

# The Physiological Pathways Portal: A new interactive online tool providing efficient access to genomic and phenomic information through biological pathway analysis

Diane H. Munzenmaier, Melinda Dwinell, Victoria Petri, Mary Shimoyama, and Howard J. Jacob  
Department of Physiology, Human and Molecular Genetics Center, Medical College of Wisconsin, Milwaukee, Wisconsin

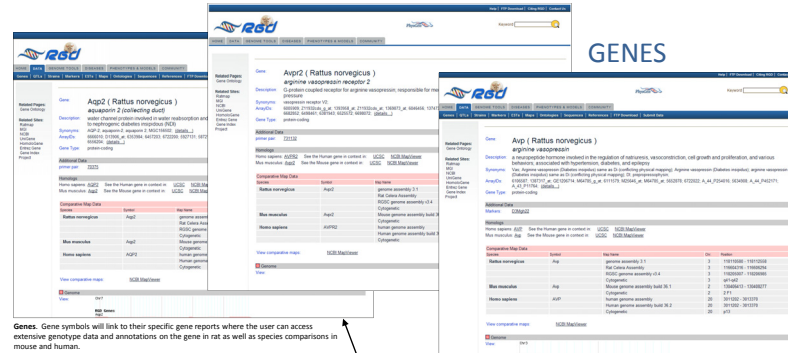
## Abstract

**Aim:** The Rat Genome Database (RGD, <http://rgd.mcw.edu>) has been developing tools and resources to aid investigators in the integration of genotype and phenotype data derived from rat research for the past 10 years. The new Physiological Pathway Portal consists of navigational hubs which allow physiologists to easily link phenotype and genotype data through intuitive mechanistic pathway flowcharts.

**Methods:** RGD has always contained valuable information for physiologists, however the focus has been primarily on genomic data, making it somewhat challenging for physiologists to navigate. The Physiological Pathway Diagrams provide a familiar map for the user, including links to relevant genotype and phenotype data through flowcharts depicting related physiological and regulatory mechanisms and pathways. Additionally, pharmacological actions and drug-gene interactions that influence these pathways are depicted within the diagrams and also link to related phenotype and genotype data. The diagrams are also linked to reports for individual genes involved in any of the pathways. In addition, links from the diagram to phenotype data allow the user to compare physiological measurements across multiple rat strains under a variety of experimental conditions or to access strain-specific variation data such as SNPs and other polymorphisms for direct linkage of the genotype and phenotype data. Examples of the types of pathways included in this portal are varied and complex regulatory and physiological systems such as blood pressure regulation, hematopoiesis and angiogenesis.

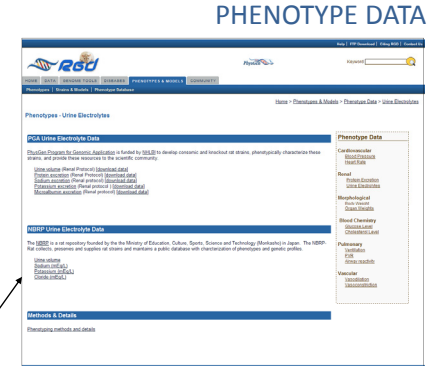
**Conclusion:** The new Physiological Pathways Portal at RGD promises to be an effective and user-friendly means to access and review physiological and genomic data for researchers who use the rat as a model to study specific physiological processes and pharmacological modulation of these processes.

Physiological Pathways are graphical depictions of multi-organ biological processes that provide the user with a systems biology approach to RGD. Physiologists will find the Physiological Pathways logically organized making it easy to locate and access pertinent information. Discrete steps within each process are arranged temporally and regionally with organ/tissue location of each step indicated by symbol and text label for clarity. Each pathway consists of clickable elements leading to information regarding genes involved in the process, experimental data at specific points in the process, associated diseases due to dysfunction of a step in the process, genetic strains that have been characterized as disease models, drugs classes that can favorably or adversely affect the process, and associated intracellular pathways.



**GENES**

The screenshots show the RGD Genes page for *Aqp2* (Rattus norvegicus) and *Avp* (Rattus norvegicus). The *Aqp2* page includes a description of the aquaporin-2 channel, its function in water reabsorption, and a list of associated diseases and phenotypes. The *Avp* page includes a description of the arginine vasopressin receptor, its function in regulating physiological processes, and a list of associated diseases and phenotypes.

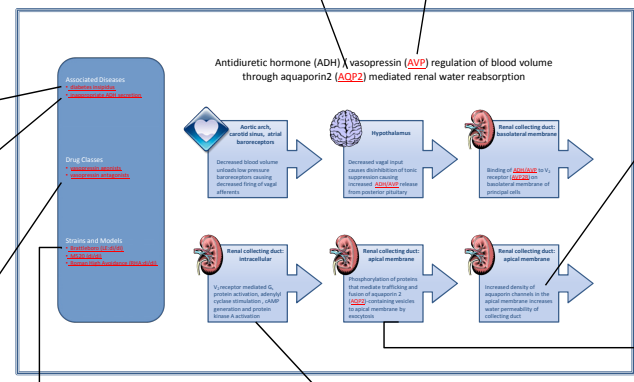
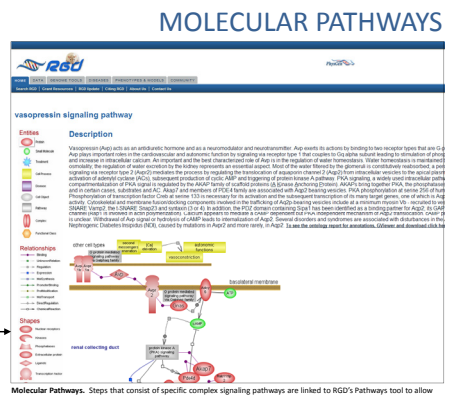


**PHENOTYPE DATA**

The screenshot shows the RGD Phenotype Data page for *Aqp2*. It displays a list of phenotypes associated with the gene, including "Renal collecting duct: aquaporin-2 expression" and "Renal collecting duct: aquaporin-2 localization". The page also includes a section for "Phenotypes & Models" where users can click on discrete functional steps in the process to view the associated page of the new Phenotypes & Models tool.

Genes. Gene symbols will link to their specific gene reports where the user can access extensive genotype data and annotations on the gene in rat as well as species comparisons in mouse and human.

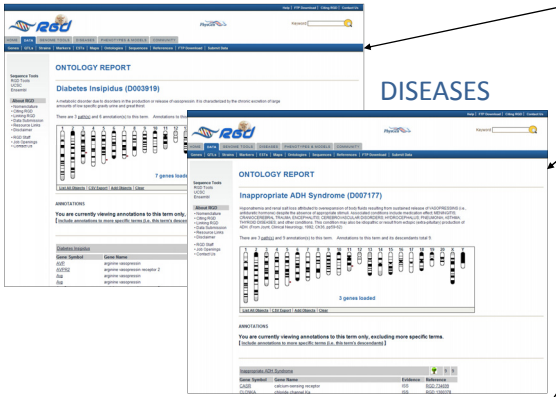
Phenotypes & Models. Clicking on discrete functional steps in the process takes the user to the associated page of the new Phenotypes & Models tool where specific values for related phenotypes can be accessed.

**MOLECULAR PATHWAYS**

The screenshot shows the RGD Molecular Pathways page for the "vasopressin signaling pathway". It includes a description of the pathway, a diagram of the signaling cascade, and a list of associated diseases and phenotypes. The diagram shows AVP binding to its receptor, activating G-proteins, which then activate phospholipase C-beta, leading to the production of diacylglycerol and inositol trisphosphate, which activate protein kinase C and calcium release, respectively.

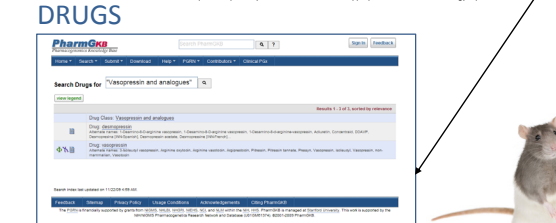
Molecular Pathways. Steps that consist of specific complex signaling pathways are linked to RGD's pathway tool to allow the user to drill down further to access information on the individual molecular signaling components of the pathways.



**DISEASES**

The screenshots show the RGD Diseases and Strain Reports pages. The Diseases page lists "Diabetes Insipidus (D003918)" and "Inappropriate ADH Syndrome (D007177)", providing links to associated physiological pathways and genomic data. The Strain Reports page shows details for the "Wistar-Kyoto" strain, including its genetic background and associated phenotypes.

Diseases. The sidebar of each physiological pathway contains useful links to information associated with the pathway. For instance, diseases known to be associated with dysfunction of a step or steps in the pathway are listed and link to the appropriate RGD disease ontology reports.



**DRUGS**

The screenshot shows the RGD Drugs page, which lists various drug classes and their associated physiological pathways. The sidebar lists classes of pharmaceuticals that are used in rat research and clinically, such as "Vasopressin analogs" and "Osmotic diuretics".

Drugs. The sidebar lists generic classes of pharmaceuticals that are used in rat research and clinically. The classes link to the PharmGKB ([www.pharmgkb.org](http://www.pharmgkb.org)) website where information on specific drugs in each class can be found.



**MODELS**

The screenshot shows the RGD Models page, which lists specific rat strains that have been characterized as disease models. The sidebar indicates strains that have been characterized as suitable rat research models for diseases associated with the physiological pathway of interest. For example, the "Wistar-Kyoto" strain is linked to the "Diabetes Insipidus" model.

Models. The sidebar also indicates specific strains that have been characterized as suitable rat research models for diseases associated with the physiological pathway of interest. These strain names link to their strain report page in RGD.



**SIGNALING PATHWAYS**

The screenshot shows the RGD Signaling Pathways page for the "protein kinase A (PKA) signaling pathway". It includes a description of the pathway, a diagram of the signaling cascade, and a list of associated diseases and phenotypes. The diagram shows a ligand binding to a G-protein coupled receptor, activating G-proteins, which then activate phospholipase C-beta, leading to the production of diacylglycerol and inositol trisphosphate, which activate protein kinase C and calcium release, respectively.

Signaling pathways. Steps that consist of classic second messenger intracellular signaling pathways link to RGD's existing Pathways tool to give the user a closer look.

## Conclusion

The new *Physiological Pathways* portal serves as a gateway into RGD for researchers in the biological sciences searching for gene function annotation and links to information regarding genotypes, phenotypes and disease associations. It is organized in a systems biology context through sequential temporal and regional steps in physiological processes with links to gene reports, phenotype data, intracellular molecular pathways. The genetics researcher will also find it a valuable resource for determining the functional aspects and potential interactions of a particular gene of interest. New pathways will continually be added on a regular basis.

Physiological Pathways seamlessly ties together many of the best features of RGD into a functionally coherent access point making it easier and more efficient than ever to navigate through the diverse but extensive wealth of genomic and phenomic information that is RGD.