Additional File 1

Prioritizing genes responsible for host resistance to influenza using network approaches

Suying Bao^{1*}, Xueya Zhou^{2*}, Liangcai Zhang³, Jie Zhou⁴, Kelvin Kai-Wang To⁴, Liqiu Wang^{5,6}, Xuegong Zhang², You-Qiang Song^{1§}

¹Department of Biochemistry, The University of Hong Kong, Hong Kong, China

²Bioinformatics Division and Center for Synthetic and Systems Biology, TNLIST,

MOE Key Lab of Bioinformatics / Department of Automation, Tsinghua University,

Beijing, China

³Department of Biophysics, College of Bioinformatics Science and Technology,

Harbin Medical University, Harbin, China

⁴Department of Microbiology, The University of Hong Kong, Hong Kong, China

⁵Department of Mechanical Engineering, The University of Hong Kong, Hong Kong ⁶Zhejiang Institute of Research and Innovation, The University of Hong Kong, Hong Kong

*These authors contributed equally to this work

[§]Corresponding author: YQS: songy@hku.hk

Mathematical details of methods

Seed-based prioritization methods

In the mathematical derivations below, we use a symmetrical adjacency matrix **A** to represent the gene network containing *n* genes. The entry $a_{ij} > 0$ if two genes *i* and *j* are linked with associated score of a_{ij} ; otherwise, $a_{ij} = 0$. The seed-based methods rank genes according to their similarities (closeness) to seed genes in the gene-network. The similarity measure can be computed by the following two algorithms.

1) Random Walk with Restart (RWR)

The random walk on networks is defined as an iterative transition from the current node to a randomly selected neighbor [1]. To obtain the transition probability, Tong suggested using the following normalization of the adjacency matrix [2]:

$$\tilde{\mathbf{A}} = \mathbf{D}^{-1/2} \mathbf{A} \mathbf{D}^{-1/2} \tag{1}$$

where **D** is an $n \times n$ diagonal matrix, with $d_{i,i} = \sum_{j=1}^{n} a_{ij}$.

The random walk method was applied to the gene prioritization problem by Köhler *et al.* [3] with the modification to allow restart from source nodes with probability r (we used r = 0.5 as suggested by the author). It is defined by

$$\mathbf{p}^{t+1} = (1-r)\mathbf{\hat{A}}\mathbf{p}^t + r\mathbf{p}^0$$
(2)

where \mathbf{p}^{t} is a vector with *i*-th element p_{i}^{t} representing the probability of being at node *i* at step *t*. The vectors is initialized with $p_{i}^{0} = \frac{1}{s}$ if node *i* is one of the *s* seed genes; and $p_{i}^{0} = 0$ otherwise. This enables random walk to start from each seed gene with

equal probabilities. After enough steps, random walk will enter the steady-state when the probability of being at each node become stabilized. We then rank the candidates according to their values in the steady-state probability vector \mathbf{p} . It can be approximated by iterating (1) until the probability vector converges:

$$\sum_{i=1}^{n} \left| p_i^{t+1} - p_i^{t} \right| < 10^{-6} \, .$$

2) Seed-based Heat Kernel Diffusion Ranking (sHKDR)

The heat kernel diffusion matrix was introduced by Chung *et al.* [4] defined as $\mathbf{H} = e^{-s\mathbf{L}}$, where is a diffusion factor controlling the magnitude of the diffusion. And matrix \mathbf{L} is the normalized Laplacian of the graph defined as $\mathbf{L} = \mathbf{I} - \mathbf{D}^{-1}\mathbf{A}$, where \mathbf{I} is the identity matrix, \mathbf{A} and \mathbf{D} were defined as above. The kernel diffusion matrix computes the similarity of two nodes in the network as the probability of reaching one node at some time point after a random walk starting from another node. To simplify the computation, here we used the discrete approximation introduced by Yang et al. [5].

$$\mathbf{H} = \left(\mathbf{I} + \frac{-\mathbf{S}}{N}\mathbf{L}\right)^{N} \tag{3}$$

with *N* being the number of iterations. The candidate genes are ranked by their average similarities to seeds:

$$score(j) = \frac{1}{s} \sum_{i \in seeds} H_{ij}$$
 (4)

We tried several sets of parameters of (N, \cdot) in cross-validation studies to evaluate their performances.

3) Direct Interaction Ranking (DIR) and STRING Association Ranking (SAR)

To demonstrate the advantage of similarity measures that take both direct and indirect links into account, we also used two methods that only consider direct interaction partners for comparison: Direct Interaction Ranking (DIR) [6] and STRING Association Ranking (SAR). In the DIR method, the candidate genes are ranked by the number of directly linked seed genes. To implement the method, we only used links with scores greater than 0.4 which represents the "medium" confidence in STRING database. In SAR method, the candidate genes are ranked by the sum of interaction scores (weights) with their direct neighbors.

Differential expression (DE)-based prioritization methods

1) Differential expression-based Heat Kernel Diffusion Ranking (deHKDR)

This method was first proposed by Nitsch et al [7] to prioritize genes for diseases with little prior knowledge about their underlying genes, and extended in a subsequent study [8]. Recall the scoring function for the seed-based HKDR(4). It can be alternatively expressed using a vector form as

$$\mathbf{p}_{\Gamma} = \mathbf{p}_0 \mathbf{H} \tag{5}$$

where \mathbf{p}_0 stands for a preference vector, which is initialized the same way as the probability vector in seed-based HKDR. The final score for each candidate gene can be found in \mathbf{p} . DE-based HKDR method has the same weighting scheme as equation (5), but instead of relying on seed genes, \mathbf{p}_0 is initialized by the differential expression levels comparing the cases and controls. In this way, each candidate gene is scored by a weighted sum of DE levels of itself and its neighbors, with the weights for neighbor genes equaling to their similarities to the candidate.

The assumption behind this approach is that the true disease genes tend to be surrounded by differentially expressed neighbors. We tested if the assumption is valid for the seed genes when evaluating the performance of the method. We also tried several sets of parameters to fine tune the performance on predicting known host resistance genes.

2) Direct Neighborhood Ranking (DNR)

As a comparison, we also implemented a network analysis method of differential expression based on Direct Neighborhood Ranking (DNR) matrix. In this method, neighbors of a candidate gene *i* are defined as all genes directly linked to the candidate in the network with confidence score $a_{ij} > V$. Here we set = 0.15 as suggested by Nitsch [8]. The candidate gene *i* is scored by

$$\hat{x}_i = \mathbf{r} \cdot x_i + \frac{1 - \mathbf{r}}{N} \sum_{j \neq i, j: \mathbf{r}_{ij} > \mathbf{v}} x_j$$
(6)

where x_i is the differential expression level of gene *i*. The parameter controls the contribution of a candidate gene's own expression to its score, which is named as steady factor relative to the diffusion factor in heat kernel diffusion models. *N* denotes the number of direct neighbors near candidate gene *i*.

Supplementary Tables

Table S1 - Parameter optimization forand *m* in seed-based Heat KernelDiffusion Ranking model

m = 1	AUC of sHKDR	= 0.5	AUC of sHKDR
= 0.25	0.904	m = 1	0.912
= 0.5	0.912	m = 2	0.895
= 0.75	0.907	m = 3	0.906
= 1	0.890	m = 5	0.903

TableS2 - Parameter optimization forandminthedifferentialexpression-basedHeatKernelDiffusionRanking model

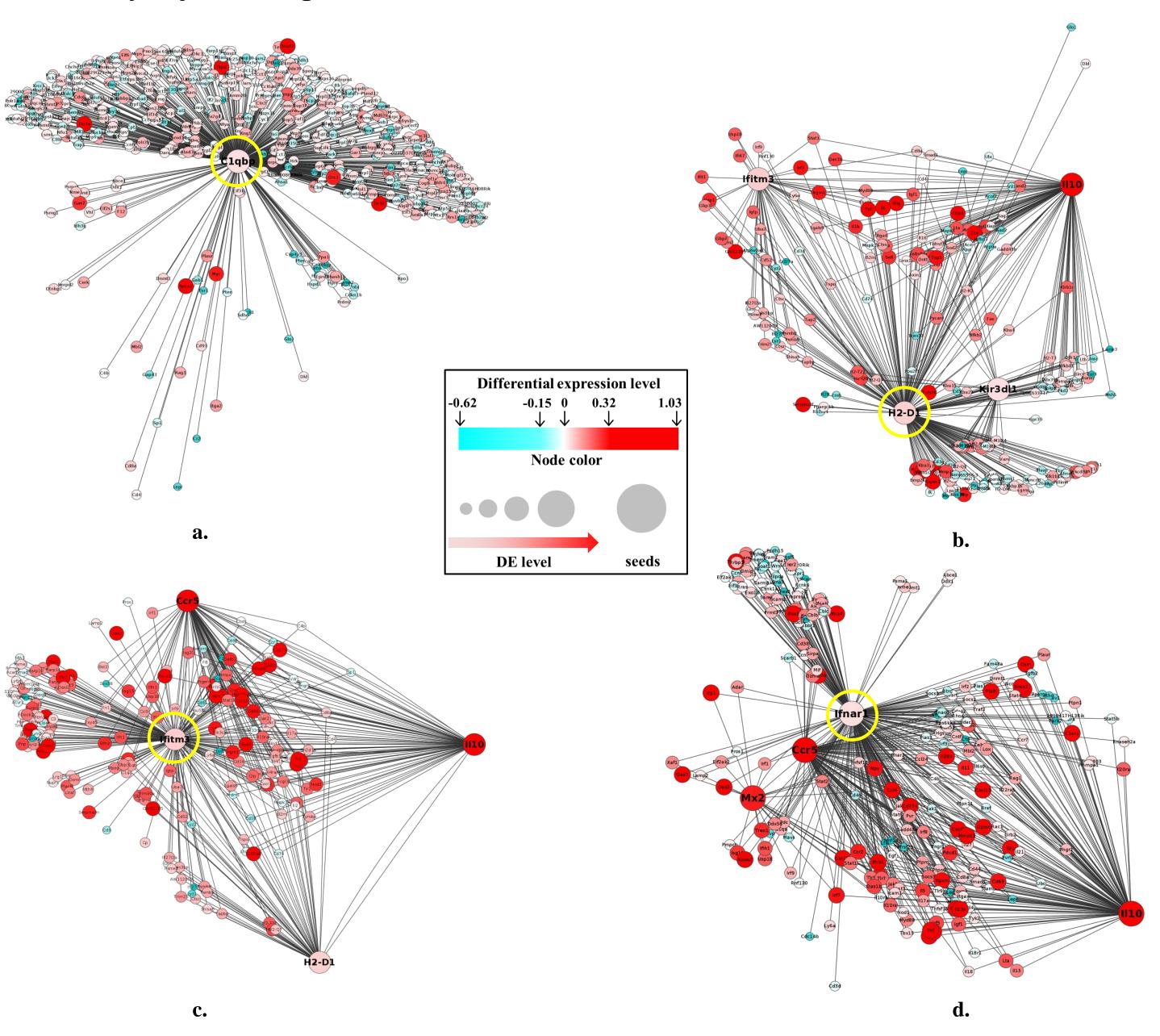
m = 1	AUC of deHKDR	= 0.5	AUC of deHKDR
= 0.25	0.869	m = 1	0.915
= 0.5	0.887	m = 2	0.897
= 0.75	0.915	m = 3	0.891
= 1	0.908	m = 5	0.888

Table S3 - Parameter optimization forin the Direct Neighborhood Rankingmodel

	AUC of DNR
= 0.75	0.845
= 0.5	0.864
= 0.25	0.854
= 0	0.829

Supplementary Figures

Supplementary Figure S1: The STRING sub-networks consisting of a single seed gene and its directly adjacent neighbors



Supplementary Figure S2: Heatmaps of functional enrichment for different winner groups

Biological Process

			ulai ru	inction	l	
	GO:0043281~regulation of caspase activity					GO:0001871~pattern binding
	GO:0052548~regulation of endopeptidase activity GO:0052547~regulation of peptidase activity					GO:0030247~polysaccharide binding
	GO:0050778~positive regulation of immune response					GO:0005125~cytokine activity
	BP00255:Cytokine/chemokine mediated immunity GO:0002252~immune effector process					GO:0005539~glycosaminoglycan binding
	GO:0002460~adaptive immune response based on somatic r					GO:0046983~protein dimerization activity
	GO:0002250~adaptive immune response BP00115:NF-kappaB cascade					GO:0030246~carbohydrate binding
	GO:0006959~humoral immune response					GO:0042802~identical protein binding
	GO:0006956~complement activation GO:0002541~activation of plasma proteins involved in acute i					GO:0042803~protein homodimerization activ
	BP00153:Complement-mediated immunity					GO:0008289~lipid binding
	GO:0002520~immune system development GO:0007169~transmembrane receptor protein tyrosine kinase					GO:0020037~heme binding
	GO:0033674~positive regulation of kinase activity			1		GO:0046906~tetrapyrrole binding
	GO:0051347~positive regulation of transferase activity GO:0016477~cell migration					MF00173:Defense/immunity protein
	GO:0048534~hemopoietic or lymphoid organ development GO:0030097~hemopoiesis					GO:0003823~antigen binding
	GO:0002521~leukocyte differentiation					MF00020:Peptide hormone
	GO:0001666~response to hypoxia GO:0043085~positive regulation of catalytic activity					MF00005:Cytokine receptor
	GO:0051254~positive regulation of RNA metabolic process					GO:0019955~cytokine binding
	GO:0031328~positive regulation of cellular biosynthetic proce GO:0009891~positive regulation of biosynthetic process					GO:0019825~oxygen binding
	GO:0051173~positive regulation of nitrogen compound metab					MF00174:Complement component
	GO:0010557~positive regulation of macromolecule biosynthe GO:0010033~response to organic substance					MF00175:Major histocompatibility complex a
	GO:0010604~positive regulation of macromolecule metabolic					GO:0046979~TAP2 binding
	GO:0051674~localization of cell GO:0048870~cell motility					GO:0046978~TAP1 binding
	GO:0006928~cell motion					GO:0046977~TAP binding
	GO:0045944~positive regulation of transcription from RNA po GO:0009967~positive regulation of signal transduction					GO:0015197~peptide transporter activity
	GO:0002684~positive regulation of immune system process					MF00006:Interleukin receptor
	GO:0048660~regulation of smooth muscle cell proliferation GO:0050795~regulation of behavior		-			GO:0042287~MHC protein binding
	GO:0032103~positive regulation of response to external stimu BP00209:Blood circulation and gas exchange					GO:0042288~MHC class I protein binding
	GO:0048661~positive regulation of smooth muscle cell prolife					GO:0030547~receptor inhibitor activity
	GO:0006915~apoptosis GO:0012501~programmed cell death					GO:0048019~receptor antagonist activity
	GO:0008219~cell death					GO:0032393~MHC class I receptor activity
	GO:0016265~death GO:0043067~regulation of programmed cell death					GO:0005344~oxygen transporter activity
	GO:0010941~regulation of cell death					GO:0050700~CARD domain binding
	GO:0042981~regulation of apoptosis BP00148:Immunity and defense	RWR	sHKDR	deHKDR	2-strategy	
	GO:0010647~positive regulation of cell communication					
	GO:0009611~response to wounding GO:0006955~immune response	Cellul	ar Com	nonen	t	
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death	Cellula	ar Com	ponen	t	
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis	Cellula	ar Com	ponen	t	GO:0048770~pigment granule
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis	Cellula	ar Com	ponen	t	GO:0048770~pigment granule GO:0042470~melanosome
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation	Cellula	ar Com	ponen	t	GO:0042470~melanosome
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex
Image: second	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex assembly GO:0065003~macromolecular complex assembly	Cellula	ar Com	ponen	t	GO:0042470~melanosome
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis GO:0043933~macromolecular complex assembly GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of multicellular organismal pr	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex assembly GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of multicellular organismal pr GO:0008285~negative regulation of cell proliferation	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of cell proliferation GO:0004461~protein complex assembly GO:00065003~macromolecular complex assembly GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00071:Proteolysis	Cellula	ar Com	ponen	t 	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of molecular function GO:0044127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis GO:0043933~macromolecular complex assembly GO:0051240~positive regulation of multicellular organization GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space
Image: section of the section of th	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of cell proliferation GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage	Cellula	ar Com	ponen	t 	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex assembly GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of cell proliferation GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage GO:0002443~leukocyte mediated immunity	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region
	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:00070271~protein complex assembly GO:0043933~macromolecular complex assembly GO:0043933~macromolecular complex subunit organization GO:00051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0002697~regulation of cellular response to stress GO:0002443~leukocyte mediated immunity GO:0002526~acute inflammatory response	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part
	GO:0009611~response to wounding GO:0006955~immune response GO:0010942~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:000461~protein complex assembly GO:0006461~protein complex assembly GO:0006461~protein complex assembly GO:00070271~protein complex assembly GO:0043933~macromolecular complex subunit organization GO:00051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0002443~leukocyte mediated immunity GO:0002266~acute inflammatory response to stress GO:0002526~acute inflammatory response	Cellula	ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region
Image: set of the	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis GO:0065003~macromolecular complex subunit organization GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of multicellular organismal pr GO:008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP0071:Proteolysis BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage GO:0002443~leukocyte mediated immunity GO:0080135~regulation of cellular response to stress GO:00016485~protein processing GO:0016485~protein maturation		ar Com	ponen	t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane
Image: set of the	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex biogenesis GO:0065003~macromolecular complex assembly GO:0051240~positive regulation of multicellular organization GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage GO:0002443~leukocyte mediated immunity GO:0002526~acute inflammatory response to stress GO:0016485~protein processing GO:0016485~protein maturation		ar Com		t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane
Image: section of the section of th	GO:0009611~response to wounding GO:0006955~immune response GO:0010942~positive regulation of programmed cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of cell proliferation GO:0044093~positive regulation of cell proliferation GO:0006461~protein complex assembly GO:00065003~macromolecular complex assembly GO:00051240~positive regulation of cell proliferation GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of cellular response to stress GO:0002697~regulation of cellular response to stress GO:0001443~protein maturation by peptide bond cleavage GO:0002697~regulation of cellular response to stress GO:0002697~regulation of stress-activated protein kinase sig GO:0002266~acute inflammatory response GO:00016485~protein maturation GO:0002266~acute inflammatory response GO:0002449~lymphocyte mediated immunity GO:0002449~lymphocyte mediated immunity GO:0002449~lymphocyte mediated immunity GO:0006958~complement activation, classical pathway				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane
Image: section of the section of th	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0042127~regulation of cell proliferation GO:006461~protein complex assembly GO:0065003~macromolecular complex subunit organization GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0002697~regulation of cellular response to stress GO:0002607~regulation of cellular response to stress GO:0002526~acute inflammatory response GO:00016485~protein maturation GO:00070302~regulation of stress-activated protein kinase sig GO:0002449~lymphocyte mediated immunity GO:0002449~lymphocyte mediated immunity				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface
Image: section of the section of th	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0043065~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of molecular function GO:00044093~positive regulation of molecular function GO:00006461~protein complex assembly GO:00070271~protein complex assembly GO:000503~macromolecular complex subunit organization GO:00051240~positive regulation of multicellular organismal pr GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0002267~regulation of cellular response to stress GO:0002267~acute inflammatory response GO:0002226~acute inflammatory response GO:0002226~regulation of stress-activated protein kinase sig GO:0002443~lymphocyte mediated immunity GO:0002245~hymorel maturation GO:0002245~complement activation, classical pathway GO:0002443~regulation of JNK cascade GO:0002455~hymorel immune response mediated by circu				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex
Image: set of the	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0043065~positive regulation of cell death GO:0044093~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:006601~protein complex assembly GO:0070271~protein complex assembly GO:0065003~macromolecular complex subunit organization GO:0043933~macromolecular complex subunit organization GO:0008285~negative regulation of multicellular organismal pr GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00071:Proteolysis BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0002443~leukocyte mediated immunity GO:0080135-regulation of cellular response to stress GO:00016485~protein naturation by peptide bond cleavage GO:00016485~protein maturation GO:0002526~acute inflammatory response GO:0016485~protein maturation GO:00051604~protein maturation GO:00051604~protein maturation GO:00051604~protein maturation GO:000526~acute inflammatory response GO:00051604~protein maturation GO:000552~regulation of stress-activated protein kinase sig GO:0002449~lymphocyte mediated immunity GO:0006958~complement activation, classical pathway GO:0006958~complement activation, alternative pathway GO:0006957~complement activation, alternative pathway GO:0006952~defense response GO:0006952~inflammatory response				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface
Image: set of the	GO:0009611~response to wounding GO:00043068~positive regulation of programmed cell death GO:0043066~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0044093~positive regulation of cell proliferation GO:00461~protein complex assembly GO:0070271~protein complex biogenesis GO:0065003~macromolecular complex assembly GO:0051240~positive regulation of multicellular organismal pr GO:0008285~negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00071:Proteolysis BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage GO:00025126~acute inflammatory response GO:0002526~acute inflammatory response GO:00025126~acute inflammatory response GO:00025126~acute inflammatory response GO:00025126~acute inflammatory response GO:00025126~acute inflammatory response GO:000251604~protein maturation GO:000251604~protein maturation GO:0006958~complement activation, classical pathway GO:0006958~complement activation, alternative pathway GO:0006957~complement activation, alternative pathway GO:0006954~inflammatory response GO:0006954~inflammatory response to stimulus				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex
Image: style s	GO:0009611~response to wounding GO:0006955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0006461~protein complex assembly GO:00051240~positive regulation of multicellular organization GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:00051605~protein maturation by peptide bond cleavage GO:0002566~acute inflammatory response GO:0002566~acute inflammatory response GO:0002582~regulation of stress-activated protein kinase sig GO:0002582~regulation of stress-activated protein kinase sig GO:0002582~regulation of stress-activated protein kinase sig GO:0002582~regulation of JNK cascade GO:0002582~regulation of JNK cascade GO:0002455~humoral immune response mediated by circulal GO:0002455~complement activation, classical pathway GO:0002455~complement activation, alternative pathway GO:0006957~complement activation of response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa GO:00045087~innate immune response				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex
Image: state s	GO:0009611~response to wounding GO:00043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0006461~protein complex assembly GO:0070271~protein complex assembly GO:0065003~macromolecular complex assembly GO:0051240~positive regulation of multicellular organization GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of cell proliferation BP00102:Signal transduction GO:0002589~regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BO:0002697~regulation of cellular response to stress GO:00051605~protein maturation by peptide bond cleavage GO:0002543~leukocyte mediated immunity GO:00051604~protein maturation GO:0002547~regulation of stress-activated protein kinase sig GO:0002449~lymphocyte mediated immunity GO:0006958~complement activation, classical pathway GO:0002455~humoral immune response mediated by circulal GO:0002455~humoral immune response to stimulus BP00103:Cell surface regulation of JNK cascade GO:0006958~complement activation, alternative pathway GO:0006958~complement activation, alternative pathway GO:0006957~response to bacterium GO:0006954~inflammatory response GO:00045884~positive regulation of response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa GO:00045087~innate immune response				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex GO:0005833~hemoglobin complex
<tt><tt><tt><tt><tt><tt><tt><tt><tt><tt< td=""><td>GO:0009611~response to wounding GO:00043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:00042127~regulation of cell proliferation GO:00065003~macromolecular complex assembly GO:00070271~protein complex biogenesis GO:0065003~macromolecular complex assembly GO:0005240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of cellular response to stress GO:00051605~protein maturation by peptide bond cleavage GO:00026443~leukocyte mediated immunity GO:000264*regulation of stress-activated protein kinase sig GO:0016485~protein maturation GO:0002443~leukocyte mediated immunity GO:000268*cegulation of JNK cascade GO:0016485~protein maturation GO:0002455~humoral antruation, classical pathway GO:0004538*complement activation, classical pathway GO:0006958*complement activation, alternative pathway GO:0006958*complement activation, alternative pathway GO:0006957*cegulation of JNK cascade GO:0006958*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation of response to stimulus BP00107*Cytokine and chemokine mediated signaling pathwa GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response to stimulus BP00107*Cytokine and chemokine mediated signaling pathwa GO:00043123*positive regulation of rtspapaB kinase/NF-kappaB casci</td><td></td><td></td><td></td><td>t</td><td>GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex</td></tt<></tt></tt></tt></tt></tt></tt></tt></tt></tt>	GO:0009611~response to wounding GO:00043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:00042127~regulation of cell proliferation GO:00065003~macromolecular complex assembly GO:00070271~protein complex biogenesis GO:0065003~macromolecular complex assembly GO:0005240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of cellular response to stress GO:00051605~protein maturation by peptide bond cleavage GO:00026443~leukocyte mediated immunity GO:000264*regulation of stress-activated protein kinase sig GO:0016485~protein maturation GO:0002443~leukocyte mediated immunity GO:000268*cegulation of JNK cascade GO:0016485~protein maturation GO:0002455~humoral antruation, classical pathway GO:0004538*complement activation, classical pathway GO:0006958*complement activation, alternative pathway GO:0006958*complement activation, alternative pathway GO:0006957*cegulation of JNK cascade GO:0006958*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation, alternative pathway GO:0006957*complement activation of response to stimulus BP00107*Cytokine and chemokine mediated signaling pathwa GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response GO:0004508*rintlammatory response to stimulus BP00107*Cytokine and chemokine mediated signaling pathwa GO:00043123*positive regulation of rtspapaB kinase/NF-kappaB casci				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma memb GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex
Image: state s	GO:000911~response to wounding GO:0004955~immune response GO:0043068~positive regulation of programmed cell death GO:0010942~positive regulation of cell death GO:0044093~positive regulation of apoptosis BP00179:Apoptosis GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:000461~protein complex assembly GO:00065003~macromolecular complex sasembly GO:0065003~macromolecular complex subunit organization GO:0043933~macromolecular complex subunit organization GO:00051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00071:Proteolysis BP00102:Signal transduction GO:0002697~regulation of cell proliferation BP00016155~protein maturation by peptide bond cleavage GO:000243~leukocyte mediated immunity GO:0002443~leukocyte mediated immunity GO:000256~acute inflammatory response GO:0016165~protein maturation GO:000243~leukocyte mediated immunity GO:000243~leukocyte mediated immunity GO:000243~leukocyte mediated immunity GO:000256~acute inflammatory response GO:0016485~protein maturation GO:0002435~humoral immune response mediated by circulal GO:0002455~humoral immune response to stress GO:0002455~humoral immune response to stimulus BO:0006957~complement activation, classical pathway GO:0006957~complement activation, alternative pathway GO:0006957~insponse to bacterium GO:0006957~insponse to bacterium GO:00045087~inflammatory response GO:00045087~inflammatory response GO:00045087~inflammatory response GO:00045087~inflammatory response GO:00045087~inste immune response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa GO:0045087~inste immune response to stimulus BP00149:T-cell mediated immunity				t	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0005886~plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex GO:0005833~hemoglobin complex
Image: state s	GO:0009611~response to wounding GO:00043068~positive regulation of programmed cell death GO:0043066~positive regulation of cell death GO:0044093~positive regulation of cell death GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation GO:0042127~regulation of cell proliferation GO:0042127~regulation of cell proliferation GO:0065003~macromolecular complex assembly GO:0065003~macromolecular complex assembly GO:0065003~macromolecular complex subunit organization GO:0051240~positive regulation of multicellular organismal pr GO:0051240~positive regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697~regulation of immune effector process GO:0051605~protein maturation by peptide bond cleavage GO:0002526~acute inflammatory response GO:0002526~acute inflammatory response GO:0002443~leukocyte mediated immunity GO:0006485~protein maturation GO:0002443~leukocyte mediated immunity GO:0002443~leukocyte mediated immunity GO:0002443~leukocyte mediated immunity GO:0006958~complement activation, classical pathway GO:0002455~humoral immune response mediated by circulal GO:0006958~complement activation, alternative pathway GO:0006958~complement activation, alternative pathway GO:0006957~response to bacterium GO:0006957~complement activation, alternative pathway GO:0006957~complement activation, alternative pathway GO:0006957~complement activation, alternative pathway GO:0006957~complement activation, alternative pathway GO:00045087~innate immune response GO:00045087~innate immune response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa GO:00043123~positive regulation of I-kappaB kinase/NF-kappaB casc: BP00149:T-cell mediated immunity BP00253:Induction of apoptosis GO:00049615~response to virus					GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:000986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex GO:005833~hemoglobin complex GO:0042824~MHC class I peptide loading c
Image: state s	GO:0009615-immune response GO:0043068-positive regulation of programmed cell death GO:0043068-positive regulation of apoptosis BP00179:Apoptosis GO:0044093-positive regulation of apoptosis GO:0044093-positive regulation of molecular function GO:0042127-regulation of cell proliferation GO:0070271-protein complex assembly GO:0004611-protein complex assembly GO:0043933-macromolecular complex assembly GO:0005003-macromolecular complex subunit organization GO:0008285-negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697-regulation of cellular response to stress GO:0002697-regulation of cellular response GO:0002647-regulation of cellular response GO:0002647-regulation of cellular response GO:0002626-acute inflammatory response GO:0002526-acute inflammatory response GO:0002443-ieukocyte mediated immunity GO:0002449-iymphocyte mediated immunity GO:0002449-iymphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmpho	RWR	SHKDR		t 	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:000986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex GO:005833~hemoglobin complex GO:0042824~MHC class I peptide loading c
Image: state s	GO:0009615-immune response GO:0043068-positive regulation of programmed cell death GO:0043068-positive regulation of apoptosis BP00179:Apoptosis GO:0044093-positive regulation of molecular function GO:0042127-regulation of cell proliferation GO:0042127-regulation of cell proliferation GO:0006461-protein complex assembly GO:0007271-protein complex assembly GO:0005003-macromolecular complex subunit organization GO:00051240-positive regulation of cell proliferation BP00173:Cell surface receptor mediated signal transduction BP0012:Signal transduction GO:0002697-regulation of cellular response to stress GO:0002697-regulation of cellular response to stress GO:0002697-regulation of cellular response to stress GO:0002697-regulation of stress-activated protein kinase sig GO:0002697-regulation of stress-activated protein kinase sig GO:0002697-regulation of stress-activated protein kinase sig GO:00026443-leukocyte mediated immunity GO:0002526-acute inflammatory response GO:00070302-regulation of JNK cascade GO:00026449-lymphocyte mediated immunity GO:00026449-lymphocyte mediated immunity GO:00026449-lymphocyte mediated immunity GO:00046328-regulation of JNK					GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:000986~cell surface GO:0043235~receptor complex GO:0042612~MHC class I protein complex GO:0042101~T cell receptor complex GO:005833~hemoglobin complex GO:0042824~MHC class I peptide loading c
Image: stateImage: state </td <td>GO:0009615-immune response GO:00043068-positive regulation of programmed cell death GO:0043068-positive regulation of cell death GO:0043065-positive regulation of cell death GO:0044093-positive regulation of cell proliferation GO:0044093-positive regulation of cell proliferation GO:0042127-regulation of cell proliferation GO:006601-protein complex assembly GO:0070271 - protein complex assembly GO:0043933-macromolecular complex subunit organization GO:0051240-positive regulation of multicellular organismal pr GO:0002885-negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697-regulation of immune effector process GO:0002443-leukocyte mediated immunity GO:0002443-leukocyte mediated immunity GO:0002455-rotein maturation by peptide bond cleavage GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002452-regulation of stress-activated protein kinase sig GO:0002449-rositive regulation of response to stimulus GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:00046328-re</td> <td></td> <td></td> <td>deHKDR</td> <td>2-strategy</td> <td>GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0042612~MHC class I protein complex GO:0042612~MHC class I protein complex GO:0042833~hemoglobin complex GO:0042824~MHC class I peptide loading c GO:0042825~TAP complex</td>	GO:0009615-immune response GO:00043068-positive regulation of programmed cell death GO:0043068-positive regulation of cell death GO:0043065-positive regulation of cell death GO:0044093-positive regulation of cell proliferation GO:0044093-positive regulation of cell proliferation GO:0042127-regulation of cell proliferation GO:006601-protein complex assembly GO:0070271 - protein complex assembly GO:0043933-macromolecular complex subunit organization GO:0051240-positive regulation of multicellular organismal pr GO:0002885-negative regulation of cell proliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GO:0002697-regulation of immune effector process GO:0002443-leukocyte mediated immunity GO:0002443-leukocyte mediated immunity GO:0002455-rotein maturation by peptide bond cleavage GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002452-regulation of stress-activated protein kinase sig GO:0002449-rositive regulation of response to stimulus GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:0002449-ipmphocyte mediated immunity GO:00046328-re			deHKDR	2-strategy	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0042612~MHC class I protein complex GO:0042612~MHC class I protein complex GO:0042833~hemoglobin complex GO:0042824~MHC class I peptide loading c GO:0042825~TAP complex
Image: stateImage: stateImage	GC:0009611-response to wounding GC:00043065-positive regulation of programmed cell death GC:0043065-positive regulation of apoptosis BP00179:Apoptosis GC:0044093-positive regulation of molecular function GC:0044093-positive regulation of molecular function GC:000461-protein complex assembly GC:006461-protein complex assembly GC:0051240-positive regulation of cell proliferation BP00173:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GC:0002697-regulation of cell uproliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GC:0002697-regulation of cellular response to stress GC:00021605-protein maturation by peptide bond cleavage GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:000302-regulation of tress-activated protein kinase sig GC:0002449-lymphocyte mediated immunity GC:0006958-complement activation, classical pathway GC:0002455-humoral immune response mediated by circulat GC:0006957-complement activation, alternative pathway GC:0006957-complement activation, alternative pathway GC:0004557-humoral immune response mediated signaling pathwa GC:0004557-innate immune response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa: GC:0048584-positive regulation of 1-kappaB kinase/NF-kappaB casc: BP00149:12-regulation of 1-kappaB kinase/NF-kappaB casc: BP00149:12-regluation processing and pres			deHKDR		GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0042612~MHC class I protein complex GO:0042612~MHC class I protein complex GO:0042833~hemoglobin complex GO:0042824~MHC class I peptide loading c GO:0042825~TAP complex
Image: state s	GC:0009611-response to wounding GC:00043068-positive regulation of cell death GC:0043068-positive regulation of cell death GC:0044093-positive regulation of molecular function GC:0044093-positive regulation of molecular function GC:0044093-positive regulation of molecular function GC:006461-protein complex assembly GC:0070271-regulation of cell proliferation GC:0006461-protein complex assembly GC:0043933-macromolecular complex assubunit organization GC:00043933-macromolecular complex subunit organization GC:00051240-positive regulation of multicellular organismal pr GC:0008285-negative regulation of cell proliferation BP0013:Cell surface receptor mediated signal transduction BP00102:Signal transduction GC:0002697-regulation of immune effector process GC:0051605-protein maturation by peptide bond cleavage GC:0002697-regulation of istress-activated protein kinase sig GC:0002526-acute inflammatory response to stress GC:00116445-protein maturation GC:0002243-leukocyte mediated immunity GC:0002497-regulation of stress-activated protein kinase sig GC:00016445-protein maturation GC:0002467-regulation of stress-activated protein kinase sig GC:0002499-regulation of stress-activated protein kinase sig GC:0002499-lymphocyte mediated immunity GC:0006958-complement activation, alternative pathway GC:0006958-complement activation, classical pathway GC:0006958-complement activation, classical pathway GC:0006957-response to bacterium GC:0006954-inflammatory response GC:00048084-positive regulation of response to stimulus BPP0017:Cytokine and chemokine mediated signaling pathwa GC:00048084-positive regulation of response to stimulus BPP00132:2-regulation of 1-kappaB kinase/NF-kappaB casc: BP001149:T-cell mediated immunity BP00253:Induction of apoptosis GC:0004802-antigen processing and presentation of peptide GC:0004802-antigen processing and presentation of peptide GC:0015671-coxygen transport			deHKDR	2-strategy	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0042612~MHC class I protein complex GO:0042612~MHC class I protein complex GO:0042833~hemoglobin complex GO:0042824~MHC class I peptide loading c GO:0042825~TAP complex
Image: state s	GC:0009611-response to wounding GC:00043065-positive regulation of programmed cell death GC:0043065-positive regulation of apoptosis BP00179:Apoptosis GC:0044093-positive regulation of molecular function GC:0044093-positive regulation of molecular function GC:000461-protein complex assembly GC:006461-protein complex assembly GC:0051240-positive regulation of cell proliferation BP00173:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GC:0002697-regulation of cell uproliferation BP00103:Cell surface receptor mediated signal transduction BP00102:Signal transduction GC:0002697-regulation of cellular response to stress GC:00021605-protein maturation by peptide bond cleavage GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:0002443-leukocyte mediated immunity GC:000302-regulation of tress-activated protein kinase sig GC:0002449-lymphocyte mediated immunity GC:0006958-complement activation, classical pathway GC:0002455-humoral immune response mediated by circulat GC:0006957-complement activation, alternative pathway GC:0006957-complement activation, alternative pathway GC:0004557-humoral immune response mediated signaling pathwa GC:0004557-innate immune response to stimulus BP00107:Cytokine and chemokine mediated signaling pathwa: GC:0048584-positive regulation of 1-kappaB kinase/NF-kappaB casc: BP00149:12-regulation of 1-kappaB kinase/NF-kappaB casc: BP00149:12-regluation processing and pres			deHKDR	2-strategy	GO:0042470~melanosome GO:0042611~MHC protein complex GO:0009897~external side of plasma membra GO:0005615~extracellular space GO:0044421~extracellular region part GO:0044459~plasma membrane part GO:0005576~extracellular region GO:0005887~integral to plasma membrane GO:0031226~intrinsic to plasma membrane GO:0005886~plasma membrane GO:0009986~cell surface GO:0042612~MHC class I protein complex GO:0042612~MHC class I protein complex GO:0042833~hemoglobin complex GO:0042824~MHC class I peptide loading c GO:0042825~TAP complex

Molecular Function

				GO:0001871~pattern binding
				GO:0030247~polysaccharide binding
				GO:0005125~cytokine activity
				GO:0005539~glycosaminoglycan binding
				GO:0046983~protein dimerization activity
				GO:0030246~carbohydrate binding
				GO:0042802~identical protein binding
				GO:0042803~protein homodimerization activity
				GO:0008289~lipid binding
				GO:0020037~heme binding
				GO:0046906~tetrapyrrole binding
		L		MF00173:Defense/immunity protein
				GO:0003823~antigen binding
				MF00020:Peptide hormone
				MF00005:Cytokine receptor
				GO:0019955~cytokine binding
				GO:0019825~oxygen binding
				MF00174:Complement component
				MF00175:Major histocompatibility complex antigen
				GO:0046979~TAP2 binding
				GO:0046978~TAP1 binding
				GO:0046977~TAP binding
				GO:0015197~peptide transporter activity
				MF00006:Interleukin receptor
				GO:0042287~MHC protein binding
				GO:0042288~MHC class I protein binding
				GO:0030547~receptor inhibitor activity
				GO:0048019~receptor antagonist activity
				GO:0032393~MHC class I receptor activity
				GO:0005344~oxygen transporter activity
				GO:0050700~CARD domain binding
RWR	sHKDR	deHKDR	2-strategy	·

				GO:0043068~positive regulation of programmed cell death	Centula		ponent	<i>y</i>				
				GO:0010942~positive regulation of cell death GO:0043065~positive regulation of apoptosis					GO:0048	3770~pigment g	ranule	
				BP00179:Apoptosis						470~melanoso		
				GO:0044093~positive regulation of molecular function GO:0042127~regulation of cell proliferation					GO.00424	470~melanosoi	ne	
				GO:00042127~regulation of cell promeration GO:0006461~protein complex assembly			/		GO:0042	2611~MHC prote	ein complex	
				GO:0070271~protein complex biogenesis								_
				GO:0065003~macromolecular complex assembly			1		GO:0009	897~external si	ide of plasma m	embrane
				GO:0043933~macromolecular complex subunit organization GO:0051240~positive regulation of multicellular organismal pr					000005	C1E. ovtropollu		
				GO:0008285~negative regulation of cell proliferation					GO.0005	615~extracellul	ar space	
				BP00103:Cell surface receptor mediated signal transduction					GO:0044	421~extracellul	ar region part	
				BP00071:Proteolysis							0	
				BP00102:Signal transduction GO:0002697~regulation of immune effector process					GO:0044	459~plasma me	embrane part	
			4	GO:002697~regulation of infinitule enector process GO:0051605~protein maturation by peptide bond cleavage					00.0005			
				GO:0002443~leukocyte mediated immunity					GO:0005	576~extracellul	ar region	
				GO:0080135~regulation of cellular response to stress					GO:0005	887~integral to	plasma membra	ano
			<u> </u>	GO:0002526~acute inflammatory response					GO.0003	00/ milegrar to	plasma memori	ane
				GO:0016485~protein processing GO:0051604~protein maturation					GO:0031	226~intrinsic to	plasma membr	rane
				GO:0070302~regulation of stress-activated protein kinase sig								
				GO:0002449~lymphocyte mediated immunity					GO:0005	886~plasma me	embrane	
				GO:0046328~regulation of JNK cascade					GO:0000	986~cell surfac		
				GO:0006958~complement activation, classical pathway GO:0002455~humoral immune response mediated by circulat					GO.0009	900~cell sunac	e	
				GO:0006957~complement activation, alternative pathway					GO:0043	235~receptor c	omplex	
				GO:0006952~defense response	_					-	-	
				GO:0009617~response to bacterium			1		GO:0042	.612~MHC clas	s I protein comp	Jex
				GO:0006954~inflammatory response GO:0048584~positive regulation of response to stimulus					00.0040			
				BP00107:Cytokine and chemokine mediated signaling pathwa					GO:0042	2101~T cell rece	ptor complex	
				GO:0045087~innate immune response					GO:0005	833~hemoglobi	in complex	
				GO:0001819~positive regulation of cytokine production					u0.0000	000 memogiou	II complex	
				GO:0043123~positive regulation of I-kappaB kinase/NF-kapp GO:0043122~regulation of I-kappaB kinase/NF-kappaB casc					GO:0042	824~MHC clas	s I peptide loadi	ing comple
				BP00149:T-cell mediated immunity								
				BP00253:Induction of apoptosis					GO:0042	825~TAP comp	lex	
				GO:0009615~response to virus				O strate and				
				GO:0001816~cytokine production	RWR	sHKDR	deHKDR	2-strategy				
				GO:0048002~antigen processing and presentation of peptide GO:0019882~antigen processing and presentation								
				GO:0002474~antigen processing and presentation of peptide				- . .	_			
				GO:0070206~protein trimerization			Fold	d enrichme	ent			
				BP00150:MHCI-mediated immunity								
				GO:0015671~oxygen transport GO:0051953~negative regulation of amine transport								
				GO:0051953~negative regulation of amine transport GO:0016045~detection of bacterium					T			
				GO:0015669~gas transport	•	10	00			10	50	
RWR	sHKDR	deHKDR	2-strategy		0	10	20	;	30	40	>50	

Reference

- Can T, Çamoğlu, O., and Singh, A.K: Analysis of protein-protein interaction networks using random walk. In: In BIOKDD '05: Proceedings of the 5th international workshop on Bioinformatics: 2005; New York, USA: Association for Computing Machinery; 2005.
- Tong HH, Faloutsos C, Pan JY: Random walk with restart: fast solutions and applications. *Knowl Inf Syst* 2008, 14(3):327-346.
- Kohler S, Bauer S, Horn D, Robinson PN: Walking the interactome for prioritization of candidate disease genes. *American journal of human genetics* 2008, 82(4):949-958.
- 4. Chung F YS: Coverings, heat kernels and spanning trees. *Electron J Comb* 1999.
- Yang H KI, Lyu MR: Diffusion rank: a possible penicillin for web spamming.
 In: 30th annual international ACM SIGIR conference on Research and development in information retrieval: 2007; Amsterdam: ACM; 2007.
- Oti M, Snel B, Huynen MA, Brunner HG: Predicting disease genes using protein-protein interactions. *J Med Genet* 2006, 43(8).
- Nitsch D, Tranchevent LC, Thienpont B, Thorrez L, Van Esch H, Devriendt K, Moreau Y: Network analysis of differential expression for the identification of disease-causing genes. *PloS one* 2009, 4(5):e5526.
- Nitsch D, Goncalves JP, Ojeda F, de Moor B, Moreau Y: Candidate gene prioritization by network analysis of differential expression using machine learning approaches. *BMC bioinformatics* 2010, 11:460.