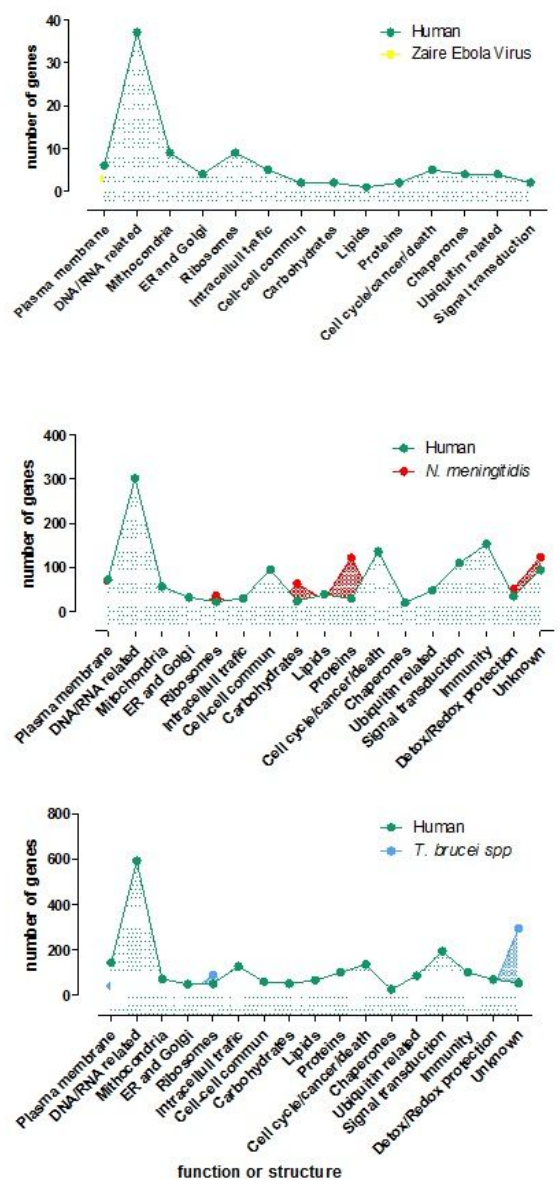
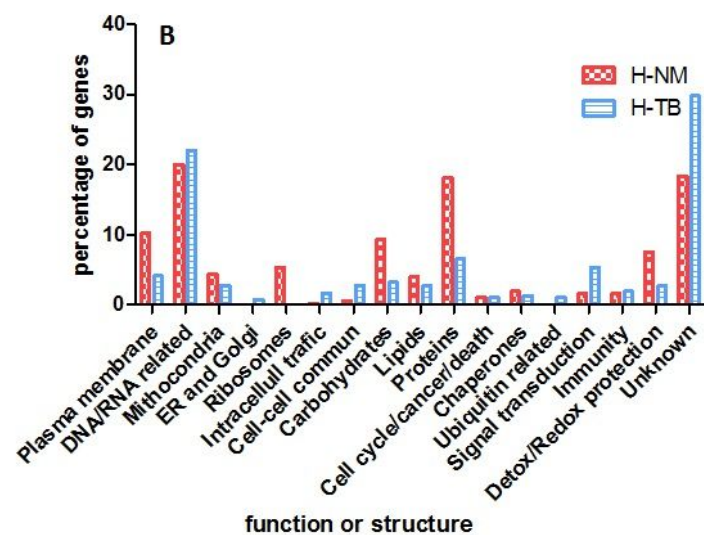
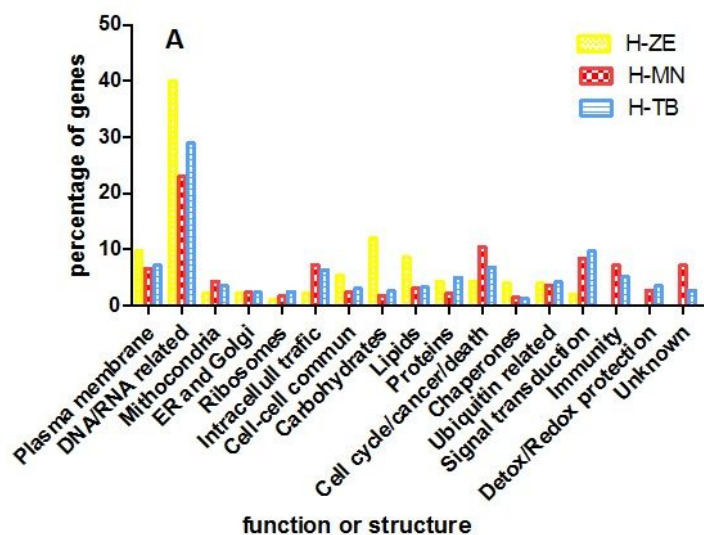


Figure 1

Number of genes involved in each pathogen interactome and its counterpart in humans as detailed.

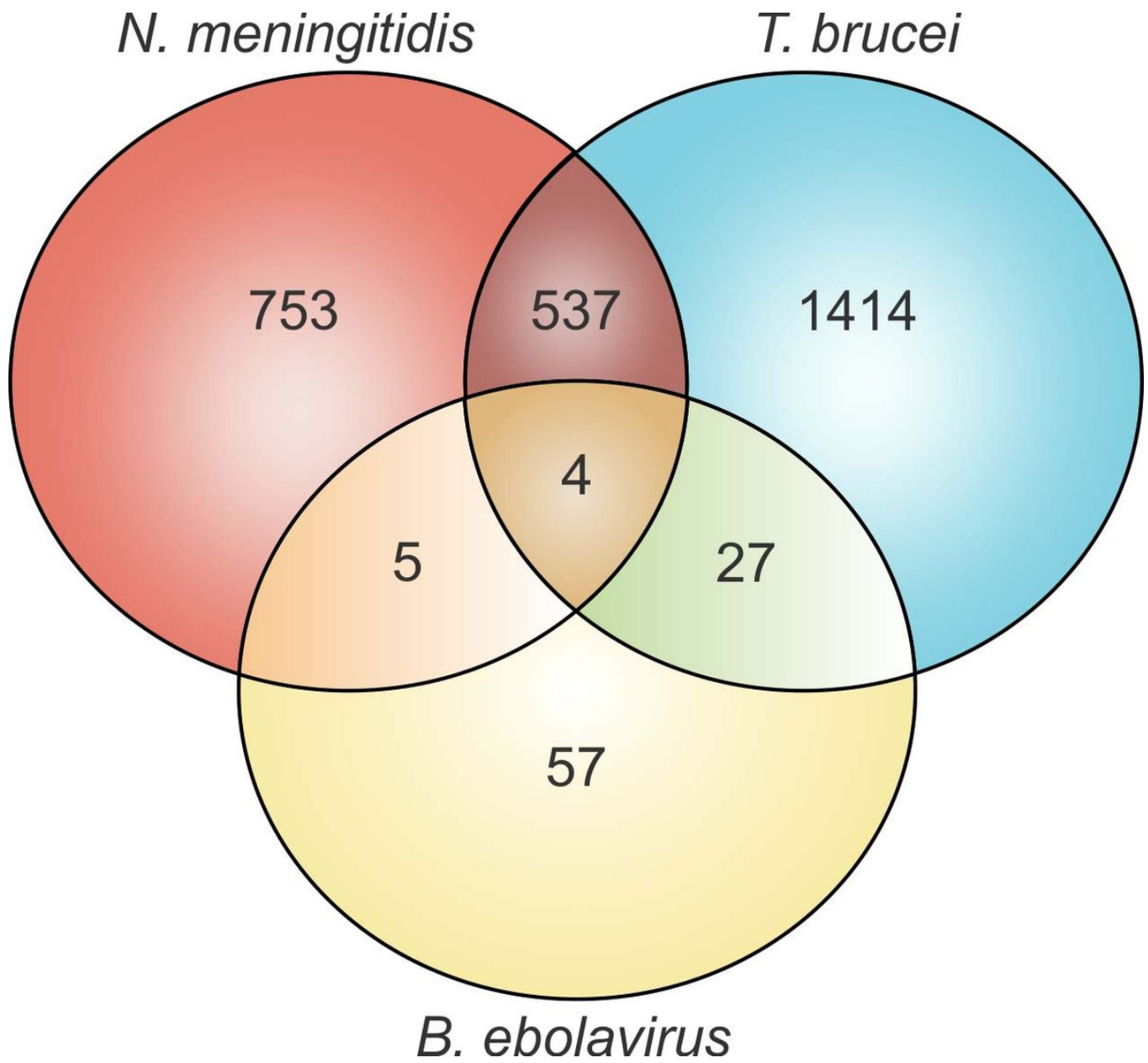


**Figure 2**

Comparison of percentages of genes participating in the interactome. A.-Human genes involved in the interactome for each disease. B.- Pathogen genes related to their function or structure.



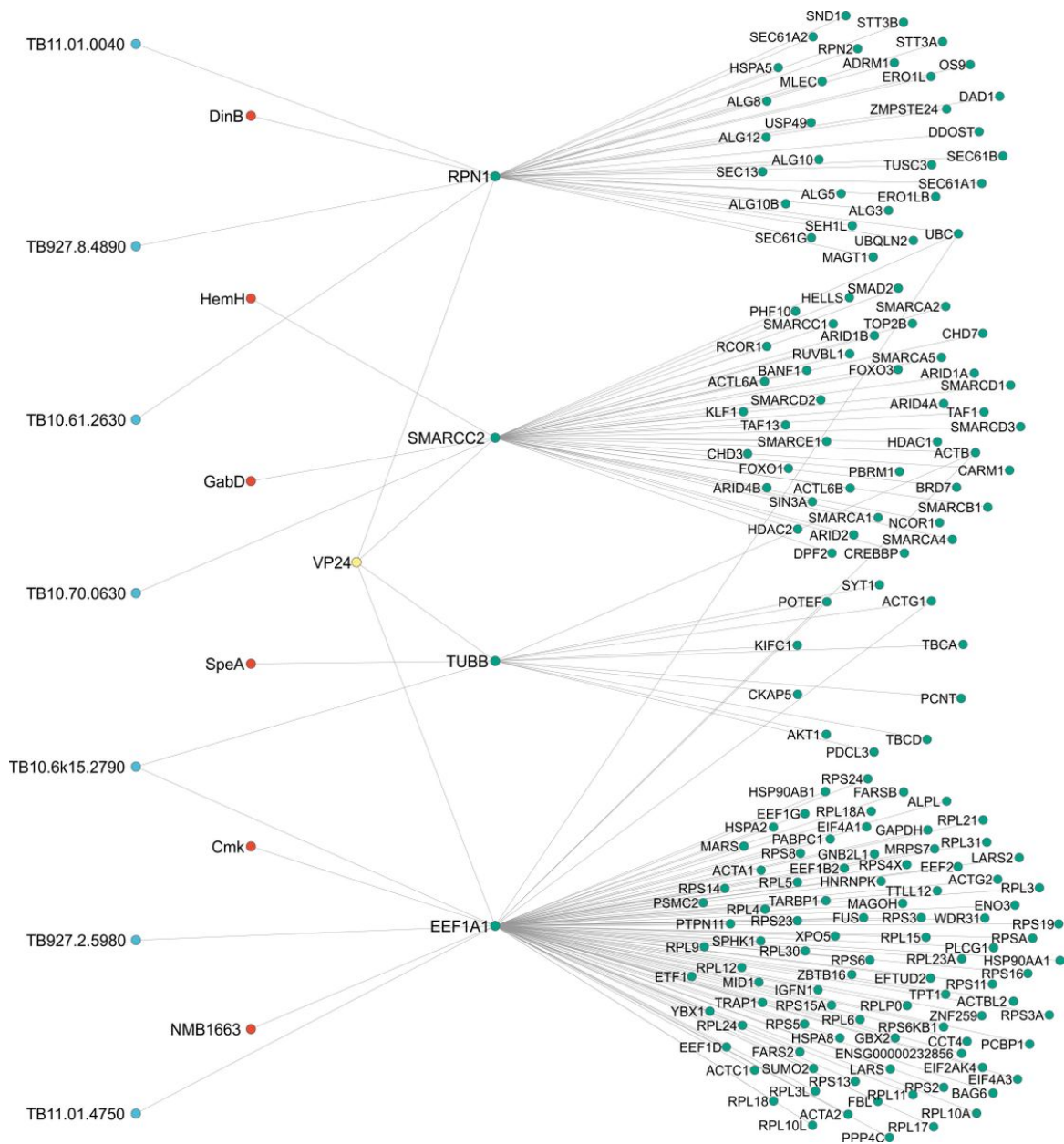




**Figure 4**

Unique and common targeted human proteins by three pathogens. The figure details the targeted human proteins *Neisseria meningitidis*, *Trypanosoma brucei* and *Zaire ebolavirus*, highlighting those that are unique from those that are commonly targeted proteins.





**Figure 5**

Pathogen targeting common hubs of human interactome. Only the primary interactors of common hubs are shown. The color of the nodes indicates the different organism's proteins (blue = *Trypanosoma brucei*; red = *Neisseria meningitidis*; yellow = Zaire ebolavirus; and green = Human).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement.zip](#)