

Guide to Creating New Pathways

Version 1.0

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Contents

Introduction.....	2
Pathways	2
Purpose	2
Contents	2
Pathway drawing procedure	3

Tables

Table 1. Naming convention, features and links used for molecules in SMPDB pathways.	3
Table 2. Standard font styles and sizes to be used in pathways.	7

Introduction

This guide contains information for the pathway artists contributing to the Small Molecule Pathway Database (SMPDB). It describes the purpose of SMPDB pathways, contents of the pathways, and the pathway drawing procedure. Additionally, lists of references that should be used for each pathway are included. A supplementary legend with pathway items and descriptions can be found [here](#).

1 Pathways

This section explains the purpose of SMPDB pathways, describes pathway contents and the drawing procedure.

2.1 Purpose

To create a research and educational tool that provides comprehensive, detailed information on human metabolic, disease, drug and signalling pathways. SMPDB pathways are linked interactive pathway maps with an emphasis on human small molecules.

2.2 Contents

Pathways in SMPDB are focused on human metabolism, disease, drug, and signalling mechanisms. All pathways should depict subcellular locations as well as cell, tissue and organ specificity where relevant. Metabolic, disease and signalling pathways may be linked to other pathways in SMPDB.

Metabolic pathways should contain a minimum of five metabolites.

Disease pathways show the enzyme(s) involved in etiology of the disease and identify the metabolites that accumulate or are depleted as a result of the disease.

Drug pathways illustrate the major drug targets involved in the observed pharmacological effects. Drug pathways may contain additional information on drug entry to target sites, *in vivo* activation of pro-drugs, resultant accumulation or depletion of metabolites, and effect on physiological processes. Links to other pathways in SMPDB may be added where relevant.

Signalling pathways depict the mechanisms by which small molecule ligands participate in cellular communication and affect biological responses.

Table 1. Naming convention, features and links used for molecules in SMPDB pathways.

Molecules	Naming Convention	Features	Links
Human metabolites and small molecules	Name recommended by Human Metabolome Database (HMDB)	Chemical structure HMDB ID	HMDB - http://www.hmdb.ca/HMDBID (e.g. HMDBxxxxx)
Protein metabolites	Name recommended by UniProt	Protein structure if available UniProt ID	UniProt - http://www.uniprot.org/uniprotID (e.g. Pxxxxx)
Enzymes, receptors, and non-metabolite proteins	Name recommended by UniProt	Subunit structure Subcellular location UniProt ID	UniProt - http://www.uniprot.org/uniprotID (e.g. Pxxxxx)
Channel proteins	Gene name (per UniProt)	Subunit structure Subcellular location UniProt ID	UniProt - http://www.uniprot.org/uniprotID (e.g. Pxxxxx)
Drugs	Name recommended by DrugBank	Chemical structure DrugBank ID	DrugBank - http://www.drugbank.ca/DrugBankID (e.g. DBxxxxx)

2.3 Pathway drawing procedure

All pathways should be drawn using the standard shapes, colours, and font sizes set out in the [Legend](#). All pathways should be drawn using Microsoft PowerPoint. Shape sizes may be adjusted to fit the pathway.

Metabolites (chemical) Create chemical MetaboCards for each chemical metabolite using the recommended names, chemical structures and HMDB IDs from HMDB (<http://www.hmdb.ca/>). Chemical structures should be cropped and re-sized appropriately. The blue MetaboCard background should be re-sized so the chemical structure can be centered evenly on the card. A solid black 2.25 pt border should frame each chemical structure.

Small molecules Create small molecule cards for each small molecule using standard atom colours to depict atomic structure. Use appropriate chemical abbreviations to name the small molecules (e.g. water should be denoted as H₂O). Use subscripts and superscripts where appropriate. Include the HMDB ID of the small molecule. (<http://www.hmdb.ca/>).

Protein metabolites	<p>Create protein MetaboCards using the UniProt recommended names and IDs (http://www.uniprot.org/).</p> <p>Include crystal structures of proteins if available from the NCBI Structure Database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Structure&itool=toolbar). Otherwise, use a generic protein structure. Proteins structures should be cropped and resized appropriately. The MetboCard background should be re-sized so the chemical structure can be centered evenly on the card. A white or black 2.25 pt border should frame all protein structures on a black or white background, respectively.</p>
Enzymes and receptors	<p>Search for all enzymes in UniProt. Information to be shown in pathway:</p> <ul style="list-style-type: none"> • Recommended name • UniProt ID • Enzymatic or receptor activity • Subunit structure • Cofactors required for activity • Subcellular location • Associated proteins where relevant
Channel proteins	<p>Search for all channel proteins in UniProt. Information to be shown in pathway:</p> <ul style="list-style-type: none"> •Gene name of each subunit •UniProt ID •Subunit structure •Cofactors required for activity •Subcellular location •Associated proteins when relevant •Transported metabolite and direction of transport
DrugCards	<p>Create DrugCards using the recommended name and chemical structure in DrugBank (http://www.drugbank.ca/). DrugCards should be created in the same manner as chemical MetaboCards. The blue MetaboCard background should be substituted for the yellow DrugCard background and image of two capsules should be added to the bottom right corner of the DrugCard.</p>
Organs	<p>Specific organs should be depicted in organ-specific pathways. An image of the organ should be used with a zoom box (see instructions below on how to use zoom boxes).</p>

Pathways that occur ubiquitously in cells throughout the human body or in multiple organs do not require tissue or organ specificity to be shown.

If segments of a pathway take place in multiple organs, connectors should be used to show transport between the organs.

Organelles

Organelles should be used to show the subcellular location of pathway constituents (e.g. enzymes, receptors, accessory proteins, etc.) in the cell. If only a small number of pathway constituents are located within an organelle, the organelle should be placed behind the constituents. If a significant portion of a pathway takes place in an organelle, a zoom box should be used within the cell. Information boxes should be used to label all subcellular structures.

Zoom boxes

Extracellular: Organs (see [Legend](#) for example)

Intracellular: Organelles

A small white box should be placed on the organ or organelle that will be zoomed in on. A large white box should be placed around the portion of the pathway that is located in the organ or organelle. A representative portion of the phospholipid bilayer pertaining to the organ or organelle should be shown in the pathway box. The faint blue triangle should be used to connect the small and large boxes.

Cellular membranes

Phospholipid bilayers should be used to divide intracellular and extracellular spaces. They may also be used to create membranous organelles where a pathway might require greater subcellular details (e.g. if a significant portion of the pathway takes place within an organelle or on the organelle membrane). See instructions on Organelles and Zoom boxes above for how to show greater subcellular detail. The colour of the phospholipids should correspond to the organelle or cell membrane as set out by the [Legend](#). Phospholipid bilayers may also be used to differentiate between different cell types within a pathway.

Multiple cells

Different cell types may be depicted by using different coloured ovals to represent each cell type (see [Legend](#)). These may be used to show the movement of metabolites and drugs from one cell to another. They may also be used to depict the pharmacological actions of drugs or effects of a disease or signalling cascade in different cell types or to show transport, movement or signalling between different cells.

Connectors

Connectors are an essential part of all pathways. Connectors represent enzymatic reactions, activation or inhibition of receptors and proteins, transport of drugs and metabolites, protein binding and other biochemical events that occur in the

human body. Please see the [Legend](#) for specific connector styles and colours used to depict these events.

Drug activity

See [Legend](#) for specific connectors that should be used to depict inhibition or activation by a drug. When a drug affects a processes (e.g. muscle contraction or enzyme activity), a purple or blue star should be placed behind the affected to denote increased or decreased activity. See [Legend](#) for the specific shapes and colours that should be used.

Disease effects

Many diseases have been attributed to enzyme deficiencies. A red "X" symbol should be placed over enzymes whose decreased activity has been associated with the disease. A yellow or orange star should be placed behind metabolites that subsequently accumulate or are depleted as a result of the disease. See [Legend](#) for specific shapes that should be used.

Fonts and borders

Font sizes should be standardized according to Table 2. All borders should be created according to the standards set out by the [Legend](#).

Table 2. Standard font styles and sizes to be used in pathways.

Pathway titles	Arial 60, bold, white with shadow
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MetaboCards: Metabolite name HMDB ID	Arial 12, bold, blue Arial 12, underline, black
DrugCards: Drug name DrugBank ID	Arial 12, bold, red Arial 12, underline, black
Small molecules: Element name HMDB ID	Arial 12, underline, white Arial 12, bold use superscript and subscript where appropriate (e.g. H ⁺ , H ₂ O)
Enzymes	Calibri 12, black
Enzyme cofactors and channel proteins	Calibri 15, bold, black use elemental abbreviations from periodic table use superscript and subscript where appropriate (e.g. Fe ²⁺ , H ₂ O) illustrate number of cofactors that bind per subunit (e.g. if two Mg ²⁺ bind per subunit on a homodimeric enzyme, show "2 Mg ²⁺ " on each co-factor shape)
Protein transporters, ATP, NAD, etc.	Calibri 15, bold use superscript and subscript where appropriate (e.g. NAD ⁺)
Text boxes for receptors	Calibri 12, black