Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Connecting viral with cellular interactomes
SM Bailer¹ and J Haas¹,²

Genome-scale screens for intraviral and virus–host protein interactions and the analysis of literature-curated datasets are able to provide a novel, comprehensive perspective of viruses, and virus-infected cells. Until now, large-scale interaction screens were predominantly performed with the yeast-two-hybrid (Y2H) system; however, alternative high-throughput technologies detecting binary protein interactions or protein complexes have been developed. Although many of the previous studies suffer from a rather poor validation of the results and few biological implications, these technologies potentially lead to a plethora of novel hypotheses. Here, we will give an overview of current approaches and their technical limitations, present recent examples and novel developments.

Addresses
¹ Max-von-Pettenkofer Institut, Ludwig-Maximilians-Universität München, Pettenkoferstrasse 9a, 80336 Muenchen, Germany
² Division of Pathway Medicine, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK

Corresponding author: Bailer, SM (Bailer@mvp.uni-muenchen.de) and Haas, J (juergen.haas@ed.ac.uk)

The Y2H system as the standard assay for the evaluation of interactomes
Essentially all high-throughput approaches to identify binary protein interactions on a genome-scale currently rely on the Gal4-based yeast-two-hybrid (Y2H) system (Figure 1) developed in 1989 [1]. In principle, two proteins are fused to separately expressed and nonfunctional domains of the Gal4 transcription factor, either the Gal4 DNA binding domain (bait) or the Gal4 activation domain (prey). Upon interaction of the two proteins of interest, the transcription factor activity is reconstituted in the yeast nucleus leading to the activation of one or several reporter genes. A major improvement was the introduction of a mating protocol in which pretransformed haploid yeast cells form diploids that carry both the bait and prey vector [2]. Compared to the previously used transformation protocol, this novel strategy is easier to perform and allows automated screening and the crosscombination of a large number of pretransformed bait and prey pairs. Another major improvement that further boosted genome-scale Y2H approaches was the combination with the highly efficient Gateway recombinational cloning system for the generation of larger clone collections [3]. Over the last 10 years, the interactomes of several previously sequenced organisms like H. pylori [4], C. jejuni [5], M. tuberculosis [6], P. falciparum [7], T. pallidum [8], S. cerevisiae [9,10], C. elegans [11], D. melanogaster [12], and humans [13,14] could be generated using the Y2H system. In most cases arrays were generated to test either individual or defined pools of open reading frames (ORFs) for interaction with each other (matrix screens). Alternatively, a number of individual baits were used to screen cDNA libraries. More recently, several viral interactomes with the herpesvirus family being by far the largest group analyzed have been generated (refs. [15**,16**,17,18**,19**] and [E Fossum et al., in revision]).

Limitations of the Y2H system
The reliability and the biological relevance of the Y2H system in general have been challenged repeatedly. Despite certain limitations the Y2H system is used by the majority of groups because of its enormous efficacy and the data discussed in this review are all based on Y2H screens as all currently published large-scale studies on intraviral or virus–host protein interactions are based on them. Clearly, since based on the nuclear localization of a transcriptional reporter system, it is limited in the analysis of transcriptional activators and proteins localized to membrane compartments. However, although the proteins to be tested are forced into the yeast nucleus for interaction, no bias between nuclear or non-nuclear proteins was observed [20**]. Interestingly, while the yeast system is not expected to provide translational modifications comparable to the mammalian cell, it is nonetheless able to introduce and report modification-dependent interactions up to a certain extent. Thus, the yeast cell offers an environment sufficiently natural for the analysis of protein interactions of other species [20**].

A major concern of the Y2H system particularly in its high-throughput application is the small overlap of identified interactions in comparative studies. This is exemplified by two S. cerevisiae proteome-wide Y2H approaches in which the screening of 6000 gene products identified 682 (Uetz-screen) and 843 (Ito-core) binary interactions [9,10]. However, only 19% of the Uetz-screen and 15% of the Ito-core interactions were found in the respective other screen [9,10]. A similarly small overlap was observed in several independently performed...
genome-wide herpesviral protein interaction screens [15**,16**,19**,21,22] (E Fossum et al., in revision). Recent large-scale efforts demonstrated by reinvestigating a set of random protein interactions of the *S. cerevisiae* and human interactomes that the low coverage is the result of low sensitivity rather than low specificity [20**,23**,24**]. Several validation protocols performed in parallel (see below) confirmed 25–30% of the Y2H interactions suggesting that the Y2H approach does not yield more false positives than other assays that detect binary interactions and is comparable in quality to literature-curated data [25**].

Several reasons are likely to account for the low sensitivity of Y2H approaches [25**]. First, only a fraction of all possible pairwise combinations are actually tested in a given screening situation. Second, depending on the assay or screening protocol applied different spaces are screened. This is demonstrated by studies on Hepatitis C virus (HCV) where the same set of proteins was screened by a yeast mating (IMAPI) as well as a transformation protocol (IMAPII) using two different human cDNA libraries [18**]. Although performed in the same laboratory, IMAPI and IMAPII shared only 22 interactions indicating that different screening protocols, vectors, and yeast strains as well as the quality and composition of cDNA libraries have a greater impact on the screening success than generally assumed. Third, high-throughput approaches are often hampered by technical limitations that can be improved for example by multiple screenings of the same space. Multiple sampling of the same search space allowed the identification of 80–90% while a single round revealed only 60% of all possible Y2H interactions [23**]. The ORFeomes of five evolutionarily related herpesviruses were used to systematically address the low coverage of Y2H screens by comparing the interactions identified in individual species followed by secondary methods [15**] (E Fossum et al., in revision). In the initial Y2H screens 283 interactions of the 41 core orthologous proteins were observed and 113 interactions...
were found in more than one species (E Fossum et al., in revision). On the basis of 55 Y2H interactions detected in KSHV, 59 of 92 interactions predicted for the corresponding orthologs in HSV-1, mCMV, and EBV could be identified by coprecipitation. In conclusion, the low coverage of the Y2H system — currently its major drawback — can be addressed either by technical improvements or the combination with other assays.

Alternative technologies
To address the biological significance of an interaction identified by Y2H, validation by one or more biochemical methods is required (Figure 1). Technologies similar to the Y2H, for example an assay based on closeness of two proteins if not their direct interaction likely leads to high confirmation rates, however be little complementary [20**]. Coexpression in mammalian cells of two proteins fused to distinct tags followed by immuno-coprecipitation or affinity-coprecipitation (CoP) was successfully applied to validate several Y2H studies [15**,17] (E Fossum et al., in revision). This method, however, is time consuming and thus not applicable to analyze large sets of interactions. Recently, a tool-box for high-throughput validation of Y2H interactions was developed (Figure 1; [20**]). Expression of proteins on array-printed template DNA using a coupled in vitro transcription–translation reaction (nucleic acid programmable protein array, NAPPA, [26]) follows a principle similar to the CoP. However, since performed in vitro under a defined but artificial environment it is technically challenging. A second method used on a rather large scale is the LUMIER (luminescence-based mammalian interactome mapping) pull-down assay where two proteins are expressed in mammalian cells. While the bait protein is expressed as a fusion to the protein A-tag or Flag-tag to immobilize the complex, the prey protein is expressed as a fusion with luciferase allowing the detection of the coisolated prey [27]. Protein fragment complementation assays (PCA), for example the split-YFP system in which interacting bait and prey proteins are fused to YFP domains, reconstitute an enzyme or a fluorescent protein and generally do not require an enrichment of the interactors. Thus, they might be more easily performed in an automated large-scale fashion [28]. Finally, the MAPPTT (mammalian protein–protein interaction trap) uses a bait protein fused to a hybrid erythropoietin–leptin receptor located to the plasmamembrane and a prey protein fused to gp130, which drives a signaling cascade resulting in the read-out of an endogenous transcriptional reporter [29].

Proteomic approaches that are able to detect indirect interactions are complementary to the Y2H system rather than confirmatory, and are therefore well suited to increase the coverage of a Y2H interactome. In the tandem affinity purification (TAP) approach individual proteins are fused to a cleavable tandem tag composed for example of protein A or G and a calmodulin binding peptide (CBP), and the isolated proteins present in the pulled-down complex are subsequently identified by mass spectrometry as done for yeast (Figure 1; [30–32]). Similarly, smaller subsets of human proteins have been analyzed in higher eukaryotic cells [33–35]. Since the systematic tagging of chromosomal genes is currently not feasible in these cells, tagged proteins have been introduced in addition to the endogenous proteins and thus compete with them in the pull-down analysis. Genetic systems are now available for many viral genomes (including large DNA viruses), and systematic functional TAP-tagging of viral proteins might be addressed in the near future. Proteomic analyses of purified virus particles have recently been performed for a few virus species and may provide further evidence for the interaction between viral proteins, particularly in conjunction with Y2H data (Figure 2) [36,37].

Protein interaction networks in viruses
Initial ‘genome-wide’ studies concentrated on intraviral protein interactions of small RNA and DNA viruses. However, owing to the rather small number of proteins and protein interactions identified (Figure 3), a detailed network analysis could not be applied (reviewed by [38]). More recent approaches on intraviral interactomes include several members of the herpesvirus family [15**,16**,19**,21,22] (E Fossum et al., in revision) and the human SARS coronavirus (SARS-CoV, [17*]).
first combined virus–host interactomes were investigated in HCV [18**, EBV [16**], VZV and KSHV (Haas and collaborators). Virus–host protein interactions have been included into several public databases, or novel databases specific for virus–host interactions like VirHostNet have been set up [39].

**Hepatitis C virus (HCV)**
In a systematic screen of 27 full-length proteins or domains of HCV against two human cDNA libraries, 314 virus–host interactions were identified [18**]. Taking published interactions into account, this is the first analysis on RNA viruses producing a large enough dataset to constitute a virus–human interaction network composed of 481 interactions involving 11 HCV and 421 human proteins. The most highly connected proteins were the NS3, NS5A, and core proteins with 214, 96, 76 interactors, respectively. Intriguingly, the insulin, Jak/STAT, and TGFβ signaling pathways were particularly enriched, which might be consistent with the metabolic disorders observed during chronic HCV infection. Focal adhesion complexes could represent a novel target of HCV suggesting a role of several HCV proteins in viral spreading, cell–cell interaction, and tissue reorganization. This analysis may thus help to identify potential new targets for HCV therapy.

**Herpesviruses**
The largest high-throughput approaches involving viruses have been performed with herpesviruses. Equipped with moderately large-sized genomes encoding a manageable but complex set of genes these viruses represent the ideal candidates for genome-wide Y2H approaches followed by bioinformatical analysis. Intraviral interactomes have been generated for several herpesviruses including the α-herpesviruses Herpes simplex virus type 1 (HSV-1, [21,22], E Fossum et al., in revision) and Varicella zoster virus (VZV [15**]), the β-herpesvirus mouse Cytomegalovirus (mCMV), and the γ-herpesviruses Epstein–Barr virus (EBV [16**], E Fossum et al., in revision) and Kaposi’s sarcoma herpesvirus (KSHV [15**;19**]). In a comparison of the interactomes...
of five herpesviral species including 1007 intraviral inter-
actions a core set of highly conserved protein interactions
has been identified. Intriguingly, the interactions be-
tween the orthologous proteins were found to be con-
served independent of their sequence homology. The
topology of all herpesviral networks differed from cellular
networks; however, it is difficult to judge whether this
really reflects biological differences or artefacts caused by
different setups used to evaluate them. In EBV [16**],
HCV [18**], VZV and KSHV (Haas and collaborators),
and KSHV (Haas and collaborators) viral proteins tend to
interact with highly connected cellular proteins, which
could be a general hallmark of many pathogen–host
interactions [40**]. The datasets available to date are
hampered by the low coverage of the Y2H screens per-
formed, which makes it difficult to draw general biological
conclusions. To reveal significant differences how different
pathogens interact with the host proteome, protein
interaction data with a considerably higher coverage of
the screening space have to be generated.

To provide an example of the power of this approach, a
comparison of the five herpesviral core networks ident-
ified the highly connected HSV-1 UL33 ortholog (VZV
Orf27, mCMV M53, EBV BFLF2, and KSHV Orf69) which in turn were found and pre-
viously published to interact with the HSV-1 UL34
orthologs (VZV Orf24, mCMV M50, EBV BFRF1, and
KSHV Orf67) was highly conserved [41–45]. Likely these
proteins form a large protein complex that mediates
budding of capsids at the inner nuclear membrane of
the host (Figure 4). The role of UL33 in DNA packaging
and cleavage could point to a role in connecting capsid
maturation with nuclear egress [46]. This is in line with
these proteins being crucial for capsid formation and
nuclear egress [41,46–49]. The identification of this
protein complex thus demonstrates the potential of sys-
tems virology to reveal targets for alternative herpesviral
therapies. This could be achieved by peptides or other
small molecules introduced to interfere with targeting or
assembly of the complex components.

SARS coronavirus (SARS-CoV)
Discovered in 2002, the SARS-CoV is thus far the largest
RNA virus analyzed for genome-wide intraviral protein
interactions [17*]. Its genome consists of approximately
29 700 nt and is predicted to encode 14 functional ORFs
leading to approximately 30 structural and nonstructural
protein products. Of the 900 pairwise interactions tested
by a Y2H matrix analysis, 65 were positive and 35% of

---

Figure 4

Nuclear egress of HSV-1 capsids. Herpesviral capsids are formed in the host nucleus and released to the cytoplasm by budding through the nuclear
envelope. Primary envelopment at the inner nuclear membrane (INM) requires the membrane anchored UL34/UL31 family of proteins. The UL33
protein family interacts with this nuclear egress complex and may connect capsid packaging and nuclear egress (ER: endoplasmic reticulum; INM:
inner nuclear membrane; ONM: outer nuclear membrane; NPC: nuclear pore complex).
these could be confirmed by CoP. The intraviral interaction network revealed network parameters similar to herpesviruses [15**] and the combined published and experimental virus–host interactions suggest that SAR-S-CoV targets host functions like apoptosis, cell communication, and signaling.

Outlook
Large-scale protein interaction screens are able to provide large amounts of novel and unbiased data, but the extraction of biological implications from these screens is difficult, particularly if they are based on a technology with a rather low coverage as the Y2H system. In the near future, however, improved ‘deep’ screening technologies will lead to more comprehensive interaction maps of both intraviral and virus–host protein interactions, which, in combination with other genome-scale technologies like siRNA knock-down screens, transcriptional profiling, and spatial/temporal distribution studies may allow to setup improved models of virus-infected cells. The comparison of different viruses and, possibly, other pathogens may allow the identification of common strategies for infection and replication used by divergent pathogen groups, and the identification of targets for novel broad-spectrum antibiotics. On the other hand, it might reveal strategies that are specific for individual pathogens and help explain the characteristics of the infection with this particular pathogen. In combination with a genetic profiling of the infected host this approach will be even more powerful and might potentially lead to a step change in our understanding of viral infections.

Acknowledgements
The work of the authors has been supported by grants provided by BayGene (Bayerisches Staatsministerium für Wissenschaft, Forschung und Kunst JH), DFG (SFB 576 JH, BA 1165/5-1 SB/JH), BMBF (NGFN+ JH), MRC (G050145, JH), and Scottish Funding Council (ICHAIR, JH).

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Fields S, Song O: A novel genetic system to detect protein–protein interactions. Nature 1989, 340:245-246.
2. Fromont-Racine M, Rain JC, Legrain P: Toward a functional analysis of the yeast genome through exhaustive two-hybrid screens. Nat Genet 1997, 16:277-282.
3. Walhout AJ, Temple GF, Brasch MA, Hartley JL, Lorson MA, van den HS, Vidal M: GATEWAY recombinational cloning: application to the cloning of large numbers of open reading frames or ORFeomes. Methods Enzymol 2000, 328:575-592.
4. Rain JC, Selig L, De RH, Battaglia V, Reverdy C, Simon S, Lenzen G, Petel F, Wojcik J, Schachter V et al.: The protein–protein interaction map of Helicobacter pylori. Nature 2001, 409:211-215.
5. Parrish JR, Yu J, Liu G, Hines JA, Chan JE, Mangiola BA, Zhang H, Pacifico S, Fouchi F, DiRita VJ et al.: A proteome-wide protein interaction map for Campylobacter jejuni. Genome Biol 2007, 8:R130.
6. Raman K, Chandra N: Mycobacterium tuberculosis interactome analysis unveils potential pathways to drug resistance. BMC Microbiol 2008, 8:234.
7. LaCount DJ, Vignali M, Chettier R, Phansaikler A, Bell R, Hesselberth JR, Schoenefeld LW, Ota I, Sahasrabudhe S, Kurschner C et al.: A protein interaction network of the malaria parasite Plasmodium falciparum. Nature 2005, 436:103-107.
8. Titz B, Rajagopalla SV, Goll J, Hauser R, McKevitt MT, Palzikil T, Uetz P: The binary protein interaction map of Treponema pallidum — the syphilis spirochete. PLoS ONE 2008, 3:e2292.
9. Uetz P, Giot L, Cagney G, Mansfield TA, Judson RS, Knight JR, Lockshon D, Narayan V, Sinivasan M, Pochart P et al.: A comprehensive analysis of protein-protein interactions in Saccharomyces cerevisiae. Nature 2000, 403:623-627.
10. Ito T, Chiba T, Ozawa R, Yoshiida M, Hattori M, Sakaki Y: A comprehensive two-hybrid analysis to explore the yeast protein interactome. Proc Natl Acad Sci U S A 2001, 98:4569-4574.
11. Li S, Armstrong CM, Bertin N, Ge H, Milstein S, Boxem M, Vidalain PO, Han JD, Chesneau A, Hao T et al.: A map of the interactome network of the metazoan C. elegans. Science 2004, 303:540-543.
12. Uetz P, Bader JS, Biehl M, Brunner M, Cagney G, Chen L, Demartis S, Don rivella M, Giot L, Godwin B, Guarino O, Hao Y, Heiss JD, Hendzel MJ, Cagney G, Mansfield TA, Judson RS, Knight JR, Lockshon D, Narayan V, Sinivasan M, Pochart P et al.: A comprehensive analysis of protein–protein interactions in Saccharomyces cerevisiae. Nature 1998, 393:159-170.
20. Braun P, Tasan M, Dreze M, Barrios-Rodiles M, Lemmens I, Yu H, Sahalie JM, Murray RR, Roncarli L, de Smet AS et al.: An experimentally derived confidence score for binary protein-protein interactions. Nat Methods 2009, 6:91-97.

A tool-box of high-throughput methods was tested for the validation of Y2H interactions including the mammalian protein-protein interaction trap (MAPPIT), the luminescence-based mammalian interactome (LUMIER), the yellow fluorescent protein (YFP) protein complementation assay (PCA), and the nucleic acid programmable protein array (NAPPA). This analysis aims at defining a confidence score for binary protein-protein interactions.

21. Vittone V, Diefenbach E, Triffett D, Douglas MW, Cunningham AL, Diefenbach RJ: Determination of interactions between tegument proteins of herpes simplex virus type 1. J Virol 2005, 79:9566-9571.

22. Lee JH, Vittone V, Diefenbach E, Cunningham AL, Diefenbach RJ: Identification of structural protein-protein interactions of herpes simplex virus type 1. Virology 2008, 378:347-354.

23. Yu H, Braun P, Yildirim MA, Lemmens I, Venkatesan K, Sahalie J, Hirozane-Kishikawa T, Gebreab F, Li N, Simonis N et al.: High-quality binary protein interaction map of the yeast interactome network. Science 2008, 322:104-110.

These two sets of data define high-quality binary interaction maps of yeast and human protein networks. In particular, these datasets suggest that the Y2H data are more reliable than generally believed and that the Y2H screens currently performed suffer from low sensitivity rather than low specificity. Moreover, the distinct nature of binary versus cocomplex derived interactions is pointed out.

24. Venkatesan K, Rual JF, Vazquez A, Stelzl U, Lemmens I, Hirozane-Kishikawa T, Hao T, Zenkner M, Xin X, Goh KI et al.: An empirical framework for binary interactive mapping. Nat Methods 2009, 6:83-90.

These two sets of data define high-quality binary interaction maps of yeast and human protein networks. In particular, these datasets suggest that the Y2H data are more reliable than generally believed and that the Y2H screens currently performed suffer from low sensitivity rather than low specificity. Moreover, the distinct nature of binary versus cocomplex derived interactions is pointed out.

25. Cusick ME, Yu H, Smolyar A, Venkatesan K, Carvunis AR, Simonis N, Rual JF, Borick H, Braun P, Dreze M et al.: Literature-curated protein interaction datasets. Nat Methods 2009, 6:39-46.

Curation of protein interactions from literature is a method applied to obtain comprehensive protein networks. However this analysis critically evaluates the current literature curation and shows that it is more error-prone and possibly of lower quality than generally assumed.

26. Ramachandran N, Hainsworth E, Bhullar B, Eisenstein S, Rosen B, Lau AY, Walter JC, LaBaer J: Self-assembling protein microarrays. Science 2004, 305:86-90.

27. Barrios-Rodiles M, Brown KR, Ozdamar B, Bose R, Liu Z, Donovan RS, Shinjo F, Liu Y, Dembovy J, Taylor IW et al.: High-throughput mapping of a dynamic signaling network in mammalian cells. Science 2005, 307:1621-1625.

28. Nyfeler B, Michnick SW, Hauri HP: Capturing protein interactions in the secretory pathway of living cells. Proc Natl Acad Sci U S A 2006, 102:6350-6355.

29. Eyckerman S, Verhee A, der Heyden JV, Lemmens I, Oostve DV, Vandenbergh J, Tavernier J: Design and application of a cytokine-receptor-based interaction trap. Nat Cell Biol 2001, 3:1114-1119.

30. Gavin AC, Bosche M, Krause B, Grandi P, Marzioch M, Bauer A, Schultz J, Rick JM, Michon AM, Cruciat CM et al.: Functional organization of the yeast proteome by systematic analysis of protein complexes. Nature 2002, 415:141-147.

31. Ho Y, Gruhler A, Heilbut A, Bader GD, Moore L, Adams SL, Millar A, Taylor P, Bennett K, Boutiller K et al.: Systematic identification of protein complexes in Saccharomyces cerevisiae by mass spectrometry. Nature 2002, 415:180-183.

32. Krogan NJ, Cagney G, Yu H, Zhong G, Guo X, Ignatchenko A, Li J, Pu S, Datta N, Tikuisis AP et al.: Global landscape of protein complexes in the yeast Saccharomyces cerevisiae. Nature 2006, 440:637-643.

33. Bouwmeester T, Bauch A, Ruffner H, Angrand PO, Bergamini G, Grooten K, Cruciat C, Eberhard D, Gagneur J, Ghidelli S et al.: A physical and functional map of the human TFN-alpha/NF-kappa B signal transduction pathway. Nat Cell Biol 2004, 6:97-105.

34. Burckstummer T, Bennett KL, Preradovic A, Schutze G, Hantschel O, Superti-Furga G, Bauch A: An efficient tandem affinity purification procedure for interaction proteomics in mammalian cells. Nat Methods 2006, 3:1013-1019.

35. Ewing RM, Chu P, Elisma F, Li H, Taylor P, Clime S, Broom-Caraway L, Robinson MD, O’Connor L, Li M et al.: Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol Syst Biol 2007, 3:89.

36. Viswanathan K, Fruh K: Virus proteomics: global evaluation of viruses and their interaction with the host. Expert Rev Proteomics 2007, 4:815-829.

37. Loret S, Guay G, Lippe R: Comprehensive characterization of extracellular herpes simplex virus type 1 virions. J Virol 2008, 82:8605-8618.

38. Uetz P, Rajagopala SV, Dong YA, Haas J: From ORFeomes to protein interaction maps in viruses. Genome Res 2004, 14:2029-2033.

39. Ivavrali V, de CB, Meynie L, Delmotte G, Gautier C, Andre P, Lotteau V, Raboudin-Combe C: VirHostNet: a knowledge base for the management and the analysis of proteome-wide virus-host interaction networks. Nucleic Acids Res 2009, 37:D661-D668.

40. Dyer MD, Murali TM, Sobral BW: The landscape of human proteins interacting with viruses and other pathogens. PLoS Pathog 2008, 4:e93.

This paper integrates proteome interaction networks of several pathogens and identifies certain cellular processes that participate in interactions with different pathogen groups. This global view on infectious diseases may be a first step toward the identification of multiviral or multibacterial treatments.

41. Mettenleiter TC: Budding events in herpesvirus morphogenesis. Virus Res 2004, 106:167-180.

42. Lake CM, Hutt-Fletcher LM: The Epstein–Barr virus BFRF1 and BFLF2 proteins interact and coexpression alters their cellular localization. Virology 2004, 320:99-106.

43. Gonnella R, Farina A, Santarelli R, Raffa S, Feederle R, Bryant A, Granato M, de Luca A, Delucelle HJ et al.: Characterization and intracellular localization of the Epstein–Barr virus protein BFLF2: interactions with BFRF1 and with the nuclear lamina. J Virol 2005, 79:3713-3727.

44. Granato M, Feederle R, Farina A, Gonnella R, Santarelli R, Hub B, Faggioni A, Delucelle HJ: Deletion of Epstein–Barr virus BFLF2 leads to impaired viral DNA packaging and primary egress as well as to the production of defective viral particles. J Virol 2008, 82:4642-4651.

45. Santarelli R, Farina A, Gonnella R, Santarelli R, Hub B, Faggioni A, Delucelle HJ: Identification and characterization of the product encoded by ORF69 of Kaposi’s sarcoma-associated herpesvirus. J Virol 2008, 82:4562-4572.

46. Yang K, Poon AP, Roizman B, Baines JD: Temperature-sensitive mutations in the putative herpes simplex virus type 1 terminase subunits pUL15 and pUL33 preclude viral DNA cleavage/packaging and interaction with pUL28 at the nonpermissive temperature. J Virol 2008, 82:487-494.

47. Bubeck A, Wagner M, Ruzicsz Z, Lotzchier M, Iglesias M, Singh IR, Koszinowski UH: Comprehensive mutational analysis of a herpesvirus gene in the viral genome context reveals a region essential for virus replication. J Virol 2004, 78:8026-8035.

48. Farina A, Feederle R, Raffa S, Gonnella R, Santarelli R, Frati L, Angeloni A, Torrisi MR, Faggioni A, Delucelle HJ, BFLF1 of Epstein–Barr virus is essential for efficient primary viral envelopment and egress. J Virol 2005, 79:3703-3712.

49. Lotzchier M, Ruzicsz Z, Koszinowski UH: Functional domains of murine cytomegalovirus nuclear egress protein M53/p38. J Virol 2006, 80:73-84.