

Training course on
the BIOBASE Knowledge Library™
and
the ExPlain™ Analysis System

BKL session

July 2010

本セッションでは、BKL データベースに慣れていただく目的で、機能の一部のご使用方法を紹介いたします。HELP アイコンをクリックして頂くと、詳細なマニュアルがご覧いただけますが、まずは本セッションの内容に沿って BKL の一部機能を使用してみてください。



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Overview



This session provides an introduction to contents and interface of the BIOBASE Knowledge Library™.

After encouraging to try out the possibilities of the Ontology Search tool, we are going to take a tour through the many different ways in which the BKL presents and connects biological knowledge and in which it provides means to access that knowledge.

Starting with from the Quick Search functionality, we visit the information curated for main concepts of interest. These are compiled in Disease Reports, Locus Reports and Pathways, for which the BKL also offers report forms.

Overview of the BKL™ interface

Quick search の以下の 5 カテゴリーは、最も使用頻度が高いものです。

The screenshot displays the BIOBASE Knowledge Library interface. The main content area is titled "Quick search for genes, diseases, ..." and features a "Quick Search" section with five category buttons: "Gene/Protein", "Disease", "Pathway", "Drug", and "Keyword". Below these buttons is a search input field with radio buttons for "Name" and "Identifier", a "Set species preferences" link, and a "Search all species" dropdown menu. A "Find" button is located at the bottom of the search section.

The left sidebar contains several search and tool options, with "Quick Search" highlighted by a red circle and a red line pointing to the "Quick Search" button in the main content area. The sidebar options include:

- Quick Search
- Advanced Search
- TRANSFAC Module Search
- Ontology Search
- Upload Gene List
- Help
- Tools
 - Pathfinder
 - BLAST
 - MATCH
 - ExPiate
- Saved Search Results

Below the sidebar, there is a promotional box titled "Get the most out of your subscription!" with a "Learn more about ..." link. The box lists three features:

- Using the Set Analysis feature of the Ontology tool to identify statistically over-represented term assignments
- Exporting term assignments for genes and proteins into Excel spreadsheets for further analysis
- Overlaying disease and drug assignments on custom-built signaling networks

Text overlays on the left side of the image describe the sidebar categories:

- Tool bar offering
- Advanced search interfaces
- Ontology search
- Gene list query
- Analysis tools like Pathfinder, BLAST, MATCH

Ontology Search

Ontology Search では、複雑なドリル検索が可能です。
以下の日本語の説明サイトでご使用方法をご確認ください。

Try the powerful BKL Ontology Search to *drill* through manually curated knowledge and get the protein list you are looking for.

<http://www.biobase.co.jp/Pages/News/news%20regarding%20BKL.html> に Ontology search の方法を日本語で説明しています。
古いバージョンの BKL ですが基本的に、使用方法は同じです。インターフェイスが変更されています。

BIOBASE Knowledge Library Logout

Ontology Search Reset

Quick Search
Advanced Search
TRANSFAC Module Search
Ontology Search
Upload Gene List

Help

Tools
Pathfinder BLAST
MATCH Explain
Saved Search Results

Basic Query Detailed Query Set Analysis **Results**

Gene/Protein Search for Ontology set: 89 records found. 2 pages 1 2 > >>

Save Export Pathfinder Ontology FASTA Profiles

Hits on page 50
Composite Element
Search Within Results

Name	Species/Taxon	Description
<input type="checkbox"/> AP-2alpha	Human	Transcription factor AP-2 alpha, plays a role in apoptosis, limb morphogenesis, and in the regulation of hormone biosynthetic process, aberrant expression correlates with adenocarcinoma, astrocytoma, and thyroid neoplasms
<input type="checkbox"/> c-Ets-2	Human	Homolog 2 of v-ets erythroblastosis virus E26 oncogene, a transcription activator that acts in antiapoptosis and Ras protein signal transduction, upregulated in hyperplasia, colonic and several neoplasms; mRNA is upregulated in Down syndrome
<input type="checkbox"/> c-Fos	Human	Homolog of v-fos FBJ murine osteosarcoma viral oncogene, a transcription factor that mediates apoptosis, cell cycle, mast cell degranulation, and hemopoiesis, upregulated in atherosclerosis, asthma, Alzheimer disease, lung, prostate, and various neoplasms
<input type="checkbox"/> c-Jun	Human	Jun oncogene, a transcription activator that acts in antiapoptosis, upregulated in Alzheimer disease, multiple sclerosis, glomerulonephritis, prostatic and several neoplasms; aberrant mRNA expression is associated with schizophrenia and psoriasis

Disease Quick Search

ここからは、Quick Search の方法です。

Open the **Quick Search** interface for diseases and type "Atherosclerosis" into the text field. After the first few characters, the BKL presents several suggestions to complete term.

Click on the **Find** button below the text field.

The screenshot shows the BIOBASE Knowledge Library interface. On the left, there is a sidebar with several search options: Quick Search, Advanced Search, TRANSFAC Module Search, Ontology Search, and Upload Gene List. At the bottom of the sidebar is a Help icon. The main area is titled 'Quick Search' and features five category buttons: Gene/Protein, Disease, Pathway, Drug, and Keyword. The 'Disease' button is circled in red. Below the 'Disease' button, there is a search input field containing the text 'Atherosclerosis'. A dropdown menu is open below the input field, displaying a list of suggestions: Atherogenesis, Atheroma, Atherosclerosis, Arterial Fatty Streaks, and Atheromas. The 'Atherosclerosis' suggestion is circled in red. A red arrow points from the 'Quick Search' button in the sidebar to the 'Disease' button, and another red arrow points from the 'Disease' button to the 'Atherosclerosis' suggestion in the dropdown menu.

Disease Quick Search

The search result shows the disease name Atherosclerosis. You can click on the name to open the report form for the disease. 一度、Report を見てください。

Select the **Gene** item from the pull-down list and click on the indicated button to search for biomarkers associated with Atherosclerosis.

BIOBASE Knowledge Library Logout

Search Results

BioMarker Search for Atherosclerosis: 1 Hits on page 50

[Save](#) [Export](#) [Pathfinder](#) [Ontology](#) [FASTA](#) [Profiles](#)

Mark all on page

Disease Name
<input type="checkbox"/> Atherosclerosis

Mark all on page

Gene [Search Within Results](#)

Atherosclerosis に関連する遺伝子群の保存方法

Help

Disease Quick Search

The resulting table lists 182 genes for which an association with Atherosclerosis has been shown. You can click on gene symbols to open their BKL Locus Reports. Both Disease Reports and Locus Reports provide details about individual disease/gene interactions.

Click the **Save** button to store your search result.

Search Results







Gene Search for BioMarker Atherosclerosis->Gene: 182 records found.

4 pages ▾ 1 2 3 > »

Hits on page 50 ▾

Complex ▾

Search Within Results

 Save
  Export
  Pathfinder
  Ontology
  FASTA
  Profiles

Mark all on page

Constraint from Disease	Name	Species/Taxon	Gene type
<input type="checkbox"/> DI000015794 - Atherosclerosis	TNFSF14	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	ABCG1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	PPARGC1A	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	NFKB1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	CAV1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	SCARB1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	CHIT1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	CD40	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	PTPN22	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	ABCA1	Human	gene
<input type="checkbox"/> DI000015794 - Atherosclerosis	EDNRA	Human	gene

Disease Quick Search

The saved search result is accessible through the BKL tool bar. Click on the **Saved Search Results** button to return to the Atherosclerosis biomarker query.

Note, that saved search results are also available in ExPlain.

BIOBASE Knowledge Library Logout

Quick Search
Advanced Search
TRANSFAC Module Search
Ontology Search
Upload Gene List
Help

Tools

- Pathfinder
- BLAST
- MATCH
- ExPlain
- Saved Search Results**

Saved search results for user 'pst'

Delete
 Mark all

1 hits	Name	Entity	Query	Items	Time (sec)	Tool	Comment
<input type="checkbox"/>	Gene: BioMarker Atherosclerosis->Gene	Gene	BioMarker Atherosclerosis->Gene	182	1.031	SearchEngine	

Mark all

保存したデータは、ExPlain 等でも解析可能です。

Disease Reports

ここからは、Disease Report を見ていきましょう。

Open the Disease Report for Atherosclerosis. Click on one or more **details** links or tick marks. What are synonyms for Atherosclerosis? What types of disease/gene associations are annotated in the BKL?

現在では、187 (このスライド作成時は182) の遺伝子でこの疾患との関連が報告されている。

Disease Report Home

Atherosclerosis **Synonyms** : Arterial Fatty Streak; Arterial Fatty Streaks; Atherogenesis; Atheroma; Atheromas ; Atheroscleroses

Biomarker Associations ↑ ?

Biomarkers associated with Atherosclerosis (182 biomarkers)

Gene/Protein [details-all] [Sort alphabetically]	Type of Association				Indication		
	Causal [details] (69 associations)	Correlative [details] (423 associations)	Preventative [details] (16 associations)	Negative [details] (4 associations)	Disease Mechanism [details] (57 associations)	Prognosis [details] (105 associations)	Therapeutic Target [details] (17 associations)
CRP (16 associations) [details]	✓ (2 associations)	✓ (14 associations)			✓ (2 associations)	✓ (2 associations)	
E-selectin (14 associations) [details]		✓ (14 associations)				✓ (2 associations)	
CD91 (11 associations) [details]		✓ (11 associations)				✓ (8 associations)	

Disease Reports これ以外の色々な情報もご覧ください。

Scroll down to the **Association Characteristics** section. Which biological processes are affected by Atherosclerosis? In which cell types or tissues are Atherosclerosis associated genes expressed? Open the details about diseases associated with Atherosclerosis. By which biomarkers are **Aortic diseases** associated with Atherosclerosis?

Association Characteristics

Subtypes or forms of Atherosclerosis

more severe; increased occurrence of early stage form; advanced stage or high grade; early stage or low grade ...[\[details\]](#)

Biological processes affected by Atherosclerosis

platelet activation; proteolysis; platelet aggregation; lipoprotein biosynthetic process; response to oxidative stress ...[\[details\]](#)

Cell types or tissues affected by Atherosclerosis

serum; macrophages; smooth muscle cells; plasma; blood vessels; endothelium/endothelial cells; arteries ...[\[details\]](#)

Diseases associated with Atherosclerosis

Thrombosis; Disease Susceptibility; Disease Progression; Hypertension; Genetic Predisposition to Disease ...[\[details\]](#)

Disease Reports

Scroll to the **Biomarker Search Tool** of the Atherosclerosis Disease Report. We are going to extract biomarkers for which a correlation has been discovered on the protein level. Configure the tool as shown below and click on the **Retrieve** button to extract the biomarkers of interest.

Note, that the search result is returned in the BioKnowledge Search window.

Biomarker Search Tool

Retrieve Atherosclerosis biomarkers for analysis

Retrieve Atherosclerosis biomarkers for export or for viewing in the BKL
Pathfinder:

Retrieve all:

Limit to:

- Biomarkers with a disease relationship of
- Biomarkers with affected molecule type of
- Biomarkers expressed in

correlates with

Protein

Blood

Note: Results are returned in the BioKnowledge Search window

Disease Reports

Open the **Search Results** window. How many biomarkers were found by the Biomarker Search Tool? Find the biomarker **cyclin E1** and open its Locus Report by clicking on the link in the **Accession** column.

結果は、search results window に表示されます。

BIOBASE Knowledge Library Logout

Search Results

Biomarker Search for Atherosclerosis with a disease relationship of correlates with and with affected molecule type of Protein: Hits on page: 50

38 records found.

Save Export Pathfinder Ontology FASTA Profiles Complex Search Within Results

Mark all on page

	Accession	Biomarker	Description
<input type="checkbox"/>	GN000006468	ABCA1	ATP-binding cassette subfamily A member 1, a cholesterol transporter that acts in lipid metabolism, insulin secretion, and phagocytosis; gene polymorphism correlates with coronary artery disease, familial form of hypolipoproteinemias, and Tangier disease
<input type="checkbox"/>	GN000002440	APOB	Apolipoprotein B, acts in cholesterol metabolism and absorption, aberrantly expressed in Alzheimer disease, AIDS, arthritis, diabetes, cardiac and pulmonary diseases, hypercholesterolemia, and hepatitis; mutation correlates with hypobetalipoproteinemia
<input type="checkbox"/>	GN000003246	CAV1	Caveolin 1, a signal transducer that acts in androgen receptor signaling pathway, aging, and cholesterol metabolism, regulates blood pressure and apoptosis, aberrant expression correlates with atherosclerosis and breast and several other neoplasms

Tools


Quick Search
Advanced Search
TRANSFAC Module Search
Ontology Search
Upload Gene List
Help


Locus Reports


With how many diseases is cyclin E1 associated?

今度は、CyclinE1 が 42 の疾患に関与していることが分かります。

Locus Report Quick search [Home](#)

 **Human**

 **CCNE1 (cyclinE1)**



Cyclin E1, a cyclin-dependent protein kinase regulator that acts in G1-S transition of mitotic cell cycle, peptidyl-threonine phosphorylation, and cell cycle arrest, aberrant expression correlates with breast, ovary, and various neoplasms

Synonyms CCNE; CCNE1; cyclin E1

Biomarker Associations
Drug Interactions
Gene Ontology
Expression
Mutant Phenotype
Pathways & Interactions
Transcriptional Regulation
Protein Features
Annotations



Biomarker Associations ↑ ?

Diseases associated with CCNE1 (42 entries)

Disease <small>[details... all]</small> <small>[Sort alphabetically]</small>	Type of Association				Indication		
	<u>Causal</u> <small>[details]</small> (9 associations)	<u>Correlative</u> <small>[details]</small> (126 associations)	<u>Preventative</u> <small>[details]</small> (2 associations)	<u>Negative</u> <small>[details]</small> (9 associations)	<u>Disease Mechanism</u> <small>[details]</small> (3 associations)	<u>Prognosis</u> <small>[details]</small> (48 associations)	<u>Therapeutic Target</u> <small>[details]</small> (5 associations)
Breast Neoplasms (17 associations) <small>[details]</small>	✓ (1 associations)	✓ (15 associations)		✓ (1 associations)		✓ (5 associations)	✓ (1 associations)

Locus Reports

Scroll to the **Expression** section of the cyclin E1 Locus Report and expand the detailed view on organ or tissue, cell type, and tumor type entries. At which expression levels was cyclin E1 detected in different cell types? Click on the **details** link of the Cell Type table to further inspect the evidence behind cyclin E1 expression information.

Expression  

Tissue expression

brain	breast	colon	heart	intestine	kidney	liver	lung	muscle	ovary	pancreas	placenta	spleen	stomach	testis	thymus
	✓	✓					✓		✓						


[-] View organ or tissue, cell type, and tumor type entries in detail

Cell type

<u>Cell Type</u> [details]	<u>Form Not Determined</u>	<u>mRNA</u>	<u>Protein</u>	<u>Evidence</u>
T-lymphocytes			✓	protein detected
bladder epithelium/epithelial cells			✓	immunolocalization
blood lymphocytes monocytes mononuclear leukocytes			✓	protein detected
blood vessels smooth muscle		✓		mRNA detected

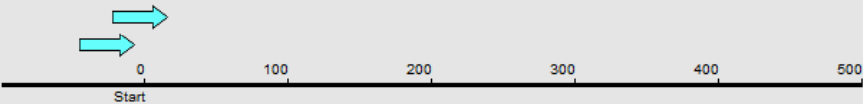
Locus Reports

Scroll to the **Transcriptional Regulation** section of the cyclin E1 Locus Report. How many binding sites are curated for E2F-1? How many in vivo fragments have been annotated? Click on the pathway icon to obtain a visualization of cyclin E1 gene regulation.

Transcriptional Regulation 




Regulation of CCNE1 gene expression

Chromosome : 19q12
 Predicted promoter sequences : [PM000003497](#)



* Note: Only binding sites whose location is relative to the TSS are graphically displayed.

Transcription factor binding sites within the CCNE1 gene (3 entries)

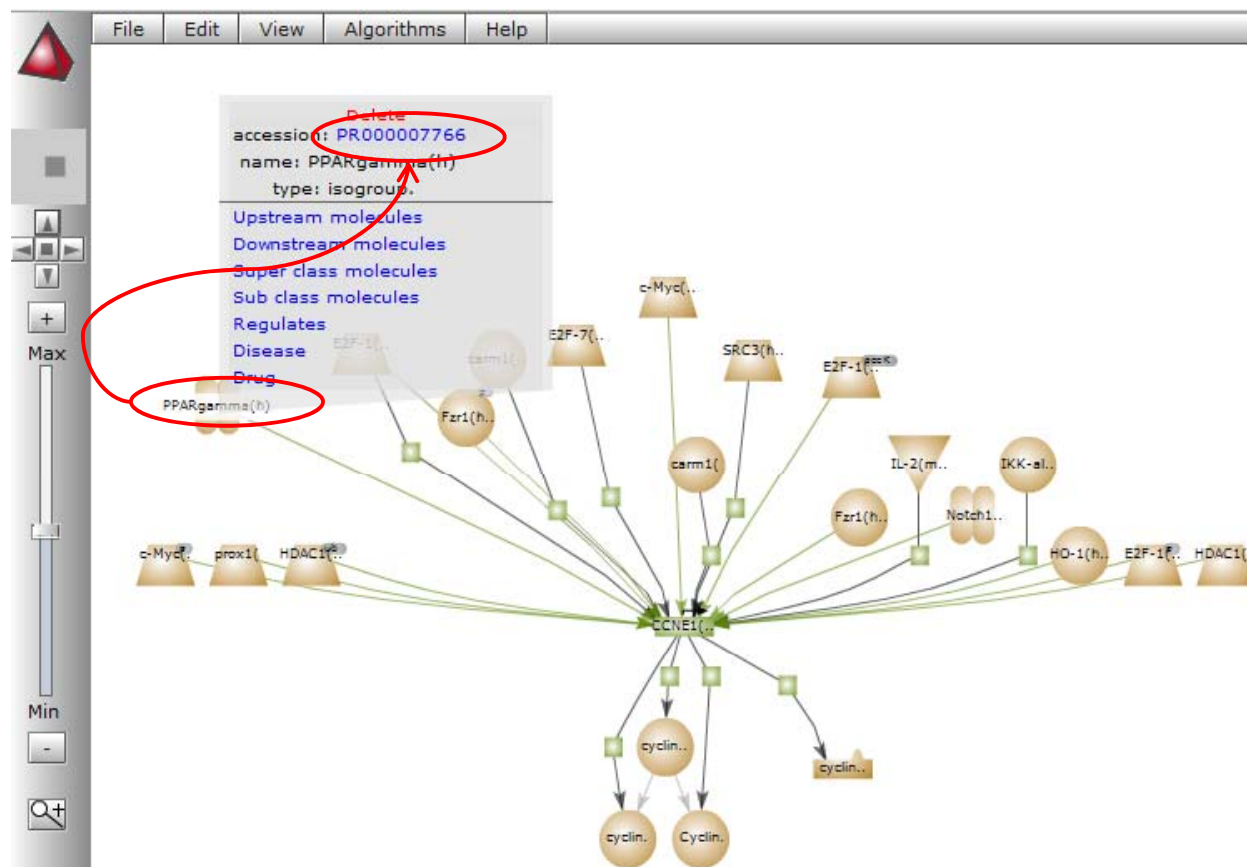
	Identifier	Location	Binding Factor(s)	DNA Binding Reaction	Effect
	HS\$CYCE_01	-16 to -9	E2F-1(h)	E2F-1(h) → cycE(h)	DNA binding
	HS\$CYCE_02	7 to 14	E2F-1(h)	E2F-1(h) → cycE(h)	DNA binding
	HS\$CYCE_03	497 to 504 *			

View in vivo fragments within the vicinity of the CCNE1 gene that are bound by transcription factors (88 entries)

Identifier	Location	Binding Factor
FR000196764	34934874..34935428	HNF3A(h)

Locus Reports

Find **PPARgamma** in the gene regulation network of the CCNE1 gene (cyclin E1) and click on its node to expand the context menu. Click on the protein accession to open its Locus Report.



Locus Reports

In the **PPARgamma** Locus Report, scroll to the **Drug Interactions** section. How many drugs are shown to interact with PPARgamma? Click on one or more of the drug names to open their **Drug Reports**.

Drug Interactions

Drug(s) targeting PPARG (6 entries)

* Indicates target provided by DrugBank.




<u>Drug(s)</u>	<u>Status</u> (provided by DrugBank)
* Atorvastatin	Approved,Small Molecule
* Icosapent	Approved,Nutraceutical,Small Molecule
* Pioglitazone	Approved,Investigational,Small Molecule
* Rosiglitazone	Approved,Investigational,Small Molecule
* Troglitazone	Small Molecule,Withdrawn

[\[more ...\]](#)

Locus Reports



Scroll to the **Pathways & Interactions** section. Open the graphic representation of the **PPAR pathway**.

Note, that the components of the opened pathway image are interactive.




Pathways & Interactions   

Pathways

Canonical pathways assembled from experiments involving orthologous proteins (1 entry)

Name	View Supporting Reactions	View Graphic Representation	Load in Pathfinder
PPAR pathway	[details]		

Subcomponents assembled from experiments involving orthologous proteins (5 entries)

Name	View Supporting Reactions	View Graphic Representation	Load in Pathfinder
15d-PGJ2 ---/ NF-ATc	[details]		
15d-PGJ2 --> PPAR-gamma	[details]		
MKK4 ---/ PPAR-gamma	[details]		

Pathways

ここでは、有名なパスウェイ情報をご覧いただけます。

Follow the steps shown below to open the **Pathway Quick Search** and to browse **Canonical Pathways** of the BKL.

BIOBASE Knowledge Library Logout

Quick Search

Quick Search (circled) | Advanced Search | TRANSFAC Module Search | Ontology Search | Upload Gene List

Gene/Protein | Disease | **Pathway** (circled) | Drug | Keyword

Pathway **Browse by Canonical Pathway** (circled)

Canonical Pathways

Regulatory pathways

Click on the icon to open the pathway in the BKL Pathfinder. To open a manually drawn map click on the pathway name.

Apoptosis	Cell cycle control	Immune response	Cell adhesion & motility
Apo2L Caspase	Aurora-A Aurora-B	B cell signaling CXCR1/2 (IL-8)	Cadherins (beta-catenin)

Pathways

Scroll to the pathway category **Growth & Differentiation** and click on the **HIF-1** pathway name.

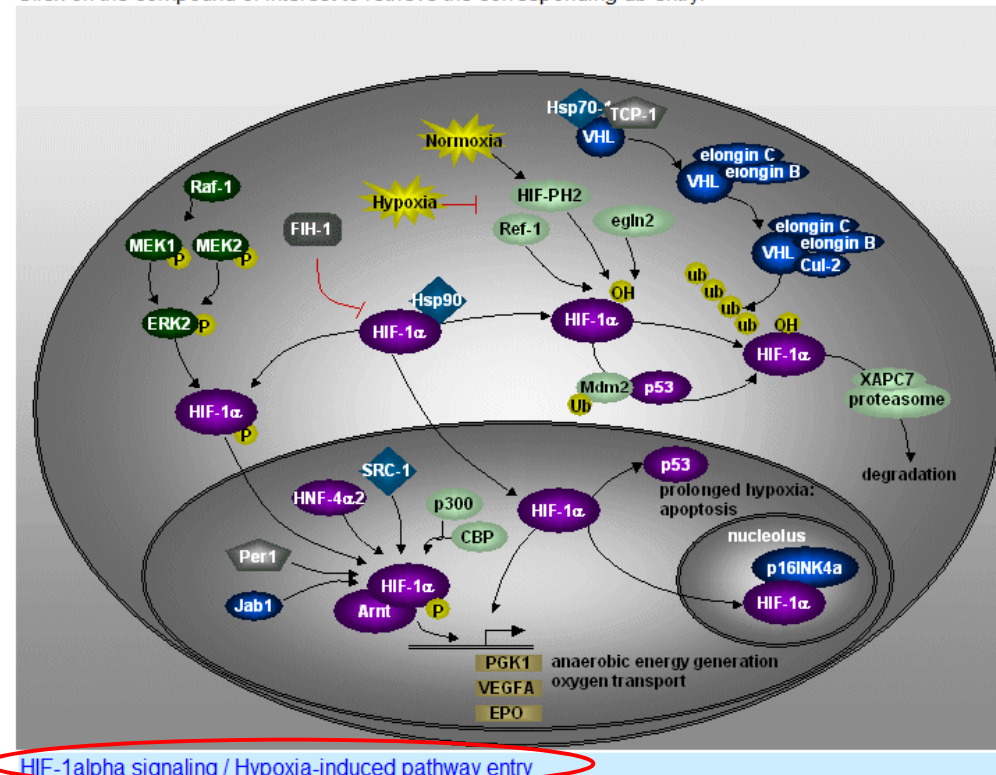
Neuronal regulation	Stem cell related pathways	Growth & Differentiation	
<ul style="list-style-type: none">APPBDNF-induced p75NTR signalingBDNF - trkB signalingBDNF ---p75NTR---> caveolin-1Htt	<ul style="list-style-type: none">NotchSonic hedgehog (Shh)	<ul style="list-style-type: none">AhRAndrogen-induced ARMAPK-affected ARAtrophin-1 (DRPLA)beta-cateninc-Kit	<ul style="list-style-type: none">HIF-1InsulinNeurotensinNotchNRG1 - ErbB3 survival pathwayPDGF

Pathways

Click on the link named **HIF-1alpha signaling / Hypoxia-induced pathway entry** below the map to open the **Pathway Report**.

HIF-1alpha signaling / Hypoxia-induced pathway

Click on the compound of interest to retrieve the corresponding db entry.



Pathways

From which subcomponents was the pathway assembled? Open the Pathway Report for **p53** → **HIF-1alpha degradation** by clicking on the link indicated below.

Pathway Report

CH000000715 HIF-1alpha pathway

Pathway Information

Overview of pathway components  [\[View hand drawn map\]](#)

Subcomponents from which this pathway was assembled

- VHL --> HIF-1alpha degradation
- MEK-1 --> HIF-1alpha
- JAB1 --> HIF-1alpha
- HIF-1alpha --/ AhR
- Trx1 --> HIF-1alpha
- p53 --> HIF-1alpha degradation**

Reactions from which this pathway or subcomponent was assembled

- └ (Hsp90)2:ITE:AhR:STIP1:TEBP:AIP:SRP1alpha + arnt --> AhR:arnt + 2 Hsp90 + ITE + STIP1 + TEBP + AIP + SRP1alpha (exchange)
- └ AhR:arnt + HIF-1alpha{p} <==> HIF-1alpha{p}:arnt + AhR (binding; competition; reversible)

Pathways

Of which Canonical Pathways is **p53 → HIF-1alpha degradation** a subcomponent? Click on the pathway icon to obtain a visualization of the reaction in the **Pathfinder**.

The image shows two parts of a software interface. On the left is a 'Pathway Report' window. It displays the pathway ID 'CH000000717' and the reaction 'p53 ----> HIF-1alpha degradation'. Under the 'Pathway Information' section, there is an 'Overview of pathway components' area with a red circle around a small orange icon. Below this, it lists 'Canonical pathway to which this subcomponent is assigned' as 'p53 pathway' and 'HIF-1alpha pathway'. On the right is the 'Pathfinder' visualization tool. It has a menu bar with 'File', 'Edit', 'View', 'Algorithms', and 'Help'. A vertical toolbar on the left contains navigation arrows and a zoom control with a '+' button and a 'Max' label. The main area shows a hierarchical diagram of the pathway. At the top is 'HIF-1alpha degradation' (orange trapezoid). Below it is 'HIF-1alpha' (green square), which is inhibited by 'p53' (orange trapezoid). 'p53' is inhibited by 'mdm2' (orange trapezoid). 'mdm2' is inhibited by 'HIF-1alpha' (green square). At the bottom, 'p53' is inhibited by 'proteasome' (orange circle), and 'HIF-1alpha' is inhibited by 'mdm2' (orange circle). A blue arrow points from the 'p53' node to the 'proteasome' node.

Congratulations

Training session completed

ご不明の点がございましたら、下記にご連絡お願いいたします。

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本セッションに記載されていない機能につきましても、お時間がある時にご使用になられてください。