# SUPPLEMENTARY INFORMATION:
# Host-pathogen protein interactions predicted by comparative modeling

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# SUPPLEMENTARY INFORMATION

### Additional examples of predicted interactions

We predicted that PFI0595c, a hypothetical *P. falciparum* protein, may interact with human CD51 (Integrin alpha-V; ENSP0000261023) based on a structure of platelet membrane glycoprotein IIIA bound to CD51 (PDB 1JV2 (Xiong et al. 2001)) (Fig S1(a)). Previous studies have observed that *P. falciparum* adherence to human microvascular endothelial cells involves CD51 (Siano et al. 1998). In addition, no interactions were predicted between integrins, such as CD51, and *P. vivax* proteins. This prediction is in agreement with previous experimental evidence that indicates *P. vivax* does not engage in microvascular sequestration (Silamut et al. 1999).

We predicted that the hypothetical *P. falciparum* meta-caspase PF13_0289 may potentially interact with several human apoptosis inhibitors, including X-linked inhibitor of apoptosis protein (XIAP), melanoma inhibitor of apoptosis protein (ML-IAP), and neuronal apoptosis inhibitory protein, based on a template structure of caspase-9 interacting with baculovirus inhibitor of apoptosis protein (PDB 1NW9) (Fig S1(b)). Animal inhibitors of apoptosis, such as XIAP, have been shown to affect cell death programs in plants, which contain meta-caspases (Dickman et al. 2001; Lincoln et al. 2002). In addition, apoptosis-like cell death has recently been observed in the mid-gut of mosquitoes as a result of malaria infection (Hurd et al. 2006). These observations suggest that apoptotic machinery cross-talk, such as the interactions predicted here, may be relevant to *in vivo* infection.

## TABLES

| | Pathogen | Pathogen Protein | Human Protein | Evidence | Predicted |
|---|---|---|---|---|---|
| 1 | *M. leprae* | histone-like protein | laminin-2 | (Soares de Lima et al. 2005) | No template |
| 2 | *M. leprae* | fibronectin-attachment protein | fibronectin | (Thole et al. 1992) | No template |
| 1 | *M. tuberculosis* | Rv3763 | TLR2 | (Lopez et al. 2003) | No template |
| 2 | *M. tuberculosis* | Rv1411c | TLR2 | (Gehring et al. 2004) | No template |
| 3 | *M. tuberculosis* | glycoprotein Apa | pulmonary surfactant protein A | (Ragas et al. 2007) | No template |
| 4 | *M. tuberculosis* | heparin-binding hemagluttanin | complement C3 | (Mueller-Ortiz et al. 2001) | No template |
| 5 | *M. tuberculosis* | fibronectin-attachment protein | fibronectin | (Abou-Zeid et al. 1991; Mueller-Ortiz et al. 2001) | No template |
| | *L. major* | none | | | |
| 1 | *T. brucei* | ornithine decarboxylase | ornithine decarboxylase | (Osterman et al. 1994) | Yes |
| 2 | *T. brucei* | serum resistance associated protein | apolipoprotein L-I | (Vanhamme et al. 2003) | No template |
| 3 | *T. brucei* | trypanopain-Tb | cystatins | (Troeberg et al. 1996) | Yes |
| 1 | *T. cruzi* | Tc85-11 (trans-sialidase) | cytokeratin 18 | (Magdesian et al. 2001) | No template |
| 2 | *T. cruzi* | Tc85-11 (trans-sialidase) | laminin | (Giordano et al. 1994; Marroquin-Quelopana et al. 2004) | No template |
| 3 | *T. cruzi* | calreticulin | complement component 1 q | (Aguilar et al. 2005) | No template |
| 4 | *T. cruzi* | cruzipain | alpha-2-macroglobulin | (Ramos et al. 1997; Ramos et al. 2002) | No template |
| 5 | *T. cruzi* | cruzipain | cystatins | (Stoka et al. 1995) | Yes |
| 6 | *T. cruzi* | cruzipain | pregnancy zone protein | (Ramos et al. 2002) | No template |
| 7 | *T. cruzi* | gp82 (trans-sialidase) | mucin | (Neira et al. 2003) | No template |
| 8 | *T. cruzi* | SA85-1.1 | mannose receptor | (Kahn et al. 1995) | No template |
| 9 | *T. cruzi* | SA85-1.1 | mannose-binding protein | (Kahn et al. 1995) | No template |
| 10 | *T. cruzi* | Tc13 (trans-sialidase) | beta-1-adrenergic receptor | (Garcia et al. 2003) | No template |
| 11 | *T. cruzi* | trans-sialidase | sialomucin cd43 | (Todeschini et al. 2002) | No template |
| 12 | *T. cruzi* | trans-sialidase | cruzin | (Prioli et al. 1987; Prioli et al. 1988) | No template |
| 13 | *T. cruzi* | gp72 | complement component C3 | (Joiner et al. 1985) | No template |
| | *C. hominis* | none | | | |
| | *C. parvum* | none | | | |
| 1 | *P. falciparum* | falcipain-2 | *G. gallus* cystatin | (Wang et al. 2006) | Yes |
| 2 | *P. falciparum* | MESA | protein 4.1 | (Waller et al. 2003) | No template |
| 3 | *P. falciparum* | PfEMP1 | CD36 | (Waller et al. 2002) | No template |
| 4 | *P. falciparum* | PfEMP1 | ICAM-1 | (Waller et al. 2002) | No template |
| 5 | *P. falciparum* | PfHRP1 | ankyrin | (Magowan et al. 2000) | No template |
| 6 | *P. falciparum* | MSP1 | band 3 | (Goel et al. 2003) | No template |

| | | | | | |
|---|---|---|---|---|---|
| 7 | *P. falciparum* | EBA-181 | erythrocyte protein 4.1 | (Lanzillotti and Coetzer 2006) | No template |
| 8 | *P. falciparum* | EBA-175 | glycophorin A | (Orlandi et al. 1992; Sim et al. 1994) | No template |
| 9 | *P. falciparum* | EBA140 | glycophorin C | (Maier et al. 2003) | No template |
| 10 | *P. falciparum* | PfEMP1 | complement receptor 1 | (Krych-Goldberg et al. 2002) | No template |
| 11 | *P. falciparum* | Circumsporozoite | LDLR-related protein | (Shakibaei and Frevert 1996) | No template |
| 1 | *P. vivax* | Duffy-binding protein | Duffy antigen | (Hans et al. 2005) | No template |
| 1 | *T. gondii* | microneme protein 2 | ICAM-1 | (Barragan et al. 2005) | No template |

**Table S1: Comparison of predicted and known host–pathogen protein interactions.** The predicted interactions were compared to known host–pathogen interactions to identify those that were found and those that were not..

| Pathogen | Data Set 1 (size) | Data Set 2 (size) | Overlap |
|---|---|---|---|
| (a) Pathogen proteins | | | |
| *M. tuberculosis* | Rachman (286) | Predictions (240) | 23 |
| *M. tuberculosis* | Sassetti (194) | Predictions (240) | 8 |
| *M. tuberculosis* | Rachman (286) | Sassetti (194) | 18 |
| (b) Host proteins | | | |
| *L. major* | Chaussabel (3060) | Predictions (2680) | 231 |
| *M. tuberculosis* | Chaussabel (2893) | Predictions (992) | 78 |
| *T. gondii* | Chaussabel (2475) | Predictions (2024) | 169 |

**Table S2: Comparison of predictions to experimental observations of proteins involved in infection.** (a) *M. tuberculosis* proteins predicted (pre-filtered) to interact with host proteins are compared to genes observed to be essential for *in vivo* growth (Sassetti and Rubin 2003) and those up-regulated in granuloma, pericavity, or distal lung infection sites (Rachman et al. 2006b). (b) *H. sapiens* proteins predicted (pre-filtered) to interact with pathogens are compared to genes that are differentially regulated in macrophages or dendritic cells upon infection by *L. major*, *M. tuberculosis*, and *T. gondii* (Chaussabel et al. 2003).

| Species | Annotation type | Coverage | | Criteria |
|---|---|---|---|---|
| M. leprae | GO annotation | 991 | (62%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 51 | (3%) | Exported, secreted, surface, extracellular |
| *M. tuberculosis* | GO annotation | 2,404 | (61 %) | Involved in defense response, host cell, pathogenesis |
| | Name match | 60 | (2%) | Exported, secreted, surface, extracellular |
| | Expression | 286 | (7%) | Differential transcription at granuloma, |

| | | | | |
|---|---|---|---|---|
| | | | | pericavity, or distal lung infection sites *vs in vitro* (Rachman et al. 2006a; Rachman et al. 2006b) |
| *L. major* | GO annotation | 3,597 | (45%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 59 | (1%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 290 | (4%) | Metacyclic, procyclic, amastigote stage-specific expression (Almeida et al. 2004; Leifso et al. 2007) |
| *T. brucei* | GO annotation | 3,825 | (43%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 327 | (4%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 120 | (1%) | Procyclic, bloodstream stage-specific expression (Brems et al. 2005) |
| *T. cruzi* | GO annotation | 6,985 | (36%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 1,156 | (6%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 1,930 | (10%) | Metacyclic, amastigote, trypomastigotes, epimastigote stage-specific expression (Atwood III et al. 2005) |
| *C. hominis* | GO annotation | 1,575 | (41%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 2 | (0%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 45 | (1%) | Sporozoite stage expression (Siddiki and Wastling 2005) |
| *C. parvum* | GO annotation | 1,687 | (44%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 156 | (4%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 84 | (2%) | Sporozoite stage expression (Siddiki and Wastling 2005) |
| *P. falciparum* | GO annotation | 3,265 | (61%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 19 | (0%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 3,902 | (73%) | Ring, trophozite, schizont, merozoite, gametocyte, sporozite stage expression (Florens et al. 2002; Le Roch et al. 2003; Le Roch et al. 2004) |
| | Organelle | 707 | (13%) | Expression in infected erythrocyte plasma membrane (Florens et al. 2004), predicted secreted (Hiller et al. 2004; Marti et al. 2004; Sargeant et al. 2006) |
| *P. vivax* | GO annotation | 36 | (1%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 301 | (6%) | Exported, secreted, surface, extracellular |
| | Organelle | 85 | (2%) | Predicted secreted (Sargeant et al. 2006) |
| *T. gondii* | GO annotation | 134 | (2%) | Involved in defense response, host cell, pathogenesis |
| | Name match | 60 | (1%) | Exported, secreted, surface, extracellular |
| | Life-cycle | 3,555 | (46%) | Bradyzoite, tachyzoite, encystation stage expression (Radke et al. 2005) |

| | | | | |
|---|---|---|---|---|
| *H. sapiens* | GO annotation | 19,646 | (61%) | Immune system |
| | Name match | 205 | (1%) | Exported, secreted, surface, extracellular |
| | Tissues | 23,331 | (73%) | Pathogen-specific (Table 4) |

**Table S3: Biological annotation and filtering criteria.** Different types of annotation data, with different proteome coverages, were used for each species. Coverage refers to the number of proteins (fraction of the proteome) that are annotated with each type of annotation. The interaction predictions are filtered according to the criteria listed in the final column. “Name match” refers to keyword matches in each protein name.

## FIGURES

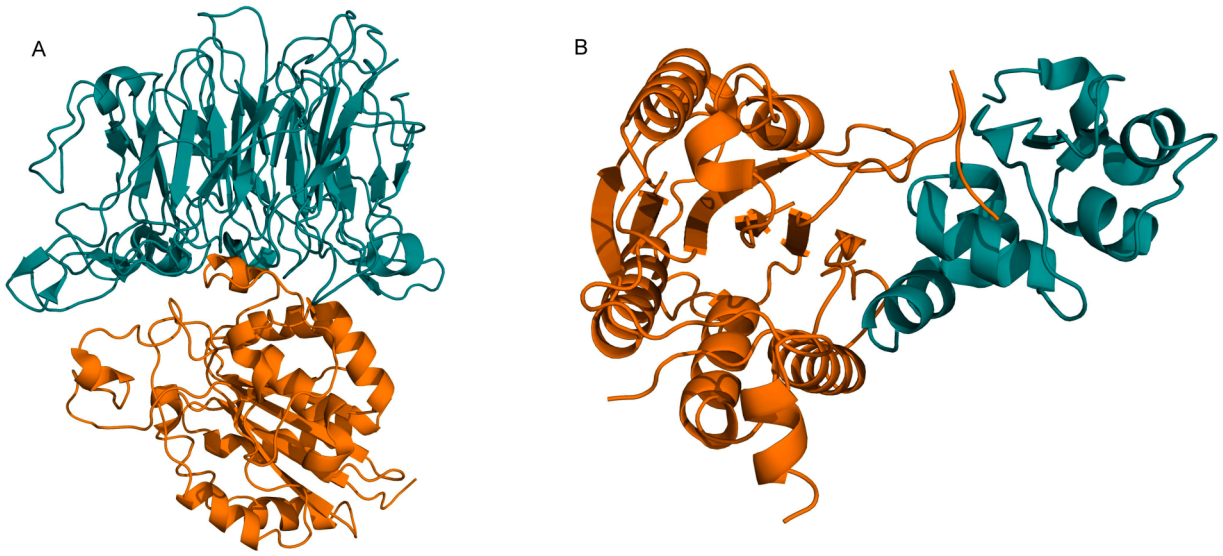


**Figure S1: Examples of predicted interactions.** (a) *P. falciparum* PFI0595c was predicted to potentially interact with human CD51 (Integrin alpha-V; ENSP0000261023) based on a structure of platelet membrane glycoprotein IIIA (orange) bound to CD51 (teal), respectively (PDB 1JV2). (b) *P. falciparum* hypothetical metacaspase PF13_0289 was predicted to potentially interact with X-linked inhibitor of apoptosis protein (XIAP) based on a template structure of caspase-9 (orange) bound to XIAP (teal), respectively (PDB 1NW9). Figures were generated by PyMOL (http://www.pymol.org).

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