RESEARCH ARTICLE



Age-related gene expression alterations by SARS-CoV-2 infection contribute to poor prognosis in elderly

UPASANA BHATTACHARYYA and B. K. THELMA* 💿

Department of Genetics, University of Delhi South Campus, New Delhi 110 021, India *For correspondence. E-mail: bktlab@gmail.com.

Received 16 July 2020; accepted 20 July 2020; published online 24 October 2020

Abstract. The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people worldwide and with notable heterogeneity in its clinical presentation. Probability of contracting this highly contagious infection is similar across age groups but disease severity and fatality among aged patients with or without comorbidities are reportedly higher. Previous studies suggest that age associated transcriptional changes in lung and immune system results in a proinflammatory state and increased susceptibility to infectious lung diseases. Similarly, SARS-CoV-2 infection could augment ageing-related gene expression alterations resulting in severe outcomes in elderly patients. To identify genes that can potentially increase covid-19 disease severity in ageing people, we compared age associated gene expression changes with disease-associated expression changes in lung/BALF and whole blood obtained from publicly available data. We observed (i) a significant overlap of gene expression profiles of patients' BALF and blood with lung and blood of the healthy group, respectively; (ii) a more pronounced overlap in blood compared to lung; and (iii) a similar overlap between host genes interacting with SARS-CoV-2 and ageing blood transcriptome. Pathway enrichment analysis of overlapping gene sets suggest that infection alters expression of genes already dysregulated in the elderly, which together may lead to poor prognosis. eQTLs in these genes may also confer poor outcome in young patients worsening with age and comorbidities. Further, the pronounced overlap observed in blood may explain clinical symptoms including blood clots, strokes, heart attack, multi-organ failure etc. in severe cases. This model based on a limited patient dataset seems robust and holds promise for testing larger tissue specific datasets from patients with varied severity and across populations.

Keywords. covid-19; SARS-CoV-2; biomarker; transcriptional changes; eQTL variants; SARS-CoV-2 poor prognosis; ageing.

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes COVID-19 in humans (Siordia 2020) has spread rapidly across the world and is classified as a global pandemic by the World Health Organization (coronavirus (COVID-19) events as they happen; https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). As of 2 July 2020, there have been 10.6 million confirmed COVID-19 cases with 519,766 deaths reported worldwide (https://

ourworldindata.org), with continuing trend of sharp rise in both these categories in many countries/regions. The disease is highly heterogenous in its clinical presentation with most common symptoms being fever, cough, shortness of breath and fatigue. In addition, myalgia, neurological symptoms, ischaemic and haemorrhagic strokes, muscle injury and gastrointestinal symptoms are also reported in a subset of patients (Harapan *et al.* 2020). Several clinical trials are ongoing but as of date, no drugs or other therapeutics have been approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19 (Sanders *et al.* 2020) and thus clinical management includes infection prevention and supportive care (Sanders *et al.* 2020). Efforts to combat COVID-19 are severely hampered by grossly inadequate knowledge of several important aspects of the illness ranging

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12041-020-01233-7) contains supplementary material, which is available to authorized users.

BKT and UB designed the study; UB performed all the data analysis; UB and BKT wrote the first draft of manuscript; and both approved the final manuscript.

from pathogen biology to host response, disease biology, target tissues and consequently treatment options. Therefore, there is an urgent need for a deeper understanding of the host–pathogen interaction biology of SARS-CoV-2, which in turn may offer important insights into general/personal-ized treatment strategies and management of the disease as well as development of new therapies.

Probability of contracting this highly contagious infection has been reported to be similar across age groups but severe clinical manifestations and increased mortality has been reported in elderly patients (Cohen et al. 2020; Hauser et al. 2020; Meyerowitz-Katz and Merone 2020; Wu et al. 2020). These observations suggest that there may be a comparatively stronger association between age and poor prognosis of COVID-19, but this may well be multifactorial. Therefore, the uncovering mechanism(s) underlying poor prognosis to SARS-CoV-2 infection among the affected elderly might be insightful for effective patient management and treatment. Several reports suggest that with the ageing, elderly population becomes more susceptible to various infectious disorders (Meyer 2001; Gavazzi and Krause 2002; López-Otín et al. 2003; Meiners et al. 2015). With ageing, transcriptional dysregulation occurs in genes involved in cellular oxidant/antioxidant systems, proinflammatory mediators (C-reactive protein, tumour necrosis factor a (TNF- α), interleukins (IL) 6, 1 β), and cell regenerations that might overlap with viral mediated dysregulation (Franceschi and Campisi 2014; Meiners et al. 2015; de Almeida et al. 2020; Fulop et al. 2018). Similarly in severe COVID-19 patients, a 'cytokine storm' comprised of TNF- α , IL 6, 1 β , 8, 12, interferon-gamma inducible protein (IP10), macrophage inflammatory protein 1A (MIP1A), and monocyte chemoattractant protein 1 (MCP1) (Cascella et al. 2020) and hypercoagulable state with increased risk of venous thromboembolism (Cevik et al. 2020) has been observed.

Based on this limited understanding, we hypothesize that SARS-CoV-2 mediated transcriptional alterations may overlap with age mediated expression changes. Thus, expression of genes that changes during ageing, might get further augmented on SARS-CoV-2 infection, leading to severe outcome in elderly patients. We attempted to explore this possibility by performing comparative transcriptomics using available data from two target tissues, namely lung and blood in healthy ageing group and COVID-19 patients. We also compared transcriptomic profile of ageing lung and blood with host genes interacting with SARS-CoV-2 protein. We observed a significant overlap between gene expression profile in both lung and blood of healthy ageing group and COVID-19 patients; which was much more pronounced in blood. Further, there was a significant overlap between host genes interacting SARS-CoV-2 proteins in ageing blood but not in lungs. These observations support previous reports that SARS-COV-2, primarily affects the respiratory system but its effects may manifest in blood leading to multiorgan failure in severe cases of COVID-19 (Cascella et al. 2020; Varga et al. 2020).

Materials and methods

Study design

Identification of candidate genes: To identify the genes that determine poor prognosis in the elderly COVID-19 patients, we performed a comparative analysis of gene expression data as collected from bronchoalveolar-lavage fluid (BALF)/lung/blood from COVID-19 patients and healthy ageing group; and data of host genes interacting with SARS-CoV-2 proteins with transcription profile of ageing lung and blood (resources are mentioned below). This methodology was adopted from previous studies (Dugo *et al.* 2016; Elko *et al.* 2019). Overlaps between the following groups were documented: (i) patients' BALF with healthy ageing lung; (ii) patients' PBMCs with healthy ageing blood; (iii) host genes interacting with viral proteins with healthy ageing lung and blood.

Statistical analysis

Statistical significance of these overlaps, if any, were tested using hypergeometric test (http://nemates.org/MA/progs/overlap_stats_prog.html). Basic equation to find the probability of finding an overlap of genes using the above-mentioned program is provided in supplementary text.

Pathway analysis

Pathway enrichment of the significantly overlapping genes identified above was done using EnrichR (Chen *et al.* 2013; Kuleshov *et al.* 2016) which is an integrative web-based and mobile software application that currently includes 180,184 annotated gene sets from 102 gene set libraries and various interactive visualization approaches to display enrichment results using the JavaScrit library, Data Driven Documents.

eQTL analysis

eQTL variants of genes from significantly overlapping genesets for respective tissues (lung and blood) were obtained from GTEx v. 8 (https://gtexportal.org). With a view to obtain a universally applicable biomarker, a comparable minor allele frequency of the markers would be ideal and such a suitability was tested using $F_{\rm ST}$ or fixation index. This was done using 1000 genome phase 1 data with the help of an online tool SPSmart (http://spsmart.cesga.es) with $F_{\rm ST}$ (i) 0 to 0.05 representing low; (ii) 0.05 to 0.15, moderate; (iii) 0.15 to 0.25, high; and (iv) > 0.25, very high, genetic differentiation.

Identification of druggable targets

Finally, these genes identified above were screened for their druggability with FDA approved drugs using DGIdb website (http://dgidb.org).

Resources

Age associated genes: (i) Differentially expressed genes (DEGs) in lung and blood tissue identified in a recently published study using RNA-Seq based transcriptome profiles from human donors of various ages from GTEx (Yang *et al.* 2015) were enlisted. (ii) DEGs from two stage transcriptomic study performed in blood, based on meta-analysis data from six different studies (n = 7074 samples) in the discovery phase and 7909 additional whole-blood samples in the replication phase (Peters *et al.* 2015) were obtained.

These two datasets were merged for blood transcriptomics and all the protein coding genes (and not any small RNAs such as miRNA, lncRNA etc.) that were reported in either study were considered. All genes showing a different direction of expression change were removed from the analysis. A total of 2877 and 2283 protein coding genes were found to be upregulated and downregulated, respectively in blood of healthy ageing group. Similarly, a total of 363 and 592 protein coding genes were found to be upregulated and downregulated, respectively in ageing lung. These genes have been subsequently referred to as 'ageassociated DEGs'.

SARS-CoV-2 associated genes: Henceforth the DEGs in COVID-19 positive patients are referred to as 'SARS-CoV-2-associated DEGs' and were obtained from two recent studies: (i) DEGs in BALFs identified comparing laboratory-confirmed COVID-19 patients (SARS2) (n = 8, median age 50.5 years) with healthy controls without known respiratory diseases (healthy) (n = 20) (Zhou *et al.* 2020). (ii) DEGs in PBMCs and BALF identified by comparing three COVID-19 patients (median age 37 years) and three healthy donors (Xiong *et al.* 2020).

BALF transcriptomics from these two datasets were merged and all the protein coding genes (and not any small RNAs such miRNA, lncRNA etc.) that are reported in either study were considered. All genes showing a different direction of expression change were removed from the analysis.

Host genes interacting with SARS-CoV-2 proteins: Host genes that were found to be interacting with SARS-COV-2 viral proteins henceforth referred as 'SARS-CoV2-interacting genes' and were collected from recent studies mentioned below. (i) Three hundred and thirty-two high-confidence SARS-CoV-2-human protein–protein interactions (PPIs) were obtained by analysing the data generated by expressing 26 of the 29 SARS-CoV-2 proteins in HEK293 cells in a

recent study (Gordon *et al.* 2020). (ii) Computation and literature based interactome data that were generated using available sequences for viral protein candidates (such as wS, wORF3a, wE, wM, wORF6, wORF7a, wORF7b, wORF8, wN and wORF10) in a recent study (Srinivasan *et al.* 2020).

Results

Test of hypothesis (figure 1) by a comparative analysis of DEGs in the different sample sets described under study design (figure 2) revealed significant overlaps between them (table 1; table 1 in electronic supplementary material at http://www.ac.in/jgenet/), which are briefly presented below (table 1; table 1 in electronic supplementary material), are briefly presented below. The most notable findings include (i) significant overlap (P < 1.4E-04) between the upregulated SARS-CoV-2 associated DEGs in patients' BALF and upregulated age associated DEGs in healthy ageing. (ii) Significant overlap (P < 6.53E-07) between the upregulated SARS-CoV-2 associated DEGs in patients' PBMCs and upregulated age associated DEGs in healthy ageing blood. (iii) Nominally significant overlap (P < 0.03) between the downregulated SARS-CoV-2 associated DEGs in patients' PBMCs and downregulated age associated DEGs in healthy ageing blood. (iv) Significant overlap between the SARS-CoV-2 interacting genes and up (P < 0.002) / down (P <1.04E-06) regulated age associated DEGs in healthy ageing blood (table 1; table 1 in electronic supplementary material).

eQTLs in these genes (A, B, E, F) might confer poor prognosis in healthy young individuals and may even worsen with age Poor Prognosis Figure 1. A schematic view of the hypothesis of cumulative gene expression changes leading to poor prognosis among the elderly

COVID-19 patients.





Figure 2. Workflow and results of the comparative transcriptomics across different study groups.

Table 1. The results of the comparative analysis of DEGs across different sample sets.

						Number of common genes between study groups; <i>P</i> value			
	SARS-Cov-2 associated genes		SARS-	Age associated DEGs		Definite?		SARS-Cov2	SARS-
Direction of DEG	Patients' BALF	Patients' PBMCs	interacting genes	Ageing lung	Ageing blood	BALF and ageing lung	Patients' PBMCs and ageing blood	genes and ageing lung	cov2_interacting genes with ageing blood
Up Down	1360 981	521 196	417	363 592	2877 2283	44; 1.4E-04 27; 0.39	116; 6.53E-07 14; 0.03	12; 0.07 18; 0.07	82; 0.002 81; 1.04E-06

Pathway enrichment

As the number of genes in each gene-set was very small to identify the enriched pathways, if any, all the genes from significant gene-sets and showing change in same direction were considered together for pathway enrichment analysis. Cytokine genes that are frequently found to be upregulated in patients and which overlapped with healthy ageing expression profiles were also included. Six of the 21 upregulated cytokine genes in patients, overlapped with ageing related genes in the blood but none with ageing lung. Upregulated genes in the healthy ageing group that overlap with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes were seen to be enriched in a range

Pathway enrichment in up-regulated genes



Figure 3. Result of pathway enrichment analysis of upregulated genes in the healthy ageing group overlapping with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes.

of signalling pathways, including p53, chemokine and cytokine mediated inflammation, EGF receptor, TGF-beta, AGE-RAGE, Toll-like receptor mediated, NF-kappa B, VEGFA-VEGFR2 and genes involved in ROS in triggering vascular inflammation, oxidoreductive damage, T cell polarization, lung fibrosis, chronic obstructive pulmonary disorder (COPD), and local acute inflammatory response (representative pictures at figure 3; table 2 in electronic supplementary material). Downregulated genes in the healthy ageing group that overlap SARS-CoV-2 associated and SARS-CoV-2 interacting genes were seen to be enriched in pathways such as PI3K-Akt-mTOR-signalling, membrane trafficking, HIV and influenza RNA transport, ISG15 antiviral mechanism, cellular export machinery that interacts with NEP/NS2 (representative pictures at figure 4; table 3 in electronic supplementary material).

Pathway enrichment in down-regulated genes

Foca Adhesion P32 Attern TOR Algunding pathway WP3932 HV Ulfe Cycle Home sapies RHSA-142350 Hut Phase of HV Ulfe Cycle Home sapies RHSA-142350 Hut Phase of HV Ulfe Cycle Home sapies RHSA-142350 Hut Phase of HV Ulfe Cycle Home sapies RHSA-142350 Hut Phase of P32 Home Sapies RHSA-142350 Hut Phase of P32 Home Sapies RHSA-142350 Hut Phase Sapies RHSA-142350 Hut Phase Sapies RHSA-142350 Hut Phase Sapies RHSA-142351 Hut Phase Sapies RHSA-142351 Hut Phase RHSA-142352 Hut Phase RHSA		GABA-B recentor II signaling Homo saniens P05731
 HV URG Cycle Hone sapies R-H5A-L02371 HV URG Cycle Hone sapies R-H5A-L02371 HV URG Hyper RNA synthesis Hone sapies R-H5A-L02372 Hz Phase OHV URG Cycle Hone sapies R-H5A-L02373 Hz Phase OHV URG Cycle Hone sapies R-H5A-L02374 Hz Phase OHV HT HY HAR HONE Sapies R-H5A-L02374 Hz Phase OHV HT Hyper Hone sapies R-H5A-L02374 Hz Phase OHV HIM Hyper Relation Hone sapies R-H5A-L023743 Hiteractions of Hev HTh host cellular proteins Hone sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation OF HSL Activity at G2/M Transition Hore sapies R-H5A-L02374 Hz Hyper Relation Hyper Relation Hyper Relation Hyper Relation Hyper Relation Hyper R-H5A-H23374 Hz Hyper Relation Hyper Relation Hyper Relation Hyper R-H3A-H32374 Hz Hyper Relation Hyper R-H3A-H32374 Hz Hyper Relation Hyper R-H3A-H32374 Hz Hyper Relation Hyp		Encal Adhecion-DI3K-Akt-mTOR-signaling nathway WP3932
 Vis Signi Angulari Michael Schlauser And Water homesstalis via Aquaportis Home sapies RHSA-18250 Visa Massager RMS Apthesis Home sapies RHSA-18259 Aquaportis mediated transport Home sapies RHSA-18259 Aquaportis mediated transport Home sapies RHSA-18259 Visicle mediated transport Home sapies RHSA-18250 Visicle mediated transport Home sapies RHSA-18250 Visicle mediated transport Home sapies RHSA-18251 Visicle mediated transport Home sapies RHSA-18251 Visicle mediated transport Home sapies RHSA-18251 Visicle mediated transport Home sapies RHSA-18254 Translocation of GUIT4 to the phasm membrase RHSA-18254 Translocation of Visit mediated beat shock response RHSA-18254 Instructions of Visit mediated beat shock response RHSA-18254 Instructions of Visit mediated beat shock response RHSA-18254 Instructions for with host cellular proteins Home sapies RHSA-18254 Instructions Home sapies RHSA-18254 Instructions Home sapies RHSA-18254 Instructions Home sapies RHSA-18256 Regulation of HISI mediated beat shock response RHSA-18254 Instructions Home sapies RHSA-18256 Instructions HISI mediated beat shock response RHSA-18257 Transport of the SLBP bependent Mature mRMA Home sapies RHSA-18271 Transport of the SLBP bependent Mature mRMA Home sapies RHSA-18274 Transport of the SLBP bependent Mature mRMA Home sapies RHSA-18274 Transport of the SLBP bependent Mature mRMA Home sapies RHSA-18274 Transport of the SLBP bependent Mature mRMA Home sapies RHSA-18276 Instruction of RHSA Home sapies RHSA-18		HIV Life Cycle Home senions B-HSA-162587
 Viral Mussager RN Synthesis Indu Kedi Multity Status Activation Sagena RHSA 1823 Late Phase of MV Life Cycle Home sagena RHSA 1823 Late Phase of MV Life Cycle Home sagena RHSA 1823 Late Phase of MV Life Cycle Home sagena RHSA 1823 Late Phase of MV Life Cycle Home sagena RHSA 1823 Mutabelian of proteins Home sagena RHSA 1824 Mutabelian of proteins Home sagena RHSA 1824 Mutabelian of HSFI mediated heat Home sagena RHSA 18243 Home sagena RHSA 1824 Home sagena RHSA 12030 Regulation of HSFI mediated heat Home sagena RHSA 12031 Regulation of HSFI mediated heat 18243 HIV Infection Home sagena RHSA 12036 Regulation of HSI RHSA 12035 Regulation of HSI RHSA 12036 Regulation of HSI RHSA 12035 Regulation of HSI RHSA 12036 Regulation CHSI RHSA 18436 HIV Inferious AHSA 12035 Regulation of HSI RHSA 12036 Regulation of HSI RHSA 12036 Regulation CHSI RHSA 120371 Transmotherase transport of HSI RHSA 120374 Regulation CHSI RHSA 120374 R		Noronzaria sagulatas ranzi watas homoastasis via Asuanasias Homo sanions B USA 422040
Like Phase ATIVU for Cycle Homo Sapien R H5A-1523 Auguporti-mediated transport Homo Sapien R H5A-15237 Auguporti-mediated transport Homo Sapien R H5A-15555 Veticle-mediated transport Homo Sapien R H5A-15555 Veticle-mediated transport Homo Sapien R H5A-15555 Metabolism of protein Homo Sapien R H5A-15555 Hetabolism of H5I-mediated heta Hole response Homo Sapien R H5A-15233 Interactions of Work homo Sapien R H5A-16225 Hit Interactions of NSI-mediated heta Hole response Homo Sapien R H5A-15235 Interactions of NSI-mediated heta Hole response Homo Sapien R H5A-15236 Reputation of HSI-Ministre Homo Sapien R H5A-15235 Hit Interactions of Park Hithole Homo Sapien R H5A-15235 Hit Interactions of HSI Arthyla (20) Hamos Sapien R H5A-15235 Hit Interaction of HSI Arthyla (20) Hamos Sapien R H5A-15235 Hit Interaction of HSI Arthyla (20) Hamos Sapien R H5A-15235 Hit Interaction of HSI Arthyla (20) Hamos Sapien R H5A-15235 Hit Interaction of HSI Arthyla (20) Hamos Sapien R H5A-15237 Hit Mediated Effise Dependent Mature mNA Homo Sapien R H5A-15237 Hit Mediated Hit Sapien R H5A-15237 Hit Mediated Hit Sapien R H5A-15237 Hit Mediated Hit Sapien R H5A-15237 Hit Mathema		Vasopressin regulates renar water nomeostasis via Aquaporins nomo sapiens R-n5A-452040
Lite Prise Unit Cycle Minols Splane R-H5A-48272 Aquippolin mediated transport Netwo splane R-H5A-48273 Weitcher Mediated Transport Netwo Splane R-H5A-48274 Yesicle Mediated Transport Network Splane R-H5A-18286 Transport of UTU Stuth Netwo Splane R-H5A-18286 Metabolism of proteins Homo splane R-H5A-18286 Transport of UTU Stuth Network Splane R-H5A-18287 Transport Of Vir With host cellular proteins Homo splane R-H5A-18287 Interactions of Ker With host cellular proteins Homo splane R-H5A-18286 Interactions of Vir With host cellular proteins Homo splane R-H5A-18287 HIV Infection Homo Splane R-H5A-18271 Transport of HIV RNA Homos Splane R-H5A-18271 Transport of HIV RNA Homos Splane R-H5A-18272 Transport of HIV RNA Homos Splane R-H5A-182		Viral Messenger KNA Synthesis Homo sapiens R-HSA-108525
Amplitude and a set of the set of		Anumerin mediated transmet Home coniers B USA 445717
 Netherland in Finding, Nerrol Superk Nethol. 2002. Vesicie mediated transfer Al-Sol States Translection of CUY The the plasma membrane Homo sapiers RHS-145184 Aconal growth inhibition (BHOA activator) Homo sapiers RHS-17603 Regulation of HST-mediated heat shock response Homo sapiers RHS-17603 Regulation of HST-mediated heat shock response Homo sapiers RHS-17603 Regulation of HST-mediated heat shock response Homo sapiers RHS-17283 Ecocytosis: Vesici Tethering Influenza Infection Homo sapiers RHS-162364 Hivitanian RHSA-18254 Hivitanian RHSA-18255 Hivitanian RHSA-18255 Hivitanian RHSA-18255 Hivitanian RHSA-18255 Hivitanian RHSA-18255 Hivitanian RHSA-18254 Hivitanian RHSA-18254 Hivitanian RHSA-18254 Hivitanian RHSA-18255 Hivitanian RHSA-18257 Hivitanian RHSA-18257 Hivitania		Aquaporin-mediated transport nomo sapiens R-HSA-445717
Velici-mediate Transport Romo sajers R-HSA-3239 Metabolism of proteins membrane Homo sajers HSA-1465148 Translocation of KUT4 to the plasma methane Homo sajers R-HSA-1465148 Accord all growth inhibition (ROM activation) Homo sajers R-HSA-137153 heteractions of Rev with host cellular proteins Homo sajers R-HSA-137153 heteractions of Rev with host cellular proteins Homo sajers R-HSA-137153 heteractions of Rev with host cellular proteins Homo sajers R-HSA-137234 Locytosis: Velice Tethering Influence Infection Homo sajers R-HSA-138254 HIV Infection Homo sajers R-HSA-138256 Regulation of HSIT-meetine None sajers R-HSA-301254 Regulation of HSIT-meetine None sajers R-HSA-301254 Regulation of HSIT-meetine None sajers R-HSA-301254 Regulation of HXI Activity at CQ/I Transport of the SIB Protein Homo sajers R-HSA-158220 NSI Mediate Offst Control None sajers R-HSA-158276 Transport of the SIB Program Mature mRNA Homo sajers R-HSA-158270 Transport of the SIB Program Homo sajers R-HSA-158270 Transport of the SIB Program Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158270 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-158271 Transmort of Rev protein Homo sajers R-HSA-158273 Hoti Interactions with Influence Federa HSA-168274 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-168274 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-168274 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-168274 Transport of HSIS MICH Rependent Mature mRNA Homo sajers R-HSA-168273 Hoti Interactions with Influence Federa HSIS HSIS HSIS HSIS HSIS HSIS HSIS HSI		Weinde and Transcring nomo sapiens R-HSA-19991
 Translotion of protein Flore Japiens FHAS-326299 Translotion of protein Flore Japiens FHAS-13534 Acenal growth inhibition (BIOA Activity Into callular proteins Home sapiens RHSA-13534 Herteractions of Yay With host cellular proteins Home sapiens RHSA-137033 Regulation of HSF1-mediated heat shock response Home sapiens RHSA-137033 Herteractions of Rev with host cellular proteins Home sapiens RHSA-137033 Herteractions of Rev with host cellular proteins Home sapiens RHSA-137283 Locorytosis: Vexici Tethering Influenza Infection Home sapiens RHSA-13236 Regulation of HSA Tethering Influenza Infection Home sapiens RHSA-13236 Regulation of FIXA Activity at G2/M Transition Home sapiens RHSA-135230 Regulation of FIXA Activity at G2/M Transition Home sapiens RHSA-135230 Regulation of HSA Activity at G2/M Transition Home sapiens RHSA-135230 Regulation of HSA Hore Net Tahways Home sapiens RHSA-135230 Regulation of HSA Hore Net Tahways Home sapiens RHSA-135230 Revendiated nuclear caport of HW RhA Home sapiens RHSA-135231 Revendiated nuclear caport of HW RhA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature MRA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transport of Hore SIBP Independent Mature RNA Home sapiens RHSA-168274 Transcription and Regularotion Home sapiens		vesicle-mediated transport Homo sapiens R-HSA-5655656
 Handballton of HUL Tek Unite plasma in Histon Lates Jakes 1445.1485 Accord Jacob Type with host cellular proteins Homo sapiens RH5A-15033 Republication of HST-mediate heat shock response HSA-15033 Herrardions of How with host cellular proteins Homo sapiens RH5A-15033 Herrardions of Rev with host cellular proteins Homo sapiens RH5A-15035 Hittana Infection Homo sapiens RH5A-168234 Hittana Infection Homo sapiens RH5A-168234 Hittana Infection Homo sapiens RH5A-168236 Hittana Infection Homo sapiens RH5A-158236 Transport of the SLBP Dependent Mature mRNA Homo sapiens RH5A-158271 Transport of Riboundeceus Homo sapiens RH5A-158271 Transport of Riboundeceus Homo sapiens RH5A-158271 Transport of Homo Inferenceus Homo sapiens RH5A-158274 Transport of Homo Inferenceus Homo sapiens RH5A-158276 <li< th=""><th></th><th>Metabolism of proteins Homo sapiens K-HSA-392499</th></li<>		Metabolism of proteins Homo sapiens K-HSA-392499
Actional growth ministration (Heru). Actional priorits Net Share 179633 Repulsition of HST-ineditated hera thoth response Nome sapiens R-HSA-157033 Repulsition of HST-ineditated hera thoth response Nome sapiens R-HSA-157233 Exceytoris: Vesicle Tethering Influenza Infection Home sapiens R-HSA-16254 HIV Infection Home sapiens R-HSA-16256 Repulsition of Insulin secretion Home sapiens R-HSA-15256 Repulsition of Insulin secretion Home sapiens R-HSA-15256 Repulsition of Insulin secretion Home sapiens R-HSA-15256 INfluenza Infection Home sapiens R-HSA-15256 Repulsition of Insulin secretion Home sapiens R-HSA-15256 INfluenza Infection Home sapiens R-HSA-15256 Repulsition of HSI Activity at G2/M Transition Home sapiens R-HSA-152576 Transport of the SLBP Dependant Mature mRNA Home sapiens R-HSA-152571 Transport of the SLBP Dependant Nature mRNA Home sapiens R-HSA-152512 Rev-mediated nuclear export of HVI RNA Home sapiens R-HSA-152574 Influenza Life Cycle Home sapiens R-HSA-15274 Transport of the SLBP independent Mature mRNA Home sapiens R-HSA-15273 Host Interactions with Influenza R-HSA-15275 Influenza With Influenza R-HSA-152757		Transiocation of GLU14 to the plasma membrane Homo sapiens K-HSA-1445148
 Interaction 6 Yp/ with Note Campone Homo sapien X-HSA-13723 Repulation of YST-unellate heat shock response Homo sapiens R-HSA-137243 Excytosic Veide Tetering Influenza Infection Homo sapiens R-HSA-168254 Hi/U Infection Homo sapiens R-HSA-16256 Repulation of Institution Homo sapiens R-HSA-16256 Repulation of NUM Institution Homo sapiens R-HSA-16256 Repulation of Institution Homo sapiens R-HSA-16256 Repulation of Institution Homo sapiens R-HSA-16256 Nuclear Proc Compile (NPC (Dissembly Homo sapiens R-HSA-15252) NSI Mediated Effects on Hota Tawing N-HSA-168271 Transport of His SubP Opendant Mature mRNA Homo sapiens R-HSA-18251 Revealized nuclear export of Institution R-HSA-182551 Revealized nuclear export of Isoland molecules Homo sapiens R-HSA-182525 Export of Viral Ribonculeoproteins Into the Hota Nucleus Homo sapiens R-HSA-182527 Nuclear Import of Are protein Homo sapiens R-HSA-182527 Nuclear Import of Rev protein Homo sapiens R-HSA-182527 Nuclear Import of Rev protein Homo sapiens R-HSA-18253 Export of Viral Ribonculeoproteins Inform Nucleus Homo sapiens R-HSA-182527 Nuclear Import of Rev protein Homo sapiens R-HSA-18253 Export of Viral Ribonculeoproteins Homo sapiens R-HSA-18233 Hota Interactions With the Clubar Export Mature MRA Homo sapiens R-HSA-18237 Studoylation of PACL (PhLP1) and TRI/C/CCT in G-protein bets folding Homo sapiens R-HSA-158236 Studoylation of RA exploretins Homo sapiens R-HSA-158237 Histamine HZ receptor mediated signaling attway Homo sapiens R-HSA-158273		Axonal growth inhibition (RHOA activation) Homo sapiens R-HSA-193634
 Regulation of HS-1-mediated shock regions R-HSA-37743 Docytosis: Viside Tethering Influenza Infection Homo sapiens R-HSA-17243 Docytosis: Viside Tethering Influenza Infection Homo sapiens R-HSA-128256 HV Infection Homo sapiens R-HSA-123266 Regulation of Insulin secretion Homo sapiens R-HSA-32355 Regulation of PLKI Activity at CQW Transition Homo sapiens R-HSA-159200 NSI Mediated Effects on Host Pathway Homo sapiens R-HSA-159200 NSI Mediated Effects on Host Pathway Homo sapiens R-HSA-159200 NSI Mediated Effects on Host Pathway Homo sapiens R-HSA-158276 Transport of Homouleoproteins Host Nucleus Homo sapiens R-HSA-158271 Transmerbrane transport of small molecules Homo sapiens R-HSA-158271 Transmerbrane transport of Homouleoproteins Homo Nucleus Homo sapiens R-HSA-158271 Transmerbrane transport of Hill RNA Homo sapiens R-HSA-158274 Transmort of Homouleoprotein Homo sapiens R-HSA-158274 Transmerbrane transport of Hill RNA Homo sapiens R-HSA-158274 Transmerbrane transport of Hill RNA Homo sapiens R-HSA-158274 Transmerbrane RHSA-158275 Export of Uria Ribonucleoprotein Homo sapiens R-HSA-158274 Transmerbrane RHSA-158276 Collubar response to Hast trees Homo sapiens R-HSA-158276 Collubar response to Hast trees Homo sapiens R-HSA-158276 Collubar response to Hast trees Homo sapiens R-HSA-5572769 Influenza Viria RNA Transcription and Replication Homos sapiens R-HSA-158273 Hifterina Viria RNA Trans		Interactions of Vpr with nost cellular proteins Homo sapiens R-HSA-176033
 Interactions of Rev With Not Cellular proteins Home Supers R-HSA-127243 Excrycistic Visite Fathering Influenza Infection Home Supers R-HSA-126206 Regulation of Insulin secretion Home Supers R-HSA-122356 Nuclear Pore Complex (NFC) Dissembly Home Supers R-HSA-1301854 Regulation of Insulin secretion Home Supers R-HSA-1301854 Regulation of Insulin secretion Home Supers R-HSA-159230 NSI Mediated Freet Complex (NFC) Dissembly Home Supers R-HSA-159230 NSI Mediated Freets on Home Supers R-HSA-159230 Rev-mediated nuclear export of HIV RNA Home Supers R-HSA-159243 Transport of Hull Robunckeproteins from Nucleus Home Supers R-HSA-159247 Transport of Hause Transport of Supers R-HSA-159247 Transport of Hause Transport of HIV RNA Home Supers R-HSA-159247 Nuclear Import of Rev protein Home Supers R-HSA-159247 Nuclear Import of Rev protein Home Supers R-HSA-159247 Nuclear Import of Rev protein Home Supers R-HSA-159248 Coperation of Rev protein Home Supers R-HSA-168233 Antivital mechanism by IFM-Himolated genes Home Supers R-HSA-168333 Hoist Interactions with Influenza Factor Home Supers R-HSA-159356 SUMO/Jation of NNA Epilection Home Supers R-HSA-159358 SUMO/Jation of NNA Epilection Home Supers R-HSA-4515840 SUMO/Jation of NNA Epilection Home Supers R-HSA-158273		Regulation of HSF1-mediated heat shock response Homo sapiens R-HSA-33/1453
 Ecorytosis: Veside Tethering Hitlenara Infection Homo sapiems R-HSA-158254 Hitlenian Infection Homo sapiems R-HSA-158256 Regulation of Insulia secretion Homo sapiems R-HSA-3301854 Regulation of Insulia secretion Homo sapiems R-HSA-3501854 Regulation of Insulia Secretion Homo sapiems R-HSA-350265 Transport of His Dependant Mature mRNA Homo sapiems R-HSA-158270 Transport of His Dependant Mature mRNA Homo sapiems R-HSA-158270 Transmembrane transport of small molecules Homo sapiems R-HSA-158271 Transmembrane transport of Small molecules Homo sapiems R-HSA-158271 Transmembrane transport of Small molecules Homo sapiems R-HSA-158271 Transmembrane transport of His Divulce Homo sapiems R-HSA-158271 Transmembrane transport of His Divulces Homo sapiems R-HSA-158271 Transmembrane transport of His Divulces Homo sapiems R-HSA-158271 Transmembrane transport of His Divulces Homo sapiems R-HSA-158273 Transmembrane transport of His Divulces Homo sapiems R-HSA-158274 Transmerbrane transport of His Divulces Homo sapiems R-HSA-158274 Transmerbrane transport of His Divulces Homo sapiems R-HSA-158274 Transmerbrane transport of Hes Use Homo sapiems R-HSA-158273 Nuclear Import of Rev proteins Homo sapiems R-HSA-158233 Host Interactions with Influence Sapiems R-HSA-158233 Host Interactions with Influence Sapiems R-HSA-158274 Transmerbrane Sapiems R-HSA-168273 Cellular response to heat trace Homo sapiems R-HSA-158273 Host Interaction proteins Homo sapiems R-HSA-158273 Goperation of DAI replication proteins Homo sapiems R-HSA-158274 Transford/Autor Transford/Bomo sapiems R-HSA-158274 Transford/Have Transford/Homo sapiems R-HSA-158274 Transford/Homo sapiems R-HSA-215840		Interactions of Rev with host cellular proteins Homo sapiens R-HSA-177243
 Induental infection informa spiens R-HSA-182244 HVI Infection Homo sapiens R-HSA-182266 Regulation of Insulin secretion Homo sapiens R-HSA-422356 Nuclear Pore Complex (NPC) Diassembly Homo sapiens R-HSA-55592. Transport of PLKI Activity at G2/M Transition Homo sapiens R-HSA-152200 NS1 Mediated Effects on Host Pathways Homo sapiens R-HSA-158270 Transport of the SLBP Dependant Mature mRNA Homo sapiens R-HSA-158271 Transmembrane transport of small molecules Homo sapiens R-HSA-158273 Transport of Sinal Molecules Homo sapiens R-HSA-158273 Transport of Viral Ribonucleoproteins in from Nucleus Homo sapiens R-HSA-158274 Transport of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-158274 Transport of Key protein Know sapiens R-HSA-158274 Kuclear Incension by INT-Homos sapiens R-HSA-158275 Coperation of POLC (PhyLIP) and TRIC/CT In C-protein beta Soliding Homo sapiens R-HSA-158251 SGLS antiviral mechanism Know sapiens R-HSA-4507464 Ras Signaling WP4223 Genes Silomo Siphens R-HSA-158276 SGLMO JOBAN epilesa R-HSA-158250 SGLS antiviral mechanism Komo sapiens R-HSA-158273 Influenza Viral RNA Transcription and Replication Homo sapiens		Exocytosis: Vesicle Tethering
 HVI Infection Homo sapiens R-HSA-162966 Regulation of PLXI Activy a GZ/M Transition Homo sapiens R-HSA-255542 Transport of BLSIP Compared Matter mRNA Homo sapiens R-HSA-25520 NSI Mediated Effects on Note Pathways Homo sapiens R-HSA-158276 Transport of BLSIP Compared Matter mRNA Homo sapiens R-HSA-158276 Transport of Blonuckoproteins into the Host Nucleus Homo sapiens R-HSA-158271 Transport of Ribonuckoproteins into the Host Nucleus Homo sapiens R-HSA-158271 Transport of Ribonuckoproteins from Nucleus Homo sapiens R-HSA-158271 Transport of Blonuckoproteins from Nucleus Homo sapiens R-HSA-158274 Transport of HUX RNA Homo sapiens R-HSA-158274 Transport of Hux Blonuckoproteins from Nucleus Homo sapiens R-HSA-158274 Transport of Hux Blonuckoproteins from Nucleus Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Nuclear Import Rev protein Homo sapiens R-HSA-158274 Nuclear Import of Rev protein Homo sapiens R-HSA-158273 Hoti Interactions with Influenza Factors Homo sapiens R-HSA-158274 NEP/N52 Interacts with the Cellular Export Machinery Homo sapiens R-HSA-158273 Hoti Interactions with Influenza Factors Homo sapiens R-HSA-158274 SUMO/ylation of DNA replication proteins Homo sapiens R-HSA-158255 SUMO/ylation of DNA replication proteins Homo sapiens R-HSA-3528749 Hofuenza VI/RA HAM Transcriptional Replication Homo sapiens R-HSA-3527749 Hofuenza VI/RA HAM Transcriptional Replication Homo sapiens R-HSA-352752 Gene Silencing by NRA Homo sapiens R-HSA-352752 Gene Silencing Hol PAR HAM romo sapiens R-HSA-3522752 Histamine H-RA Transcriptional Replication		Influenza Infection Homo sapiens R-HSA-168254
Regulation of Insuline section Amon sources R-HSA-42256 Nucker Proc Complex (MPC) Disassembly Homo sapiens R-HSA-350854 Regulation of PLXI Activity at G2/M Transition Homo sapiens R-HSA-155200 NSI Mediated Effects on Host Pathways Homo sapiens R-HSA-155270 Transport of the SLBP Dependant Mature mRNA Homo sapiens R-HSA-155271 Transport of Ribonucleoproteins into the Host Nucleus Homo sapiens R-HSA-156271 Transmembrane transport of small molecules Homo sapiens R-HSA-156271 Transport of NUR RNA Homo sapiens R-HSA-156274 Transmembrane transport of small molecules Homo sapiens R-HSA-156274 Transport of the SLBP Independent Mature mRNA Homo sapiens R-HSA-158270 Nuckear Import of the SLBP Independent Mature mRNA Homo sapiens R-HSA-158274 Transport of the SLBP Independent Mature mRNA Homo sapiens R-HSA-158271 Nuckear Import of the SLBP Independent Mature mRNA Homo sapiens R-HSA-158273 Nuckear Import of Rev protein Homo sapiens R-HSA-158273 Nuckear Import of Rev protein Homo sapiens R-HSA-158273 Not Interactions with Influenza Edotor Machinery Homo sapiens R-HSA-158273 Antiviral mechanism by IFN-stimulated genes HesA-1169408 SUMOVjation of DNA replication proteins Homo sapiens R-HSA-4615885 SUSI Santiviral mechanism Homo sapiens R-HSA-158273 Antiviral RA Transcription and Replication Homo sapiens R-HSA-158273 Influenza Vir		HIV Infection Homo sapiens R-HSA-162906
Nuclear Pore Complex Pore Complex Nome sapiens R-HSA-3301854 Regulation of PLKL Activity at G2/M Transition Home sapiens R-HSA-255942 Transport of the SLBP Dependant Mature mRNA Home sapiens R-HSA-158276 NS1 Mediated Effects on Host Pathways Home sapiens R-HSA-168271 Transmerbrane transport of Risourdeopreteins into the Host Nuclear Home sapiens R-HSA-18251 Rev-mediated muclear export of NIV RNA Home sapiens R-HSA-168274 Transmerbrane transport of anall molecules Home sapiens R-HSA-168274 Influenza Life Cycle Home sapiens R-HSA-168274 Transport of W1 RNA Home sapiens R-HSA-168274 Transport of W2 RNA Home sapiens R-HSA-168274 Transport of the SLBP Independent Mature mRNA Home sapiens R-HSA-168274 Transport of the VIR RNA Home sapiens R-HSA-168274 Transport of the SLBP Independent Mature mRNA Home sapiens R-HSA-168274 Transport of the SLBP Independent Mature mRNA Home sapiens R-HSA-168273 Nte/RSI Interacts with the Cellular Export Machinery Home sapiens R-HSA-168273 Hot Interactions with Influenza Factors Home sapiens R-HSA-168273 Hot Interactions of POCL (Ph.PJ) and TRI/C/CT in G-protein Home sapiens R-HSA-4615885 SUMOylation of DNA Lighting Theorem Sapiens R-HSA-4615885 SUMOylation of RNA Home sapiens R-HSA-451584 SUMOylation of RNA Home sapiens R-HSA-45168273 Influenza Viral RNA Transcription and Replication Home		Regulation of insulin secretion Homo sapiens R-HSA-422356
Regulation of PLK SLIP Dependent Mature mRNA Homo sapiens R-HSA-158230 NS1 Mediated Effects on Host Pathways Homo sapiens R-HSA-158230 NS1 Mediated Effects on Host Pathways Homo sapiens R-HSA-168271 Transport of Ribounceporteins into the Host Nucleus Homo sapiens R-HSA-168271 Transmethrane transport of Nilonuceporteins into the Host Nucleus Homo sapiens R-HSA-168273 Rev-mediated nuclear export of HIV RNA Homo sapiens R-HSA-168274 Transport of the SIBP Independent Mature mRNA Homo sapiens R-HSA-168274 Transport of the SIBP Independent Mature mRNA Homo sapiens R-HSA-168274 Transport of DVI/al Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274 Transport of the SIBP Independent Mature mRNA Homo sapiens R-HSA-168333 Hot Interactions with Influenza Effective Homo sapiens R-HSA-168274 Transport of the SIBP Independent Mature mRNA Homo sapiens R-HSA-168333 Hot Interactions with Influenza Factors Homo sapiens R-HSA-168333 Hot Interactions with Influenza Factors Homo sapiens R-HSA-168273 Colouration of POLL (PhLP3) and TRIC/CCT In G-protein bara folding Homo sapiens R-HSA-168274 Colouration of POLL (PhLP3) and TRIC/CCT In G-protein Homo sapiens R-HSA-4615885 SIGIS antiviral mechanism Homo sapiens R-HSA-4615885 SIGIS antiviral mechanism Homo sapiens R-HSA-168273 Influenza Vrial RNA Homo sapiens R-HSA-165205 Gene Silencing VR NA Homo sapiens R-HSA-1652		Nuclear Pore Complex (NPC) Disassembly Homo sapiens R-HSA-3301854
Transport of the SIBP Dependant Mature mRNA Homo sapiens RHSA-158276 NSI. Mediated Effects on Host Pathways Homo sapiens RHSA-158271 Transport of Rib Doucleoproteins into the Host Nucleus Homo sapiens RHSA-158271 Transmembrane transport of small molecules Homo sapiens RHSA-158251 Rev-mediated nuclear export of HIV RNA Homo sapiens RHSA-158254 Influenca Life Cycle Homo sapiens RHSA-168274 Transport of Key protein Homo sapiens RHSA-158274 Nuclear import of Rev protein Homo sapiens RHSA-168274 Nuclear import of Rev protein Homo sapiens RHSA-168273 Hott Interactions With House SHSA-168273 Hott Interactions With Influenza Factors Homo sapiens RHSA-168233 Hott Interactions With Influenza Factors Homo sapiens RHSA-168255 Cellular response to the st tress Homo sapiens RHSA-168256 SUMOylation of DNA replication proteins Homo sapiens RHSA-161885 SUMOylation of DNA replication Homo sapiens RHSA-168278 Hiftenza Viral RNA Homo sapiens RHSA-168273 Influenza Viral RNA Homo sapiens RHSA-168273 Influenza Viral RNA Homo sapiens RHSA-168274 Ras Signaling WPA223 Gene Silenida by RNA Homo sapiens RHSA-1682		Regulation of PLK1 Activity at G2/M Transition Homo sapiens R-HSA-2565942
NSI. Mediated Flexts on Host Pathways Homo sapiens R-HSA-168276 Transport of Ribonucleoproteins into the Host Nucleus Homo sapiens R-HSA-168271 Transmembrane transport of small molecules Homo sapiens R-HSA-168271 Rev-mediated nuclear export of HVI RNA Homo sapiens R-HSA-168274 Transport of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274 Transport of Rev protein Homo sapiens R-HSA-168274 Transport of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274 Transport of Viral Ribonucleoproteins from SA-168274 Transport of Viral Ribonucleoproteins Homo sapiens R-HSA-168273 Nuclear Import of Rev protein Homo sapiens R-HSA-168233 Host Interactions with Influenza Factor Homo sapiens R-HSA-168233 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168233 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168233 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168255 Cooperation of POL (PhLIP1) and RIC/CCT In G-protein beta folding Homo sapiens R-HSA-168255 Coldular response to heat stress Homo sapiens R-HSA-169408 SUMOylation of DNA replication proteins Homo sapiens R-HSA-156404 Rass Signaling WP4233 Gene Silencing by RNA Homo sapiens R-HSA-156404 Rass Signaling WP423 Gene Silencing by RNA Homo sapiens R-HSA-578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-156273 Inflectious disease Homo sapiens R-HSA-156273 Inflectious disease Homo sapiens R-HSA-156275 G Leta-gamma signalling through PJKgamma Homo sapiens R-HSA-156273 Inflectious disease Homo sapiens R-HSA-250766 G-protein beta-gamma signalling Homos sapiens R-HSA-397755		Transport of the SLBP Dependant Mature mRNA Homo sapiens R-HSA-159230
Transport of Rev Protein Status Homo sapiens R-HSA-168271 Transport of HUR NRA Homo sapiens R-HSA-155054 Influenza Uirc Qivel Homo sapiens R-HSA-156274 Transport of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Transport of Rev protein Homo sapiens R-HSA-158274 Nuclear import of Rev protein Homo sapiens R-HSA-158274 Nuclear import of Rev protein Homo sapiens R-HSA-158233 Hot Interactions with the Cellular Export Machinery Homo sapiens R-HSA-168333 Hot Interactions with Interactions with Interactions sapiens R-HSA-168333 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168333 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168335 SUMO/ylation of DNA replication proteins Homo sapiens R-HSA-4515885 ISG15 antiviral mechanism Homo sapiens R-HSA-4505464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-252752 Histamine H2 receptor mediated signaling pathway Homo sapiens R-HSA-15825 SIGID antiviral RNA Transcription and Replication Homo sapiens R-HSA-2528752 Histamine H2 receptor mediated signaling pathway Homo sapiens R-HSA-352851 SIGID are converted and sapiens R-HSA-2528752 Histamine H2 receptor mediated signaling pathway Homo sapiens R-HSA-352855 Netabolism of non-coding RNA Homo sapiens R-HSA-2528752 Histamine H2 receptor mediated signaling pathway Homo sapiens R-HSA-35855 Nuclear Evelope Breakdown Homo sapiens R-HSA-350766 G-protein beta:gamma signalling Homo sapiens R-HSA-397755		NS1 Mediated Effects on Host Pathways Homo sapiens R-HSA-168276
Transmetrate transport of small molecules Home sapiens R-HSA-382551 Rev-mediated nuclear export of HIV RNA Home sapiens R-HSA-168054 Influenza Life Cycle Home sapiens R-HSA-168255 Export of Viral Ribonucleoproteins from Nucleus Home sapiens R-HSA-168274 Transport of Rev protein Home sapiens R-HSA-168273 Nuclear import of Rev protein Home sapiens R-HSA-168273 Nuclear import of Rev protein Home sapiens R-HSA-168273 Antiviral mechanism by IFN-stimulated genes Home sapiens R-HSA-168233 Host Interactions with Influenza Factors Home sapiens R-HSA-168273 Antiviral mechanism by IFN-stimulated genes Home sapiens R-HSA-168233 Host Interactions with Influenza Factors Home sapiens R-HSA-168273 Antiviral mechanism by IFN-stimulated genes Home sapiens R-HSA-4159410 Cooperation of DNA replication proteins Home sapiens R-HSA-457064 Ras Signaling WP4223 Gene Silencing by RNA Home sapiens R-HSA-457064 Ras Signaling WP4223 Gene Silencing by RNA Home sapiens R-HSA-158273 Influenza Viral RNA Transcription and Replication Home sapiens R-HSA-392451 siRNP Assembly Home sapiens R-HSA-2582572 Histamine H2 receptor mediated signaling pathway Home sapiens P04386 Metapolism of non-coding RNA Home sapiens R-HSA-392451 SiRNP Assembly Home sapiens R-HSA-392455 SiRNP Assembly Hom		Transport of Ribonucleoproteins into the Host Nucleus Homo sapiens R-HSA-168271
Re-mediated nuclear export of HIV RNA Homo sapiens R-HSA-165054 Influenza Life Cycle Homo sapiens R-HSA-168255 Export of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274 Transport of the SLBP independent Mature mRNA Homo sapiens R-HSA-168273 Nuclear import of Rev protein Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168253 Antiviral mechanism do IFN-cycle the tat folding Homo sapiens R-HSA- Cellular response to heat stress Homo sapiens R-HSA-415885 ISG15 antiviral mechanism Homo sapiens R-HSA-1169408 SUMOylation of RNA binding proteins Homo sapiens R-HSA-168273 Influenza Viral RNA Homo sapiens R-HSA-168273 Influenza Viral RNA Homos appiens R-HSA-168273 Influenza Viral RNA Homos appiens R-HSA-2578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-392451 SIRNP Assembly Homo sapiens R-HSA-168275 Cellular responses to stress Homo sapiens R-HSA-168273 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-392451 SIRNP Assembly Homo sapiens R-HSA-19346 Metabolism fomo sapiens R-HSA-19346 Metabolism fomo sapiens R-HSA-193461 Integration of energy metabolism Homo sapiens R-HSA-19365 Nuclear Envelope Breakdown Homo sapiens R-HSA-19441 Integration of energy metabolism Homo sapiens R-HSA-19365 Metabolism fomo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Transmembrane transport of small molecules Homo sapiens R-HSA-382551
Influenza Life Cycle Homo sapiens R-HSA-168255 Export of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-159227 Nuclear Import of Rev protein Homo sapiens R-HSA-159227 Nuclear Import of Rev protein Homo sapiens R-HSA-159227 Nuclear Import of Rev protein Homo sapiens R-HSA-159237 Nuclear Import of Rev protein Homo sapiens R-HSA-168333 Hoff Unteract with the Cellular Export Machinery Homo sapiens R-HSA-168333 Hoff Unteract with the Cellular Export Machinery Homo sapiens R-HSA-168333 Hoff Unteract Stress Homo sapiens R-HSA-168253 Antiviral mechanism by IRV-stimulated genes Homo sapiens R-HSA-168253 Cellular response to heat stress Homo sapiens R-HSA-158255 SUMOVJation of DNA replication proteins Homo sapiens R-HSA-158256 SUMOVJation of RNA binding proteins Homo sapiens R-HSA-156286 SUMOVJation of RNA Homo sapiens R-HSA-156286 SUMOVJation of RNA Homo sapiens R-HSA-1562704 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infleenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infleenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infleenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infleenting HY Assembly Homo sapiens		Rev-mediated nuclear export of HIV RNA Homo sapiens R-HSA-165054
Export of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274 Transport of the SLBP independent Mature mRNA Homo sapiens R-HSA-159227 Nuclear import of Rev protein Homo sapiens R-HSA-168233 Host Interactions with influenza Factors Homo sapiens R-HSA-168253 Antiviral mechanism by IRN-stimulated genes Homo sapiens R-HSA-168253 Cooperation of PDCL (PhLP1) and TRic/CCT in G-protein beta folding Homo sapiens R-HSA-168254 Cellular response to heat stress Homo sapiens R-HSA-168255 SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism by IRN-stimulated genes Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Inflectious disease Homo sapiens R-HSA-2663205 Gene Silencing by RNA Homo sapiens R-HSA-2620752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-2980766		Influenza Life Cycle Homo sapiens R-HSA-168255
Transport of the SLBP independent Mature mRNA Homo sapiens R-HSA-159227 Nuclear import of Rev protein Homo sapiens R-HSA-180746 NEP/NS2 Interacts with the Cellular Export Machinery Homo sapiens R-HSA-168333 Host Interactions with Influenza Factors Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-168253 Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding Homo sapiens R-HSA-168253 SUMOVjation of PDA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-169408 SUMOVjation of NA binding proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-2562755 Geb taragemma signalling through PI3Kgamma Homo sapiens R-HSA-2682752 Influenza Viral RNA Transcription and Replication Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-2980766 Geno Silencing by RNA Homo sapiens R-HSA-2980766 Gene Televiope Breakdown Homo sapiens R-HSA-2980766		Export of Viral Ribonucleoproteins from Nucleus Homo sapiens R-HSA-168274
Nuclear import of Rev protein Homo sapiens R-HSA-180746 NEP/NS2 Interacts with the Cellular Export Machinery Homo sapiens R-HSA-168333 Host Interactions with Influenza Factors Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-1169410 Cooperation of POCL (PhLP1) and TRIC/CCT in G-protein beta folding Homo sapiens R-HSA-3371556 SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-4615885 SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Influenza Viral RNA Transcription and Replication Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-163865 Cellular responses to stress Homo sapiens R-HSA-2508766 G-protein beta-gamma signalling Homo sapiens R-HSA-397795		Transport of the SLBP independent Mature mRNA Homo sapiens R-HSA-159227
NEP/NS2 Interacts with the Cellular Export Machinery Homo sapiens R-HSA-168333 Host Interactions with Influenza Factors Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-1169410 Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding Homo sapiens R-HSA- Cellular response to heat stress Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription al Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-2563205 G beta: gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193441 Integration of energy metabolism Homo sapiens R-HSA-2380766 G-protein beta: gamma signalling Homo sapiens R-HSA-3907795		Nuclear import of Rev protein Homo sapiens R-HSA-180746
Host Interactions with Influenza Factors Homo sapiens R-HSA-168253 Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-1169410 Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding Homo sapiens R-HSA- Cellular response to heat stress Homo sapiens R-HSA-4515885 ISG15 antiviral mechanism Homo sapiens R-HSA-4515885 ISG15 antiviral mechanism Homo sapiens R-HSA-450464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-262752 Histamine H2 receptor mediated signaling pathway Homo sapiens R-HSA-194411 Integration of energy metabolism for on cooling RNA Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-19307795		NEP/NS2 Interacts with the Cellular Export Machinery Homo sapiens R-HSA-168333
Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-1169410 Cooperation of PDCL (PLP1) and TRIC/CCT in G-protein beta folding Homo sapiens R-HSA Cellular response to heat stress Homo sapiens R-HSA-415885 ISG15 antiviral mechanism Homo sapiens R-HSA-4159408 SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-563205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-163859 Cellular responses to stress Homo sapiens R-HSA-163865 Metabolism of non-coding RNA Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-3937795		Host Interactions with Influenza Factors Homo sapiens R-HSA-168253
Cooperation of PDCL (Ph.P.1) and TRic/CCT in G-protein beta folding Homo sapiens R-HSA Cellular response to heat stress Homo sapiens R-HSA-3371556 SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-563205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-163685 Metabolism of non-coding RNA Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-239795		Antiviral mechanism by IFN-stimulated genes Homo sapiens R-HSA-1169410
Cellular response to heat stress Homo sapiens R-HSA-3371556 SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-169408 SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-166855 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-2980766		Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding Homo sapiens R-HSA
SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885 ISG15 antiviral mechanism Homo sapiens R-HSA-1169408 SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5563205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-390766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Cellular response to heat stress Homo sapiens R-HSA-3371556
ISG15 antiviral mechanism Homo sapiens R-HSA-1169408 SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795), 	SUMOylation of DNA replication proteins Homo sapiens R-HSA-4615885
SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464 Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-1632752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193451 Integration of energy metabolism Homo sapiens R-HSA-193455 Nuclear Envelope Breakdown Homo sapiens R-HSA-1934756 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		ISG15 antiviral mechanism Homo sapiens R-HSA-1169408
Ras Signaling WP4223 Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2110859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193451 Integration of energy metabolism Homo sapiens R-HSA-193655 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		SUMOylation of RNA binding proteins Homo sapiens R-HSA-4570464
Gene Silencing by RNA Homo sapiens R-HSA-211000 Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-2191859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193451 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Ras Signaling WP4223
Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749 Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193451 Integration of energy metabolism Homo sapiens R-HSA-19441 Integration of energy metabolism Romo sapiens R-HSA-193655 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Gene Silencing by RNA Homo sapiens R-HSA-211000
Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273 Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Transcriptional regulation by small RNAs Homo sapiens R-HSA-5578749
Infectious disease Homo sapiens R-HSA-5663205 G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-193685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Influenza Viral RNA Transcription and Replication Homo sapiens R-HSA-168273
G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451 snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Infectious disease Homo sapiens R-HSA-5663205
snRNP Assembly Homo sapiens R-HSA-191859 Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		G beta:gamma signalling through PI3Kgamma Homo sapiens R-HSA-392451
Cellular responses to stress Homo sapiens R-HSA-2262752 Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		snRNP Assembly Homo sapiens R-HSA-191859
Histamine H2 receptor mediated signaling pathway Homo sapiens P04386 Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Cellular responses to stress Homo sapiens R-HSA-2262752
Metabolism of non-coding RNA Homo sapiens R-HSA-194441 Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Histamine H2 receptor mediated signaling pathway Homo sapiens P04386
Integration of energy metabolism Homo sapiens R-HSA-163685 Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Metabolism of non-coding RNA Homo sapiens R-HSA-194441
Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766 G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Integration of energy metabolism Homo sapiens R-HSA-163685
G-protein beta:gamma signalling Homo sapiens R-HSA-397795		Nuclear Envelope Breakdown Homo sapiens R-HSA-2980766
		G-protein beta:gamma signalling Homo sapiens R-HSA-397795

0.00E+00 5.00E-03 1.00E-02 1.50E-02 2.00E-02 2.50E-02 3.00E-02 3.50E-02 4.00E-02 4.50E-02 5.00E-02

Figure 4. Result of pathways enrichment analysis of downregulated genes in the healthy ageing group overlapping with SARS-CoV-2 associated genes and SARS-CoV-2 interacting genes.

eQTL analysis

eQTL variants in genes from significantly overlapping genesets from the respective tissues namely lung and blood were identified (table 2; table 4 in electronic supplementary material). $F_{\rm ST}$ test was performed to identify the variants with low genetic differentiation among different population. A large number of eQTL variants with $F_{\rm ST}$ < 0.05 were found in each group (table 2; table 4 in electronic supplementary material). Further analysis of these may enable identification of variant(s) which could be used as a biomarker(s).

Direction of expression change in patients and		Upre	Downregulated			
healthy ageing group Gene-set common between study groups (<i>n</i>)	Patients' BALF and ageing lung (44)	Patients' PBMCs and ageing blood (116)	SARS-CoV-2 interacting genes with ageing blood (82)	Cytokine and ageing blood (6)	Patients' PBMCs and ageing blood (14)	SARS-CoV-2 interacting with ageing blood (81)
Number of eGenes in GTEx dataset (<i>n</i>)	22	58	44	3	8	49
Total number of eQTL variants	1163	2717	2118	72	90	2269
Number of variants with $F_{\rm ST} < 0.05$	395	1215	1611	40	34	1302

Table 2. Number of genes with significant eQTL variants in each group and number of variants with $F_{\rm ST}$ <0.05 among them.

Identification of druggable gene targets

It may be mentioned that SARS-CoV-2 interacting genes were excluded from this analysis since they have already been reported previously (Gordon *et al.* 2020). Efforts to identify novel druggable targets for FDA approved drugs from among 259 genes from significantly overlapping gene sets between different groups shown above (table 1), yielded a total of 48 druggable genes mostly from the immune system related pathways. A total of 205 FDA approved drugs could potentially target them (table 5 in electronic supplementary material).

Discussion

COVID-19, the recent pandemic has affected individuals of all age groups as well as all ethnicities. However, poor prognosis has been witnessed in the elderly effected group with or without comorbidities (Hauser et al. 2020; Cohen et al. 2020; Meyerowitz-Katz and Merone 2020; Wu et al. 2020). The overall case fatality rate (CFR) for cases with age 70 to 79 years is 8.0% and for cases with age 80 years and above it is 14.8%; which is strikingly higher compared to 0.4% in cases below 50 years of age, based on a study that included 72314 cases from China (Wu and McGoogan 2020). It is well known that with ageing there is a notable increase in circulating proinflammatory cytokines even in the absence of an immunological threat and also a reduction in proteins that maintain homeostasis of the immune system, thus entailing a greater risk for many diseases (cancer, cardiovascular and neurodegenerative disorders, COPD, lung cancer, interstitial lung disease etc.) (Panda et al. 2009; López-Otín et al. 2013; Meiners et al. 2015; Angelidis et al. 2019). Thus, we reasoned that comparing naturally occurring, age-dependent transcriptional changes with those observed in COVID19 patients and/or known SARS-COV-2 interacting proteins may provide insights into the age-associated poor prognosis in COVID-19.

Three noteworthy findings emerged from our study: (i) a significant overlap was witnessed between DEGs in patients' BALF/blood and in ageing lung and blood; (ii) this overlap was more pronounced in blood compared to lung; and (iii) a similar overlap between SARS-CoV-2 interacting proteins and DEGs in ageing blood but not in lung (table 1) and warrant discussion. Pathway enrichment analysis of the overlapped gene sets suggest that genes involved in pathways such as proinflammatory, apoptotic, T cell polarization, viral replication suppression (figures 3 & 4; tables 2 & 3 in electronic supplementary material) remain dysregulated in elderly patients. Upon SARS-CoV-2 infection, expression of these genes gets further dysregulated resulting in poor prognosis in case of elderly patients.

As for the second novel observation, the higher extent of overlap between SARS-CoV-2 associated / SARS-CoV-2 interacting genes and DEGs in blood among the heathy ageing group, may explain the range of clinical symptoms including high prevalence of blood clots, strokes and heart attack as well as multi-organ failure in a subset of severe patients reported in this disorder (Harapan et al. 2020; Cevik et al. 2020). Our observations are corroborated by a recent report of SARS-CoV-2 mediated damage to endothelial cells lining the blood vessels probably leading to blood clotting, strokes and heart attacks (Varga et al. 2020). We observed that proinflammatory genes such as IFNG, CCL4, CCR9, BCL2, TIMP1, TNF, C2, CCR2, VEGFA (table 1 in electronic supplementary material) remain upregulated in aged individuals which might cause the 'cytokine storm' observed in severe patients. Further, higher expression of these genes may lead to over activation of T cell polarization and TGFbeta pathways in affected elderly patients (figure 3), which can cause functional exhaustion of T cells (Swain et al. 2012; Kahan et al. 2015) that has been reported in elderly patients (Diao et al. 2020). Of note, one of these genes, namely CCR9 was found to be significantly ($P = 1.15 \times$ 10^{-10}) associated with COVID-19 in a recent genomewide association study that included 835 patients and 1255 control participants from Italy and 775 patients and 950 control

subjects from Spain (Ellinghaus *et al.* 2020), lending support to our findings.

Taken together these observations, eQTLs in the genes identified in our study (table 2; table 4 in electronic supplementary material) may also confer poor prognosis in young patients but this may worsen with age and comorbidities. However, their utility as prognostic biomarkers across different populations may be assessed only when more data of patients become available and these genes are characterized as COVID-19 patients. On the other hand, variants with $F_{\rm ST} > 0.05$ may be tested for correlation with population specific severity. Additionally, identification of genes involved in influenza and HIV infection in our study (figures 3&4; tables 2&3 in electronic supplementary material) may be of considerable relevance for drug repurposing for treatment of COVID-19 patients.

In summary, our analysis (i) identified probable candidate genes for poor prognosis among the affected elderly group; (ii) identified potential druggable targets as well as FDA approved drugs opening the possibility of drug repurposing; and (iii) seems to provide early explanation for manifestation of blood related symptoms and probably multiorgan damage. Finally, although these leads are preliminary based on a very limited patient dataset, the model holds promise to be tested as and when more tissue specific patient derived data from different age groups and/or from different populations become available. Our study is limited by nonavailability of large tissue specific transcriptomic datasets of COVID-19 patients across age groups, and with varying severity and from different populations to validate the hypothesis.

Acknowledgments

Central Instrumentation Facility, University of Delhi South Campus provided the computational facility. Special Assistance Programme and Department of Science and Technology, New Delhi, through FIST and DU-DST PURSE programmes to the Department of Genetics, UDSC, Non-NET Fellowship from UGC; and Senior Research Fellowship from Indian Council of Medical Research, New Delhi to UB are gratefully acknowledged. The authors have declared that there are no conflicts of interest in relation to the subjects of this study.

References

- Angelidis I., Simon L. M., Fernandez I. E., Strunz M., Mayr C. H., Greiffo F. R. *et al.* 2019 An atlas of the aging lung mapped by single cell transcriptomics and deep tissue proteomics. *Nat. Commun.* 10. https://doi.org/10.1038/s41467-019-08831-9.
- Cascella M., Rajnik M., Cuomo A., Dulebohn S. C., Di Napoli R. 2020 Features, evaluation and treatment of coronavirus (COVID-19). *StatPearls*; http://www.ncbi.nlm.nih.gov/pubmed/ 32150360.
- Cevik M., Bamford C. and Ho A. 2020 COVID-19 pandemic A focused review for clinicians. *Clin. Microbiol. Infec.* 26, 842–847.

- Chen E. Y., Tan C. M., Kou Y., Duan Q., Wang Z., Meirelles G. V. et al. A. 2013 Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics 14. https://doi.org/10.1186/1471-2105-14-128.
- Cohen J. F., Korevaar D. A., Matczak S., Brice J., Chalumeau M. and Toubiana J. 2020 COVID-19-related mortality by age groups in Europe: A meta-analysis. *MedRxiv*, https://doi.org/10.1101/ 2020.04.11.20061721.
- de Almeida A. J. P. O., de Almeida Rezende M. S., Dantas S. H., de Lima Silva S., de Oliveira J. C. P. L. *et al.* 2020 Unveiling the role of inflammation and oxidative stress on age-related cardiovascular diseases. *Oxid. Med. Cell. Longev.* 2020, 1–20.
- Diao B., Wang C., Tan Y., Chen X., Liu Y., Ning L. et al. 2020. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front. Immunol. 11, 827.
- Dugo M., Cotroneo C. E., Lavoie-Charland E., Incarbone M., Santambrogio L., Rosso L. *et al.* 2016 Human lung tissue transcriptome: influence of sex and age. *PLoS One* **11**, e0167460.
- Elko E. A., Mahoney J. M., Vacek P., van der Vliet A., Anathy V., van der Velden L. J. L. *et al.* 2019 Age-dependent dysregulation of redox genes may contribute to fibrotic pulmonary disease susceptibility. *Free Radic. Biol. Med.* **141**, 438–446.
- Ellinghaus D., Degenhardt F., Bujanda L., Buti M., Albillos A., Invernizzi P. et al. 2020 Genomewide association study of severe covid-19 with respiratory failure. N. Engl. J. Med. https://doi.org/ 10.1056/nejmoa2020283.
- Franceschi C. and Campisi J. 2014 Chronic inflammation (Inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. 69, S4–S9.
- Fulop T., Witkowski J. M., Olivieri F. and Larbi A. 2018 The integration of inflammaging in age-related diseases. *Semin. Immunol.* 40, 17–35.
- Gavazzi G. and Krause K. H. 2002 Ageing and infection. *Lancet Infect. Dis.* 2, 659–666.
- Gordon D. E., Jang G. M., Bouhaddou M., Xu J., Obernier K., White K. M., O'Meara M. J. *et al.* 2020 A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 583, 459–468.
- Harapan H., Itoh N., Yufika A., Winardi W., Keam S., Te H. et al. 2020 Coronavirus disease 2019 (COVID-19): A literature review. J. Infect. Public Heal. 13, 667–673.
- Hauser A., Counotte M. J. J., Margossian C. C. C., Konstantinoudis G., Low N. *et al.* 2020 Estimation of SARS-CoV-2 mortality during the early stages of an epidemic: a modelling study in Hubei, China and northern Italy. *MedRxiv.* Preprint, https://doi. org/10.1101/2020.03.04.20031104.
- Kahan S. M., Wherry E. J., and Zajac A. J. 2015 T cell exhaustion during persistent viral infections. *Virology* 479–480. 180–193.
- Kuleshov M. V., Jones. M. R., Rouillard A. D., Fernandez N. F., Duan Q., Wang Z. *et al.* 2016 Enrichr: a comprehensive gene set enrichment analysis. *Nucleic Acids Res.* 44, W90-W97.
- López-Otín C., Blasco M. A., Partridge L., Serrano M. and Kroemer G. 2013 The hallmarks of aging. *Cell.* **153**, 1194.
- Meiners S., Eickelberg O. and Königshoff M. 2015 Hallmarks of the ageing lung. *Eur Respir J*, 45, 807–827.
- Meyer K. C. 2001 The role of immunity in susceptibility to respiratory infection in the aging lung. *Respir.* **128**, 23–31.
- Meyerowitz-Katz G. and Merone L. 2020 A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates. *Medrxiv*. Preprint, https://doi.org/10.1101/ 2020.05.03.20089854.
- Panda A., Arjona A., Sapey E., Bai F., Fikrig E., Montgomery R. R. et al. 2009 Human innate immunosenescence: causes and consequences for immunity in old age. *Trends Immunol.* 30, 325–333.

- Peters M. J., Joehanes R., Pilling L. C., Schurmann C., Conneely K. N., Powell J. *et al.* 2015 The transcriptional landscape of age in human peripheral blood. *Nat. Commun.* 6, 1–14.
- Sanders J. M., Monogue M. L., Jodlowski T. Z. and Cutrell J. B. 2020 Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *Jama-J AM Med. Assoc.* 323, 1824–1836.
- Siordia J. A. 2020 Epidemiology and clinical features of COVID-19: A review of current literature. J. Clin. Virol. 127.
- Srinivasan S., Cui H., Gao Z., Liu M., Lu S., Mkandawire W. et al. 2020 Structural genomics of SARS-COV-2 indicates evolutionary conserved functional regions of viral proteins. *Viruses* 12, 360.
- Swain S. L., McKinstry K. K. and Strutt T. M. 2012 Expanding roles for CD4⁺ T cells in immunity to viruses. *Nat. Rev. Immunol.* 12, 136–148.
- Varga Z., Flammer A. J., Steiger P., Haberecker M., Andermatt R., Zinkernagel A. S. *et al.* 2020 Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395, 1417–1418.
- Wu J. T., Leung K., Bushman M., Kishore N., Niehus R., de Salazar P. M. et al. 2020 Estimating clinical severity of COVID-

Corresponding editor: H. A. RANGANATH

19 from the transmission dynamics in Wuhan, China. *Nat. Med.* **26**, 506–510.

- Wu Z. and McGoogan J. M. 2020 Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *Jama-J AM Med. Assoc.* 323, 1239–1242.
- Xiong Y., Liu Y., Cao L., Wang D., Guo M., Jiang A. et al. 2020 Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg. Microbes Infect.* 9, 761–770.
- Yang J., Huang T., Petralia F., Long Q., Zhang B., Argmann C. et al. 2015 Synchronized age-related gene expression changes across multiple tissues in human and the link to complex diseases. Sci. Rep. 5, 1–16.
- Zhou Z., Ren L., Zhang L., Zhong J., Xiao Y., Jia Z. *et al.* 2020 Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe.* 27, 883–890.