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Featured Resource: The BioSystems Database of Biological Pathways

NCBI BioSystems is a new database that collects information on interacting sets of biomolecules involved in metabolic and signaling pathways, disease states, and other biological processes. BioSystems currently contains biological pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the EcoCyc (*Escherichia coli* K-12 MG1655) subset of the BioCyc databases and is designed to accommodate other data in the future. BioSystems is fully integrated with other databases in the Entrez system with links to related literature, genes, protein sequences, structures, chemical data, and to related BioSystems. Along with links to related data at the NCBI site, each BioSystem record provides links to detailed diagrams and annotations for individual pathways on the Web sites of the source databases. BioSystems adds an important new aspect to the NCBI system by linking many different kinds of molecular records in biochemical pathways and providing means to compare these pathways across organisms.

Searching BioSystems

BioSystems is available as part of the NCBI Entrez system and can be searched directly from the database page:

www.ncbi.nlm.nih.gov/BioSystems/

As with other Entrez databases, field-restricted queries in BioSystems give more precise search results. Many of the fields that work in the other Entrez molecular databases such as Organism and Title also are useful in BioSystems. All of the available fields can be browsed through the Preview/Index tab on the search page. The Limits tab provides a simple way to limit to certain types of records through pre-set fields. For example, the search can be limited to a specific source database, currently KEGG or EcoCyc. There is also a checkbox that allows restricting to organism-specific BioSystems, those with links to molecular records for a single species, or conserved BioSystems that group together orthologous organism specific pathways derived from KEGG reference pathways.

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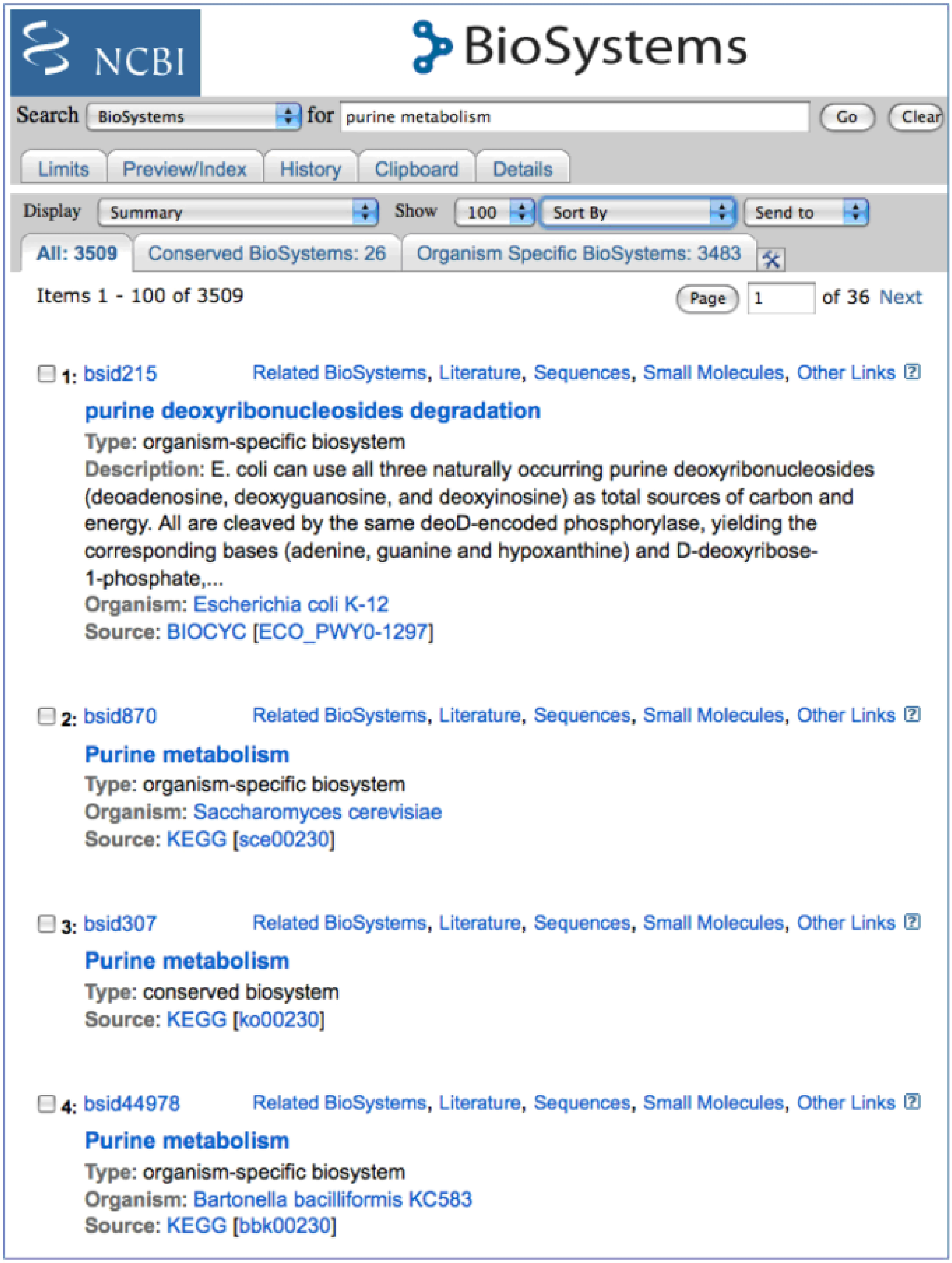

Search BioSystems for purine metabolism

Display Summary Show 100

All: 3509 Conserved BioSystems: 26 Organism Specific BioSystems: 3483

Items 1 - 100 of 3509

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□ 1: bsid215 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

purine deoxyribonucleosides degradation

Type: organism-specific biosystem

Description: E. coli can use all three naturally occurring purine deoxyribonucleosides (deoadenosine, deoxyguanosine, and deoxyinosine) as total sources of carbon and energy. All are cleaved by the same deoD-encoded phosphorylase, yielding the corresponding bases (adenine, guanine and hypoxanthine) and D-deoxyribose-1-phosphate,...

Organism: Escherichia coli K-12

Source: BIOCYC [ECO_PWY0-1297]

□ 2: bsid870 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Purine metabolism

Type: organism-specific biosystem

Organism: Saccharomyces cerevisiae

Source: KEGG [sce00230]

□ 3: bsid307 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Purine metabolism

Type: conserved biosystem

Source: KEGG [ko00230]

□ 4: bsid44978 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Purine metabolism

Type: organism-specific biosystem

Organism: Bartonella bacilliformis KC583

Source: KEGG [bbk00230]

Figure 1. **Search results in BioSystems using purine metabolism as a query.** Both EcoCyc (BioCyc) and KEGG source records are found. The Conserved BioSystems filter tab at the top of the results selects KEGG reference pathways that summarize orthologous pathways for large numbers of organisms.

Limiting to Conserved BioSystems provides more concise results and access to an overall summary of the pathway in all organisms. For example, a search with the phrase "purine metabolism" retrieves 3,509 records while limiting to conserved BioSystems or clicking the Conserved BioSystems filter tab provides a more concise set of only 26 records (Figure 1). As another example, the organism-specific record for purine metabolism in mouse is found directly with the following field-restricted query.

purine metabolism[Title] AND mouse[Organism]

BioSystems Records: Photosynthesis

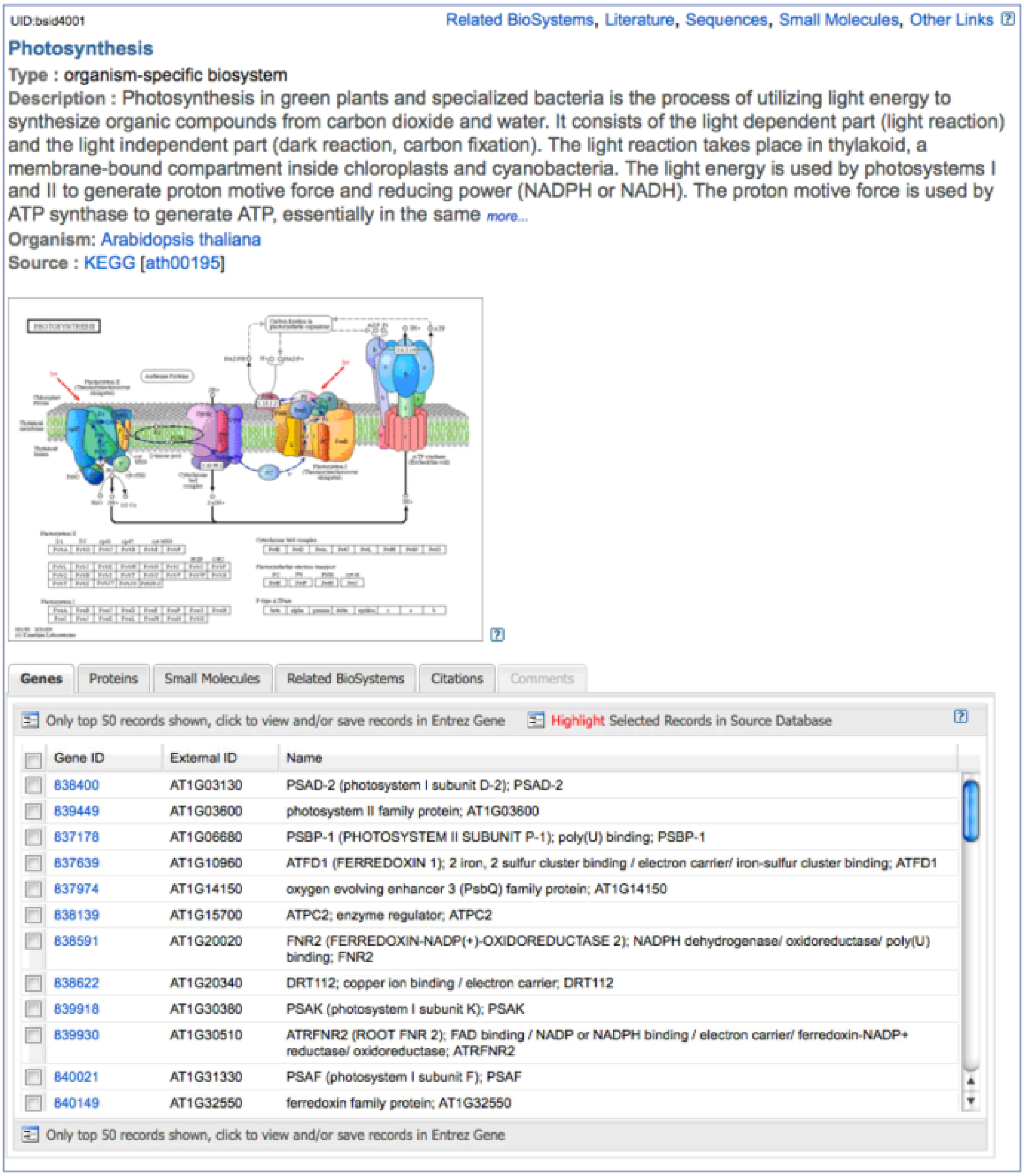
The BioSystems database currently contains over 95 thousand pathways from the KEGG database including 255 conserved BioSystems and 286 *Escherichia coli* K-12 pathways from the EcoCyc portion of the BioCyc database. Figure 2 shows the BioSystems organism-specific record for photosynthesis from *Arabidopsis thaliana* (BioSystems ID 4001). The record has a description of the process from the source database, a thumbnail graphic that links to the larger diagram in the KEGG database, and a Tabbed Table of components and other aspects of the pathway (Genes, Proteins, Small Molecules, Related BioSystems, Citations and Comments). These components link to records in the NCBI Gene, Protein, PubChem, BioSystems, and PubMed databases.

Pathway Diagram

The full photosynthesis diagram is available at the KEGG site and is linked to the thumbnail image in the BioSystems record. The cartoon of the chloroplast thylakoid membrane at the KEGG site shows the multi-subunit protein complexes of the photosynthetic system (photosystems I and II, cytochrome b6/f, electron transport system, and the f-type ATPase). The boxes in the tables below the cartoon represent the genes or protein components of the system. Each of the green-filled boxes represents one or more *Arabidopsis* genes. The unfilled boxes represent genes or functions that are not known from *Arabidopsis*. In this case these missing components (PsbU, PsbV, PsbX, Psb28-2, PsaM, PsaX, PetL, and PetM) are specific to certain cyanobacterial systems and are available in the corresponding Conserved BioSystem or reference pathway.

Tabbed Table of BioSystem Components

The Tabbed Table provides access to the components and other information linked to the pathway in the NCBI databases. Tabs include Genes, Proteins, Small Molecules, Related BioSystems, and Citations. The *Arabidopsis* genes and proteins corresponding to the filled boxes in the pathway diagram are listed in the Genes and Proteins tabbed sections of the table. The Small Molecule tab provides access to substrates, inhibitors, cofactors, and other non-protein entities involved in pathways from the NCBI PubChem database. Clicking on any entry will link to the corresponding Gene, Protein, or PubChem record. The link at the top of the table retrieves all records in the active tab. For example, clicking the top link in the Genes tab easily retrieves all 73 *Arabidopsis* genes involved in the photosynthetic pathway; clicking this link in the Small Molecules tab retrieves cofactors



UID:bsid4001

Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Photosynthesis

Type : organism-specific biosystem

Description : Photosynthesis in green plants and specialized bacteria is the process of utilizing light energy to synthesize organic compounds from carbon dioxide and water. It consists of the light dependent part (light reaction) and the light independent part (dark reaction, carbon fixation). The light reaction takes place in thylakoid, a membrane-bound compartment inside chloroplasts and cyanobacteria. The light energy is used by photosystems I and II to generate proton motive force and reducing power (NADPH or NADH). The proton motive force is used by ATP synthase to generate ATP, essentially in the same *more...*

Organism: Arabidopsis thaliana

Source : KEGG [ath00195]

Genes | Proteins | Small Molecules | Related BioSystems | Citations | Comments

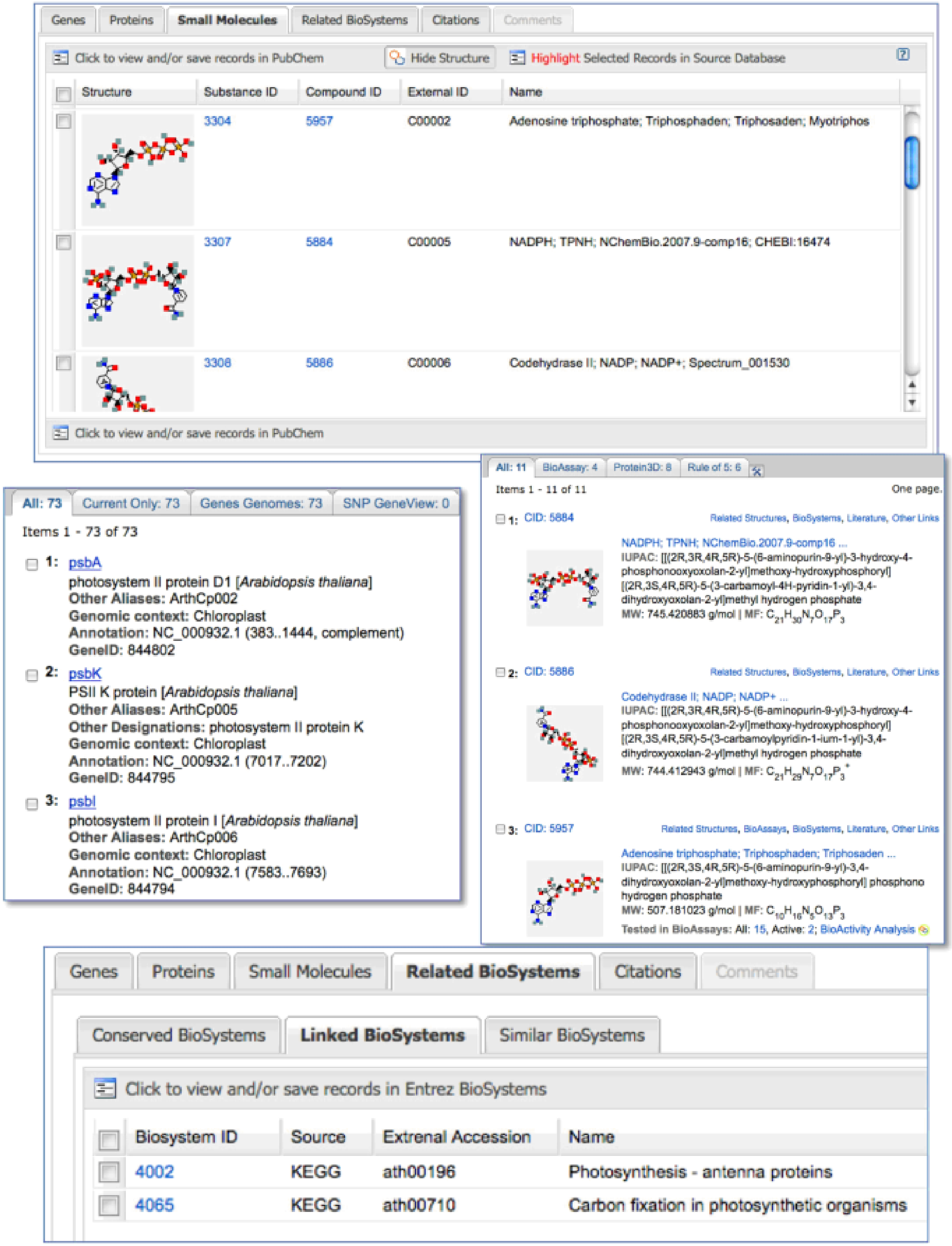
Only top 50 records shown, click to view and/or save records in Entrez Gene   Highlight Selected Records in Source Database

□	Gene ID	External ID	Name
□	838400	AT1G03130	PSAD-2 (photosystem I subunit D-2); PSAD-2
□	839449	AT1G03600	photosystem II family protein; AT1G03600
□	837178	AT1G06680	PSBP-1 (PHOTOSYSTEM II SUBUNIT P-1); poly(U) binding; PSBP-1
□	837639	AT1G10960	ATFD1 (FERREDOXIN 1); 2 iron, 2 sulfur cluster binding / electron carrier/ iron-sulfur cluster binding; ATFD1
□	837974	AT1G14150	oxygen evolving enhancer 3 (PsbQ) family protein; AT1G14150
□	838139	AT1G15700	ATPC2; enzyme regulator; ATPC2
□	838591	AT1G20020	FNR2 (FERREDOXIN-NADP(+)-OXIDOREDUCTASE 2); NADPH dehydrogenase/ oxidoreductase/ poly(U) binding; FNR2
□	838622	AT1G20340	DRT112; copper ion binding / electron carrier; DRT112
□	839918	AT1G30380	PSAK (photosystem I subunit K); PSAK
□	839930	AT1G30510	ATRFNR2 (ROOT FNR 2); FAD binding / NADP or NADPH binding / electron carrier/ ferredoxin-NADP+ reductase/ oxidoreductase; ATRFNR2
□	840021	AT1G31330	PSAF (photosystem I subunit F); PSAF
□	840149	AT1G32550	ferredoxin family protein; AT1G32550

Only top 50 records shown, click to view and/or save records in Entrez Gene

Figure 2. The full BioSystems record for photosynthesis for *Arabidopsis thaliana*. The description and thumbnail image are from the KEGG database and link to the KEGG site. The Tabbed Table at the bottom provides access to corresponding Gene, Protein, Small Molecule (PubChem), Related BioSystem, and Citations (PubMed) records for components of the pathway at NCBI

and substrates from PubChem (Figure 3). The Related BioSystems tab expands to display three types of related BioSystems: Linked BioSystems, Similar BioSystems, and Conserved BioSystems. Linked BioSystems are pathways that interact with the current pathway often


Genes
Proteins
Small Molecules
Related BioSystems
Citations
Comments
Click to view and/or save records in PubChem
Hide Structure
Highlight Selected Records in Source Database

□ Structure	Substance ID	Compound ID	External ID	Name
□	3304	5957	C00002	Adenosine triphosphate; Triphosphaden; Triphosaden; Myotriphos
□	3307	5884	C00005	NADPH; TPNH; NChemBio.2007.9-comp16; CHEBI:16474
□	3308	5886	C00006	Codehydrase II; NADP; NADP+; Spectrum_001530

Click to view and/or save records in PubChem
All: 73
Current Only: 73
Genes Genomes: 73
SNP GeneView: 0

Items 1 - 73 of 73

□ 1: psbA
photosystem II protein D1 [*Arabidopsis thaliana*]
Other Aliases: ArthCp002
Genomic context: Chloroplast
Annotation: NC_000932.1 (383..1444, complement)
GeneID: 844802

□ 2: psbK
PSII K protein [*Arabidopsis thaliana*]
Other Aliases: ArthCp005
Other Designations: photosystem II protein K
Genomic context: Chloroplast
Annotation: NC_000932.1 (7017..7202)
GeneID: 844795

□ 3: psbI
photosystem II protein I [*Arabidopsis thaliana*]
Other Aliases: ArthCp006
Genomic context: Chloroplast
Annotation: NC_000932.1 (7583..7693)
GeneID: 844794

Items 1 - 11 of 11 One page.

□ 1: CID: 5884 Related Structures, BioSystems, Literature, Other Links
NADPH; TPNH; NChemBio.2007.9-comp16 ...
IUPAC: [[(2R,3R,4R,5R)-5-(6-aminopurin-9-yl)-3-hydroxy-4-phosphonooxyoxolan-2-yl]methoxy-hydroxyphosphoryl] [(2R,3S,4R,5R)-5-(3-carbamoyl-4H-pyridin-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl hydrogen phosphate
MW: 745.420883 g/mol | MF: $C_{21}H_{30}N_7O_{17}P_3$

□ 2: CID: 5886 Related Structures, BioSystems, Literature, Other Links
Codehydrase II; NADP; NADP+ ...
IUPAC: [[(2R,3R,4R,5R)-5-(6-aminopurin-9-yl)-3-hydroxy-4-phosphonooxyoxolan-2-yl]methoxy-hydroxyphosphoryl] [(2R,3S,4R,5R)-5-(3-carbamoylpyridin-1-ium-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl hydrogen phosphate
MW: 744.412943 g/mol | MF: $C_{21}H_{29}N_7O_{17}P_3^+$

□ 3: CID: 5957 Related Structures, BioAssays, BioSystems, Literature, Other Links
Adenosine triphosphate; Triphosphaden; Triphosaden ...
IUPAC: [[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl] phosphono hydrogen phosphate
MW: 507.181023 g/mol | MF: $C_{10}H_{16}N_5O_{13}P_3$
Tested in BioAssays: All: 15, Active: 2; BioActivity Analysis

□ Biosystem ID	Source	Extrenal Accession	Name
□ 4002	KEGG	ath00196	Photosynthesis - antenna proteins
□ 4065	KEGG	ath00710	Carbon fixation in photosynthetic organisms

Figure 3. The Tabbed Table and linked records from the *Arabidopsis* photosynthesis BioSystem. *Top panel.* Tabbed Table with the Small Molecules tab selected showing PubChem records linked to the pathway. *Center panel.* Linked Gene and PubChem records in the corresponding Entrez databases. All genes and cofactors are available in Entrez. *Bottom panel.* The Related BioSystems tab with the Linked BioSystems tab selected showing the two systems or pathways, antenna proteins and carbon fixation, that connect to photosynthesis.

providing substrates or receiving products of the current pathway. In this case, these are the antennal proteins light collecting system of photosynthesis (BioSystems ID 4002) and carbon fixation in photosynthetic organisms (BioSystems ID 4065). Similar BioSystems are pathways that share at least one identical protein sequence from the same source organism. Oxidative phosphorylation (BioSystems ID 4000) is the Similar Pathway to photosynthesis because it shares the subunits of the f-type ATPase. Finally, the Conserved BioSystem (BioSystems ID 340) is the reference pathway record for photosynthesis that gathers all orthologous pathways. The Conserved BioSystem includes the cyanobacterial components represented by unfilled boxes in the organism-specific pathway at the KEGG site. The remaining populated tab for the photosynthesis record, Citations, provides literature citations from the source database with links to the corresponding records in PubMed.

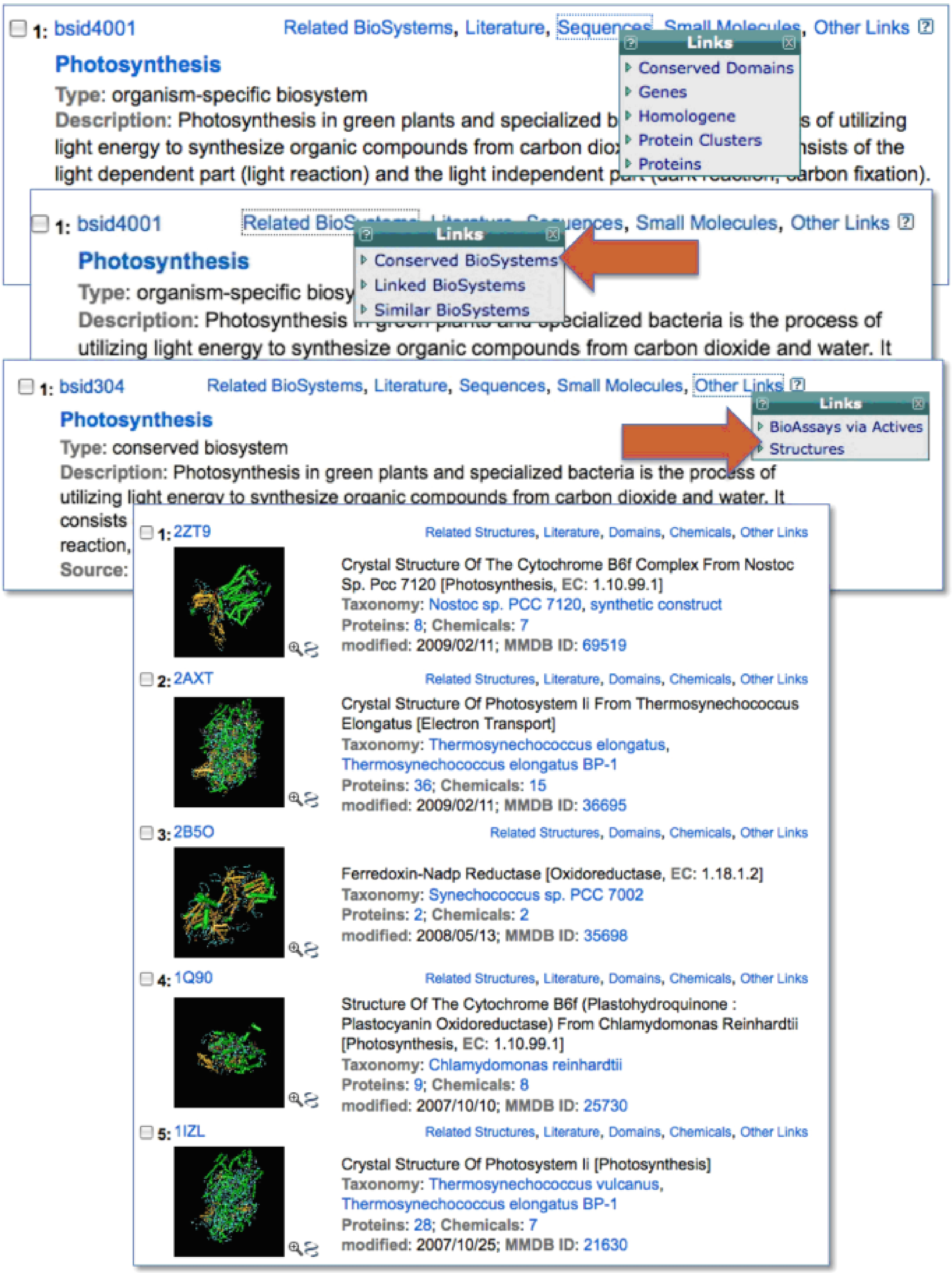
Links Menus: Related Data

In addition to the linked data available in the Tabbed Table, each BioSystems record has related data available as Links menus at the upper right of the summary or full BioSystems record (Figure 4). These are the Related BioSystems, Literature, Sequences, Small Molecules, and Other Links menus. The BioSystems, Literature, and Small Molecules menus access the same related data available in the Tabbed Table. Additional related data in the Sequences menu that are not available in the Tabbed Table are HomoloGene, Protein Clusters, and Conserved Domain records that are linked from the proteins in the pathway.

The HomoloGene and Protein Clusters related data identify homologs from selected eukaryotic and microbial genomes and allow comparisons of pathways across taxa. The linked Conserved Domains can give additional structural and functional information about the proteins in the pathway. The Other Links menu connects the BioSystem to the PubChem BioAssay database for small molecules in the pathway that have been classified as active in one of the assays. There are also links to the NCBI taxonomy database for organism-specific BioSystems, and to the Structure database if any of the proteins in the pathway are linked to a three-dimensional structure. The following example shows how to use these related data to find structures for the photosynthetic complexes starting from the *Arabipdopsis* organism-specific record.

Example: Using Related Data to Find Three-Dimensional Structures

The links to data available through the Tabbed Table and Links menus can be used to find important related data such as homologous pathways, genes, and proteins in other species as well additional structural and functional information. For example, using the Tabbed Table and the Links menus, it is easy to find the three-dimensional structures of some of the protein complexes involved in photosynthesis. As mentioned previously, structure records are linked to the BioSystems pathway through the “Other Links” menu. However, the *Arabidopsis* photosynthesis pathway has no direct structure links because none of the photosynthesis proteins with structures are from this species. Following the Related BioSystems link to the Conserved BioSystem gives access to proteins from orthologous



□ 1: bsid4001 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Photosynthesis

Type: organism-specific biosystem

Description: Photosynthesis in green plants and specialized b… s of utilizing light energy to synthesize organic compounds from carbon dio… nsists of the light dependent part (light reaction) and the light independent p… arbon fixation).

Links
- Conserved Domains
- Genes
- Homologene
- Protein Clusters
- Proteins

□ 1: bsid4001 Related BioS… …ences, Small Molecules, Other Links

Photosynthesis

Type: organism-specific biosy…

Description: Photosynthesis … ecialized bacteria is the process of utilizing light energy to synthesize organic compounds from carbon dioxide and water. It

Links
- Conserved BioSystems
- Linked BioSystems
- Similar BioSystems

□ 1: bsid304 Related BioSystems, Literature, Sequences, Small Molecules, Other Links

Photosynthesis

Type: conserved biosystem

Description: Photosynthesis in green plants and specialized bacteria is the process of utilizing light energy to synthesize organic compounds from carbon dioxide and water. It consists … reaction, …

Source: …

Links
- BioAssays via Actives
- Structures

□ 1: 2ZT9 Related Structures, Literature, Domains, Chemicals, Other Links

Crystal Structure Of The Cytochrome B6f Complex From Nostoc Sp. Pcc 7120 [Photosynthesis, EC: 1.10.99.1]
Taxonomy: Nostoc sp. PCC 7120, synthetic construct
Proteins: 8; Chemicals: 7
modified: 2009/02/11; MMDB ID: 69519

□ 2: 2AXT Related Structures, Literature, Domains, Chemicals, Other Links

Crystal Structure Of Photosystem Ii From Thermosynechococcus Elongatus [Electron Transport]
Taxonomy: Thermosynechococcus elongatus, Thermosynechococcus elongatus BP-1
Proteins: 36; Chemicals: 15
modified: 2009/02/11; MMDB ID: 36695

□ 3: 2B5O Related Structures, Domains, Chemicals, Other Links

Ferredoxin-Nadp Reductase [Oxidoreductase, EC: 1.18.1.2]
Taxonomy: Synechococcus sp. PCC 7002
Proteins: 2; Chemicals: 2
modified: 2008/05/13; MMDB ID: 35698

□ 4: 1Q90 Related Structures, Literature, Domains, Chemicals, Other Links

Structure Of The Cytochrome B6f (Plastohydroquinone : Plastocyanin Oxidoreductase) From Chlamydomonas Reinhardtii [Photosynthesis, EC: 1.10.99.1]
Taxonomy: Chlamydomonas reinhardtii
Proteins: 9; Chemicals: 8
modified: 2007/10/10; MMDB ID: 25730

□ 5: 1IZL Related Structures, Literature, Domains, Chemicals, Other Links

Crystal Structure Of Photosystem Ii [Photosynthesis]
Taxonomy: Thermosynechococcus vulcanus, Thermosynechococcus elongatus BP-1
Proteins: 28; Chemicals: 7
modified: 2007/10/25; MMDB ID: 21630

Figure 4. The Links menus from BioSystems records. The Sequences menu has Conserved Domains, HomoloGene, and Protein Clusters links in addition to the Proteins that are also in the Tabbed Table. Following the Conserved BioSystems link (*left arrow*) from the Arabidopsis record allows access through the Other Links menu to protein structures (*right arrow*) from the reference pathway for photosynthesis.

pathways in all species including those with structure records. The Conserved BioSystem for photosynthesis (BioSystems ID 340) has links to five structures of photosynthetic protein complexes through the Other Links menu (Figure 4). Four of these structures are from cyanobacteria, and one is from the green alga, *Chlamydomonas reinhardtii*.

Summary

The BioSystems database adds a new dimension to NCBI resources by connecting molecular, bioassay, and literature data to biological pathways and processes. This enables searches that for the first time can find all gene, protein records, and small molecules in a pathway for a particular organism. Moreover, integration with other NCBI databases allows comparisons of pathways across taxa and provides access to other data on structure and function of the biomolecules involved. Expanding the coverage of the Entrez system to pathways provides new connections among databases that should greatly increase the power of Entrez as a discovery system.

New Databases and Tools

New BankIt Submission Tool

A new version of the BankIt sequence submission tool is available for testing. The new tool will eventually replace current version of BankIt after the test period. Please see the New BankIt page for more information: www.ncbi.nlm.nih.gov/WebSub/?tool=genbank

Bookshelf

The book, *Familial Cancer Syndromes* has been added to the NCBI Bookshelf. To browse this book go to www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=famcan

Microbial Genomes

Twenty-one finished microbial genomes were released between May 29 and July 6, 2009. The original sequence data files submitted to GenBank/EMBL/DDBJ are available on the FTP site: ftp.ncbi.nih.gov/genbank/genomes/Bacteria/. The RefSeq provisional versions of these genomes are also available: ftp.ncbi.nih.gov/genomes/Bacteria/.

GenBank News

GenBank release 172.0 is available on the NCBI Web and FTP sites. The current release includes information available as of June 10, 2009. Release notes are available on the on the NCBI ftp site: ftp.ncbi.nih.gov/genbank/gbrel.txt

NCBI is considering ceasing support for the index files; affected users are encouraged to review the discussion of this change in the release notes and provide comments to the GenBank group.

Updates and Enhancements

PubChem

The American Library Association has selected PubChem as one of the Best Free Reference Web Sites 2009. More PubChem announcements are available at: pubchem.ncbi.nlm.nih.gov/pcnews.html and as an RSS feed.

BLAST

As previewed in the May 2009 NCBI News, COBALT multiple-sequence alignments can now be generated from protein BLAST results by clicking on the "Multiple Alignment" link. A direct submission form for generating protein multiple alignments using COBALT is also available in the Specialized BLAST section of the BLAST Homepage. The BLAST News page provides additional details about COBALT. The BLAST homepage also provides a "Tip of the Day" for more efficient use of the BLAST tool.

Announce Lists and RSS Feeds

Fifteen topic-specific mailing lists are available which provide email announcements about changes and updates to NCBI resources including dbGaP, BLAST, GenBank, and Sequin. The various lists are described on the Announcement List summary page: www.ncbi.nlm.nih.gov/Sitemap/Summary/email_lists.html. To receive updates on the *NCBI News*, please see: www.ncbi.nlm.nih.gov/About/news/announce_submit.html

Seven RSS feeds are now available from NCBI including news on PubMed, PubMed Central, NCBI Bookshelf, PubChem, LinkOut, HomoloGene, and NCBI Announce. Please see: www.ncbi.nlm.nih.gov/feed/

Comments and questions about NCBI resources may be sent to NCBI at: info@ncbi.nlm.nih.gov, or by calling 301-496-2475 between the hours of 8:30 a.m. and 5:30 p.m. EST, Monday through Friday.