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**Interactomics : dozens of viruses, co-evolving with humans, including the influenza A virus,
may actively distort human ageing**

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1 **Abstract**

2 Some viruses (e.g. HIV-1, SARS-CoV-2) have been experimentally proposed to accelerate features
3 of human ageing and of cellular senescence. These observations, along with evolutionary
4 considerations on viral fitness, raised the more general puzzling hypothesis that, beyond
5 documented sources in human genetics, ageing in our species may also depend on virally-encoded
6 interactions distorting our ageing to the benefits of diverse viruses. Accordingly, we designed
7 systematic network-based analyses of the human and viral protein interactomes, which unraveled
8 dozens of viruses encoding proteins experimentally demonstrated to interact with proteins from
9 pathways associated with human ageing, including cellular senescence. We further corroborated
10 our predictions that specific viruses interfere with human ageing using published experimental
11 evidence and transcriptomic data; identifying influenza A virus (subtype H1N1) as a major
12 candidate age-distorter, notably through manipulation of cellular senescence. By providing original
13 evidence that viruses may convergently contribute to the evolution of numerous age-associated
14 pathways through co-evolution, our network- and bipartite network-based methodology supports
15 an ecosystemic study of ageing, also searching for genetic causes of ageing outside a focal ageing
16 species. Our findings, predicting age-distorters and targets for anti-ageing therapies amongst
17 human viruses, could have fundamental and practical implications for evolutionary biology, ageing
18 study, virology, medicine and demography.

19

20 **Introduction**

21

22 Some viruses, such as the human immunodeficiency virus (HIV-1) (Reynoso et al. 2012;
23 Pfefferbaum et al. 2014; Horvath and Levine 2015; Cohen and Torres 2017; Humphreys et al.
24 2020a; Seoane et al. 2020; Schank et al. 2021; Horvath et al. 2022) and the Severe acute respiratory
25 syndrome coronavirus 2 (SARS-CoV-2) (Mongelli et al. 2021; Tripathi et al. 2021; Cao et al. 2022;
26 Tsuji et al. 2022), have been recently proposed to accelerate features of human ageing and of human
27 cellular senescence based on experimental evidence. Similar claims have been made for several
28 other viruses, such as the Dengue virus serotype 2 (DENV2) (Seoane et al. 2020). Moreover, some
29 works suggested that latent CMV-infection impairs immunity in old age and might propagate
30 immune senescence (Mekker et al. 2012), contributing to a decade of debates on the potential
31 impact, or as it presently seems, limited, impact, of latent infections of the human Cytomegalovirus
32 (HCMV) on human ageing (Redeker et al. 2018; Nikolich-Žugich et al. 2020). Together, these

1 observations, centered on specific human viruses, show that considering viruses as potentially
2 relevant agents to understand our ageing is a raising concern (Humphreys et al. 2020a; Seoane et
3 al. 2020; Teulière et al. 2021). Additional works stressed that, in a context of evolutionary arms
4 race and co-evolution, a diversity of interference, e.g. on host apoptosis, host growth and host
5 immunity, can be mediated by viral genes (Gillet and Brun 1996; Iranzo et al. 2014; Frasca and
6 Blomberg 2016; Aiello et al. 2017; Connolly and Fearnhead 2017; Kuss-Duerkop et al. 2017;
7 Schönrich et al. 2017; Mlih et al. 2018; Zamaraev et al. 2020; Teulière et al. 2021). Moreover,
8 evolutionary considerations on viral fitness (Gillet and Brun 1996; Humphreys et al. 2020a; Kelley
9 et al. 2020; Zamaraev et al. 2020; Teulière et al. 2021) brought forward the more general hypothesis
10 that human ageing might depend on interactions with a broad phylogenetic diversity of viral
11 lineages. Namely, many viruses could act as age-distorters (Teulière et al. 2021), meaning that their
12 reproduction benefits from interferences with their host ageing processes. More precisely, two
13 major kinds of age-distorting viruses were recently theorized: i) age-distorters of type 2 that alter
14 ageing as their infection generates damages and dysbalance in their hosts, yet without interfering
15 with specific host ageing-associated pathways, and ii) age-distorters of type 1, i.e., viruses whose
16 gene products directly interfere with components of their host ageing-associated pathways.
17 Furthermore, when characterised, the specific mode of age-distorsion could support more detailed
18 classifications of these two kinds of age-distorters, depending on which hallmarks of ageing
19 (López-Otín et al. 2013) are impacted by the age-distorting virus (e.g. within age-distorters of type
20 2, one could imagine “resource-depleting viruses”, and within age-distorters of type 1, one could
21 imagine distinguishing “cellular senescence-inducing viruses”, or “mitochondrial dysfunction-
22 inducing viruses”, or “generalist age-distorters” that impact multiple hallmarks of ageing). In
23 principle, such virus-host interaction could accelerate ageing, but it could also delay ageing.

24 Owing to the considerable number of human viruses, this evolutionary-minded view
25 encourages a reconceptualisation of the locus of ageing, no longer exclusively focused on our own
26 genetic material but expanded towards a larger set of genetic entities interacting with our species,
27 such as viruses (Johnson et al. 2019; Teulière et al. 2021). While this reconceptualisation suggests
28 a worrying diversity of possible sources of threats to our healthy ageing, the hypothesis that some
29 viruses distort human ageing also appreciably comes with a unique potential to offer novel anti-
30 ageing treatments concentrated on specific viral age-distorters, their age-distorting genes and
31 proteins, as well as their human proteic interactors. Adopting an eco-evolutionary perspective can
32 thus drive new findings of molecular evolution and enrich the understanding of both the ultimate
33 and proximal causes of critical organismal phenotypes.

1 Problematically, even though compelling cases have been reported for viral age-distortion
2 (Teulière et al. 2021), type 1 viral distorters of human ageing have not yet been systematically
3 identified. The extent and diversity of viruses able to directly interfere with pathways associated
4 with human ageing, as well as their genes and mechanisms of action, remain therefore to be
5 characterised. Fortunately, these important questions can now be effectively addressed by
6 connecting several available -omics resources. Precisely, knowledge from interactome databases,
7 reporting interactions between functionally annotated human proteins, in particular proteins
8 associated with various aspects of human ageing, e.g. cellular senescence (Tacutu et al. 2018;
9 Avelar et al. 2020) can be integrated with knowledge on experimentally supported protein-protein
10 interspecific interactions, such as interactions between human and viral proteins (Szkłarczyk et al.
11 2019; Yang et al. 2021). Experimental support for these interactions is provided by assays detecting
12 molecular interactions using affinity (e.g. coimmunoprecipitation, pull down or tandem-affinity
13 purification assays), protein complementation (e.g. yeast two-hybrid assays), biophysical (e.g. mass
14 spectrometry, X-ray crystallography) and other biochemical (e.g. electrophoretic mobility shift
15 assays. Moreover, proteic interactomes are routinely analysed using the framework of protein-
16 protein interaction networks (PPI). For instance, so-called ‘human longevity networks’ (Budovsky
17 et al. 2007; Bell et al. 2009; Fernandes et al. 2016) feature proteins associated with human ageing
18 as their nodes and represent interactions between these human proteins by direct edges.
19 Experimentally-supported interactions between human proteins can be recovered from all PPIs
20 listed in the STRING database, by filtering them based on their “experiments” subscore
21 (Szkłarczyk et al. 2019). This score reflects the amount of experimental support, i.e. provided by
22 biochemical/biophysical assays, for each interaction. Importantly, this network formalism can then
23 be exploited through network sciences approaches, allowing one to identify highly central human
24 proteins in the human longevity network, and in interspecific protein-protein interaction bipartite
25 networks to define which of these critical human proteins are targeted by viral proteins from diverse
26 phylogenetic sources.

27 Precisely, we took advantage of such data and designed a systematic network-based
28 analysis of the human and viral protein interactomes to identify viral proteins experimentally
29 demonstrated (on the basis of published supporting biochemical/biophysical assays that detect
30 molecular interactions, as indicated by STRING and HVIDB databases) to interact with human
31 proteins associated with human ageing and with human cellular senescence. Our working
32 hypothesis was that when a viral protein was demonstrated to interact with some human proteins
33 in carefully controlled experimental set-ups, then this viral protein has the potential to interfere
34 with the same human proteins during the course of its infection. Remarkably, our work unraveled

1 such interactions for viral proteins from dozens of human viruses and identified their human targets.
2 From these findings, we derived a list of top viral candidates predicted to interfere with human
3 ageing through proteic interactions with ageing-associated pathways, computed possible additive
4 effects of co-infections by multiple candidate age-distorters on human ageing-associated pathways,
5 and, when possible, we further corroborated our predictions and characterised the modes of action
6 of these viruses by providing independent published experimental evidence from molecular and
7 cellular biology, from transcriptomic data and using functional inferences. Unexpectedly, the
8 influenza A virus (subtype H1N1), emerged as a major candidate age-distorter of type 1, in
9 particular through its encoded genetic potential to interact with human cellular senescence. Overall,
10 our evolutionary-minded work provided new multi-faceted evidence to support the hypothesis that
11 many viruses interfere with many aspects of human ageing and predicted targets for anti-ageing
12 therapies amongst human viruses.

13 **Results**

14 **Hundreds of viruses connect to human ageing associated pathways via viral proteins**

15
16 Experimentally demonstrated interactions described in the STRING human protein-protein
17 interaction network were selected on the basis of published experimental support using
18 biochemical/biophysical molecular interaction detection assays (see M&M) (Szklarczyk et al.
19 2019). The selected PPIs were used to define an updated "human longevity network", comprised
20 of interacting proteins associated with human cellular senescence (Avelar et al. 2020) and human
21 longevity/ageing (Tacutu et al. 2018), as well as ageing-associated proteins for which proteic
22 interactions with other ageing-associated proteins are currently unknown and which therefore form
23 isolated nodes in the PPI longevity network. We then determined the set of viral proteins
24 experimentally demonstrated (in majority using affinity-based assays, see M&M) to interact with
25 this human longevity network using the HVIDB (fig. 1) and clustered the viral proteins interacting
26 with human age-associated proteins into homologous families. This protocol returned a list of viral
27 proteins, of homologous families of viral proteins and of viral strains with experimentally
28 characterised potential to interfere with proteins associated with several aspects of human ageing.
29 More precisely, 1031 viral proteins, distributed across 148 viral strains, displayed experimentally
30 supported interactions with 429 human proteins associated with ageing (fig. 1, supplementary table
31 S1).
32

1 A broad phylogenetic diversity of viruses (dsDNA viruses, such as Herpesviridae, like
2 HHV-4; ssRNA positive viruses, such as Retroviridae, like HIV-1; ssRNA negative viruses, such
3 as Arenaviridae, like LCMV, and one ssDNA virus, the Parvoviridae AAV-2) encodes proteins
4 reported to interact with three or more distinct human age-associated proteins (fig. 2). Some viruses
5 even connect to a high number of human proteins (e.g. >100), which are generally central in the
6 human longevity network as well as in the entire human PPI networks, as assessed by closeness
7 value analyses (supplementary fig. S2). Logically, viruses with larger genome sizes generally
8 connect to more human proteins, but there are remarkable exceptions (figs. 3 and 4 and see below
9 for a deeper discussion). This variation in the number of human proteins potentially targeted by
10 viruses with similarly sized-genomes may reflect genuinely contrasted evolutionary strategies (e.g.
11 with some viruses being more prone to hijack host ageing-associated pathways) and/or a bias in the
12 intensity by which different viral interactomes have been studied (i.e., a higher number of proteic
13 partners being described for more extensively investigated viruses). In the context of an
14 evolutionary arms race between viruses and host however, it makes sense that viruses would
15 preferentially interact with highly central host proteins, not only because interacting with such
16 proteins might allow the hijacking of important host processes, but also because such host proteins
17 are under strong evolutionary constraints and display limited potential to evade viral pressure,
18 precisely due to their high centrality.

19 We observed that some human proteins were connected to multiple viruses in HVIDB. We
20 tested the statistical significance of this pattern of convergent connection between viral and human
21 proteins. For this, we generated a distribution of 1000 random bipartite virus-human protein
22 networks, under the null hypothesis that viruses with the same genome sizes than in our dataset
23 would connect to the same number of randomly chosen human proteic interactors as in our dataset.
24 We compared the properties of these random bipartite networks with those of HVIDB (see M&M).
25 By determining which human proteins have a significantly high in-degree in the bipartite virus-
26 human protein network, defined as the number of viral proteins able to interact with these human
27 proteins in the HVIDB interspecific PPI network, we identified which human proteins were
28 significantly enriched amongst the possible targets of real viruses. 10% of the human proteins with
29 multiple reported interactions with viral proteins were connected by significantly more viruses than
30 expected by chance (using random bipartite networks to determine an empirical p-value with a
31 significance threshold set at 0.05, after Bonferroni correction, see M&M), indicating that some
32 human proteins are indeed preferentially connected by viruses. Moreover, we tested whether
33 specific human proteins, in our case ageing-associated proteins, were significantly connected by
34 more viruses than expected by chance, a pattern suggestive of convergent targeting of those ageing-

1 associated human proteins by viruses. Among 347 ageing-associated human proteins, we found
2 that 20% were connected by significantly more viruses than expected by chance ($P < 0.05$ adjusted
3 with Bonferroni correction, supplementary fig. S3), indicating that viruses preferentially target
4 ageing-associated human proteins with respect to other human proteins. Next, we tested whether
5 these ageing-associated proteins significantly connected to viruses were also amongst the most
6 central in the human PPI network. To find the most central proteins in the human PPI network, we
7 ranked human proteins by decreasing values of degree (number of direct neighbours) and observed
8 that the 20% of ageing-associated human proteins significantly connected to viruses were indeed
9 more central than the other ageing-associated proteins (p -value = $9.165e-12$, Wilcoxon rank sum
10 test). Overall, our analysis shows that viruses significantly and convergently interact with 69
11 significantly central human proteins associated with ageing (supplementary fig. S3).

12 We arbitrarily ranked the viruses connected to human ageing proteins into ranked lists of
13 candidate viral age-distorters and of candidate viral age-distorting proteins in order to highlight the
14 viral proteins connected to the highest number of human protein associated with ageing (top
15 candidate age-distorting proteins). Accordingly, the top 100 viral age-distorting proteins describe
16 which viral proteins are suspected to strongly interact with host ageing, defining future possible
17 targets of choice for anti-ageing treatments (supplementary table S4). Logically, these viral proteins
18 comprise the “usual proteic suspects”, e.g. the HIV-1 Tat protein (Cohen and Torres 2017; Seoane
19 et al. 2020; Schank et al. 2021), the E7 protein from HPV16 (Zamaraev et al. 2020), etc., often
20 mentioned in the literature in a context of viral hijacking (Forterre 2013) of host pathways. Next,
21 in order to identify the viral protein families that may interfere with human ageing and be
22 evolutionarily conserved across viruses (supplementary table S5), we determined whether these top
23 candidate age-distorting viral proteins belonged to common protein families shared across viral
24 lineages or instead formed distinct lineage-specific protein families. Interestingly, there were very
25 few candidate age-distorting protein families shared above the level of viral phyla. Specifically,
26 122 viruses from 28 different phyla independently evolved 231 different sets of gene families that
27 were demonstrated to convergently interact, based on network shuffling tests, with 69 human
28 proteins associated with ageing..

29 Interestingly, our finding that phylogenetically distant and even unrelated candidate age-
30 distorters convergently connect to the same human proteins is consistent with past experimental
31 discoveries focusing on the human PI3K-AKT-mTOR pathway, suggested to be an important
32 molecular target for both DNA and RNA viruses. Namely, the successful replication of different
33 phylogenetic lineages of viruses depends upon the activation of proteins from the PI3K-AKT-

1 mTOR pathway (Cooray 2004; Shin et al. 2007; Buchkovich et al. 2008; Murray et al. 2012) likely
2 because this pathway, associated with host ageing, achieves many functions in hosts. In brief, the
3 PI3K-AKT-mTOR pathway can regulate cellular macromolecular synthesis, metabolism, growth
4 and survival and thus its hijacking can contribute to establishing an environment accommodated to
5 the increased demand for nutrients, energy and macromolecular synthesis that comes with viral
6 infection (Buchkovich et al. 2008). From an evolutionary perspective, virus fitness was proposed
7 to benefit both from activating this pathway and from overcoming its inhibition when host cellular
8 stress responses are activated during viral infection (Buchkovich et al. 2008; Kuss-Duerkop et al.
9 2017). Our analysis generalises these observations by reporting that, among 34 human proteins
10 directly connected to mTOR and convergently connected to a diversity of viral proteins, 10 proteins
11 (beyond the known cases of Akt, or of the mTORC1 inhibitor REDD1 (Kuss-Duerkop et al. 2017),
12 namely EGFR, EP300, PML, PRKDC, RUVBL2, SQSTM1, SUMO1, TP53, VCP and YWHAZ,
13 have a significantly higher number of interactions with viral proteins/viruses than expected by
14 chance (as determined using random bipartite network permutations to determine an empirical p-
15 value with a significance threshold set at 0.05, after Bonferroni correction, see M&M,
16 supplementary fig. S6). In addition, we also report that 59 additional human proteins, not directly
17 connected to mTOR, have a higher number of interactions with viral proteins than expected by
18 chance (supplementary fig. S3). Thus, our findings strongly suggest that, in addition to the
19 evolution of mTOR signalling, which was speculated in the past to be convergently affected by
20 some pathogens through arms race (Martin et al. 2012), viruses may have also contributed to the
21 evolution of other age-associated pathways through co-evolution.

22

23 **Dozens of viruses are strongly connected to human ageing associated pathways**

24

25 As we also computed the average centrality of the human proteins targeted by each virus
26 in the human longevity network, we could sort human viruses based on their genetic potential to
27 interact with central human proteins associated with human cellular senescence (table 1) and with
28 human ageing in general (table 2). From this, we identified two lists of top 25 candidate age-
29 distorters, that we selected based on the large absolute number of candidate age-distorting proteins
30 they harboured and could use to interact with a large number of human proteins associated with
31 human ageing. As expected, these two lists of top 25 candidate age-distorters strongly overlap,
32 because the contents of the GenAge and CellAge databases are not independent, featuring a total

1 of 30 viruses. In order to highlight the most trustable of these predictions, we focused on the nature
2 of the experimental support for the interspecific PPIs associated with these 30 viruses
3 (supplementary fig. S7). Interactions were classified to reflect their level of support, from less well
4 supported, based only on protein complementation assays which comprise yeast 2 hybrid assays
5 ("protein complementation assays only"), to more stringent support based on affinity technologies
6 ("affinity technology assays only"), and better support provided by data curation ("imported from
7 Reactome") or a variety of other biochemical/biophysical assays (see M&M). This analysis
8 suggests that HIV-1, HHV-8, AAV-2, HRSV interactions have the highest quality of support, in
9 contrast to HPV1a, HPV33, HPV9, MuHV4, HPV8 or H3N2 interactions.

10 Furthermore, we compared the possible human targets for all pairs of these top candidate
11 age-distorters to evaluate their potential additive effects in case of co-infection by two such viruses.
12 Co-infection scores were computed as indicated in the M&M. These analyses suggest that some
13 viral co-infections (namely between influenza A virus (subtype H1N1), HHV-1, HHV-4, HHV-8
14 and HIV-1, supplementary fig. S8A) may be of special concern owing to their high additive
15 potential to interfere with human ageing, assuming their sites of infection overlap. Using random
16 bipartite network permutations, we could derive an empirical p-value (see M&M) pointing to
17 statistically significant high score values ($P < 0.05$ with Bonferroni adjustment), in particular for
18 HHV-8 in combination with either HPV16, HAdV-2, BPV-1, HTLV-1 or HPV1a (stars in
19 supplementary fig. S8A). We also compared the sets of human proteins connected by each pair of
20 viruses in our list of top candidates, in order to identify co-infections with the potential to reinforce
21 interactions with given human ageing-associated proteins (supplementary fig. S8B). Shared sets of
22 human interactors were observed for a cluster of papillomaviruses (HPV8, HPV33, HPV9, HPV1a,
23 HPV5, HPV16, HPV18, HPV11, HPV6b) on the one hand, and another cluster containing MeV,
24 AAV-2, HHV-1, HHV, H1N1 and HIV-1 on the other hand. For these clusters, several Jaccard
25 index values were statistically significant when compared to Jaccard indices in random bipartite
26 networks (stars in supplementary fig. S8B, $P < 0.05$ with Bonferroni adjustment), indicating which
27 pairs of viruses have a significant overlap in their sets of human interactors and a potentially
28 enhanced age-distorting effect in co-infections.

30 **Inferences of the modes of action of viral age-distorters**

31 We sought to evaluate whether our top candidate age-distorters could be further
32 characterised based on their potential interaction with proteins associated with specific hallmarks
33 of ageing. To assess this, we used a bipartite network analysis (Corel et al. 2018) to identify sets of

1 human proteins directly connected to each virus. Based on the functional annotations of these sets
2 of human proteic interactors, we performed functional inferences to gain an approximate view of
3 which host processes may be impacted during infection by each virus. For this, we associated each
4 human protein connected by a candidate viral age-distorting gene to a hallmark of human ageing,
5 or to general human ageing, based on former published evidence (Tacutu et al. 2018; Avelar et al.
6 2020; Holzschek et al. 2020; Saul et al. 2021). We used that logic to approximate the type of
7 impact on human ageing that each candidate viral age-distorter may produce, by distinguishing
8 whether these human proteins were currently reported to be associated with general human ageing
9 or more specifically with some hallmarks of ageing, including cellular senescence. Thus, for each
10 candidate viral age-distorter, we first contrasted the proportion of its human proteic interactors
11 associated with human cellular senescence according to the CellAge database (Avelar et al. 2020)
12 with the proportion of its human proteic interactors associated with general ageing, by subtracting
13 the proteins listed in the CellAge database from the more generalist GenAge database (Tacutu et al.
14 al. 2018) (supplementary fig. S9A). We also quantified the proportion of human proteic interactors
15 that belonged to a recently published list of biomarkers of human cellular senescence
16 (supplementary fig. S9A) (Saul et al. 2021). Finally, we quantified the proportion of human proteic
17 interactors associated with each hallmark of ageing, according to a classification kindly provided
18 by (Holzschek et al. 2020) (supplementary fig. S9B). We observed that all our top candidates had
19 genetic potential to interact with human proteins associated with several hallmarks of ageing, and
20 therefore could be considered as “general age-distorters”.

21 Moreover, we used published transcriptomic data to further investigate the potential of
22 several top age-distorter candidates to interfere with cellular senescence. We took advantage of the
23 recent demonstration that human cellular senescence can be empirically deduced from
24 transcriptomes through differential expression of a set of 125 biomarker genes, known as SenMayo
25 biomarkers (Saul et al. 2021), to search for evidence of an alteration of cellular senescence
26 associated with various viral infection (Kaczkowski et al. 2012; Jagya et al. 2014; Peng et al. 2014;
27 Bercovich-Kinori et al. 2016; Devadas et al. 2016; Hu et al. 2016; Tang et al. 2016; Zhang et al.
28 2016; Boldanova et al. 2017; Deshiere et al. 2017; Harden et al. 2017; Hojka-Osinska et al. 2017;
29 Klymenko et al. 2017; McGrath et al. 2017; Oberstein and Shenk 2017; Oh et al. 2017; Razooky
30 et al. 2017; Viollet et al. 2017; Zhu et al. 2017; Journo et al. 2018; Tso et al. 2018; Golumbeanu et
31 al. 2019; Mrozek-Gorska et al. 2019; Wang et al. 2019; Blanco-Melo et al. 2020; Dissanayake et
32 al. 2020; Li et al. 2020; Li et al. 2020; Seelbinder et al. 2020; Sen et al. 2020; Sheng et al. 2020;
33 Thompson et al. 2020; Winer et al. 2020; Zhuravlev et al. 2020; Bauby et al. 2021; Chandrashekar
34 et al. 2021; Chow et al. 2021; Coelho et al. 2021; Dapat et al. 2021; van der Heijden et al. 2021;

1 Hong et al. 2021; Tegtmeyer et al. 2021; Tsalik et al. 2021; Yanagi et al. 2021; Yuan et al. 2021;
2 Alberts et al. 2022; Bell et al. 2022; Montanari et al. 2022; Park et al. 2022; van Solingen et al.
3 2022; Zai et al. 2022) and GSE53993, GSE78711, GSE82232, GSE84346, GSE84897, GSE87750,
4 GSE89008, GSE92496, GSE93385, GSE97672, GSE101760, GSE102924, GSE186908,
5 GSE192528, GSE194179). We observed that amongst all human transcriptomes available to us to
6 contrast human gene expression in absence and in presence of a viral infection, differential gene
7 expression analyses under healthy and infected conditions reported a large fraction of differentially
8 expressed biomarkers of cellular senescence associated with the SARS-CoV-2 (fig. 5, columns 1-
9 6), HHV-4 (fig. 5, columns 30-34), HHV8/KSHV (fig. 5, columns 35-37), HCMV (fig. 5, columns
10 38-43) and HCV (fig.5, columns 51-54) infections, consistently with published reports of infection-
11 induced senescence for those viruses (Humphreys et al. 2020a; Seoane et al. 2020; Tripathi et al.
12 2021; Tsuji et al. 2022). Further, among viruses in the top 25 candidate senescence-distorters (table
13 1), HIV-1 (consistently with (Seoane et al. 2020)), HPV16 and ZIKV (fig.5 columns 7-13, 57-59,
14 66-69) indeed displayed differentially expressed SenMayo biomarkers in addition to HHV-4,
15 HHV-8/KSHV and HCV, whereas HPV11 and HRSV, for which we analyzed one dataset each
16 (fig.5 columns 56, 61), did not. Remarkably, this important proof of concept suggests that infection
17 by either influenza A or influenza B can also interfere with human senescence, because our heatmap
18 also reveals a large fraction of differentially expressed biomarkers of cellular senescence for
19 samples from various tissues and data collections of human infected by at least six H1N1 and one
20 H3N2 influenza A strains, as well as two influenza B strains (fig. 5, columns 15-29, supplementary
21 table S10). In details, observed variations between influenza transcriptomic studies may be partly
22 explained by their experimental designs, mainly concerning time post-infection before analysis.
23 Accordingly, most H1N1 columns showing a high number of differentially expressed biomarkers
24 of cellular senescence relates to 12h to 48h post-infection, as is especially clear for time-course
25 transcriptomic analyses of infection (fig. 5, columns 20, 22, 23), whereas H1N1 studies showing a
26 low number of differentially expressed genes have been conducted for 12h post-infection or less
27 (fig. 5, columns 15, 16, 24). Similar dynamics were observed for influenza A H3N2 strains (fig. 5,
28 columns 26, 27) and influenza B strains (fig. 5, columns 28, 29). Moreover, studies used a variety
29 of cell lines and viral strains, although the two main H1N1 strains used to compose the H1N1-
30 human PPI network (63% from A/Wilson-Smith/1933 H1N1, 27.5% from A/Puerto Rico/8/1934
31 H1N1) were amongst the viral strains tested in the transcriptomic dataset (fig. 5, columns 18, 21,
32 24, 25).

33 Interestingly, influenza B strains are barely represented in the PPI data with only 9 PPIs
34 recorded in the HVIDB and thus were logically not predicted as age-distorters in our analysis.

1 However, differential expression of many SenMayo biomarkers strongly suggests both influenza
2 A and B viruses interfere with the normal process of cellular senescence. Of note, the molecular
3 mechanisms that produce this effect on cellular senescence were not mainly due to direct
4 interactions between influenza viral proteins and the human proteins from the SenMayo biomarker
5 list (supplementary fig. S9A). Rather, some mechanisms producing this transcriptomic signature
6 suggesting altered cellular senescence associated with influenza A H1N1 infection can probably be
7 searched for amongst the 45 % of human proteins, listed in CellAge, with which H1N1 interacts
8 and experimentally known to be associated with cellular senescence (supplementary fig. S9A)
9 ([Avelar et al. 2020](#)).

10 In contrast, even though interference with cellular senescence has been associated with
11 HBV-induced hepatocellular carcinoma upon chronic infection ([Seoane et al. 2020](#); [Giannakoulis](#)
12 [et al. 2021](#)), only few differentially expressed SenMayo biomarkers were detected in cultured cells
13 upon HBV infection, or upon HBV co-infection with either HDV or HEV (fig. 5, columns 44-49),
14 nor in liver biopsies from chronically infected patients (fig. 5, column 50). These observations
15 suggest that HBV-associated cellular senescence may depend on host cell transformation rather
16 than directly result from viral infection.

17 We concluded that some viruses (HHV-4/EBV; SARS-CoV-2; influenza A, subtypes
18 H1N1 and H3N2; influenza B; HCMV; HHV-8/KSHV; RV; ZIKV; HPV16; HIV-1; HCV) affect
19 human cellular senescence, and therefore may negatively affect their host homeostasy.

20

21 **Published experimental evidence corroborate age-distorter predictions**

22 Importantly, in addition to our transcriptomic analyses, our predictions of age-distorters
23 can be backed up by published compatible experimental evidence and, in some cases, by additional
24 independent experimental support, meaning that different series of proofs of concept support our
25 predictions. Thus, emblematically, HIV-1 figures amongst the 25 viruses with the highest
26 interaction scores listed as candidate human age-distorters (tables 1, 2). The ability of HIV-1 to
27 interfere with the cell cycle and with the ageing of its hosts has long been recognised. For instance,
28 HIV-1 can induce telomerase activity in monocyte-derived macrophages, which is expected to turn
29 these infected host cells into resistant viral reservoirs ([Reynoso et al. 2012](#)). HIV-1 can also cause
30 immunosenescence ([Cohen and Torres 2017](#)) and provoke stress-induced premature senescence of
31 non-immune cells ([Cohen and Torres 2017](#)) and progressive mitochondrial damages that contribute
32 to accelerated ageing and cellular dysfunction ([Schank et al. 2021](#)). Consistently, HIV-1 infection

1 was reported to increase epigenetic age both in brain tissue and in the blood (Horvath and Levine
2 2015). In addition, morphological reports identified an acceleration of the normal ageing trajectory
3 in several regions of the human brain, such as the neocortex and the thalamus of HIV-infected
4 individuals in general good health (Pfefferbaum et al. 2014). HIV-1 infection was also causally
5 connected to cases of osteoporosis and of osteopenia (Seoane et al. 2020).

6 Likewise, several other viruses from our list of candidate age-distorters appear reasonable
7 candidates based on former independent knowledge. For example, the Mink enteritis virus (MEVB)
8 was demonstrated to significantly increase apoptosis in various mink organs as well as to induce
9 apoptosis in human embryonic kidney 293T cells (Lin et al. 2019). This is noteworthy because viral
10 interactions with apoptosis are recognised to affect host homeostasis, and dysregulation of
11 apoptosis appears as a pleiotropic driving force of tissue ageing (Mlih et al. 2018). Likewise, the
12 Lymphocytic choriomeningitis virus (LCMV) and the vaccinia virus (VACV) were demonstrated
13 to induce abundant senescent CD8 T cells in vivo in mice (Voehringer et al. 2001). Thus, some
14 compelling evidence for a contribution of HHV-1 (HSV-1) to host ageing also deserves mention.
15 While the role of this virus regarding ageing is debated, some prominent works considered HSV-1
16 as causally involved in Alzheimer's disease when present in the brain of APOE-e4 carriers (Itzhaki
17 2021). Upon infection, HSV-1 was described to induce oxidative stress resulting in neuronal
18 oxidative damages, to disrupt autophagy and to interfere with apoptosis (Itzhaki 2021).

19 More generally speaking, our list of viruses predicted to behave as human age-distorters
20 features many recognised human oncoviruses, such as HHV-4, also known as the Epstein-Barr
21 Virus (EBV); several Human papillomaviruses (HPVs); the Hepatitis C virus, also known as HCV,
22 the Human T-Cell Leukemia Virus-1, also known as HTLV-1, the Human Herpesvirus-8, also
23 known as KSHV, which have all been reported to increase the transcription of their host telomere
24 reverse transcriptase (Bellon and Nicot 2017), and all been demonstrated to interfere with human
25 cellular ageing. For instance, HPVs, in particular HPV16/18 use their viral oncoproteins E6 and E7
26 to manipulate host signaling pathways involved in cell proliferation, cell death and innate immunity
27 (Lo Cigno et al. 2020), depleting multiple innate immunity effectors. Moreover, HPV-18 protein
28 E2 can delay replicative senescence of human keratinocytes by downregulating antisense
29 noncoding mitochondrial RNA-2 (Villota et al. 2018). Consistently, HPV16/18 infections have
30 been proposed to correlate with epigenetic age acceleration of cervical squamous cell carcinoma
31 (Lu et al. 2020). Likewise, protein E7 of HPV-8 deregulates the phosphorylation status of nuclear
32 proteins involved in DNA damage repair and replication (Kirschberg et al. 2020), contributing to
33 cancer formation, and HPV6b induces cell senescence into primary human cervical epithelial cells
34 (Pecoraro et al. 1989). To our knowledge, experimental evidence independently supporting a role

1 of HPV31 in human ageing is less clear, although expressed sequence tag analyses provided
2 evidence that HPV31 encodes genes whose products can alter the activities of human cellular
3 proteins, including the regulation of cell growth (Chang and Laimins 2000), and thus may affect
4 cellular ageing.

5 In contrast with this later case, a clear connection between HTLV-1 infection and human
6 ageing has been proposed previously. Adult T-cell leukemia/lymphoma develops after a long
7 period of HTLV-1 infection, and this phenotype is associated to host ageing as well as to genetic
8 abnormalities in infected cells (Kozako et al. 2022). Significantly, this long term proliferation of
9 HTLV-1 within humans relies upon viral manipulations of apoptosis and of replicative senescence
10 of infected cells through mechanisms that are currently investigated (Harhaj and Giam 2018; Bellon
11 et al. 2021; He et al. 2021). Similarly, HHV8/KSHV has been reported to trigger hallmarks of
12 alternative lengthening of telomeres (Lippert et al. 2021) and to partly subvert autophagy in ways
13 that dampen host antiviral defenses and allow infected cells to proliferate (Leidal et al. 2012).
14 Moreover, HHV8/KSHV can overcome replicative senescence in primary lymphatic endothelial
15 cells using vCyclin (DiMaio et al. 2020). Finally, chronic Hepatitis C Virus (HCV) infection is
16 coupled to a marked up-regulation of cell cycle inhibitor and of senescence markers, and known to
17 result in enhanced senescence of hepatic T-cells compared to healthy liver tissues (Wandrer et al.
18 2018). These varied lines of evidence show that many candidate age-distorters predicted by our
19 analyses interfere with aspects of human ageing. In addition to these oncoviruses, several
20 empirically demonstrated oncosuppressive viruses, such as VACV, HAAdV-5, and HAAdV-2
21 (Pozzatti et al. 1988; Marcellus et al. 2000; Chen et al. 2011; Nguyen et al. 2018), also figure in
22 our list of candidate age-distorters. Although oncolytic viruses can in general rely upon very
23 different modes of action, their presence in our list and our functional inferences based on their
24 interactors amongst human proteins (Fig. S9) suggest that these viruses interfere with various
25 aspects of ageing, including cellular senescence and telomere attrition.

27 **Influenza A, a major candidate age-distorter manipulating human cellular senescence.**

28 Importantly, our list of viral age-distorters also contains several candidates (e.g. H3N2,
29 RSV) that, based on current published knowledge were less expected to behave as age-distorters,
30 and therefore may deserve greater considerations in future anti-ageing therapies. This is especially
31 true for the influenza A virus (subtype H1N1), which, based on its high scores in our tables, shows
32 a significant genetic potential to interfere with human ageing, alone or in co-infections, especially
33 with HHV-4, HHV-8, HHV-1 or HIV-1 (supplementary fig. S8)

1 First, we showed that H1N1 is connected to a remarkable number of human proteins for its
2 genome size, to an extent comparable to that of HIV-1 (figs. 3 and 4). In details, the genome of
3 HIV-1 is 8955 bp long and encodes 9 ORFs, which produce 4 polyproteins and 15 final proteins,
4 while the genome of H1N1 is 13133 or 13627 bp long, depending on the strain, and encodes 8
5 ORFs, which produce up to 17 known proteins. Both viruses however can interact with over a
6 hundred human ageing-associated proteins (142 for HIV-1, 130 for H1N1). In details, 253
7 interactions and 454 interactions with human proteins from the longevity network have been
8 experimentally demonstrated for HIV-1 on the one hand and for H1N1 (compiling data from 20
9 strains in HVIDB, with 2 strains representing 90.5 % of interactions) on the other hand. HIV-1 and
10 H1N1 PPIs are very minorly dependent on yeast two-hybrid assays with high false positive rates
11 (less than 5% each). Typically, HIV-1 interactions are mostly imported from Reactome curated
12 data, whereas 95% of H1N1 interactions are supported by a variety of affinity-based assays. Both
13 viruses are connected to 61 common human protein families, meaning that 43.4% of H1N1 human
14 proteic interactors are shared with that of HIV-1, but these viruses do so using entirely different
15 viral protein families. Finally, a comparison of the degree and closeness centrality metrics
16 distributions of HIV-1- and H1N1-associated human proteins in the human longevity network,
17 itself supported by a variety of molecular detection assays (see M&M), found no significant
18 differences in centrality (two-sample Kolmogorov-Smirnov test for goodness of fit), meaning that
19 both viruses can interact with equally central human proteins.

20 Interestingly, some published evidence on influenza A viruses (subtype H1N1) is
21 compatible with our prediction that the flu virus could be a genuine human age-distorter. Some
22 influenza A proteins (up to three: HA, NS1 and M2) were demonstrated to interact with a few host
23 proteins from the PI3K-AKT-mTOR pathway, e.g. mTORC1 and mTORC2 (Shin et al. 2007;
24 Murray et al. 2012; Kuss-Duerkop et al. 2017). In short, H1N1 proteins directly and indirectly
25 activate mTOR, which supports viral replication, and consistently H1N1 replication is reduced
26 when mTOR is inhibited (Wang et al. 2014; Jia et al. 2018), suggesting an evolutionary interest for
27 H1N1 to interfere with mTOR (Kuss-Duerkop et al. 2017). As mTORC1 activation supports viral
28 protein expression and replication, viral-human proteic interactions would probably be optimal for
29 the influenza A virus midway through its life cycle, considering that these expressed viral proteins
30 are likely to support the late-stages of influenza replication when infected cells undergo significant
31 stress (Kuss-Duerkop et al. 2017). While they support our claim that H1N1 can act as an age-
32 distorter, the above studies did not analyse the possible effects on host ageing of the interplay
33 between Influenza A proteins and these human proteins. However, while it is well-known that the
34 primary targets of influenza virus are airway epithelial cells, severe influenza infections result in

1 virus-induced tissue destruction and dysregulated systemic inflammation (Jia et al. 2018), two
2 phenotypes that could contribute to ageing. Moreover, some temporal relationships between
3 influenza A (subtype H1N1) infection and increased type 1 diabetes incidence have been reported
4 (Nenna et al. 2011; Watanabe 2011; Valdés et al. 2013). If beyond this correlation, the causal role
5 of influenza A in this increased type 1 diabetes incidence could be established (Ruiz et al. 2018),
6 this would provide independent evidence that influenza A infection can contribute to human ageing,
7 because type 1 diabetes can be considered as a form of accelerated muscle ageing (Monaco et al.
8 2019). Furthermore, another correlation appears compatible with the prediction that influenza A
9 (H1N1 subtype) interferes with human ageing. Recent reports show that the US cohort *in utero*
10 during the peak of the 1918 influenza pandemic experienced higher rates of depression after age
11 50, higher rates of diabetes and ischemic heart disease after age 60 and higher mortality after age
12 65 (Easterlin et al. 2021). Likewise, the Taiwanese cohort exposed to influenza A (H1N1 subtype)
13 *in utero* in 1919 experienced higher rates of renal disease, circulatory and respiratory morbidities,
14 and diabetes after age 60, while the corresponding Swedish cohort experienced a higher morbidity
15 at age 54-87, due to an excess of hospitalisations and an excessive male mortality from heart disease
16 and cancer (Easterlin et al. 2021). However, it is impossible to conclude whether such significant
17 phenotypic differences showing evidence of early decline in infected populations were due to
18 exposure of these individuals to the influenza A (H1N1 subtype) virus itself, acting as an age-
19 distorter according to our hypothesis, or were more generally provoked by the stress associated
20 with the pandemic environment (Easterlin et al. 2021).

21 Finally, as indicated above differential gene expression analyses comparing human gene
22 expression in the transcriptomes of individuals infected by Influenza A subtypes H1N1 and H3N2
23 strains as well as influenza B strains (fig.5) provide another independent line of experimental
24 evidence to demonstrate that influenza infection interferes with at least one feature of human
25 ageing: cellular senescence, suggesting that influenza A poses under-appreciated threats to human
26 ageing.

27 28 **Discussion**

29
30 Evolutionary considerations predict that viral genomes co-evolve with that of their hosts,
31 in particular in the context of the evolution of strategies of hijacking of host processes by their
32 viruses. Accordingly, we devised a systematic protocol based on interaction network analyses to
33 test the general, worrying hypothesis that various pathways associated with human ageing may be
34 impacted by direct interactions with viral proteins from a broad diversity of viral sources. For this,

1 we relied on the collection of experimentally demonstrated interactions between viral proteins and
2 human proteins from HVIDB (Yang et al. 2021) to survey viral candidate age-distorters of type 1,
3 i.e. viruses characterised by their genetic potential to encode proteins interacting with human
4 proteins from ageing associated pathways. The quality of HVIDB allowed us to unveil candidate
5 age-distorters, but this database is surely not yet exhaustive. Inevitably, the limited experimental
6 knowledge about under-studied viral proteins and human interactions limited our ability to detect
7 all viral candidate age-distorters of human ageing. For instance, although influenza B strains appear
8 to have similar associations as influenza A strains with cellular senescence biomarkers expression
9 upon infection, we could not have predicted such a role based on interspecific PPI because HVIDB
10 has only 9 PPIs recorded for influenza B.

11 Nonetheless, bearing these limits in mind, we found that dozens of viruses from different
12 phylogenetic groups harbour protein coding genes whose products have been experimentally
13 demonstrated, with the support of biochemical and biophysical assays (see M&M), to interact with
14 human proteins associated with ageing. This systematic analysis over a large phylogenetic diversity
15 of viruses offers a strong argument to generalise the observation that some viruses, such as HIV-1
16 and SARS-CoV-2 contribute to accelerating human ageing, beyond these well-known cases of viral
17 suspects of ‘age-distortion’.

18 From an evolutionary viewpoint, the large phylogenetic diversity of candidate age-distorter
19 viruses and the fact that, when they belong to different phyla, these viruses can use almost
20 completely unrelated age-distorting gene families to interact with human proteins associated with
21 ageing, demonstrates a strong evolutionary convergence in the impact viruses might have on human
22 ageing. This may be explained by the fact that since mechanisms of viral hijacking generally target
23 important human proteins, and since human proteins associated with ageing are often central in
24 human protein-protein interaction networks (Bell et al. 2009; Fernandes et al. 2016), then viral
25 hijacking should commonly interfere with human ageing. In that sense, viral evolutionary success
26 is likely to proceed at the cost of some alteration of human ageing. However, it should not simply
27 be assumed that any sort of viral illness, even if repeated or latent, will inevitably result in
28 accelerated host ageing. A host owns resources to fight viral infections and illnesses, even chronic
29 ones. Surely, viral lytic infection substantially alters cellular physiology, provoking nutrient
30 depletion, energy depletion, hypoxia and endoplasmic reticulum stress. But these alterations in
31 stress signalling activate host mechanisms that can either alleviate the problem or induce apoptosis
32 (Buchkovich et al. 2008). Therefore, while each new viral particle depletes cellular lipidic, proteic
33 or nucleic resources, which need to be replaced to maintain cellular homeostasy, such an infection
34 does not imply that the fight for limited macromolecules has to be (dramatically) lost by the host.

1 In the case of some infections at least, substrate availability may not be a limit, for the virus and
2 for the host (Smallwood et al. 2017). Consistently, the effects of human cytomegalovirus (HCMV)
3 infections on accelerated immune senescence have been debated for a long time. Some recent
4 studies demonstrated that a high infectious dose is a prerequisite for CMV-associated immune
5 senescence (Redeker et al. 2018), and that HCMV infection results in telomere erosion and
6 replicative senescence, faster and more frequently in CD8+ cytotoxic T lymphocytes compared to
7 CD4 + T helper cells (Humphreys et al. 2020b), through continuous antigen exposure. Yet, a recent
8 consensus is that CMV does not have a clear and measurable negative immune senescence impact
9 (Nikolich-Zugich et al. 2020). Furthermore, the effects of bacteriophage infection on human health
10 are still poorly known. Bacteriophages are abundant within our bodies (Popescu et al. 2021),
11 forming phage colonies that are highly temporally stable, including circulating bioactive phages,
12 remarkably well tolerated immunologically. In addition, some phage genome transcription has even
13 been reported in a eukaryotic system (Popescu et al. 2021), and some phages recently proved to
14 play unanticipated roles in the mammalian and in the human body, including some ability to
15 modulate the physiology of their host mammalian cells (Popescu et al. 2021), to the point that some
16 authors foresee a growing field of phage-mammalian cell interactions (Bodner et al. 2021). Whether
17 phage infection should necessarily lead to human ageing is therefore an open question.
18 Consequently, not all viruses may qualify as type 1 age-distorters.

19 Getting back to the concept of age-distorter, it must be recognised that the evolutionary
20 reasons for which viruses interfere with apoptosis or with cellular senescence, for instance, are
21 debated (Kelley et al. 2020). Our findings are consistent with the notion that, in some cases, the
22 hijacking of important human proteins within those associated with ageing, e.g. when viruses
23 interfere with very central proteins in human longevity networks, may be an adaptive strategy for
24 the viruses. Typically, viral survival and reproduction can be enhanced by interspecific proteic
25 interferences that weaken human antiviral defenses or that, by delaying cell death, generate human
26 cell reservoirs for viruses. For instance, the ability to delay or prevent apoptosis provides viruses
27 with more time and opportunities to replicate and assemble viral particles and promotes long-term
28 survival of viruses in the host cell as well as their spread to surrounding hosts cells, which can lead
29 to persistent infection. Thus, apoptosis induced by HIV-1 contribute, amongst many mechanisms,
30 to the gradual T cell decline that occurs in HIV-infected patients, and programmed cell death of
31 uninfected bystander T lymphocytes, including CD4+ and CD8+ T cells (Rex et al. 2022). The
32 same is true for cellular senescence, often considered a part of the host cell response to fight viruses
33 (Baz-Martínez et al. 2016; Kelley et al. 2020). Yet, on the other hand, many viruses replicate

1 optimally in senescent cells. Indeed, senescent cells offer a hospitable microenvironment with
2 persistently elevated cytosolic calcium, abundant intracellular iron, and low interferon type I. As a
3 result, in infected hosts, virus-induced immune dysfunction and premature cellular senescence may
4 predispose to ageing-related disease such as neurodegenerative disorders (Osorio et al. 2022).
5 Similarly, some viruses have been proposed to hijack the senescent machinery within the infected
6 cell to downregulate the interferon (IFN) pathway, to promote viral packaging and ultimately to
7 enhance viral replication within the cell (Kim et al. 2016; Kelley et al. 2020). This is the case for
8 the human papillomavirus or the varicella zoster virus which replicate more efficiently in senescent
9 human bronchial epithelial cells or in human dermal fibroblasts than in non-senescent cells, and
10 have evolved machinery to specifically overcome cellular senescence (Kelley et al. 2020).
11 Likewise, Giannakoulis et al. (Giannakoulis et al. 2021) recently reported that different isoforms
12 of the hepatitis B virus X (HBx) protein have different effects on senescence, yet promotes factors
13 of the SASP phenotype, which may enhance telomere shortening, and thus trigger replicative
14 senescence and cirrhosis in hosts. In addition, Camell et al. reported the SARS-CoV-2 S1 protein
15 is a PAMP that can trigger a hyperinflammatory state in senescent cells, and that senescent cells
16 could promote SARS-CoV-2 pathogenesis by decreasing viral defenses and increasing expression
17 of viral entry proteins in neighbouring non-senescent cells through amplified secretion of SASP
18 factors (Camell et al. 2021; Lee et al. 2021). These examples suggest that cellular senescence, in
19 some host conditions, may enhance rather than oppose viral infection. Therefore, to distinguish
20 between viruses that inadvertently trigger an immune response and viruses specifically causing
21 apoptosis/cellular senescence for their own purposes, quantifying the effect of the manipulated host
22 processes on viral fitness (e.g., by quantification of viral titers from supernatants of infected cells,
23 or of the intensity of viral protein synthesis in senescent cells) would be useful. Our work makes
24 one key step on that research road, by identifying a number of viruses with genetic potential to act
25 as type 1 age-distorters, even though our work does not allow to distinguish between two
26 interpretations, i.e. virally-altered human ageing as a side-effect of the hijacking of central human
27 proteins vs a selected direct viral-manipulation of human ageing. However, our work makes it clear
28 that many viruses encode genetic potential to interfere with human ageing and provides a broad,
29 updated list of key viruses, key viral proteins and human proteins, repeatedly involved in
30 interactions these viral entities (supplementary table S1), supporting testable predictions.

31 Importantly, this list of age-distorters and age-distorting proteins is, in part comforted by
32 the published literature and by experimental evidence. For instance, the report of HIV-1 as well as
33 that of many oncoviruses amongst the top candidate age-distorters offers a proof of concept that

1 our strategy succeeded in reporting first viruses known to interfere with host ageing and with the
2 human cell cycle. Interestingly, our broadscale functional inferences suggest that these top
3 candidate age-distorters may impact human ageing in general, potentially contributing to multiple
4 hallmarks of ageing, and in particular, for some viruses, such as influenza A (subtype H1N1), to
5 cellular senescence. These latter effects on cellular senescence are worth emphasising, because
6 virally-induced interference with cellular senescence is expected to affect global host ageing
7 beyond the fate of human infected cells. For instance, virally-induced manipulation of cellular
8 senescence can contribute to age-associated diseases (Kelley et al. 2020), as it induces
9 dysregulation of the host homeostasis, e.g. when senescent cells accumulate faster than they are
10 removed, and/or due to an aggravation of immunosenescence, caused by the known bystander
11 effect exerted by senescent cells on their neighbours (Karin et al. 2019). With this in mind, our
12 prediction that the influenza A virus (subtype H1N1) is likely to alter cellular senescence,
13 reinforced by transcriptomic evidence, raises the possibility that, although H1N1 (but maybe not
14 its genes (Tesoriero et al. 2016)) has usual short latency periods (Cori et al. 2012), it encodes a rich
15 under-appreciated genetic potential to distort human ageing. Therefore, although the majority of
16 influenza infections are acute self-resolving episodes, the long term effects on human ageing of
17 both recurrent infections by influenza A (Möst et al. 2019; Memoli et al. 2020; Wang et al. 2022)
18 and of longer episodes of acute infections in some immuno-suppressed individuals (Pinsky et al.
19 2010) (but see (Tang 2010)) may deserve further investigations. In particular, it would be worth
20 determining whether the severity of age-distortion by H1N1 viruses, by aggravating the load of
21 senescent cells and by provoking other host damages, may not be in itself an age-dependent process,
22 e.g. with stronger effects on ageing in older infected humans. Indeed, as cellular senescence,
23 particularly in cells of the immune system, is the hallmark of elderly adults, the further induction
24 of immunosenescence may cause older individuals to be more susceptible to infection (Hsieh et al.
25 2020).

26 On that front, our original heatmap analysis of the differential gene expression of SenMayo
27 markers upon viral infection provides novel evidence that many viruses beyond the influenza A
28 virus affect cellular senescence, and may also contribute to host-ageing in an age-dependent way.
29 Consistently, SARS-CoV-2 has been experimentally demonstrated i) to indirectly induce cellular
30 senescence in humans and ii) to have aggravated effects in elderly humans with respect to younger
31 humans. These two observations have been causally connected in some papers that propose that
32 because older humans already harbour an elevated proportion of pre-existing senescent cells in
33 their tissues, the additional cellular senescence provoked by SARS-CoV-2, by aggravating the load
34 in senescent cells and their SASPs beyond a certain threshold, leads to a switch past which there is

1 an exacerbation of the infection, an aggravation of age-related pathologies and further
2 immunosenescence (Camell et al. 2021; Lee et al. 2021; Lynch et al. 2021; Schmitt et al. 2022).
3 This claim was further supported by the observation that treatments with senolytics, i.e. that remove
4 senescent cells from aged organisms, can decrease the effects of SARS-CoV-2 infection,
5 confirming that (pre-existing) senescent cells are critical mediators for the disease (Camell et al.
6 2021). In addition, such an accumulation of senescent cells, when insufficient to trigger an
7 exacerbation of the disease during the course of the infection, may still have a longer-term impact,
8 as proposed (although debated) for ‘long Covid’ (Schmitt et al. 2022). If that logic holds for other
9 viruses that induce cellular senescence, either by direct viral protein interactions with human
10 proteic interactors associated with cellular senescence pathways, or indirectly, by triggering an
11 immune response that the host uses to clear the virus, then the effects of these viruses should be
12 more dramatic when they infect hosts with higher proportion of pre-existing senescent cells.
13 Consistently, the impact of viruses that induce cellular senescence should be higher on older
14 individuals, as well as in some younger individuals affected by chronic diseases, who can also
15 harbour higher proportion of pre-existing senescent cells in their tissues than healthy members from
16 their age classes (Schmitt et al. 2022).

17 By bringing into light the large diversity of viruses that could genetically alter our ageing,
18 our predictions of candidate age-distorters set the stage to subsequent experimental analyses of the
19 contribution of viral age-distorting genes, of viral age-distorters and of their human targets to
20 human ageing to determine which are the major viral threats to our ageing. It also sets the stage to
21 determine which of the human proteic interactors of these viruses may, as a result of evolution,
22 constitute human molecular Achilles’ heels, leading to altered ageing patterns upon viral infection.
23 Indeed, as our approach supports the hypothesis that many viruses interfere with human ageing and
24 may genetically contribute to the progressive weakening of our organisms, by the same token, our
25 protocol opens an avenue for the research of novel targets through innovative anti-ageing therapies.
26 Knowing which key proteic interactors in humans can be affected by age-distorters is of high
27 interest to shape evolutionary medicine, as it defines a pool of human cellular targets, critical for
28 the success of viral infection, which may be used as (less evolutionarily dynamic) targets than the
29 viral proteins for pharmacological interventions (König et al. 2010; Kuss-Duerkop et al. 2017).
30 Alternatively, new medical anti-ageing treatments could possibly be devised with the aim to
31 counter the negative effects of some interactions between viral and human proteins, e.g. by
32 designing molecules mimicking human target proteins to alleviate the effects of viral proteins
33 (Karoyan et al. 2021). Moreover, some existing vaccines developed to fight acute viral infections
34 could be re-purposed to fight against virally-induced ageing, leading to future novel health policies.

1 Likewise, it may appear desirable to routinely monitor the environmental load in viral age-
2 distorters and in viral age-distorting genes using targeted metagenomics approaches, for instance
3 to quantify the abundance of key viral age-distorters or of key age-distorting genes in the
4 environments (hospital, schools, public waters, etc.) to determine whether and where humans are
5 being exposed to significantly high age-distorting threats. A similar procedure could also be used
6 in the context of personalised medicine to monitor the dynamics of the load of age-distorters
7 associated with various individual medical conditions (e.g., through targeted -omics analyses of
8 blood samples).

9 On a more theoretical level, recognising that some viruses are age-distorters could also
10 change our perception of these viruses on our health, by recognising that these viruses may cause
11 more deaths than currently assumed. Quantifying the number of people that die from a virus (such
12 as the seasonal flu) is both important from a medical and societal viewpoint and challenging from
13 a demographic perspective (Charbonneau and James 2019). For seasonal viruses, measures of
14 excess deaths during infection periods is a common strategy to address this problem (Iuliano et al.
15 2018; Paget et al. 2019). However, should influenza A (subtype H1N1) be considered as an
16 age-distorter as suggested by our work, this would mean that infections by influenza A may also
17 lead to additional deaths, delayed in time, i.e., occurring after, rather than during, the flu season,
18 through host ageing and aggravated senescence. This additional death-toll induced by influenza
19 infection would then deserve to be accounted for, possibly by an explicit modelling of age-
20 distortion potential in demographic/epidemiological models, to quantify short- and long-term
21 deaths induced by the influenza A virus. To conclude, because our strategy to mine for candidate
22 age-distorters and age-distorting genes is very generic, our work paves the way for future,
23 phylogenetically expanded surveys of viral age-distorters and viral age-distorting, which are likely
24 to be prompted by the ever-increasing flow of -omics viral (including bacteriophages) and human
25 data. And beyond, by moving away from an anthropocentric view towards a more fundamental
26 understanding of the impact of viral interactions on ageing for a diversity of hosts across the Web
27 of Life, we anticipate that our study could be extended to many other species for which genes and
28 proteins have been associated with ageing (currently, *Mus musculus*, *Caenorhabditis elegans*,
29 *Saccharomyces cerevisiae*, etc.). Thereby, our work should further enhance the classic views on
30 the locus of organismal ageing from current mainstream evolutionary theories of ageing (Johnson
31 et al. 2019), moving it towards a more communal, ecological perspective to explain both the
32 ultimate and proximal causes of ageing, which could have implications for many fields, including
33 evolutionary biology, ageing research, virology, medicine and demography studies.

1

2 **Materials and Methods**

3

4 **Construction of ageing-associated PPI networks**

5 The human protein-protein interaction network used in this study was downloaded from
6 the STRING ('Search Tool for Retrieval of Interacting Genes/Proteins') database v11.5
7 (<https://string-db.org/>, Szklarczyk 2019). The CellAge set (Build 2) of 279 cell senescence human
8 genes (<http://genomics.senescence.info/cells/cellAge.zip>, Avelar 2020) and the GenAge set (Build
9 20) of 307 ageing-related human genes (https://genomics.senescence.info/genes/human_genes.zip,
10 Tacutu 2018) were retrieved. A "longevity network" was derived from this human PPI network by
11 keeping only the interactions between proteins corresponding to the cellular senescence-associated
12 CellAge and longevity/aging-associated GenAge gene sets. Only edges indicating experimental
13 support (see next section for details) were integrated in the longevity network.

14 Interspecific bipartite PPI networks were derived from PPI data from the HVIDB ('Human-
15 Virus protein Interaction DataBase') updated 25 June 2020 (<http://zzdlab.com/hvidb/>, Yang 2021)
16 restricted to interactions involving human proteins corresponding to the CellAge an GenAge gene
17 sets. The HVIDB experimentally supported (see next section for details) human-virus protein-
18 protein interactions (7,796 human proteins, 2,104 viral proteins, 48,643 human-virus PPIs) was
19 downloaded in June 2021 from the following URL:
20 http://zzdlab.com/hvidb/download/HVIDB_PPIs.txt. To identify viral proteins interacting with
21 senescence- and/or ageing-related human proteins, PPIs involving human proteins encoded by
22 genes present in the CellAge (212 human proteins, 771 viral proteins, 1,783 PPIs) and GenAge
23 (269 human proteins, 913 viral proteins, 2,958 PPIs) gene sets, respectively, were extracted from
24 the HVIDB PPI dataset (forming a total of 4154 total interactions). HIV-1 and H1N1-specific
25 interspecific PPI networks were built by combining interactions from the STRING human
26 longevity network with HIV-1-associated and H1N1-associated, respectively, HVIDB interspecific
27 PPI-interactions.

28

29 **Details of the experimental PPI support**

30 All PPIs used are supported by experimental data obtained using a large variety of molecular
31 interaction detection techniques. Experimental data supporting STRING and HVIDB PPI were
32 simplified using high level categories in the HUPO PSI's "experimental interaction detection"

1 ontology (Hermjakob et al. 2004). These categories were “affinity technology”
2 (immunoprecipitation assays; competition binding; display technology; enzyme linked
3 immunosorbent assay; far western blotting; filter binding; interactome parallel affinity capture;
4 luminescence based mammalian interactome mapping; phage display; proximity ligation; pull
5 down assays; saturation binding; solid phase assay; tandem affinity purification), “protein
6 complementation assay” (adenylate cyclase complementation; barcode fusion genetics two hybrid;
7 beta galactosidase complementation; beta lactamase complementation; bimolecular fluorescence
8 complementation; cytoplasmic complementation assay; gal4 vp16 complementation; lex-a
9 dimerization; lex-a b52 complementation; mammalian protein protein interaction trap; prey pooling
10 approach; protein three hybrid; split luciferase complementation; two hybrid; two hybrid array; two
11 hybrid bait; two hybrid pooling approach; ubiquitin reconstruction), “imported from Reactome”
12 (Reactome Curated interaction data), and high confidence biochemical/biophysical assays grouped
13 as “other techniques”.

14 The detail of this supporting data is crucial to determine if these interactions are to be
15 trusted: yeast two-hybrid based techniques, for instance, tend to have high rates of false positives
16 (Huang et al. 2007). PPIs in the human longevity network were selected because their
17 “experiments” STRING score channel (comprised between 0 and 1000) was greater than 0. The
18 scores in the extracted PPI network ranged from 42 to 999, with a mean of 416.54 and a standard
19 deviation of 246.45. 61.3 % were of low confidence (score < 400), 21.3 % of medium confidence
20 ($400 \leq \text{score} < 700$) and 17.4 % of high confidence (score ≥ 700), using STRING criteria. To
21 compute these scores, STRING integrated experimental support from 16231 datasets from other
22 protein interaction databases (BioGRID: 9409; IntAct: 5530; HPRD: 810; PDB: 368; DIP: 114).
23 899 interaction datasets (5.5%) were constituted using only yeast two-hybrid (Y2H) techniques,
24 whereas 10816 datasets (66%) used more reliable affinity based techniques (including
25 coimmunoprecipitation, pull down and tandem affinity purification). The remaining datasets used
26 diverse biochemical and biophysical techniques to define PPIs. Similarly, two thirds of HVIDB
27 PPIs were supported by affinity based assays (66,6% of 4154 selected PPIs), with 4% being in
28 addition supported by other categories of assays, and 16.5% were only based on protein
29 complementation assays (685/4154). Overall, the experimental support for the STRING human
30 PPIs and HVIDB interspecific PPIs gathered for this study is varied and does only marginally rely
31 on Y2H-type screens.

32
33

1 **Computation and curation of viral protein families**

2 The sequences of the 1,031 viral proteins found to interact with human protein(s) involved
3 in senescence and/or ageing were retrieved from the Uniprot database via the following string
4 concatenation: “<https://www.uniprot.org/uniprot/>” + Uniprot ID of the viral protein provided by
5 HVIDB + “.fasta”. Upon remapping of obsolete identifiers and removal of 197 sequences annotated
6 as (Fragment), 834 viral sequences were then aligned to each other in an all-against-all BLASTP
7 and families of viral proteins were defined as connected components in the sequence similarity
8 network connecting proteins showing at least 30% identity over at least 80% mutual length
9 coverage. 174 (Fragment) sequences were subsequently mapped to the families containing the
10 corresponding complete sequences, and the remaining short fragments manually curated based on
11 their annotation. Further curation identified multiple families corresponding either to unannotated
12 incomplete sequences, low-complexity sequences failing to be aligned, to hypervariable proteins
13 or to polyproteins, that were thus merged together: HIV-1/SIV/SIV-agm.gri/HIV-2: Nef; Tat; Vif;
14 Vpu; Gag/Gag-Pol/Matrix protein P17, HHV-8/MuHV-4: Latent nuclear antigen and HHV-4:
15 EBNA1. The resulting protein families were arbitrarily numbered from 1 to 314 to annotate viral
16 proteins in supplementary table S1.

17

18 **Centrality metrics computation**

19 The closeness and degree centrality metrics were computed for each human protein in the
20 entire experimentally-supported human PPI networks and in the derived longevity network using
21 the NetworkAnalyser plugin in Cytoscape (Doncheva 2012) or the networkx Python module
22 (<https://networkx.org>). In bipartite interspecific networks, the in-degree of human proteins
23 represents the number of viral proteins, viruses or viral families (as indicated) recorded interactions
24 and the out-degree of viral proteins, viruses or viral families (as indicated) is the number of recorded
25 human proteic interactors. In-degrees and Out-degrees were also computed using networkx.

26

27 **Identification of human ageing-associated proteins connecting with significantly high** 28 **numbers of viruses**

29 To determine whether some human proteins are significantly more connected than by
30 chance to viral proteins in the interspecific bipartite PPI network, we generated a distribution of
31 1000 random bipartite virus-human protein networks: in each random network, nodes representing
32 viruses and human proteins were sampled at random from the set of all viruses and all human

1 proteins, respectively, found in the reference network. The same number of edges than in the
2 reference network were then connected at random to viral and human protein nodes. The in-degree
3 of human protein nodes (number of viruses connected) was computed for each random network
4 and compared to the reference in-degree (absent proteins in random networks had an in-degree of
5 0). For each human node, a counter was incremented each time the random in-degree value was
6 greater than the reference value. Empirical p-values were then calculated by the ratio counter/1000,
7 and adjusted for multiple testing using the Bonferroni method.

8 9 **Metrics identifying candidate age-distorters in single infection and co-infection**

10 To determine the top 25 candidate age-distorters, viruses were ranked by decreasing score,
11 computed by multiplying the number of viral proteic sequences able to interact with human proteins
12 belonging to the indicated gene sets by the number of connected human proteins. The same formula
13 was used to calculate a combined score for co-infections by any two viruses from these top 25 lists.
14 For each pair of viruses, this score was obtained by multiplying the number of combined viral
15 proteins from the two viruses with the number of combined connected human proteins. To measure
16 the similarity between pairs of viruses in terms of virus-connected human proteins, we used their
17 Jaccard index, calculated as the size of the intersection of the two sets of connected human proteins
18 divided by the size of the union of these two sets. We used bipartite random network permutations,
19 as described above for the identification of proteins with significantly high in-degrees, to compute
20 random values of combined scores and Jaccard indices, which were compared to the reference
21 values. For each pair of viruses, a counter was incremented each time a random value was greater
22 than a reference value. Empirical p-values were then calculated by the ratio counter/1000, and
23 adjusted for multiple testing using the Bonferroni method.

24 25 **Determination of viral genome sizes**

26 For each virus in the HVIDB, a genome size was determined from the size of the
27 corresponding reference genome in the NCBI genome database (listed at
28 https://ftp.ncbi.nlm.nih.gov/genomes/GENOME_REPORTS/viruses.txt).

1 **Identification of biomarkers of senescence among differentially expressed genes associated**
2 **with a viral infection**

3 Published transcriptomic analyses were gathered from the literature, from the RNAseq
4 HVIDB and from the Gene Expression Omnibus repository (<https://www.ncbi.nlm.nih.gov/geo/>),
5 providing a list of differentially expressed genes (DEGs) for infected and non-infected humans for
6 a selection of viruses, several found amongst our top 25 candidate age-distorting viruses
7 (supplementary table S10). For studies with published RNAseq gene expression count matrices
8 only, differential gene expression analyses were performed using DESeq2
9 (<https://bioconductor.org/packages/DESeq2/>) using $f|\log_2FC|>1$ and adjusted p-value <0.05 as
10 cutoff. This \log_2FC and adjusted p-value filter, conservatively within the thresholds used in
11 stringent studies, was also applied to standardize the significance thresholds used across published
12 studies of predicted DEGs. When available in a given study, separated time points and/or replicates
13 were treated as separate individual samples and the number of DEGs associated with each
14 individual sample was computed. The resulting list of DEGs was intersected with the SenMayo
15 senescence gene dataset (Saul et al., 2021) to indicate which of these senescence biomarkers were
16 differentially expressed during a given condition of viral infection.

17
18
19 **Data availability statement**

20
21 The data underlying this article are available in the article and in its online supplementary
22 material.

23
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25
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33
34

1 **Figure legends**

2

3 **Figure 1. Overview of the research protocol implemented in our analysis.**

4

5 **Figure 2. Virus-human proteins bipartite network.**

6 In the bipartite network extracted from the human-virus PPI database HVIDB, 190 human
7 proteins associated to longevity, ageing and/or cellular senescence connected to three or more virus
8 strains (degree ≥ 3) are displayed as circular nodes on the right. 75 viruses connected to three or
9 more human proteins are displayed as square nodes on the left, and grouped by viral family in
10 alphabetical order from top to bottom. The type of viruses is indicated by a hexagonal symbol next
11 to each viral family. For each type of nodes, the degree is indicated by node size and colour as
12 indicated. A total of 1350 virus-human protein interactions are represented as coloured edges
13 connecting nodes. Edges colour correspond to the arbitrary colour used for the viral family
14 corresponding to the virus involved in the interaction.

15

16 **Figure 3. Relationship between viral genome size and number of human interactors.**

17 For each virus connected to three or more human proteins, the reference Log10-
18 transformed genome size was plotted against the Log10-transformed degree (number of
19 documented interacting human proteins) of the virus in the bipartite network from figure 2. Virus
20 names are indicated for each data point and names in bold indicate viruses from the top25 candidate
21 age-distorters in tables 1 and 2. For influenza A (subtype H1N1), the number of human interactors
22 is determined by the aggregation of the interactions associated with the 20 H1N1 strains present in
23 HVIDB.

24

25 **Figure 4. Interspecific protein-protein interactions for HIV-1 and H1N1.**

26 PPI networks represent the documented intraspecific interactions between human proteins
27 associated to longevity, ageing and/or cellular senescence (white edges), and interspecific
28 interactions between these human proteins and viral proteins from (A) HIV-1 and (B) influenza A
29 (subtype H1N1) (blue edges). Interactions for H1N1 correspond to the aggregation of the
30 interactions associated with the 20 H1N1 strains present in HVIDB, with the most frequently used
31 strains being A/Wilson-Smith/1933 H1N1 (63% of interactions) and A/Puerto Rico/8/1934 H1N1

- 1 chronologically from left to right in the heatmap. Over- and under-expressed SenMayo biomarkers
- 2 are represented by red and blue squares, respectively. The total number of DEGs associated with
- 3 each sample is indicated by the shade of blue at the top of the figure.

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1 **Table 1. Top 25 viruses able to interact with human cellular senescence-associated proteins**
 2 **in the HVIDB.**

Virus¹	Viral family	Viral sequences	Human interactors	Score²	Degree³
HHV-4	<i>Herpesviridae</i>	35	45	1575	28.8
H1N1	<i>Orthomyxoviridae</i>	11	64	704	24.0
HIV-1	<i>Retroviridae</i>	10	57	570	29.3
HHV-8	<i>Herpesviridae</i>	17	29	493	28.9
HHV-1	<i>Herpesviridae</i>	15	22	330	48.5
HPV16	<i>Papillomaviridae</i>	5	37	185	55.4
HPV18	<i>Papillomaviridae</i>	5	26	130	45.6
HPV31	<i>Papillomaviridae</i>	6	19	114	56.0
HPV11	<i>Papillomaviridae</i>	6	18	108	52.1
H3N2	<i>Orthomyxoviridae</i>	6	16	96	29.9
HPV8	<i>Papillomaviridae</i>	3	24	72	43.4
SV40	<i>Polyomaviridae</i>	4	18	72	61.1

¹ Virus names are those used in the human-virus PPI database HVIDB.

² Viruses were ordered by decreasing score (Score), computed for each virus by multiplying the number of viral proteic sequences able to interact with human proteins (Viral sequences) by the number of human proteins connected to the virus (Human interactors).

³ The average degree of human proteic interactors in the longevity network is indicated (Degree).

HHV-5	<i>Herpesviridae</i>	9	8	72	53.1
HPV1a	<i>Papillomaviridae</i>	4	17	68	33.4
HTLV-1	<i>Retroviridae</i>	4	16	64	34.4
MeV	<i>Paramyxoviridae</i>	5	10	50	41.6
HAdV-5	<i>Adenoviridae</i>	6	8	48	65.2
ZIKV	<i>Flaviviridae</i>	4	11	44	23.2
HPV33	<i>Papillomaviridae</i>	3	13	39	51.3
HPV5	<i>Papillomaviridae</i>	3	13	39	36.9
HPV9	<i>Papillomaviridae</i>	3	12	36	40.1
HPV6b	<i>Papillomaviridae</i>	3	11	33	26.6
HCV-H	<i>Flaviviridae</i>	2	16	32	46.8
HAdV-2	<i>Adenoviridae</i>	5	6	30	116.5
HCV	<i>Flaviviridae</i>	2	14	28	163.7

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1 **Table 2. Top 25 viruses able to interact with human longevity and aging-associated proteins**
 2 **in the HVIDB.**

Virus ¹	Viral family	Viral sequences	Human interactors	Score ²	Degree ³
HHV-4	<i>Herpesviridae</i>	41	56	2296	40.7
HHV-8	<i>Herpesviridae</i>	25	43	1075	58.4
HIV-1	<i>Retroviridae</i>	10	101	1010	41.4
H1N1	<i>Orthomyxoviridae</i>	12	74	888	47.3
HHV-1	<i>Herpesviridae</i>	19	36	684	56.4
HPV16	<i>Papillomaviridae</i>	7	45	315	64.0
VACV	<i>Poxviridae</i>	14	16	224	39.2
HPV31	<i>Papillomaviridae</i>	8	26	208	57.5
HAdV-5	<i>Adenoviridae</i>	8	23	184	66.0
MuHV-4	<i>Herpesviridae</i>	13	13	169	61.1
H3N2	<i>Orthomyxoviridae</i>	6	24	144	46.2
HHV-5	<i>Herpesviridae</i>	10	12	120	54.1

¹ Virus names are those used in the human-virus PPI database HVIDB.

² Viruses were ordered by decreasing score (Score), computed for each virus by multiplying the number of viral proteic sequences able to interact with human proteins (Viral sequences) by the number of human proteins connected to the virus (Human interactors).

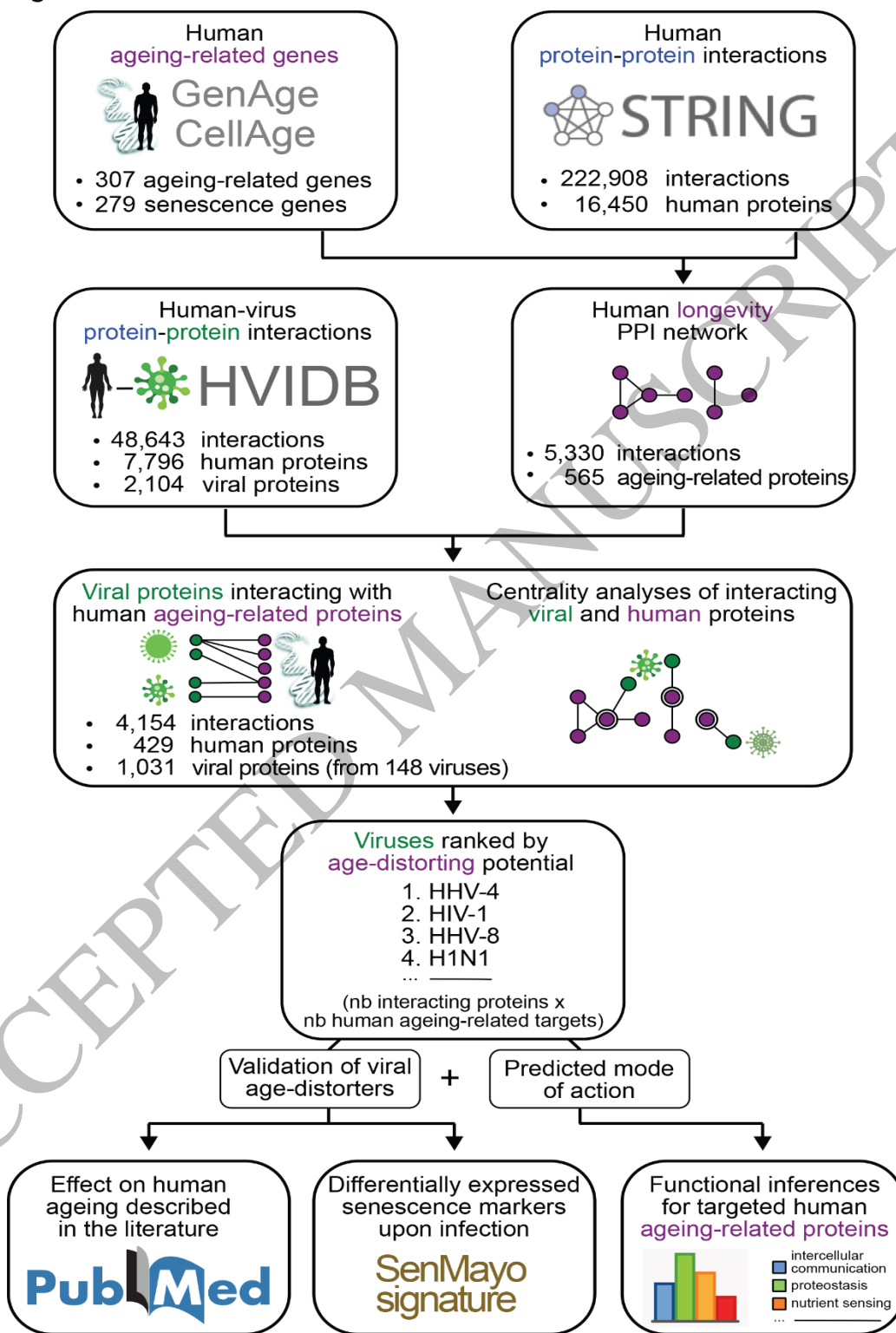
³ The average degree of human proteic interactors in the longevity network is indicated (Degree).

HPV6b	<i>Papillomaviridae</i>	6	17	102	33.7
HPV11	<i>Papillomaviridae</i>	5	19	95	63.2
SV40	<i>Polyomaviridae</i>	4	23	92	61.6
HPV18	<i>Papillomaviridae</i>	4	21	84	57.0
MeV	<i>Paramyxoviridae</i>	3	26	78	49.6
HCV	<i>Flaviviridae</i>	3	24	72	154.0
HAdV-2	<i>Adenoviridae</i>	6	12	72	88.2
HRSV	<i>Pneumoviridae</i>	5	14	70	36.8
HTLV-1	<i>Retroviridae</i>	4	16	64	48.5
HPV8	<i>Papillomaviridae</i>	3	20	60	59.0
AAV-2	<i>Parvoviridae</i>	2	25	50	66.9
ZIKV	<i>Flaviviridae</i>	4	11	44	38.1
BPV-1	<i>Papillomaviridae</i>	4	10	40	73.5

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Figure 1



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Figure 1
140x229 mm (1.3 x DPI)

Figure 2

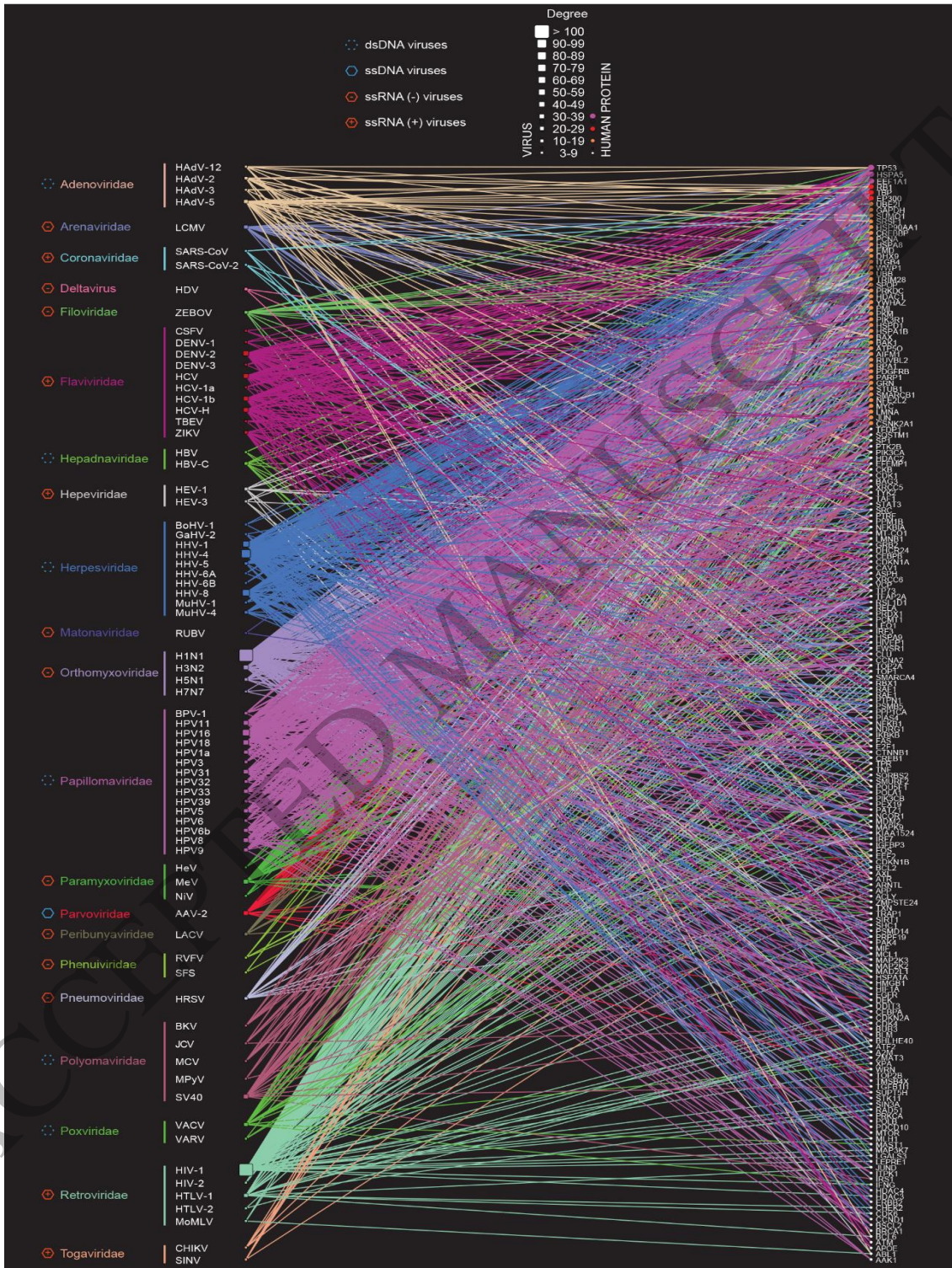


Figure 2
149x229 mm (1.3 x DPI)

Figure 3

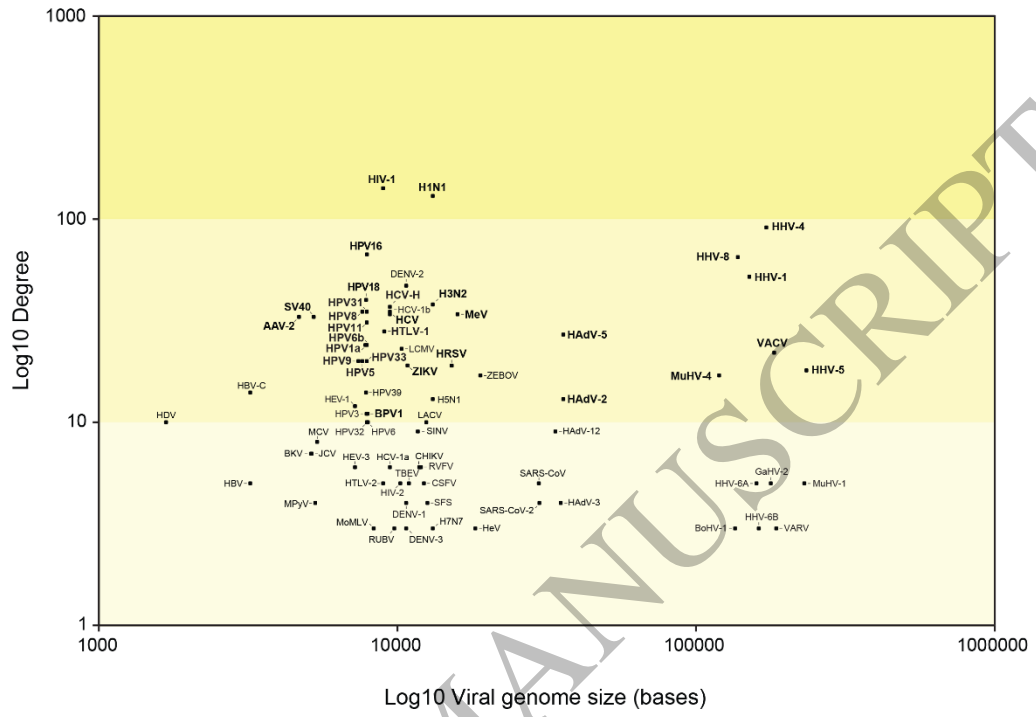


Figure 4

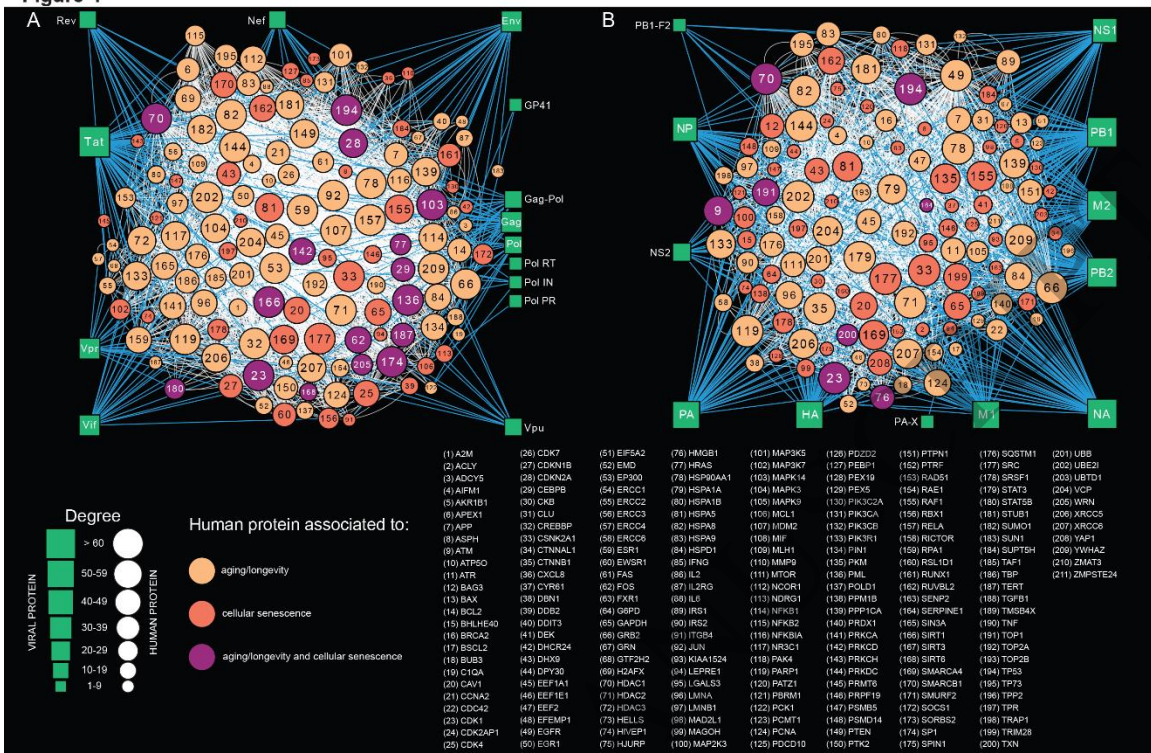


Figure 4
152x101 mm (1.3 x DPI)

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Figure 5

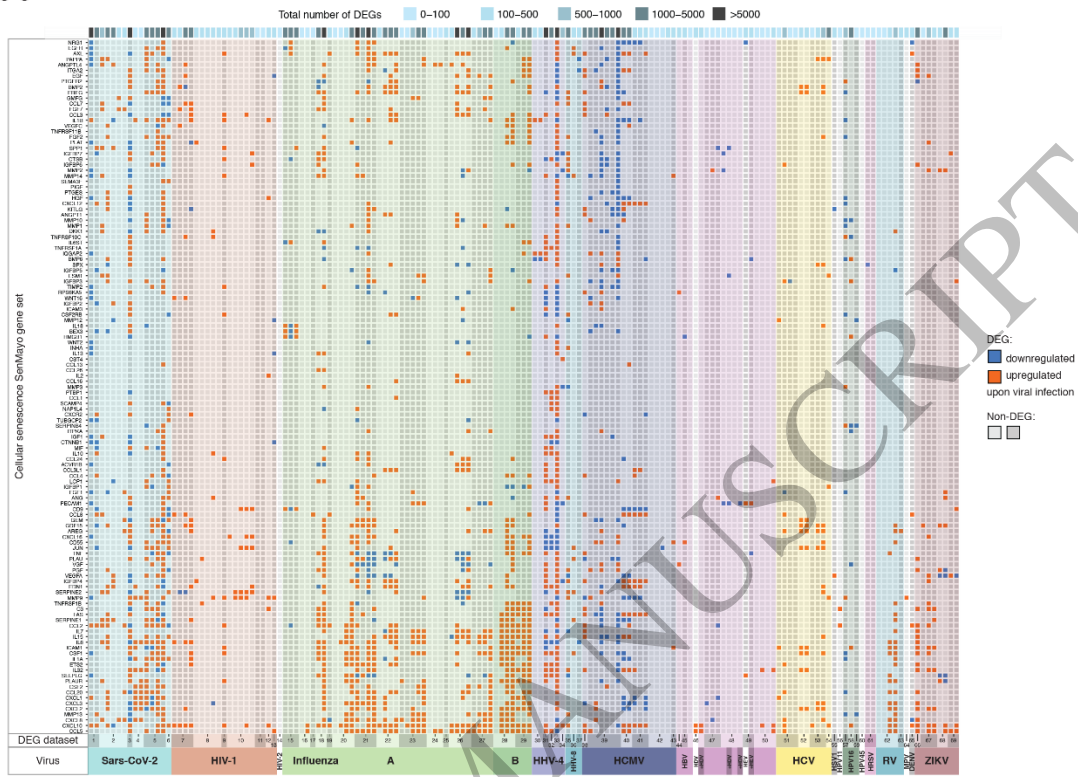


Figure 5
152x105 mm (1.3 x DPI)