

The logo for MecCog, featuring the text "MecCog" in a bright green, sans-serif font. The text is centered within a solid black rectangular background.

**A framework for representing
Disease Mechanisms**

<http://www.meccog.org>

Visualization Tutorial

Last Update: 2019/03/07

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I. About MecCog

MecCog is a web-based framework for describing biological mechanisms based on emerging concepts in the philosophy of biology. The framework is implemented in a web infrastructure that uses contemporary methods of computational biology to represent mechanism. The initial implementation focuses on capturing mechanisms relating genetic variants to disease phenotypes.

MecCog is hosted at <http://www.meccog.org>

II. MecCog Homepage

The homepage of MecCog provides a masonry layout of the all the published mechanism schemas. The page has three components:

1. Header Bar: It provides link to MecCog project overview page (*Overview*), tutorial page (*Tutorial*) and contact us form (*Contact Us*).
2. Search Bar: The user can enter a gene name or keywords to filter mechanism schemas.
3. The mechanism schema thumbnail displays the schema name, accession number, short description, and hyperlinked image of the schema. Clicking on the accession number directs to the landing page of the schema and clicking on the image directs to the *Schema Visualizer*.

The home page of MecCog appears as shown below:

The screenshot displays the MecCog homepage interface. At the top is a dark header bar with the MecCog logo on the left and navigation links for 'Overview', 'Tutorial', and 'Contact Us'. To the right of these links are input fields for 'Username' and 'Password', a search icon, and a 'Sign Up' button. Below the header is a large white search bar with the placeholder text 'Keyword or Gene name' and a magnifying glass icon. A red arrow points to this search bar with the label 'Search Bar'. The main content area features a masonry grid of eight mechanism schema thumbnails. Each thumbnail includes a title, an accession number, a short description, and a small image of the schema diagram. The thumbnails are arranged in two rows of four. The first row contains: 'Mongersen drug effectiveness schema for Crohn's disease', 'ATG16L1 and Microbiome Interaction schema for Crohn's disease', 'TREM2 R47H Schema for Alzheimer's', and 'CFTR F508del for Cystic Fibrosis'. The second row contains: 'ATG16L1 Schema for Crohn's disease', 'TLR9-NOD2 Epistasis schema for Crohn's disease', 'NOD2 Schema for Crohn's disease', and 'TLR9 Schema for Crohn's disease'.

III. Mechanism schema landing page

Each mechanism schema has a landing page that displays the meta-information of the schema such as the Schema Name, Accession, Description, Gene(s), Keywords, Schema Owner, Authors and References. It also provides links to the “*Schema Visualizer*” an interactive user interface for visualizing schemas and the “*Schema Report*” that lists the annotations of the mechanism components in the schema.

A typical landing page of a mechanism schema looks as shown below:

MecCog Overview Tutorial Contact Us Username Password Sign Up

MST1 Schema for Crohn's disease Comment

| | |
|--------------------|---|
| Accession | MS020500019.2 |
| Schema Caption | How a GWAS marker on <i>MST1/MST1</i> gene is related to increased risk of Crohn's disease |
| Schema Description | Welcome Trust Case Control Consortium (WTCCC) identified a GWAS marker for Crohn's disease at chromosome 3, in 3p21 which spans 20 genes, an unusually high number. The primary marker SNP (<i>rs9858542</i>) in this Crohn's disease locus lies in an intron of the <i>BSN</i> (bassoon, presynaptic cytomatrix protein) gene. That gene is involved in neural development and expressed in the brain, so unlikely to be relevant to Crohn's disease. Of the 20 genes spanned in this locus, the most probable candidate appears to be <i>MST1</i> (Macrophage Stimulating protein), on the grounds that it is involved in the innate immune response through alteration of macrophage activity. In later GWAS studies (pmid: 23128233), <i>rs3197999</i> in <i>MST1</i> gene is found to be significant GWAS marker. We used this SNP to address how both increase in inflammation and delayed wound healing / leaky gut are contributing towards the increase in disease risk. |
| Gene(s) | <i>MST1</i> , <i>MST1R</i> , <i>RON</i> |
| Keywords | Macrophage stimulating protein, wound healing, Barrier integrity, Leaky gut, protein-protein interaction, Crohn's disease |
| Schemas Owner | Lipika R. Pal |
| Author(s) | Lipika R. Pal, Kunal Kundu, Lindley Darden and John Moul |
| Curator(s) | John Moul |
| View Schema | Schema Visualizer Schema Report |
| References | Zhou GX, Liu Z.J. Potential roles of neutrophils in regulating intestinal mucosal inflammation of inflammatory bowel disease. <i>Journal of digestive diseases</i> 18 , 495-503 (2017) PMID:28857501 Wera O, Lancellotti P, Oury C. The Dual Role of Neutrophils in Inflammatory Bowel Diseases. <i>Journal of clinical medicine</i> 5 (2016) PMID:2799328 Liu JZ, Anderson CA. Genetic studies of Crohn's disease: past, present and future. <i>Best practice & research. Clinical gastroenterology</i> 28 , 373-86 (2014) PMID:24913378 Neurath MF. New targets for mucosal healing and therapy in inflammatory bowel diseases. <i>Mucosal immunology</i> 7 , 6-19 (2014) PMID:24084775 |

Click here to visualize schema in an interactive user interface

Click here to view schema report

IV. Schema Visualizer

The visualizer allows users to interact with the schema. The visualizer interface has four panels:

Panel A: Mechanism Schema Info Panel that shows the meta-information for a mechanism schema such as accession number, schema name, and gene name(s).

Panel B: Toolbar Panel for editing mechanism schema.

Panel C: Visualization Board is the panel where mechanism schemas are displayed.

Panel D: A Bird's Eye View Panel that facilitates navigation of big complex schemas.

 Help icon displays the Legend Key for a mechanism schema. If the help icon is not visible, try to adjust the resolution of the browser. The help icon always appears on the top right corner of the screen as shown the image below.

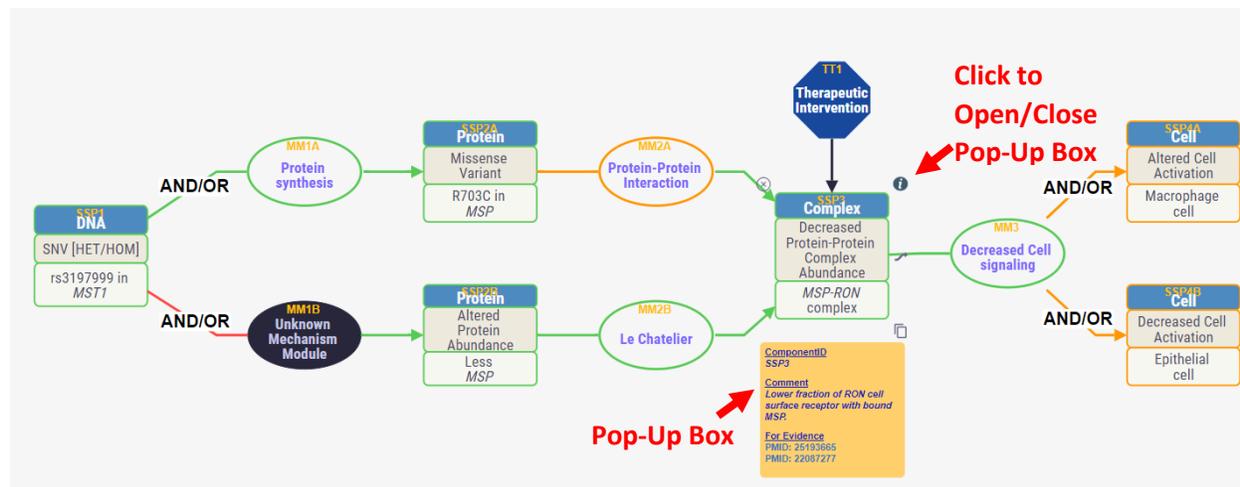
Toolbar Panel

The toolbar of *Schema Builder* provides a number of utility tools to enhance the user's interactive experience with the mechanism schema.

Below images show all the options present in the tool bar –

Interactive actions in Visualization board (Panel C)

Every mechanism component is accompanied by a pop-up box that contains evidence information. The pop-up box can be opened by first clicking on the component that display an info icon () and then clicking on the info icon as shown below:

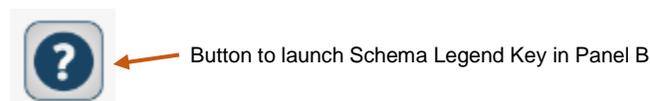


All the PubMed IDs on the pop-up box are hyperlinked to the PubMed database. The *For Evidence* lists the PMIDs that supports the fact in the schema and the *Against Evidence* lists the contradicting PMIDs. The *Comment* section in the box summarizes the evidence information based on the linked PMIDs.

Confidence Colors

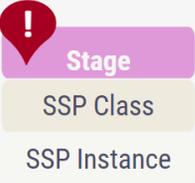
The evidence based confidence scores entered in the annotation form for the mechanism components are converted to confidence color automatically by the MecCog system. A score of **1** converts to red color, score of **5** converts to green color and any score in between converts to orange color.

Schema Key



Here is detailed description of the graphical notations in MecCog:

| Component Name | Component Notation | Description |
|------------------------------|--------------------|---|
| Sub-State Perturbation (SSP) | Stage | Notation of a sub-state perturbation (SSP) component represents three types of information – 1. Stage it belongs to. 2. SSP class name and 3. SSP instance name. The framework provides eight stages – DNA, RNA, Protein, Complex, Cell, Tissue, Organ and Phenotype. For each stage, SSP class names have been |
| | SSP Class | |
| | SSP Instance | |

| | | |
|---------------------------------|--|--|
| | | manually curated Based on the type of SSP class, an instance can be annotated. |
| Biomarker |  | Notation of a Biomarker component represents three types of information – 1. Stage it belongs to. 2. Biomarker class name and 3. Biomarker instance name. The framework provides eight stages – DNA, RNA, Protein, Complex, Cell, Tissue, Organ and Phenotype. |
| Mechanism Module (MM) |  | The graphical notation of a mechanism module (MM) component represents two types of information – 1. Mechanism module class name, 2. An optional Mechanism Module Instance name. 24 mechanism module class names have been manually curated that either operate within a stage or produce a stage transition. This list will be updated as the project progresses. |
| Unknown Mechanism Module |  | For a case, where a mechanism is known to link two substate perturbations but its class is unknown, a black oval represents it. |
| Therapeutic Intervention |  | For a putative or known therapeutic intervention site, a blue octagon represents it. |
| Environmental Factor |  | For an environmental factor that affects disease risk, a mokko shape represents it. |

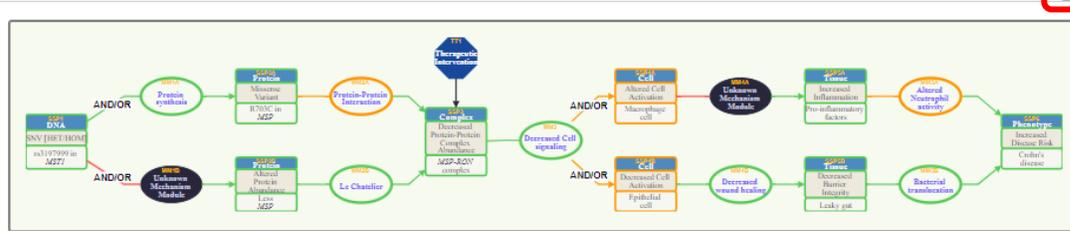
The edges in the schema are labeled with AND, OR, or AND/OR at the start of branches based on evidence supporting the logical operations.

V. Schema Report

All the annotations in the mechanism components of a schema can be converted to a text report. We call this as the schema report. In addition to the annotations, the report also contains the meta-information of the schema.

The figure below shows a typical view of a report:

Report can be saved as PDF by clicking on the print icon 



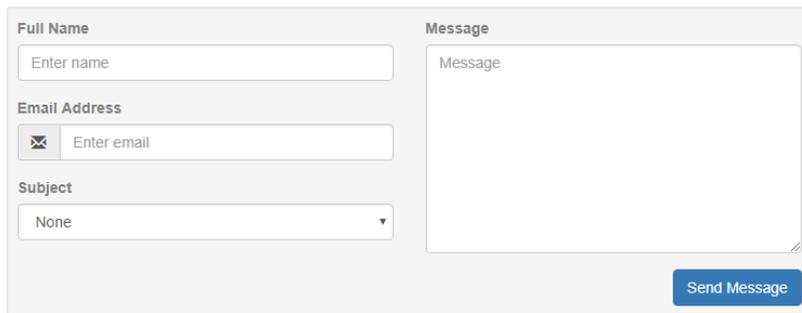
| | |
|---|--|
| Schema Name | MST1 Schema for Crohn's disease |
| Accession | MS020500019.2 |
| Gene(s) | MST1, MST1R, RON |
| Schema Caption | How a GWAS marker on MST1/MST1 gene is related to increased risk of Crohn's disease |
| Schema Description | Welcome Trust Case Control Consortium (WTCCC) identified a GWAS marker for Crohn's disease at chromosome 3, in 3p21 which spans 20 genes, an unusually high number. The primary marker SNP (rs9858542) in this Crohn's disease locus lies in an intron of the BSN (bassoon, presynaptic cytomatrix protein) gene. That gene is involved in neural development and expressed in the brain, so unlikely to be relevant to Crohn's disease. Of the 20 genes spanned in this locus, the most probable candidate appears to be MST1 (Macrophage Stimulating protein), on the grounds that it is involved in the innate immune response through alteration of macrophage activity. In later GWAS studies (pmid: 23128233), rs3197999 in MST1 gene is found to be significant GWAS marker. We used this SNP to address how both increase in inflammation and delayed wound healing / leaky gut are contributing towards the increase in disease risk. |
| Author(s) | Lipika R. Pal, Kunal Kundu, Lindley Darden and John Moul |
| Curator(s) | John Moul |
| Last Modified | Fri Aug 10 2018 15:13:18 GMT-0400 (EDT) |
| Sub-state Perturbation (SSP) Annotations | |
| Component ID: SSP1 | |
| Stage: DNA | |
| SSP Class: Other | |
| Other SSP Class: SNV [HET/HOM] | |
| Modifier: NA | |
| Ontology: | |
| SSP Instance: rs3197999 in MST1 | |
| Confidence Score: 5 | |
| Comment: Of the 20 genes spanned in this locus, the most probable candidate appears to be MST1 (macrophage stimulating protein), on the grounds that it is involved in the innate immune response through stimulation of macrophage activity. In later GWAS, rs3197999 became established GWAS marker for Crohn's disease (Jostins et al 140 loci Crohn's disease paper). As these are GWAS marker information, where relationship with increasing disease risk is based on allele frequency, so SNV can be in either heterozygous (HET) or homozygous (HOM) mode. After this SSP, there are conflicting data and theories at the protein level mechanism. Hence there is branching in the next mechanism components from this SSP. We are not sure which branch is correct - so AND/OR labeling in the branches. | |
| For Evidence: PMID:23128233 | |
| Against Evidence: | |
| Component ID: SSP2A | |
| Stage: Protein | |
| SSP Class: Other | |
| Other SSP Class: Missense Variant | |
| Modifier: NA | |
| Ontology: | |
| SSP Instance: R703C in MSP | |
| Confidence Score: 5 | |

VI. Contact Us

Users can contact MecCog Project PI and developers for suggestions, problems, and collaborations using a web form as shown below.



Contact Us

The contact form is a light grey box with a white background. It is divided into two main sections. The left section contains three input fields: 'Full Name' with the placeholder 'Enter name', 'Email Address' with a small envelope icon and the placeholder 'Enter email', and 'Subject' with a dropdown menu currently showing 'None'. The right section is a large text area labeled 'Message' with the placeholder 'Message'. At the bottom right of the form is a blue 'Send Message' button.

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