RGD: Data and Tools for Translational Research in Otitis Media

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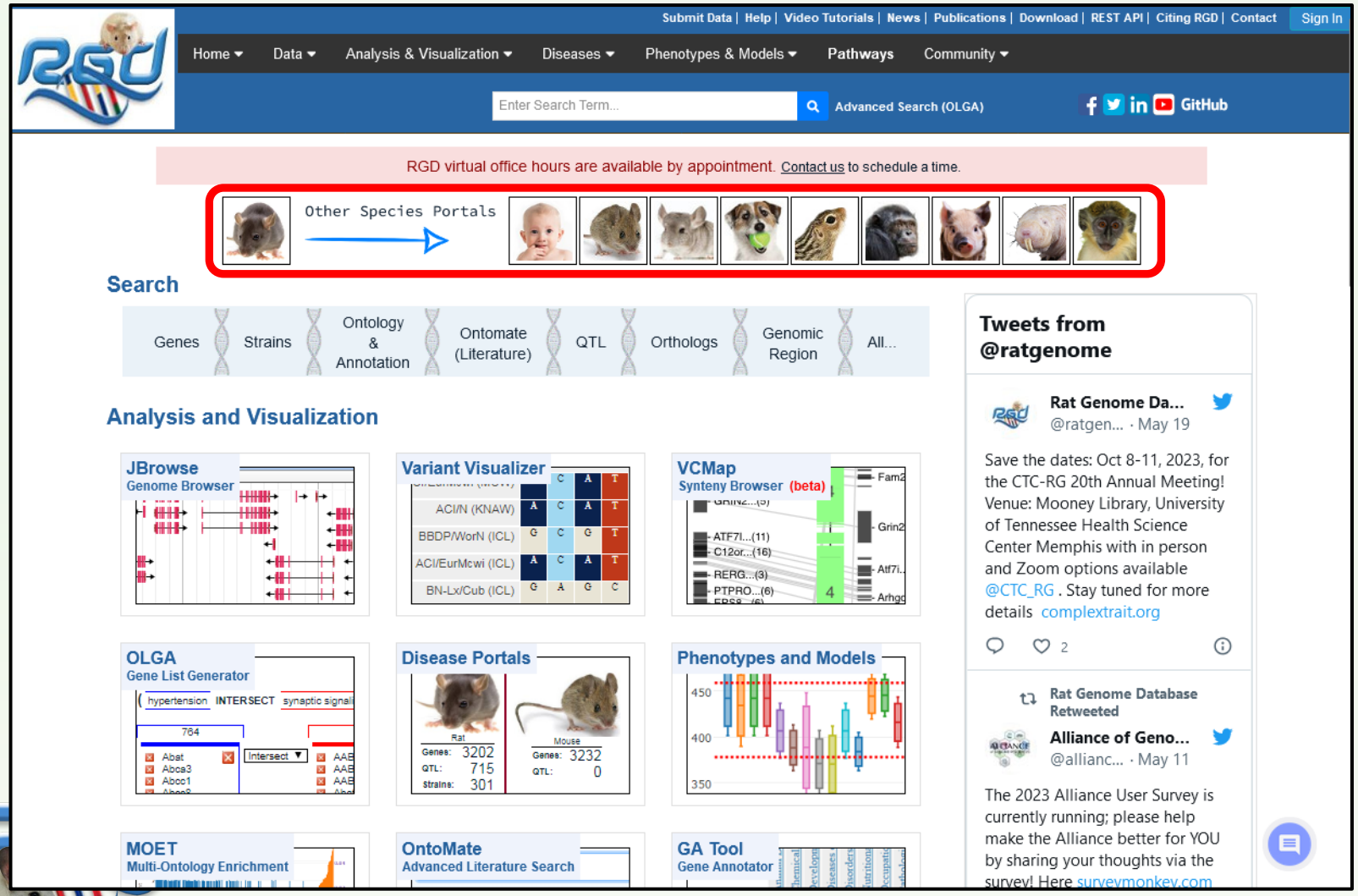
ISOM 22ND International Symposium on Recent Advances in Otitis Media

RGD is a multispecies resource for translational research and comparative genomics



- Houses data for ten mammalian species including human and chinchilla.
- Integrates data derived from expert literature curation with data imported from other sources including other databases and direct submissions from researchers.
- Provides an extensive and well-rounded corpus of genetic, genomic, disease and physiological data.
- Provides innovative tools for data analysis.

Physiology
MEDICAL COLLEGE OF WISCONSIN

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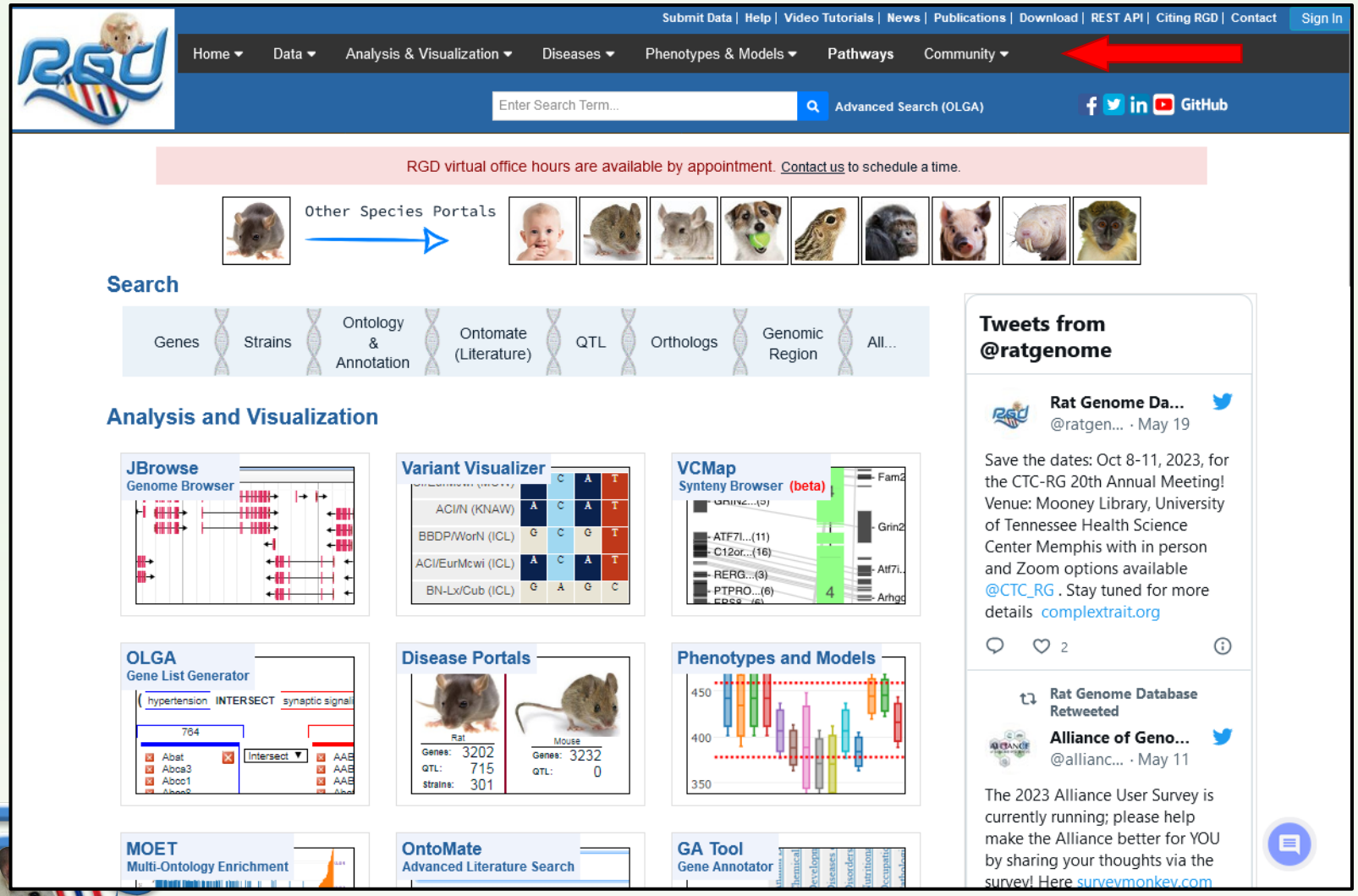

- Data and tools are accessible using the menus at the top of the page.

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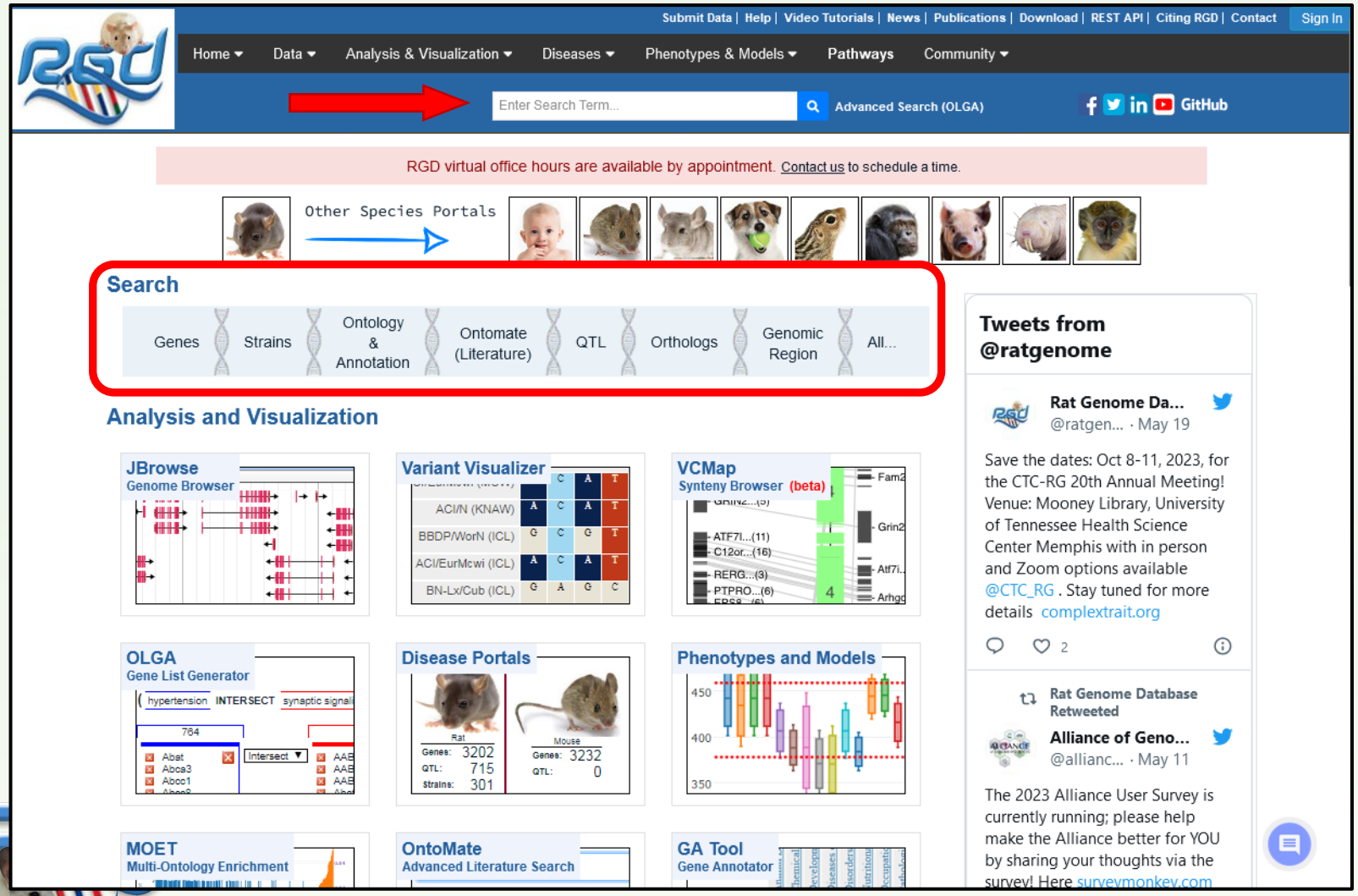

- Data and tools are accessible using the menus at the top of the page
- Data can also be accessed using the general search box or targeted searches.

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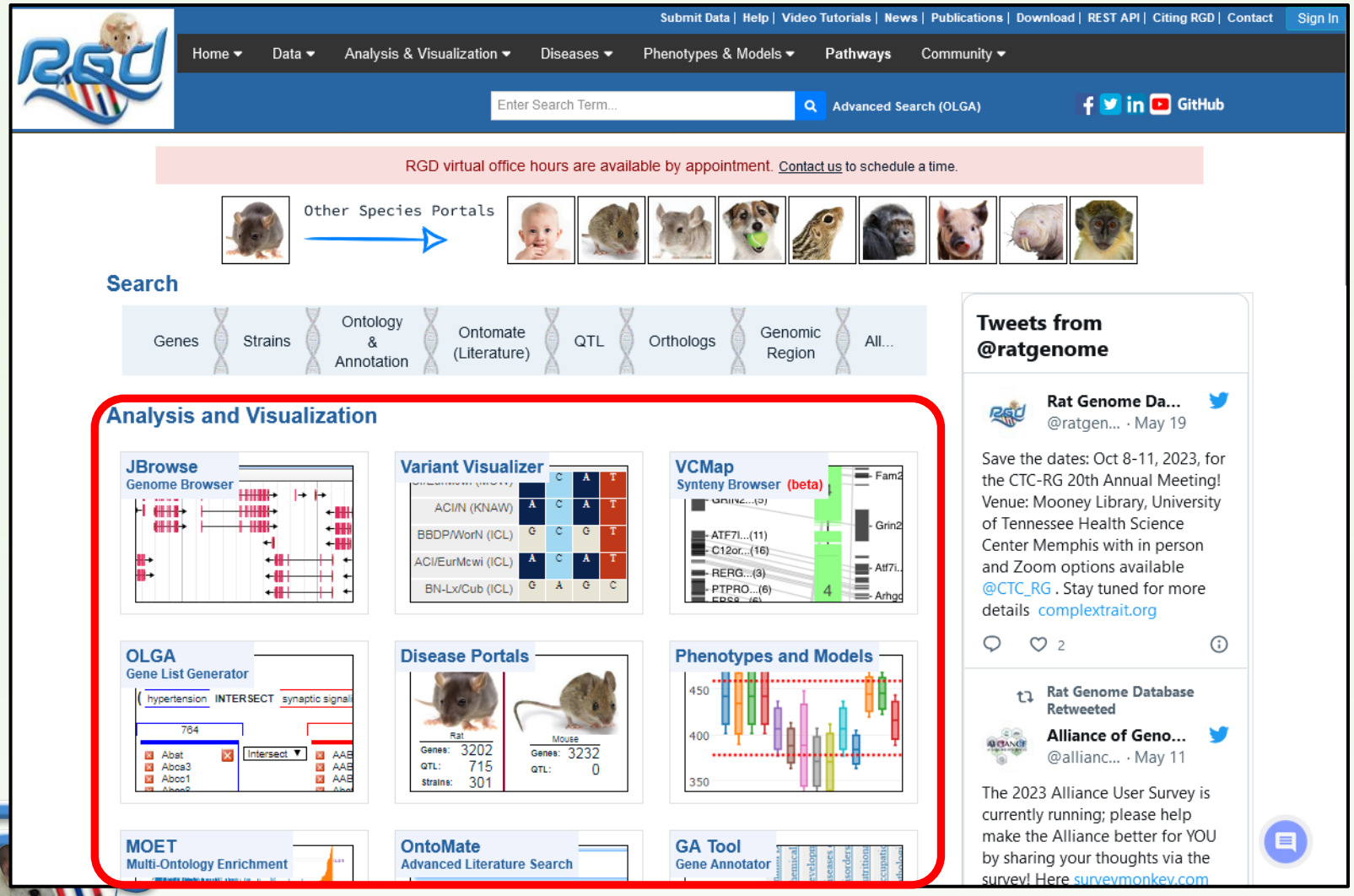

- Data and tools are accessible using the menus at the top of the page
- Data can also be accessed using the general search box or targeted searches.
- Tools can also be accessed using the Analysis and Visualization links on the front page.

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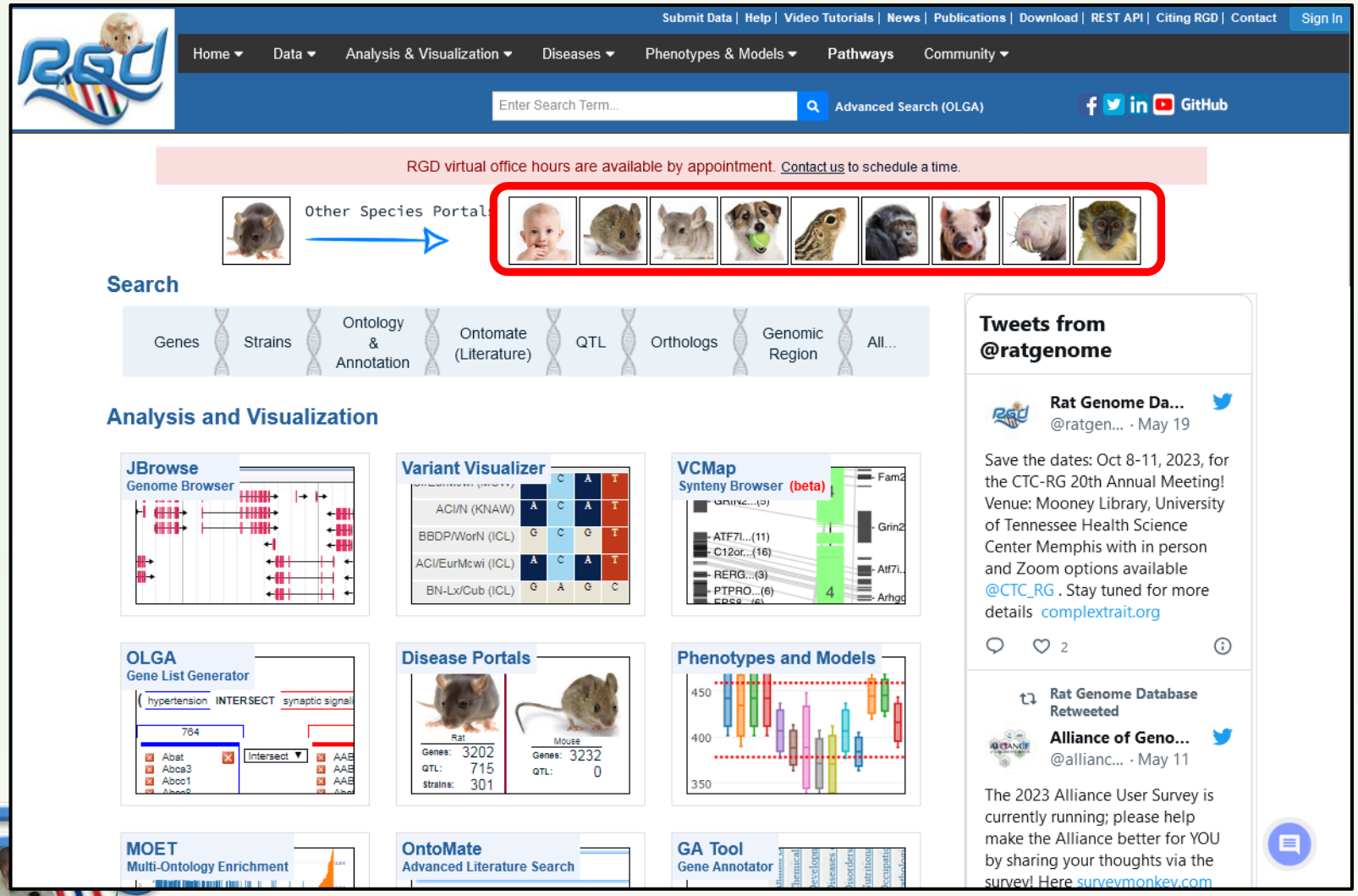

- Data and tools are accessible using the menus at the top of the page
- Data can also be accessed using the general search box or targeted searches.
- Tools can also be accessed using the Analysis and Visualization links on the front page.
- Species icons link to informational landing pages for each species.

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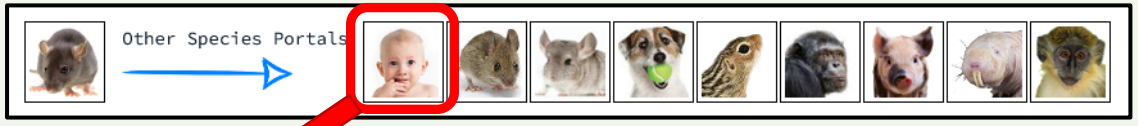
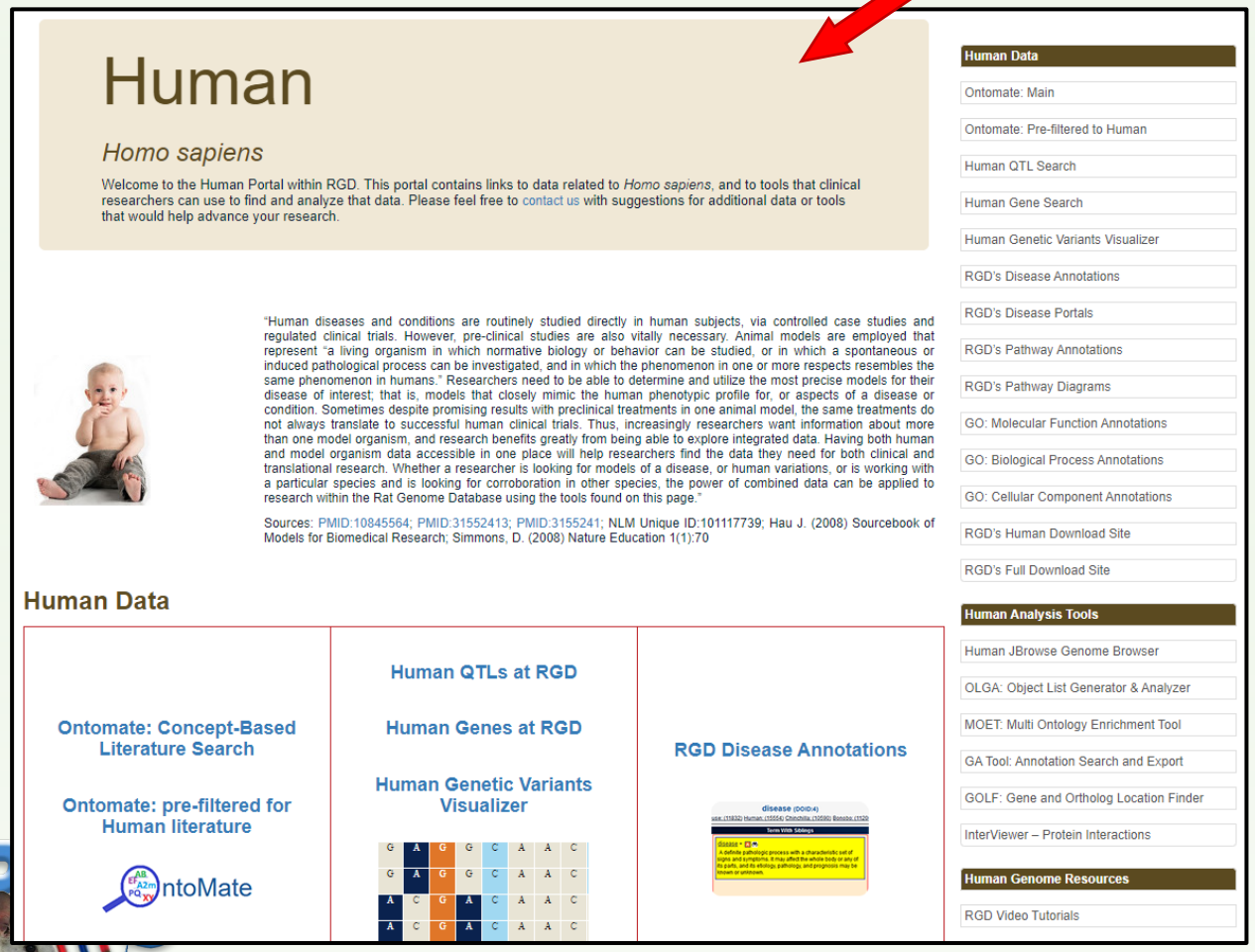
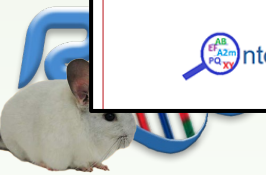
Species portals provide easy access to species-oriented information, data, and tools





As an example, this is the top of the species page for human. The layout is essentially the same for all of the species portals, although depending on the data and tools available for each, there are differences. The next few slides show the sections of the chinchilla portal.



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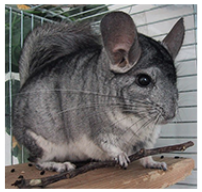
Species portals provide easy access to species-oriented information, data, and tools

Long-tailed Chinchilla

Chinchilla lanigera

Welcome to the Chinchilla Portal within RGD. This portal contains links to data related to the long-tailed chinchilla, *Chinchilla lanigera*, and to tools that chinchilla researchers can use to find and analyze that data. Please feel free to contact us with suggestions for additional data or tools that would help advance your research.



"The long-tailed chinchilla (*Chinchilla lanigera*) is used as a model for understanding the physiology, development and function of the auditory system. The chinchilla is used in several research areas, including otitis media, upper respiratory tract infections, hearing, psychoacoustics and ototoxicity. The chinchilla has been used for auditory or acoustics research because of the anatomical and physiological similarities between its inner ear and that of human (1–4). Its middle ear and Eustachian tube structures are also similar to that of humans and unlike other rodent models it is not susceptible to innate middle ear infections, making it an ideal model organism for otitis media (OM) studies (5–7). The presence of a large cephalid bulla, from which sufficient quantities of middle ear fluids can be withdrawn for microbiological and immunological assessment, is also an advantage. Most interestingly, the chinchilla has a permanently semipatulous Eustachian tube, which makes this tubal organ highly similar to the 'floppy' Eustachian tube of childhood (5). The chinchilla is recognized as an ideal model of otitis media and its use has produced critical information regarding the molecular mechanisms of pathogenesis of pneumococcal OM, the immune response to S. pneumoniae-induced OM, the efficacy of antimicrobial drugs that target S. pneumoniae, and the immunogenicity and protective efficacy of pneumococcal capsular polysaccharide vaccine antigens (8)."

Source: PMID:27173523

Chinchilla Data

Ontomate: Concept-Based Literature Search

Ontomate: pre-filtered for Chinchilla literature

Chinchilla Genes at RGD

RGD Disease Annotations

Chinchilla Otitis Media Annotations

Chinchilla Data

- Ontomate: Main
- Ontomate: pre-filtered for Chinchilla
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- RGD Disease Annotations
- Chinchilla Otitis Media Annotations
- RGD's Pathway Annotations
- RGD's Pathway Diagrams
- GO: Molecular Function Annotations
- GO: Biological Process Annotations
- GO: Cellular Component Annotations
- RGD's Chinchilla Download Site
- RGD's Full Download Site

Chinchilla Analysis Tools

- Chinchilla JBrowse Genome Browser
- OLGA: Object List Generator & Analyzer
- MOET: Multi Ontology Enrichment Tool
- GA Tool: Annotation Search and Export
- GOLF: Gene and Ortholog Location Finder
- Chinchilla PhenoMiner

Chinchilla Genome Resources

- RGD's Genome Information page
- NCBI Genome Page

The top of the chinchilla portal gives information about chinchilla as a model of human disease

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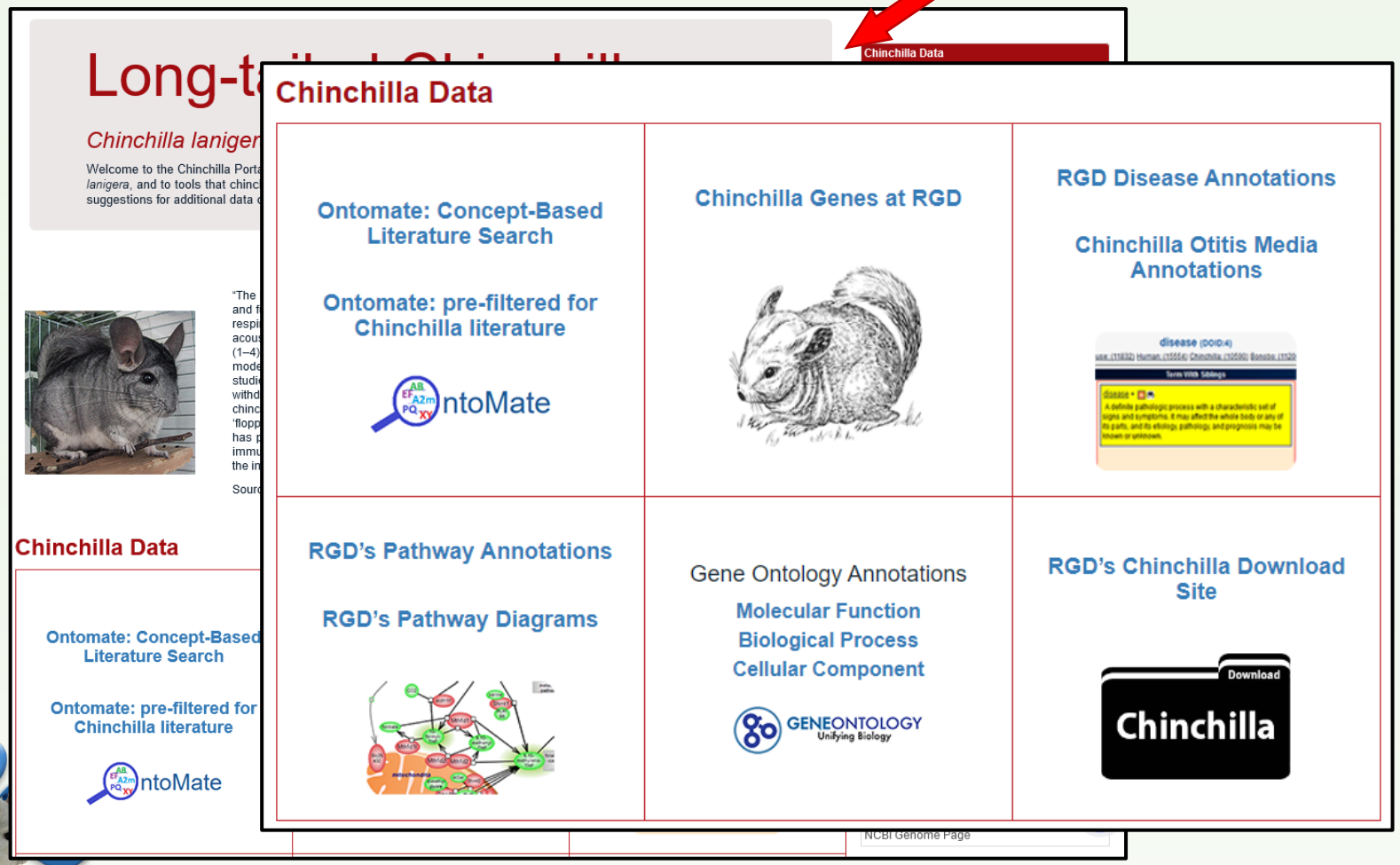

The second section provides links to chinchilla data, including a link to RGD's download site for chinchilla data.

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Species portals provide easy access to species-oriented information, data, and tools

Chinchilla Data

Tools for Chinchilla Data Analysis

Chinchilla JBrowse Genome Browser

OLGA: Object List Generator & Analyzer

MOET: Multi Ontology Enrichment Tool

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GOLF: Gene and Ortholog Location Finder

Chinchilla PhenoMiner

Quantitative Phenotypes

The third section gives links to RGD tools with chinchilla already selected as the species.

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Species portals provide easy access to species-oriented information, data, and tools

In the fourth section there are links to gene and genome information at RGD, NCBI and Ensembl.

Chinchilla Data

Chinchilla Data

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Ontomate: Concept-Based
Literature Search

Ontomate: pre-filtered for
Chinchilla literature

Tools for Chinchilla Data Analysis

Chinchilla JBrowse
Genome Browser

GA Tool:
Annotation Search and Expo

Genome and Gene Resources

RGD's Chinchilla Genome Information Page for Chinchilla

Chinchilla Taxonomy Page

Chinchilla Species Browser

Chinchilla Genome Page

ChiLan1.0 Assembly Page

Ensembl's Chinchilla Information Page

Chinchilla Assembly, Gene Annotation and Statistics at Ensembl

Quantitative Phenotypes

Physiology

MEDICAL COLLEGE OF WISCONSIN

Species portals provide easy access to species-oriented information, data, and tools

All of these are also available in the right sidebar, along with links to chinchilla research laboratories and selected publications.

Chinchilla Analysis Tools

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Chinchilla Genome Resources

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Featured Chinchilla Research

- Lauren O. Bakaletz, Ph.D.
- Garth Ehrlich, Ph.D.
- Wenzhou Hong, Ph.D.
- Joseph E. Kerschner, M.D.
- Kevin Mason, Ph.D.

RGD Publications

- The Chinchilla Research Resource Database: resource for an otolaryngology disease model.
- PhenoMiner: quantitative phenotype curation at the rat genome database.

Chinchilla Data

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Chinchilla JBrowse Genome Browser

RGD's Chinchilla Genome Information Page for Chinchilla

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Quantitative Phenotypes

NCBI

Quantitative Phenotypes

We will highlight just a few of the items listed on this page, starting with the Chinchilla PhenoMiner.

Chinchilla Data

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Ontomate: pre-filtered for Chinchilla literature

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Chinchilla Analysis Tools

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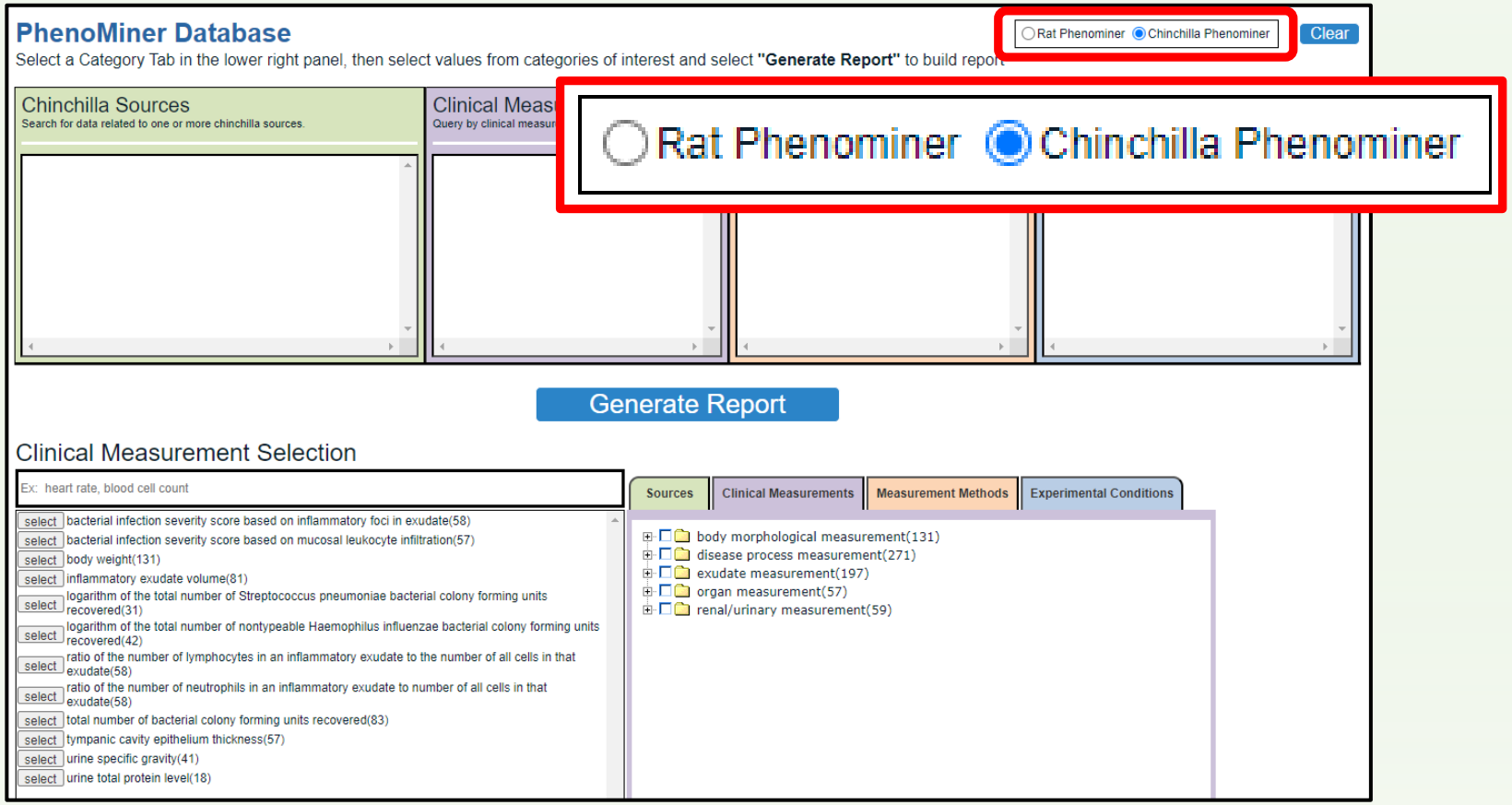
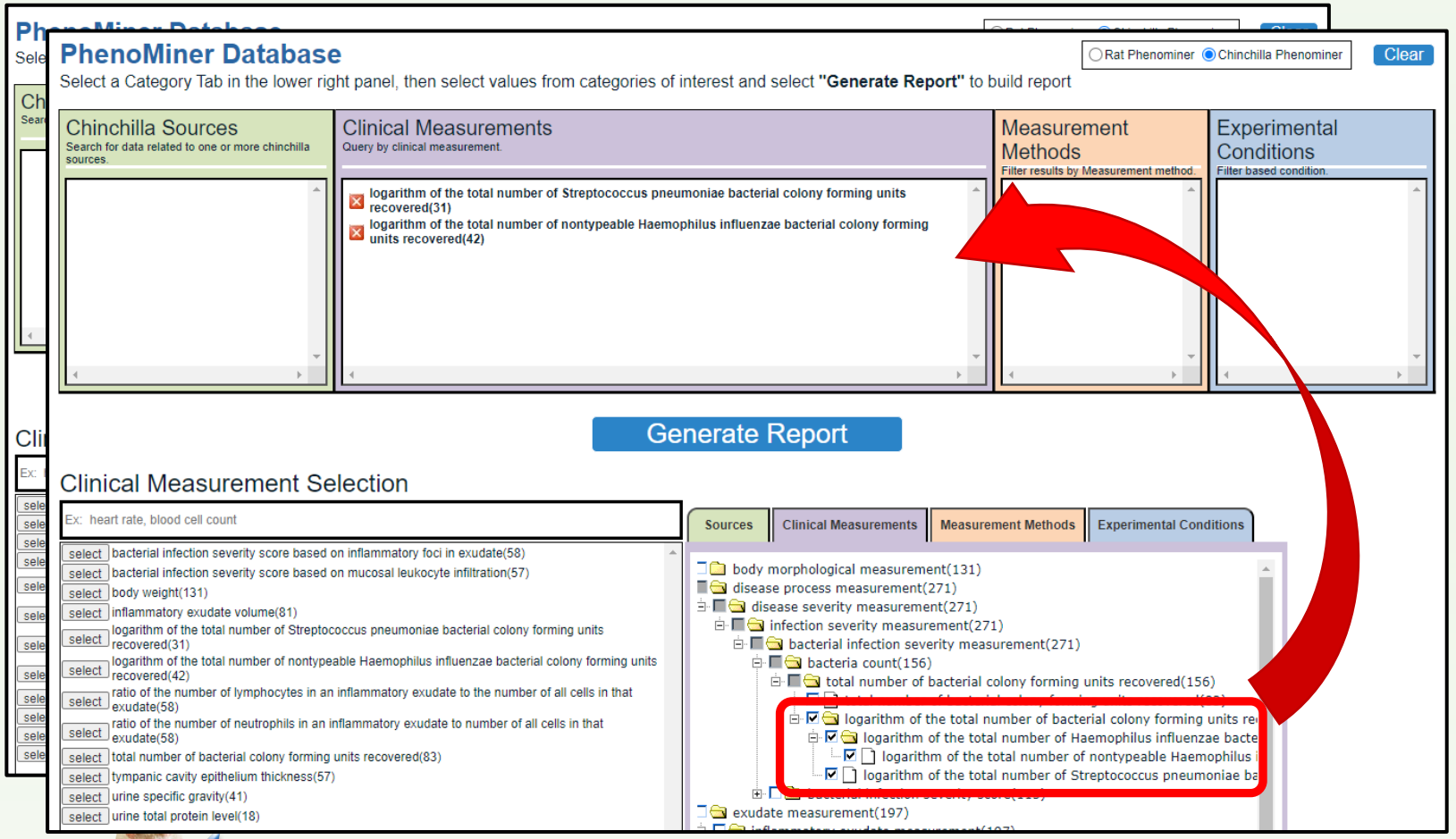
PhenoMiner is a data mining tool for quantitative phenotype measurement data for rat and chinchilla



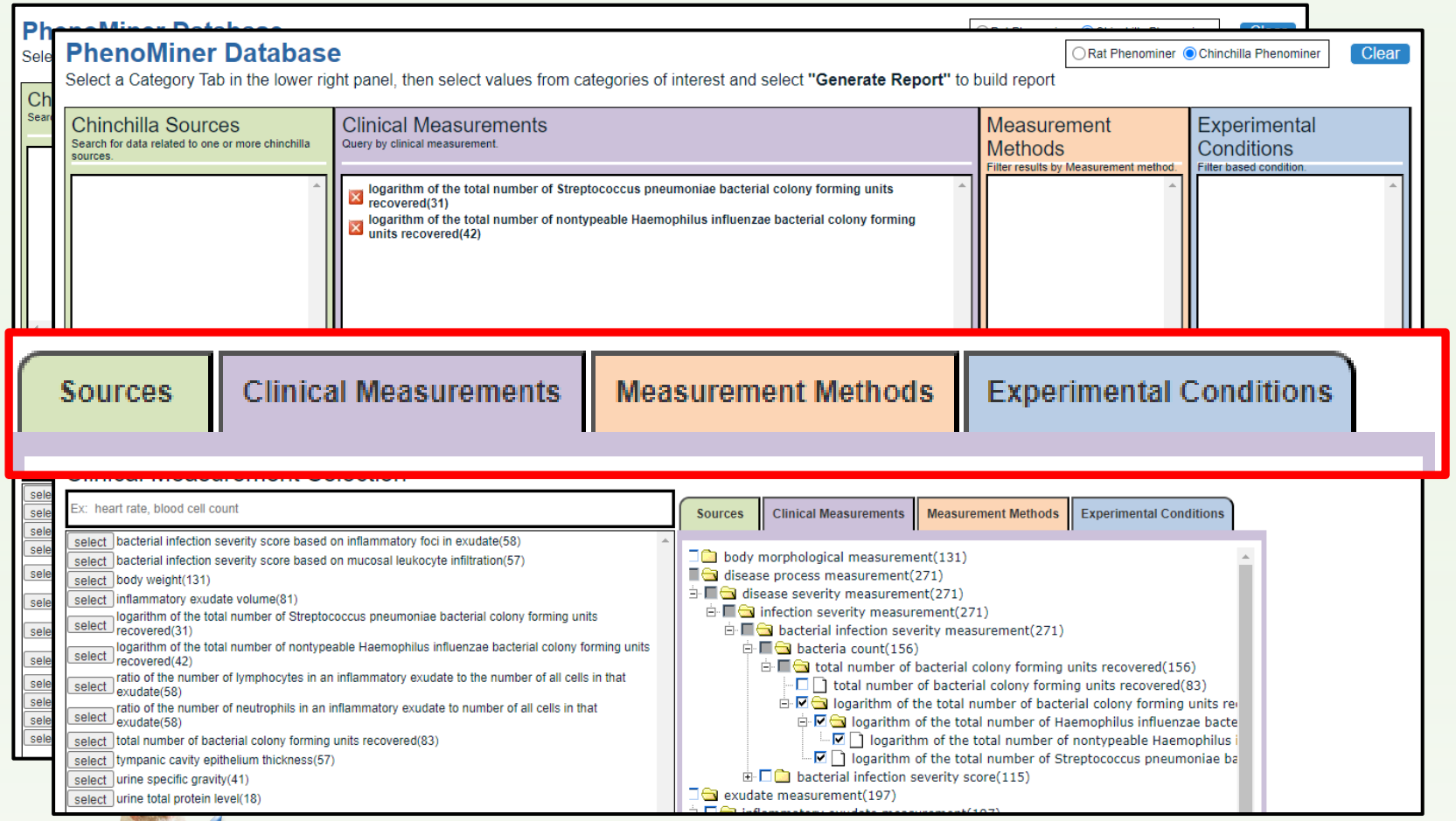
- The data in PhenoMiner is a combination of curated data from the literature and direct submissions from researchers.
- The link from the Chinchilla portal directly accesses the Chinchilla PhenoMiner.

PhenoMiner is a data mining tool for quantitative phenotype measurement data for rat and chinchilla



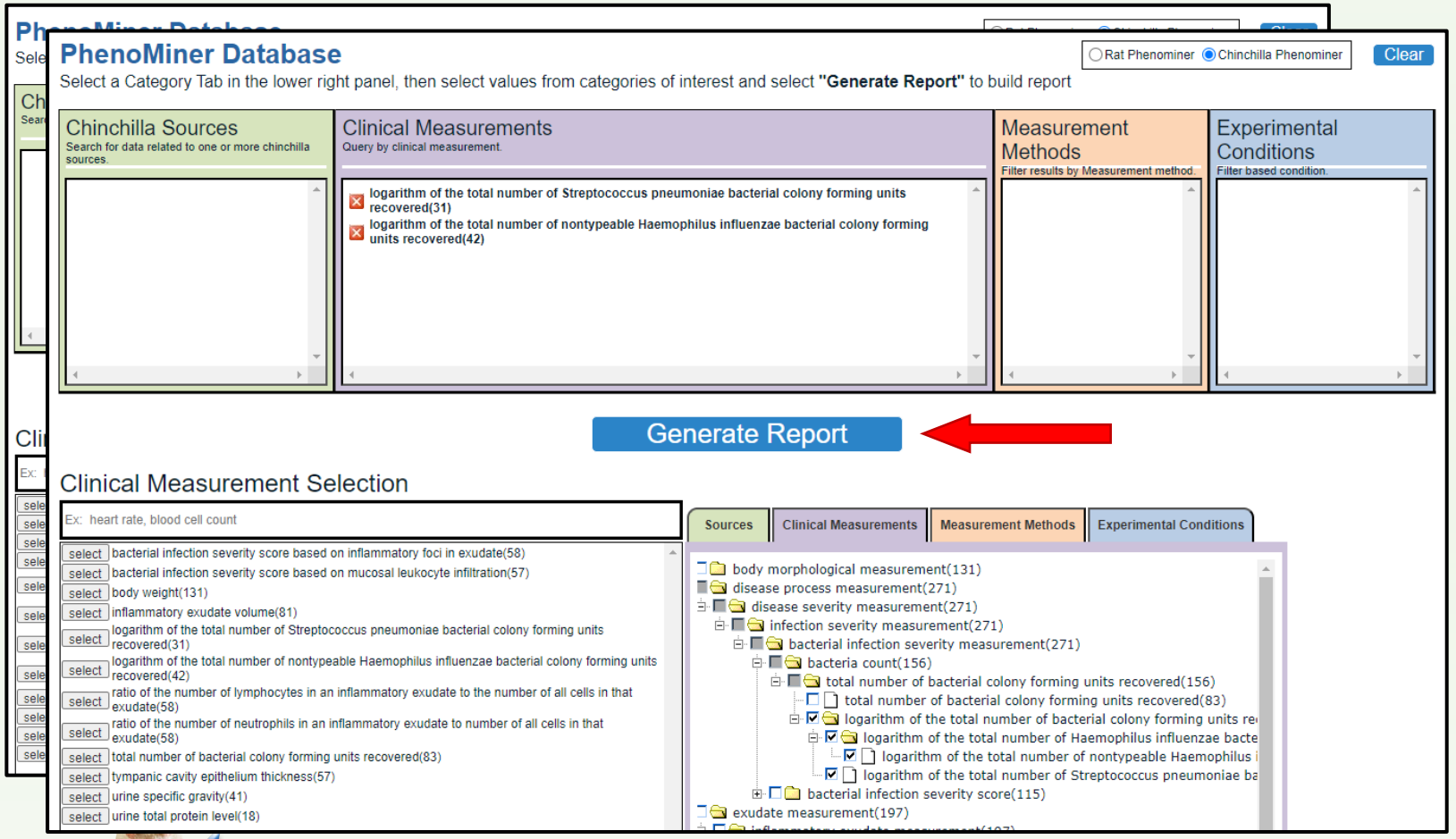
- Selecting terms in the bottom section of the PhenoMiner home page adds them to the corresponding bins in the top section.

PhenoMiner is a data mining tool for quantitative phenotype measurement data for rat and chinchilla



- Data can be chosen on the basis of any or all of four criteria:
  - Chinchilla Sources
  - Clinical Measurement (what was measured)
  - Measurement Method (how it was measured)
  - Experimental Conditions (under what condition(s) was it measured)

PhenoMiner is a data mining tool for quantitative phenotype measurement data for rat and chinchilla



- Once selections have been made, click "Generate Report" to view the associated data.

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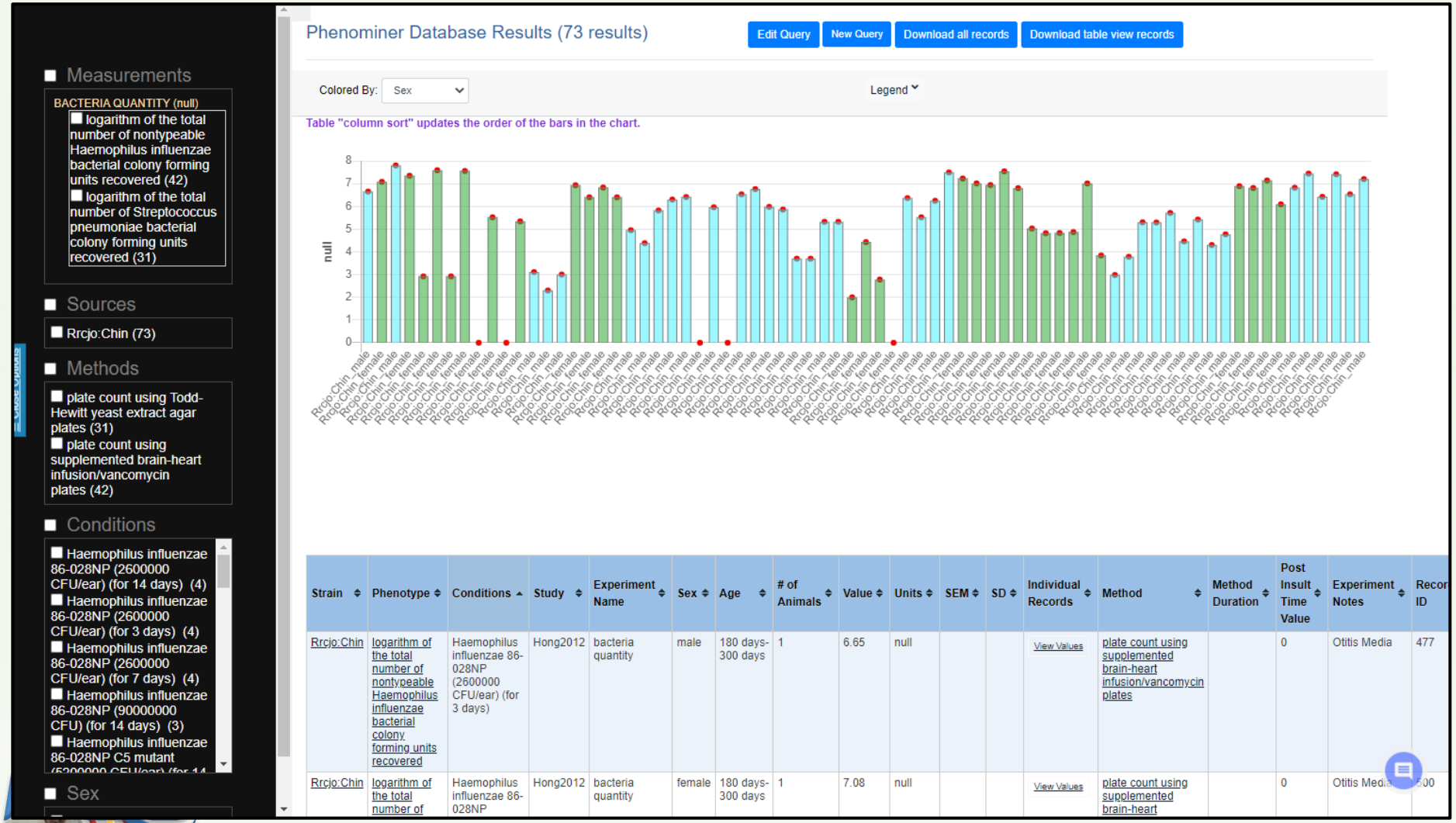
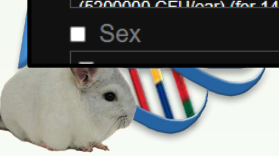


- Results consist of three parts:
  - A graph
  - A detailed table
  - Filters in the left sidebar.
- The three sections work together so filters selected on the left remove bars from the graph and rows from the table, and sorting the table reorders bars in the graph.



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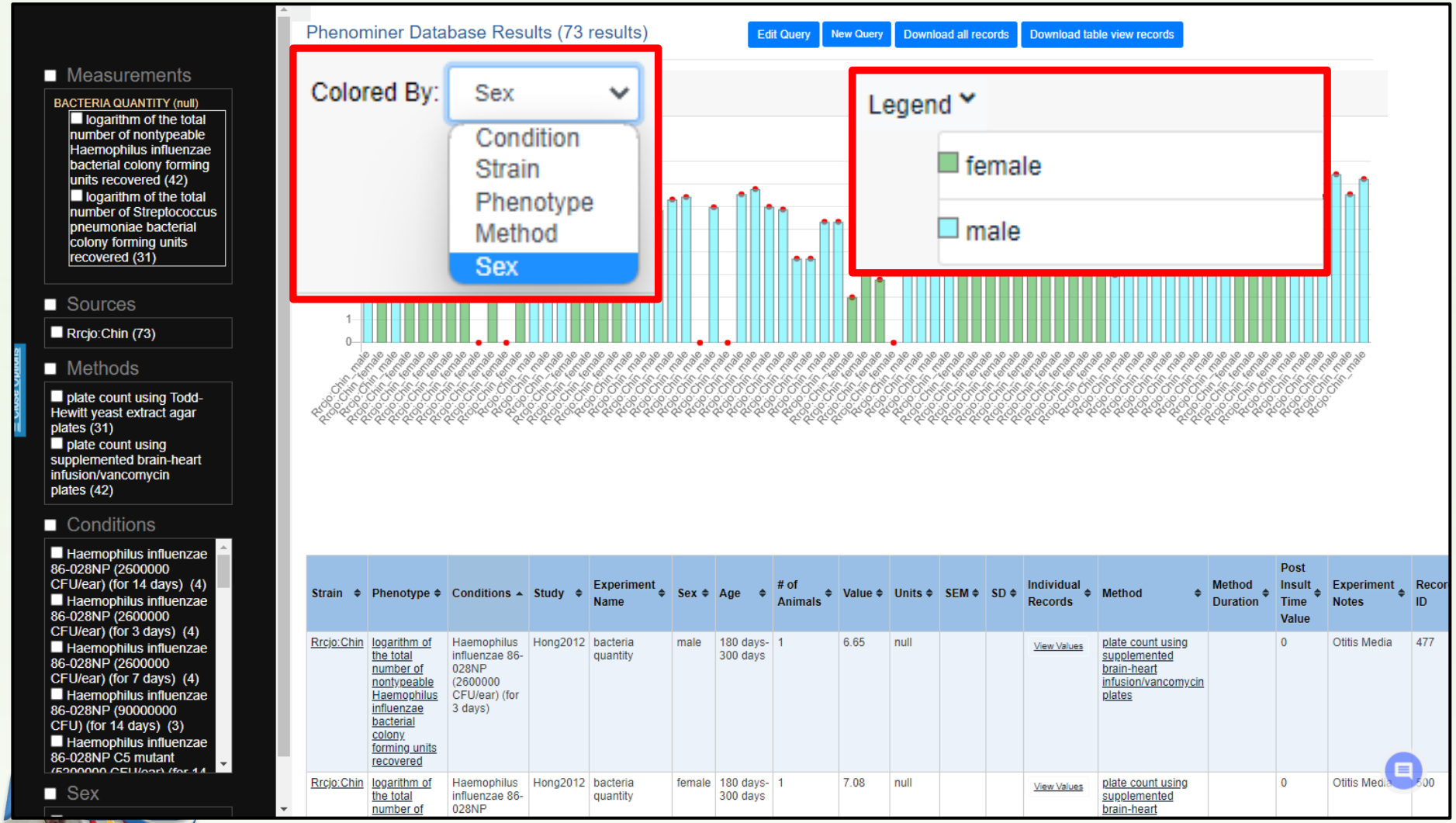
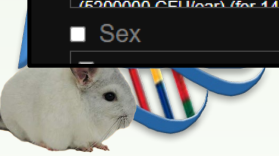


- The "Colored by"functionality gives options for coloring the bars of the graph.
- The default is to color by condition but any of the options can be selected.
- A dropdown legend is available to indicate what color corresponds to each possible value for the selected experimental variable.



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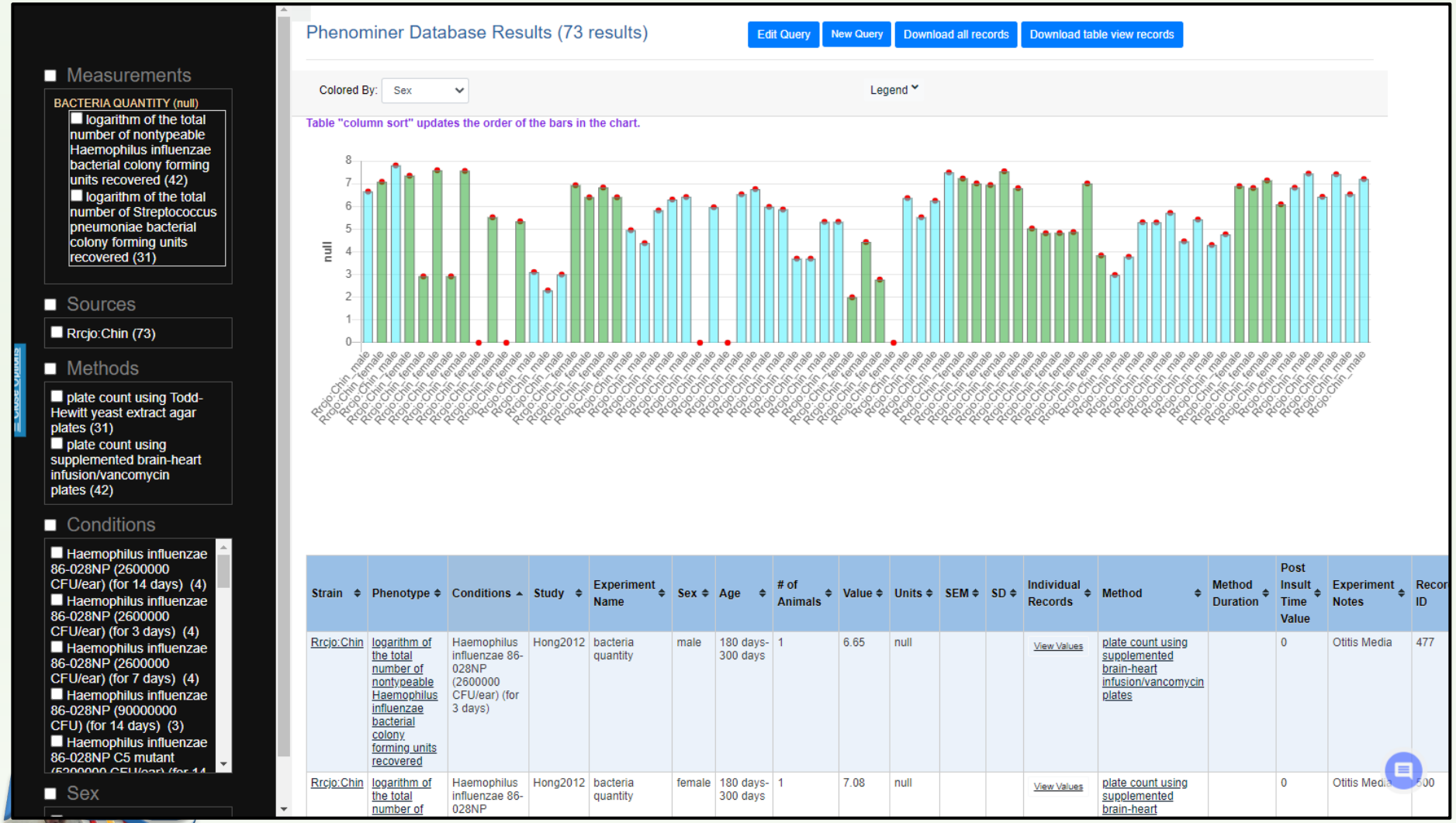
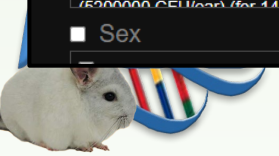


- Here the table is sorted by condition and bars are colored by the sex of the animals.



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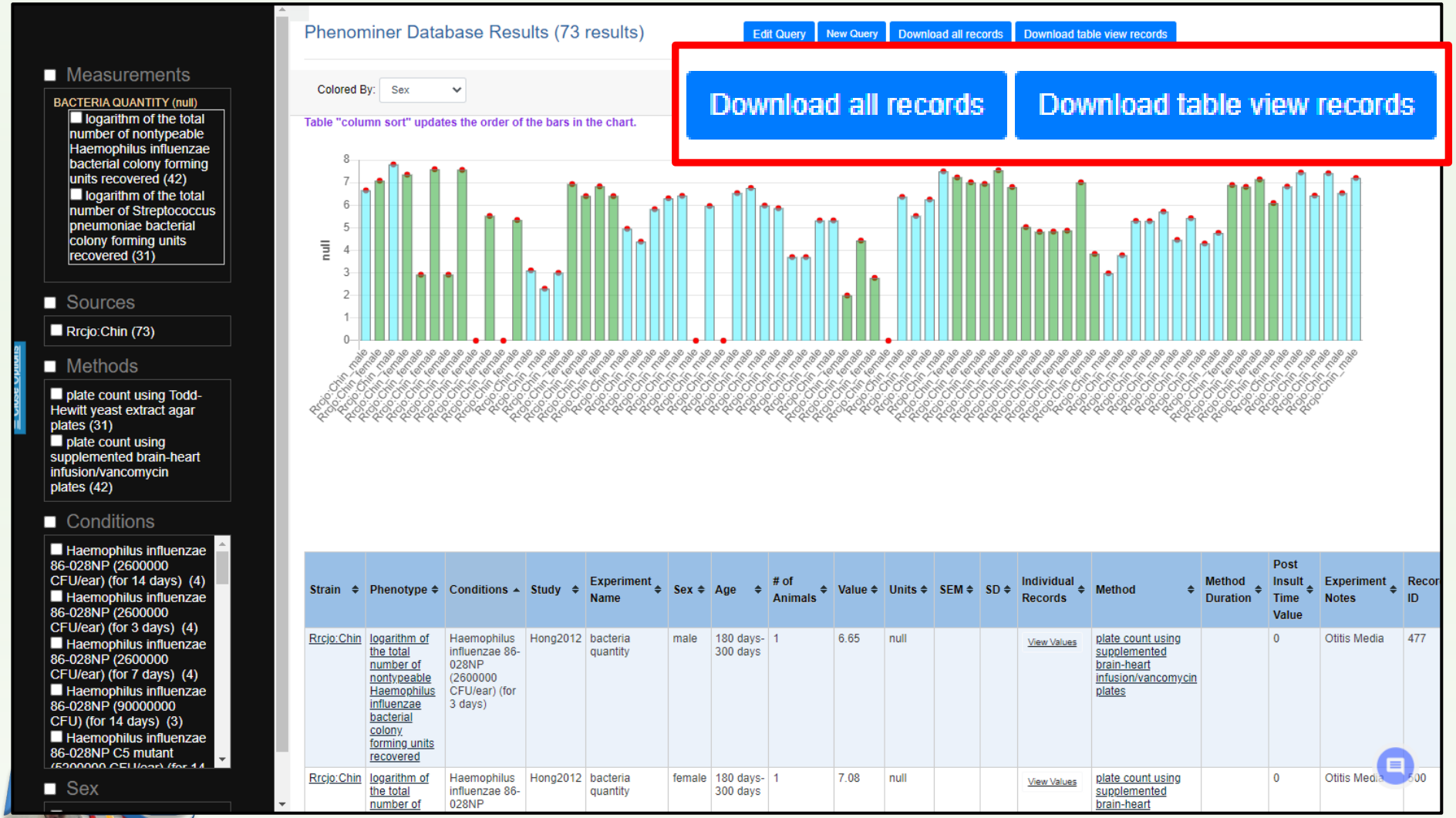
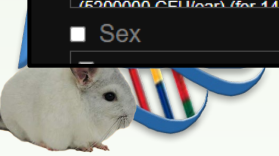


- Options are provided to download all records matching the original query or, if filters have been applied, just the filtered set of records.



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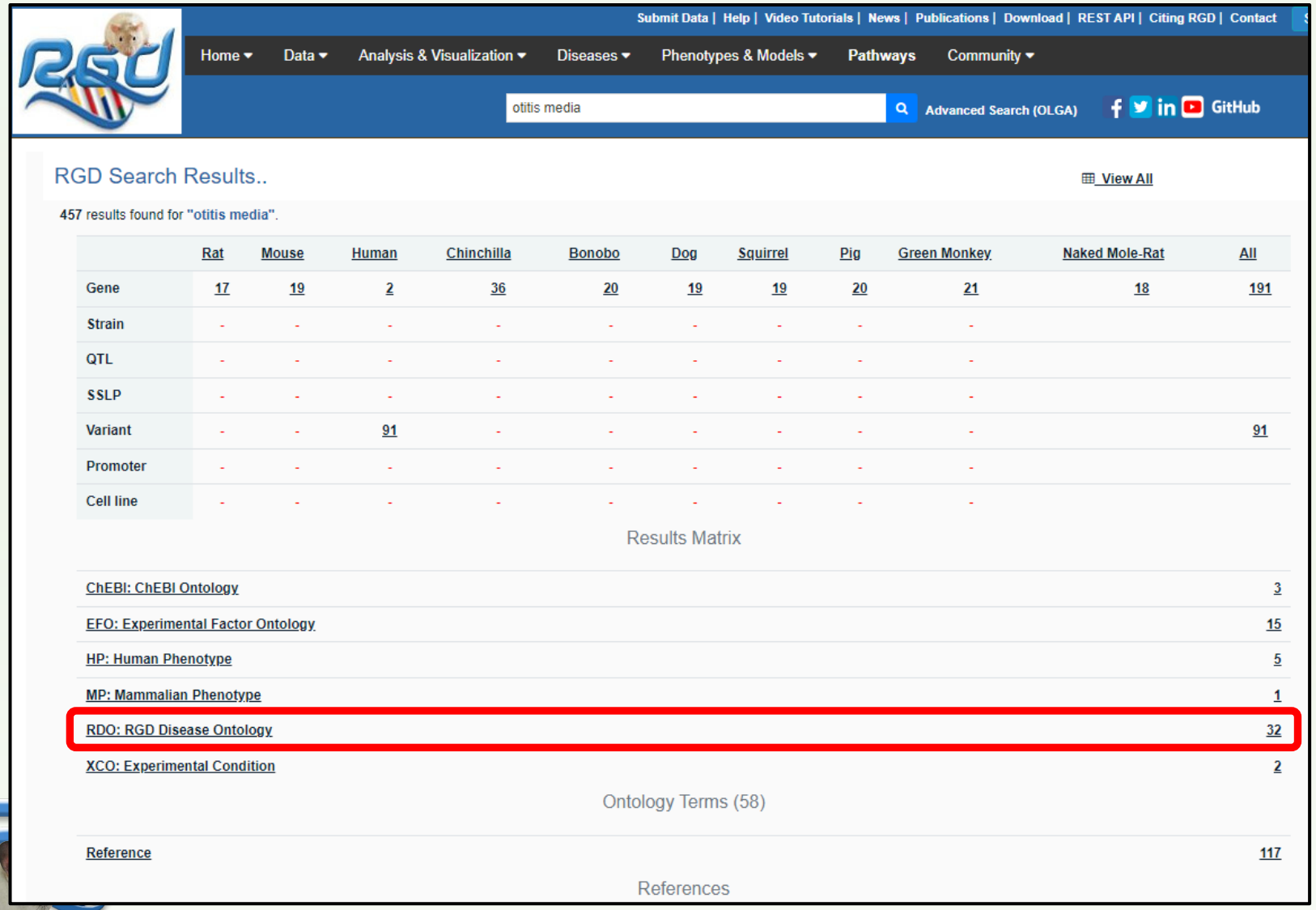
RGD's general search searches across datatypes and across species



- A search for "otitis media" returns
  - A number of genes for each species
  - Human clinical variants from NCBI's ClinVar database
  - Links to vocabularies that RGD uses for functional annotations, including the Disease Ontology.
- Clicking the line for the Disease Ontology takes you to the list of terms in that vocabulary that match the search term "otitis media".

Physiology
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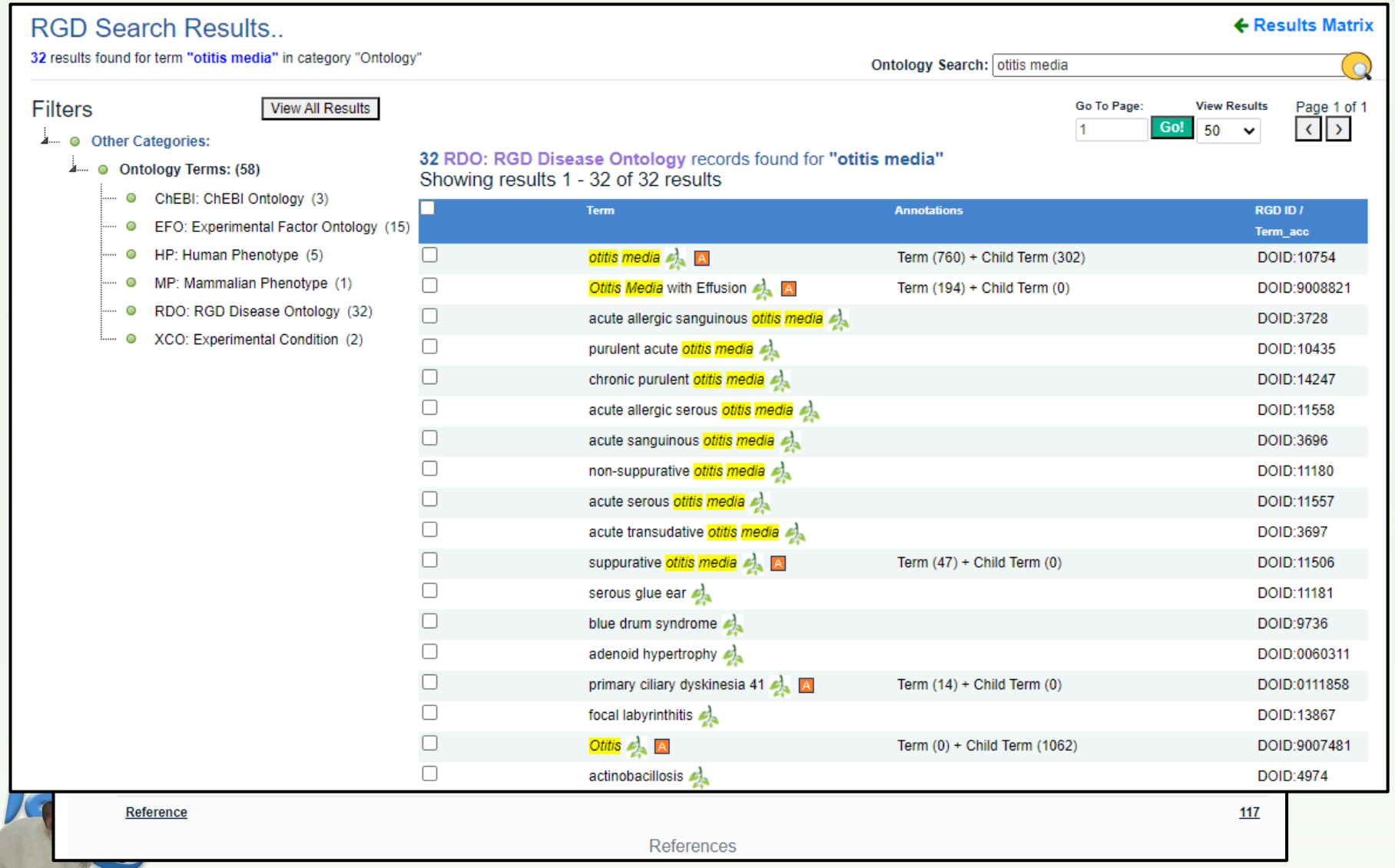
RGD's general search searches across datatypes and across species



- RGD uses ontologies for data standardization.
- An ontology is a structured vocabulary which is often shown as an upside-down tree structure with fewer more general terms toward the top and larger numbers of more specific terms as you move down the tree.

Physiology
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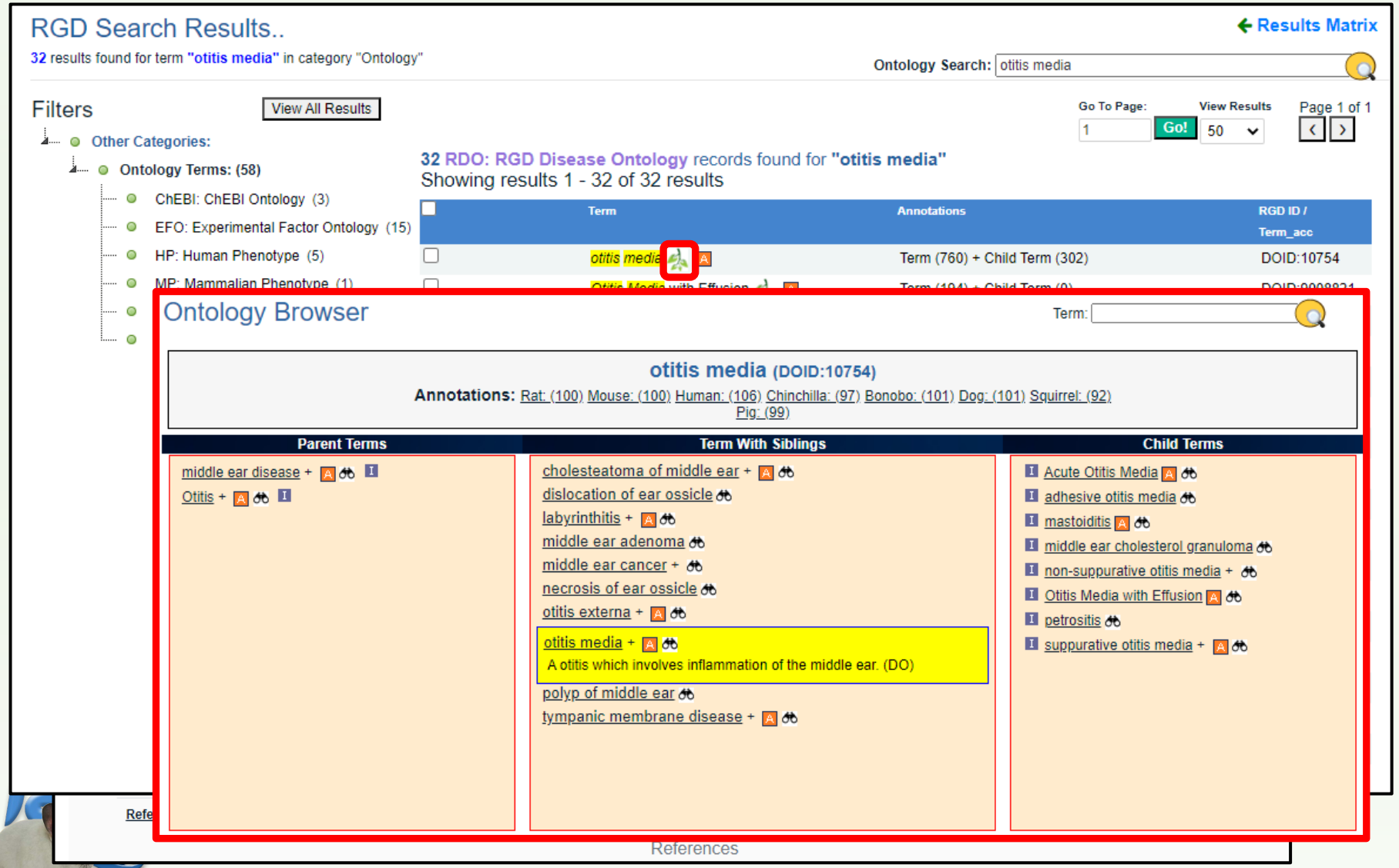
RGD's general search searches across datatypes and across species



- RGD uses ontologies for data standardization.
- An ontology is a structured vocabulary which is often shown as an upside-down tree structure with fewer more general terms toward the top and larger numbers of more specific terms as you move down the tree.
- The leaf icon in the search results list takes you to that term in RGD's ontology browser which makes it very easy to navigate up the tree to the more general term and down the tree to the more specific ones.

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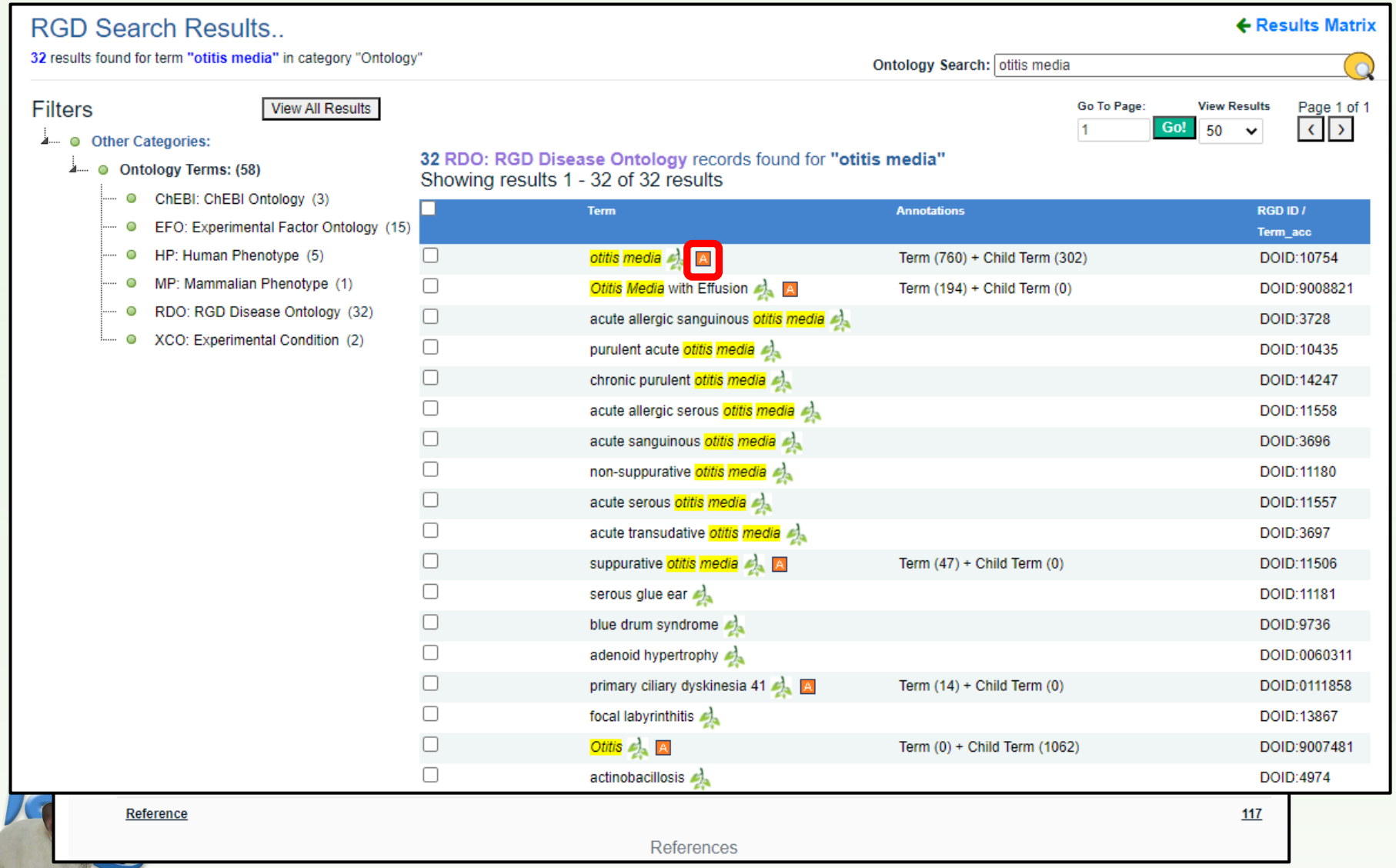
RGD's general search searches across datatypes and across species



- The "A" icon links to the ontology report page as seen in the next slide.

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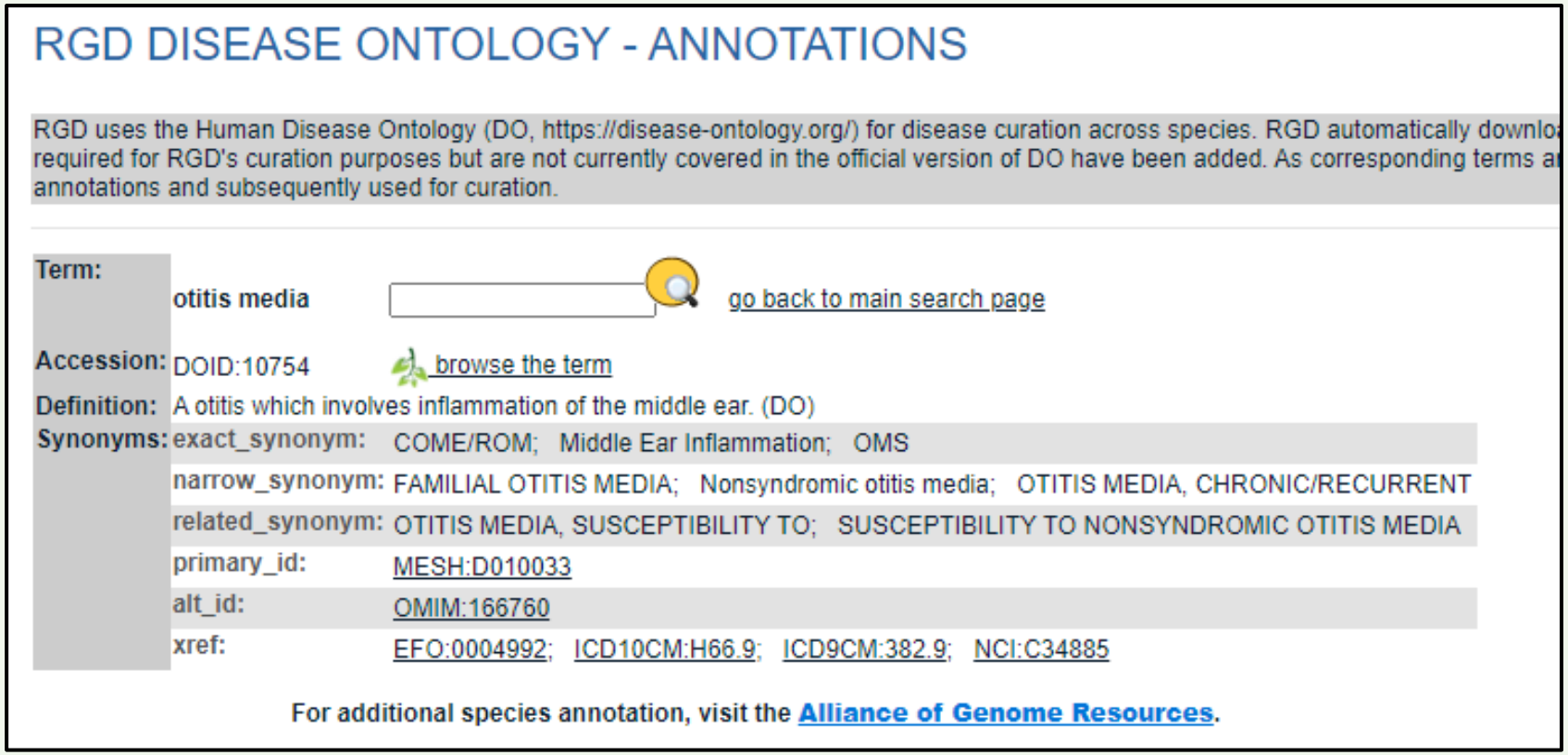
RGD's Disease Report page for Otitis Media



RGD DISEASE ONTOLOGY - ANNOTATIONS

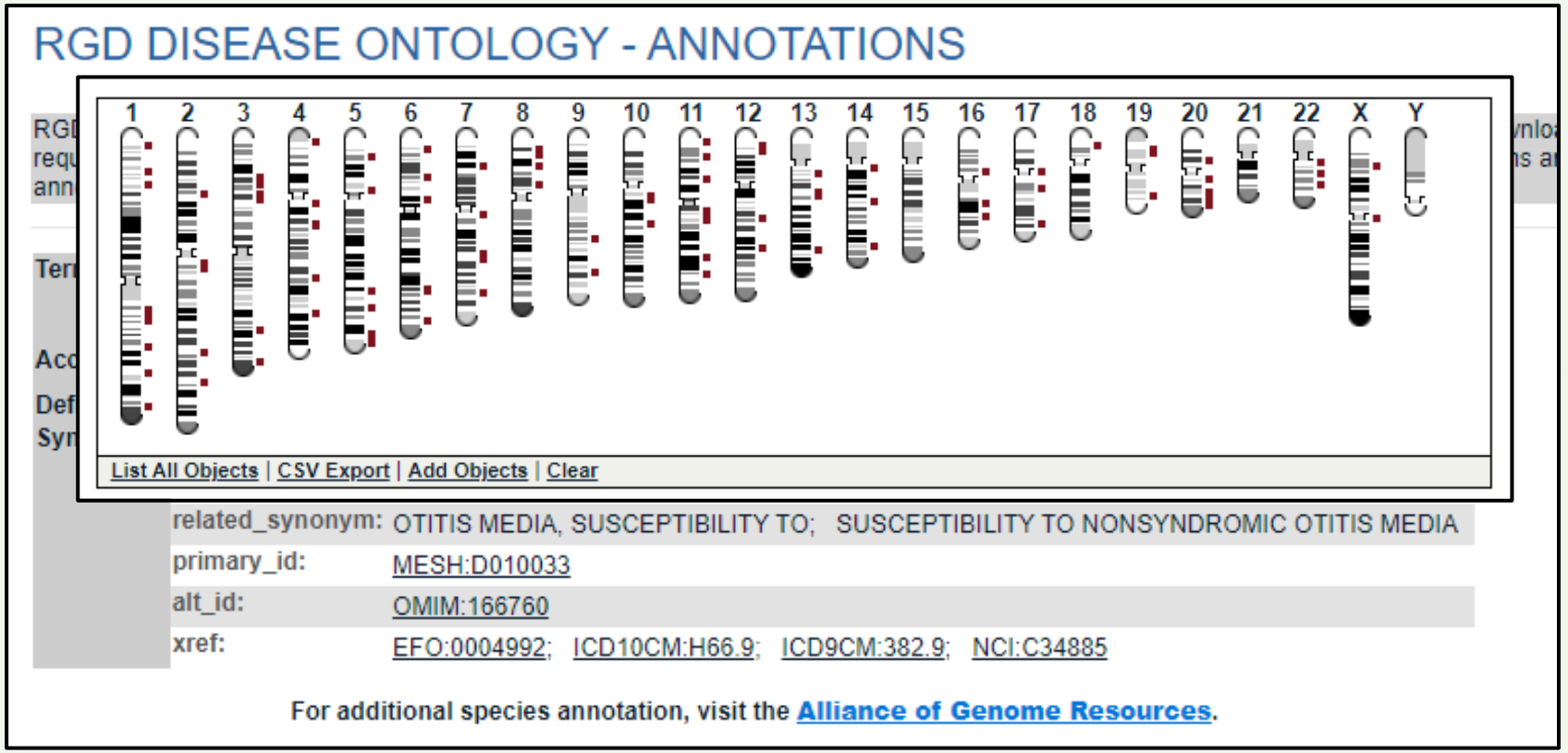
RGD uses the Human Disease Ontology (DO, https://disease-ontology.org/) for disease curation across species. RGD automatically downlo
required for RGD's curation purposes but are not currently covered in the official version of DO have been added. As corresponding terms a
annotations and subsequently used for curation.

Term:	**otitis media**	go back to main search page
Accession:	DOID:10754	browse the term
Definition:	A otitis which involves inflammation of the middle ear. (DO)	
Synonyms:	exact_synonym:	COME/ROM; Middle Ear Inflammation; OMS
	narrow_synonym:	FAMILIAL OTITIS MEDIA; Nonsyndromic otitis media; OTITIS MEDIA, CHRONIC/RECURRENT
	related_synonym:	OTITIS MEDIA, SUSCEPTIBILITY TO; SUSCEPTIBILITY TO NONSYNDROMIC OTITIS MEDIA
	primary_id:	MESH:D010033
	alt_id:	OMIM:166760
	xref:	EFO:0004992; ICD10CM:H66.9; ICD9CM:382.9; NCI:C34885

For additional species annotation, visit the Alliance of Genome Resources.

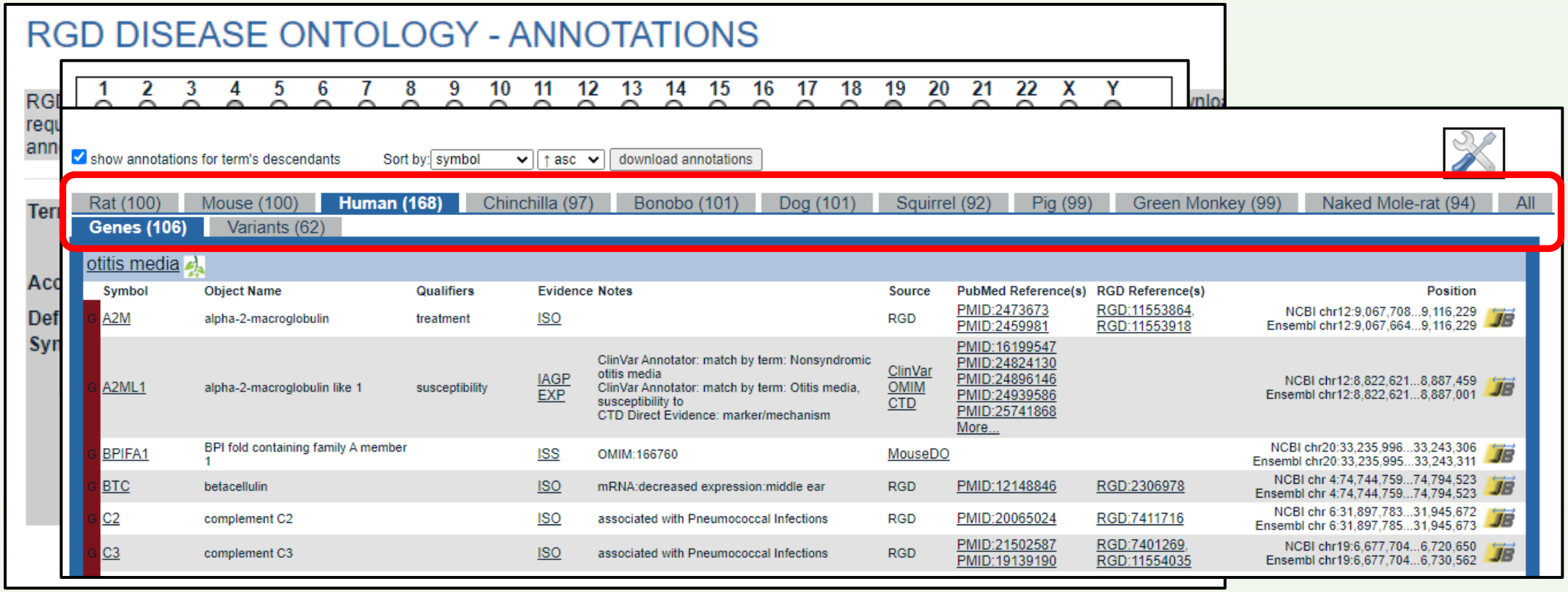
- The top of the disease report page gives information about the term, including the definition, synonyms for the term and links to related terms in other vocabularies and information in other databases such as the Online Mendelian Inheritance in Man (OMIM) database.

RGD's Disease Report page for Otitis Media



- Where possible a genome-level view of the genes annotated to the term is shown. For rat, the genome level view also shows positions for QTLs and mapped strains annotated to the selected term.

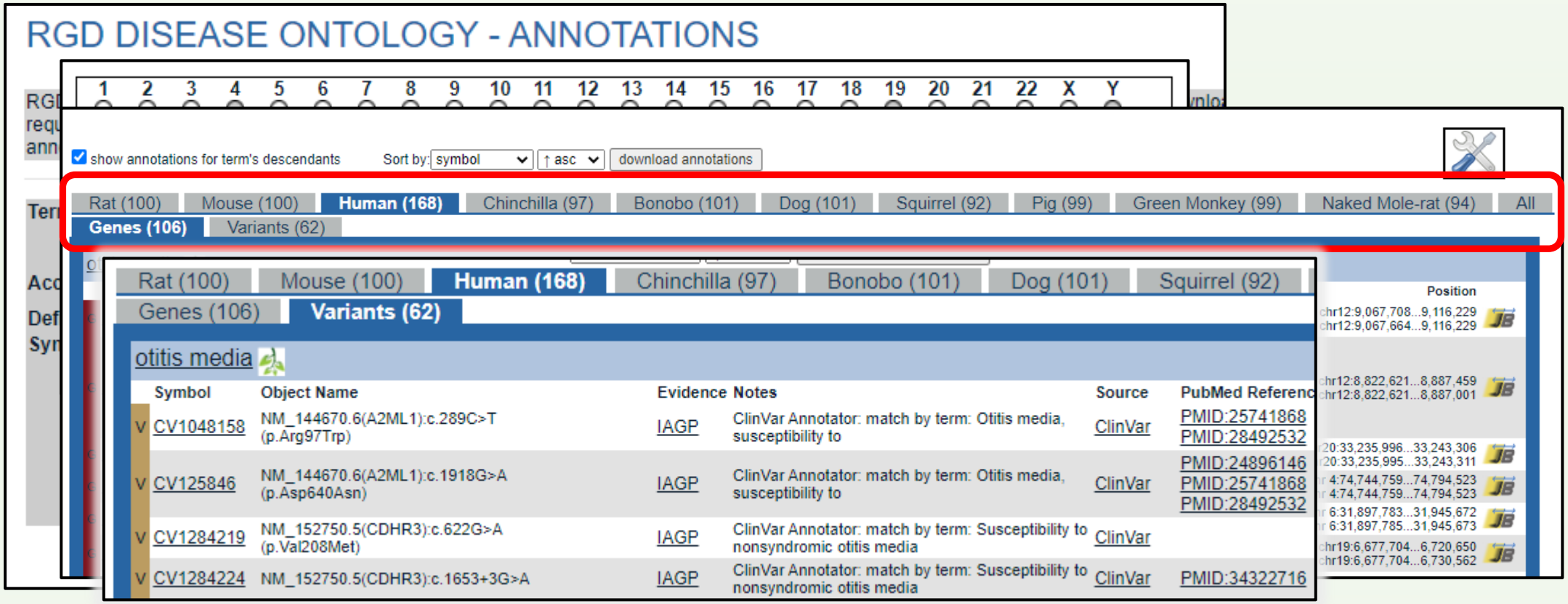
RGD's Disease Report page for Otitis Media



	Symbol	Object Name	Qualifiers	Evidence	Notes	Source	PubMed Reference(s)	RGD Reference(s)	Position
G	A2M	alpha-2-macroglobulin	treatment	ISO		RGD	PMID:2473673 PMID:2459981	RGD:11553864, RGD:11553918	NCBI chr12:9,067,708...9,116,229 Ensembl chr12:9,067,664...9,116,229
G	A2ML1	alpha-2-macroglobulin like 1	susceptibility	IAGP EXP	ClinVar Annotator: match by term: Nonsyndromic otitis media ClinVar Annotator: match by term: Otitis media, susceptibility to CTD Direct Evidence: marker/mechanism	ClinVar OMIM CTD	PMID:16199547 PMID:24824130 PMID:24896146 PMID:24939586 PMID:25741868 More...		NCBI chr12:8,822,621...8,887,459 Ensembl chr12:8,822,621...8,887,001
G	BPIFA1	BPI fold containing family A member 1		ISS	OMIM:166760	MouseDO			NCBI chr20:33,235,996...33,243,306 Ensembl chr20:33,235,995...33,243,311
G	BTC	betacellulin		ISO	mRNA:decreased expression:middle ear	RGD	PMID:12148846	RGD:2306978	NCBI chr 4:74,744,759...74,794,523 Ensembl chr 4:74,744,759...74,794,523
G	C2	complement C2		ISO	associated with Pneumococcal Infections	RGD	PMID:20065024	RGD:7411716	NCBI chr 6:31,897,783...31,945,672 Ensembl chr 6:31,897,785...31,945,673
G	C3	complement C3		ISO	associated with Pneumococcal Infections	RGD	PMID:21502587 PMID:19139190	RGD:7401269, RGD:11554035	NCBI chr19:6,677,704...6,720,650 Ensembl chr19:6,677,704...6,730,562

- For human, RGD has annotations to otitis media for both genes and ClinVar variants.

RGD's Disease Report page for Otitis Media



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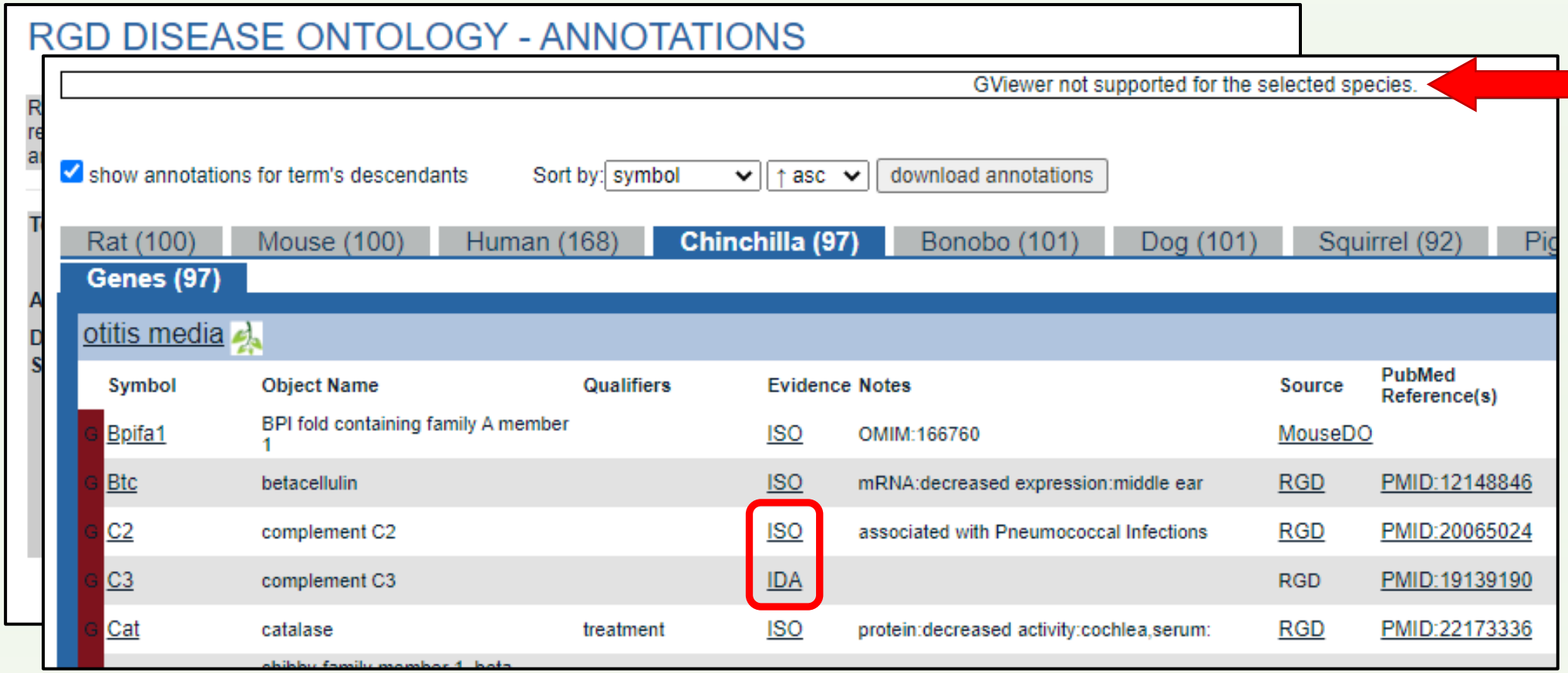
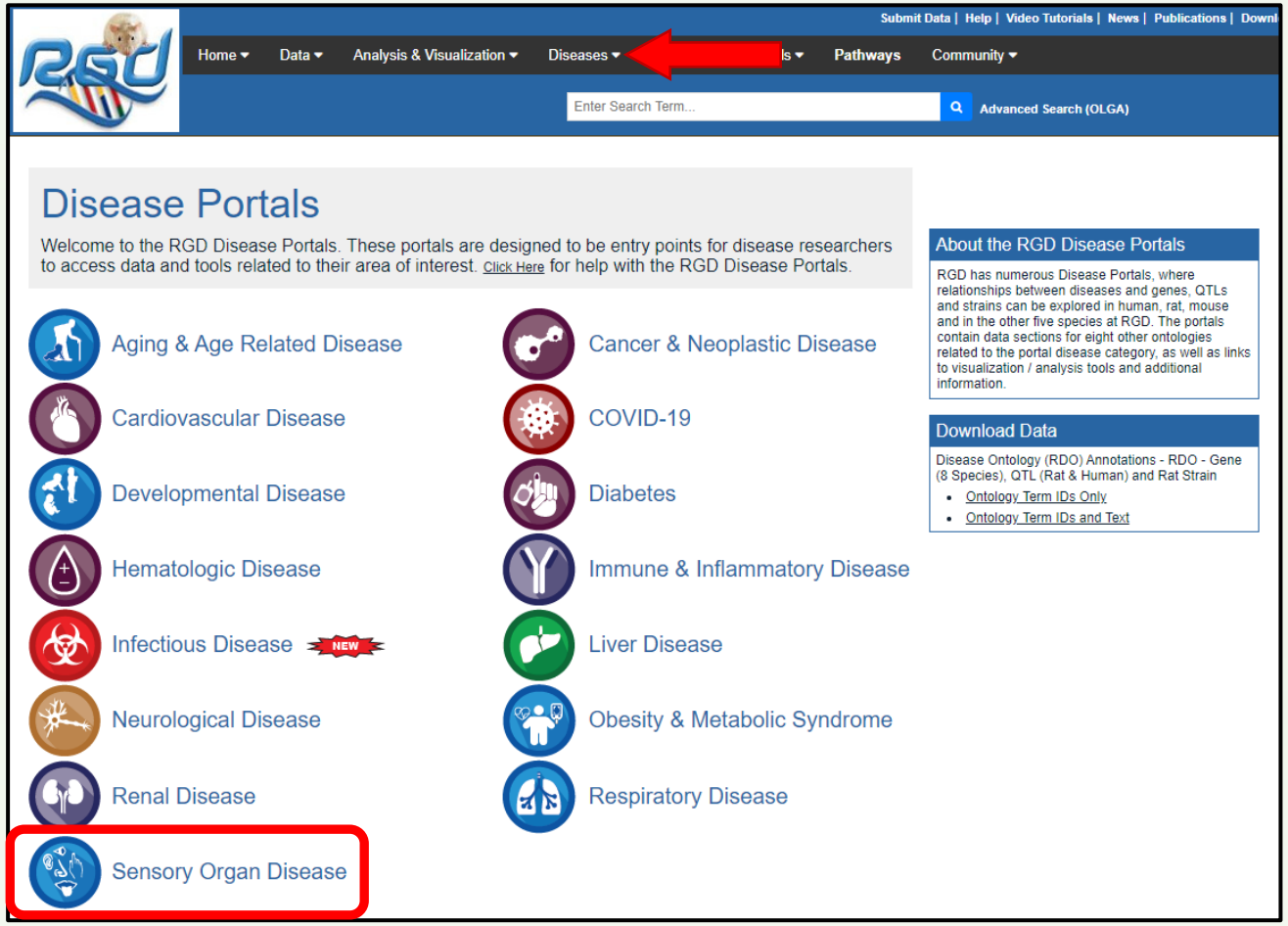
RGD's Disease Report page for Otitis Media



Note that Chinchilla does not have a genome-level view since the genome is only assembled to the point of scaffolds.

- For chinchilla, most gene annotations are derived from orthologous genes in other species ("ISO" evidence code), but RGD curators have reviewed the literature and made experimental annotations directly to chinchilla wherever possible (in this case indicated by the "inferred from direct assay" (IDA) evidence code.

RGD's Disease Portals provide consolidated views of data related to 15 disease categories



- Disease portals can be accessed via a dropdown list in the top menu bar (arrow), or by clicking the "Diseases" tab in the menu bar to go to the disease portal landing page shown here which provides links to all of the disease portals.
- We will use the Sensory Organ Disease Portal as our example.

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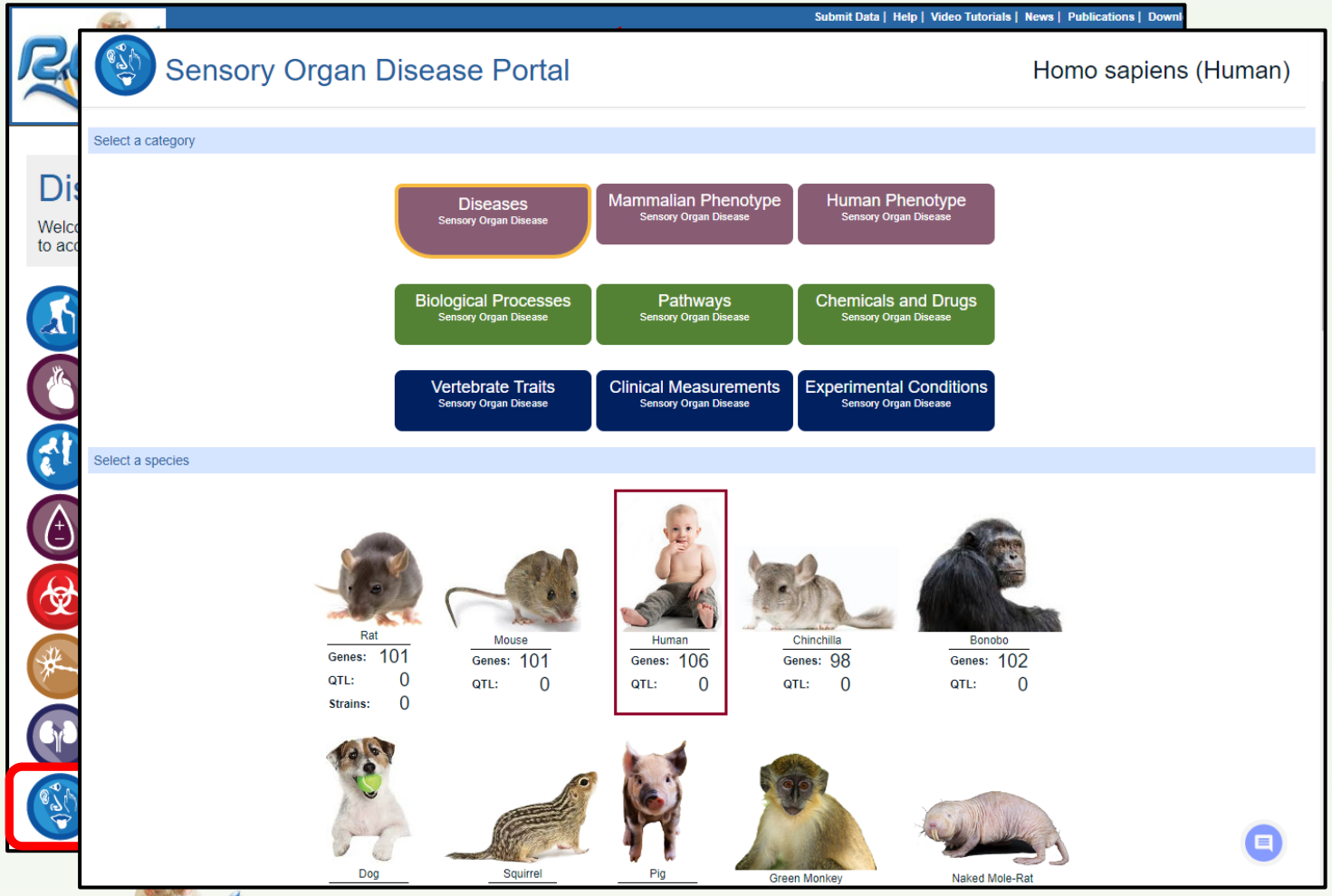

- When accessing a disease portal, first select a data type, in this case, "Diseases", which is the default.
- Select a species, here we have chosen human.

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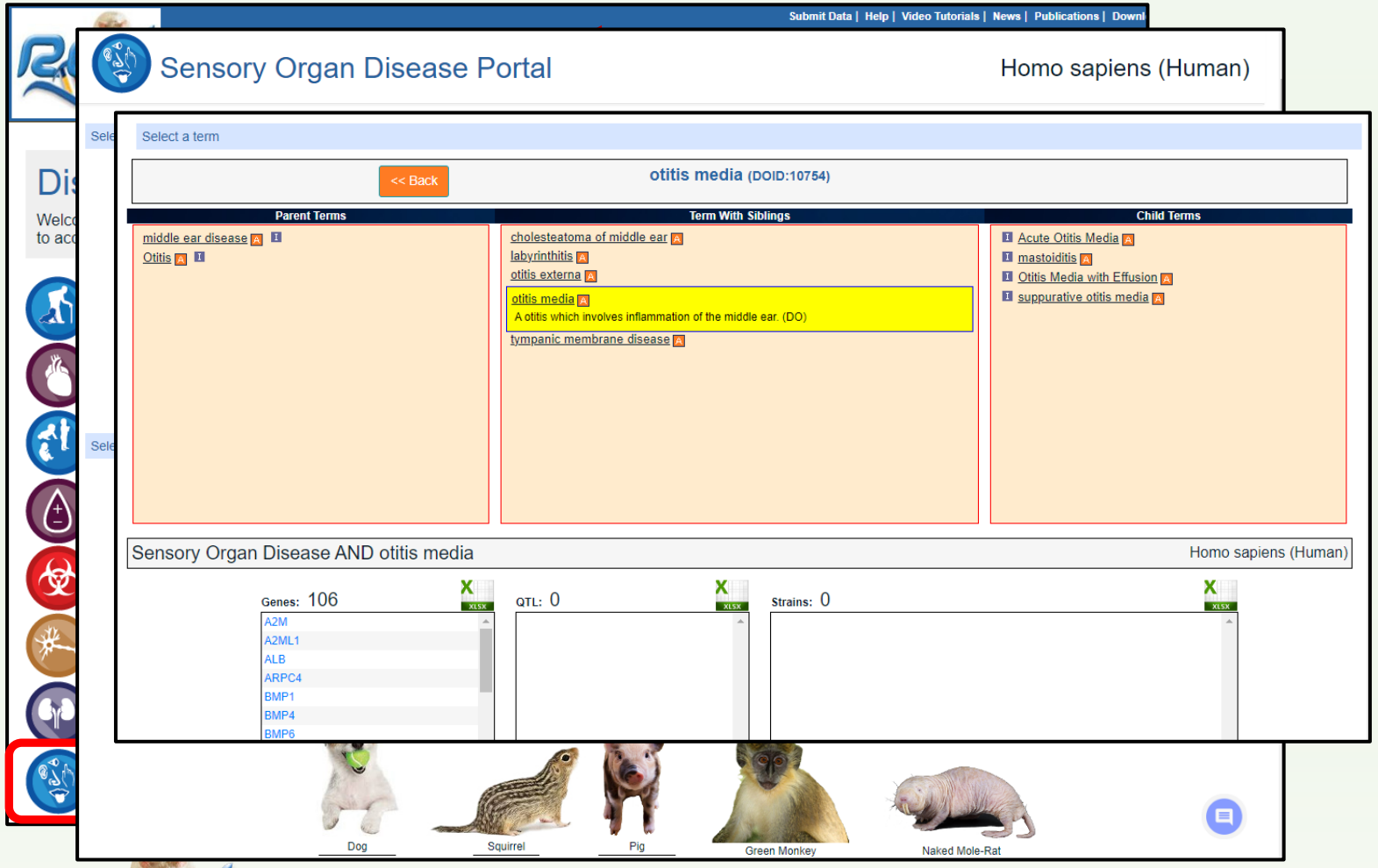

- Disease portals start with the most general term in the category, in this case, "sensory system disease".
- Use the embedded ontology browser to select a more specific term. The portals leverage the structure of the ontology to show all data, in this case, all data annotated to the selected term and it's more specific children.
- Here there are 106 human genes annotated to otitis media or a more specific child term in the list below the browser.

- As selections are made in the browser, the list of genes below and the object counts for each species above are updated on the fly.

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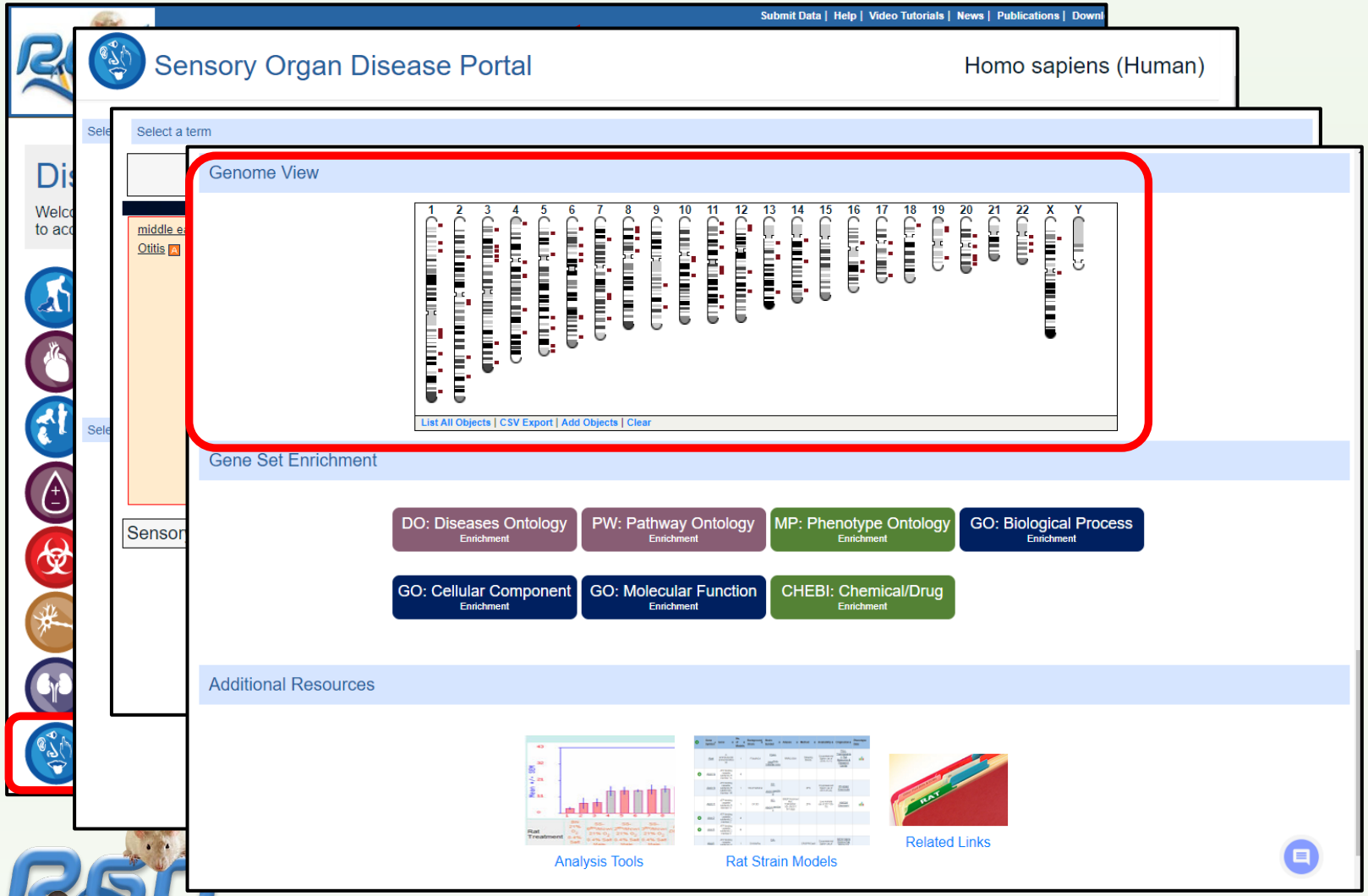

- For human and other species with chromosome-level assemblies, the genome-wide view of gene positions is shown.

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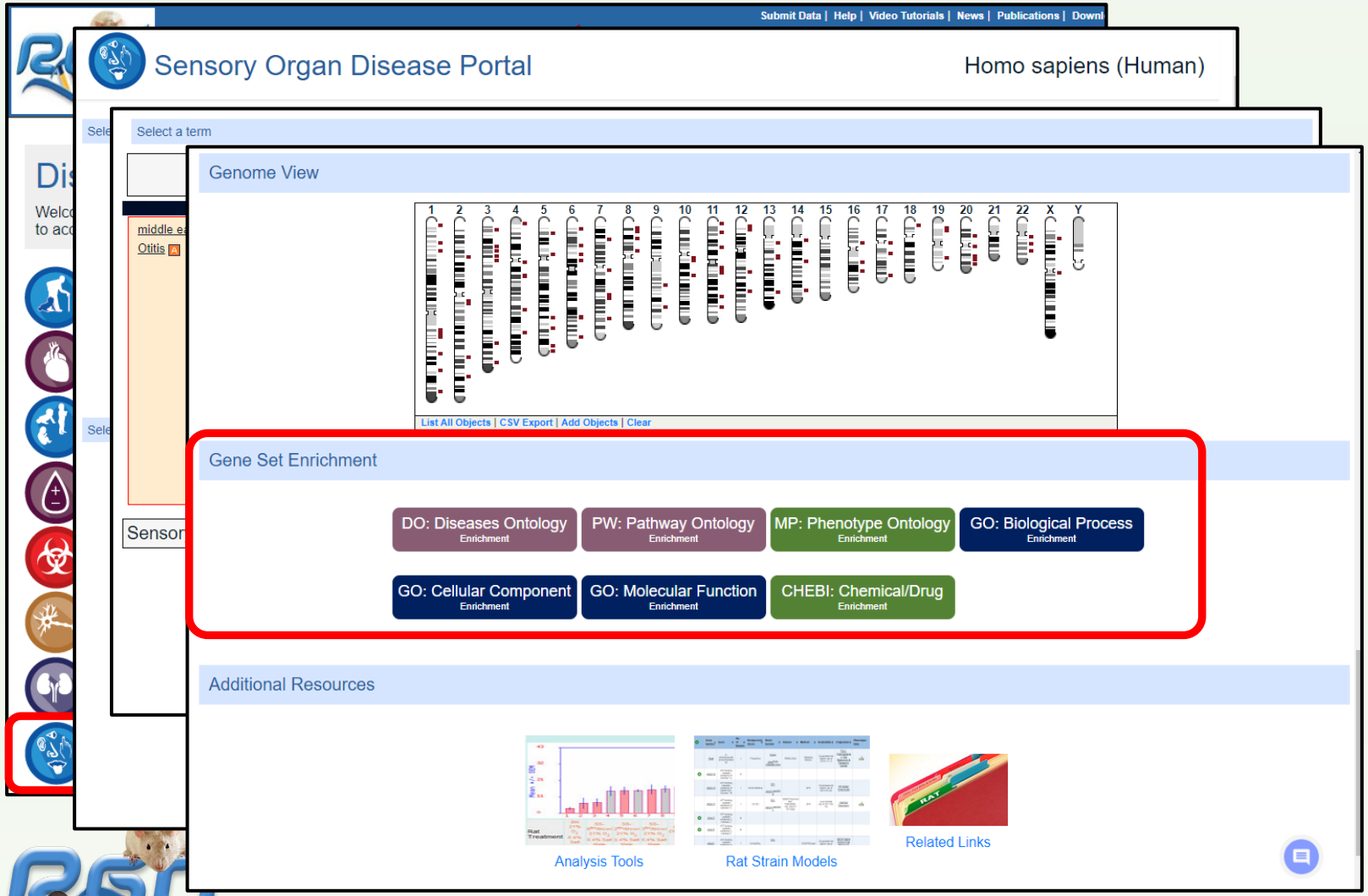

- For human and other species with chromosome-level assemblies, the genome-wide view of gene positions is shown.
- RGD's Multi-Ontology Enrichment Tool is embedded into the disease portals. *(More about this later.)*

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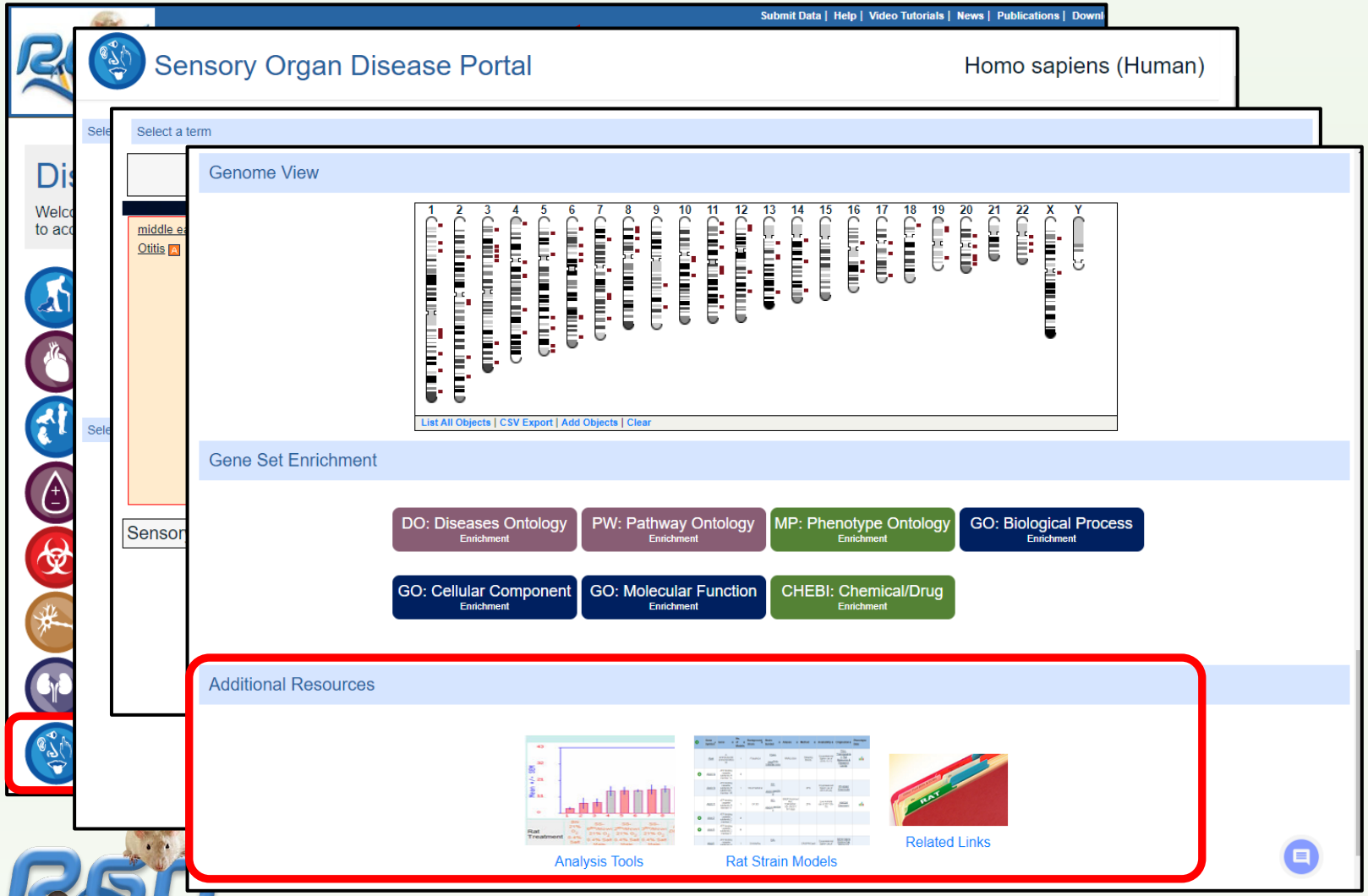

- For human and other species with chromosome-level assemblies, the genome-wide view of gene positions is shown.
- RGD's Multi-Ontology Enrichment Tool is embedded into the disease portals. *(More about this later.)*
- Links to additional information are provided at the bottom of the page.
- The same functionality is available for all species.

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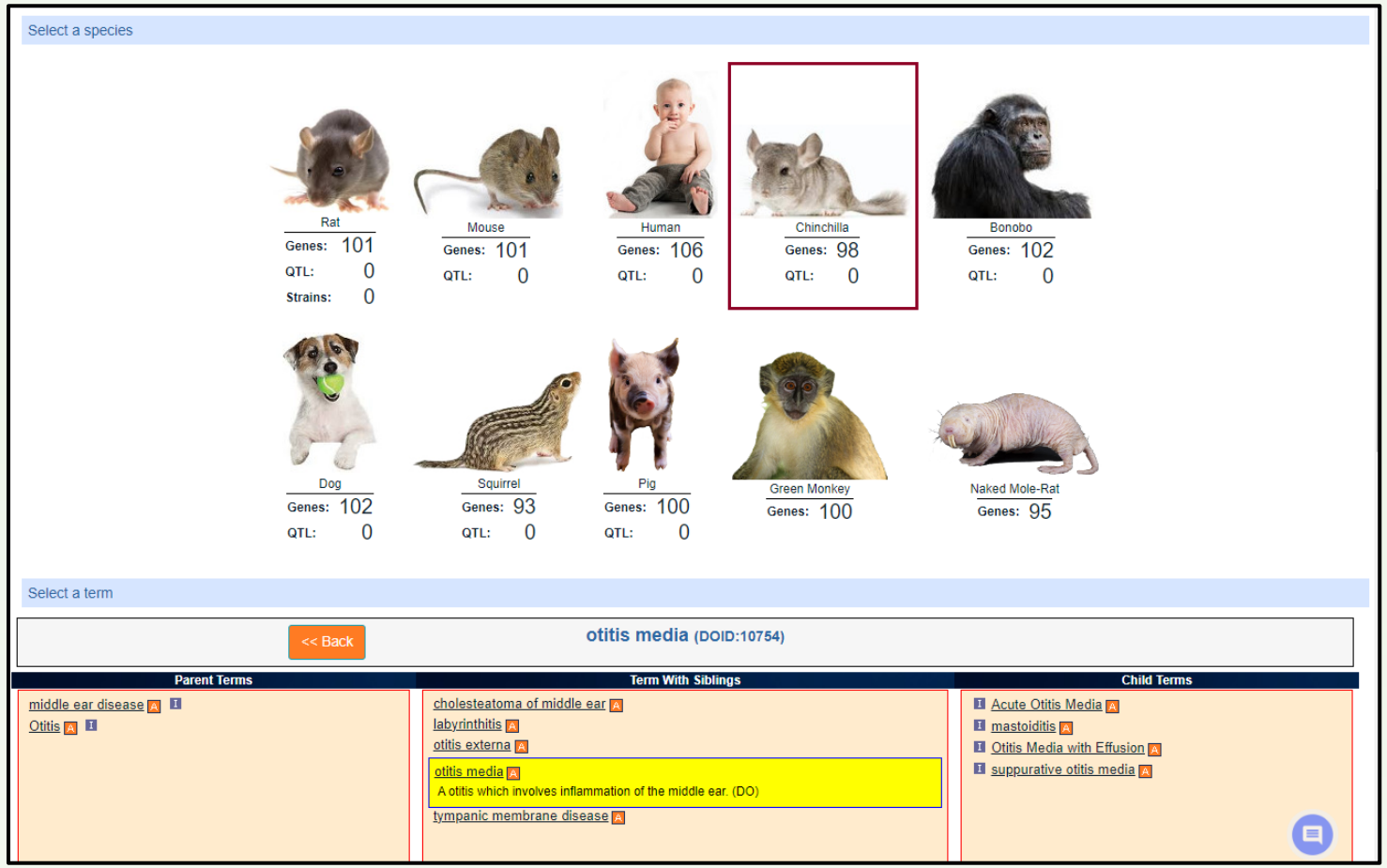
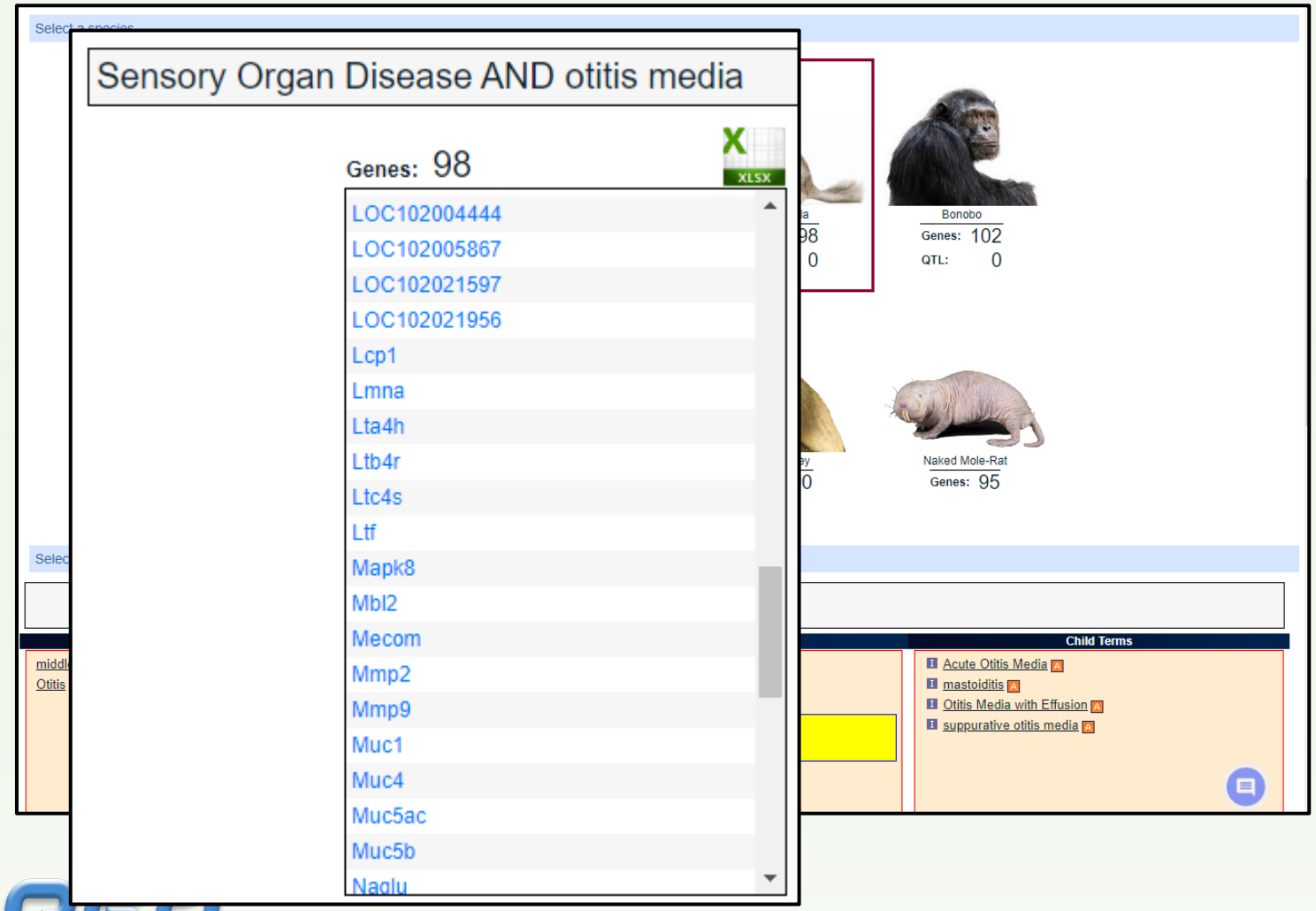
RGD's Disease Portals provide consolidated views of data related to 15 disease categories



- Going back up to the top of the page, we will select chinchilla as the species.

RGD's Disease Portals provide consolidated views of data related to 15 disease categories



- Going back up to the top of the page, we will select chinchilla as the species.
- When Chinchilla is chosen the list shows the 98 genes in chinchilla annotated to otitis media or any of its more specific children.

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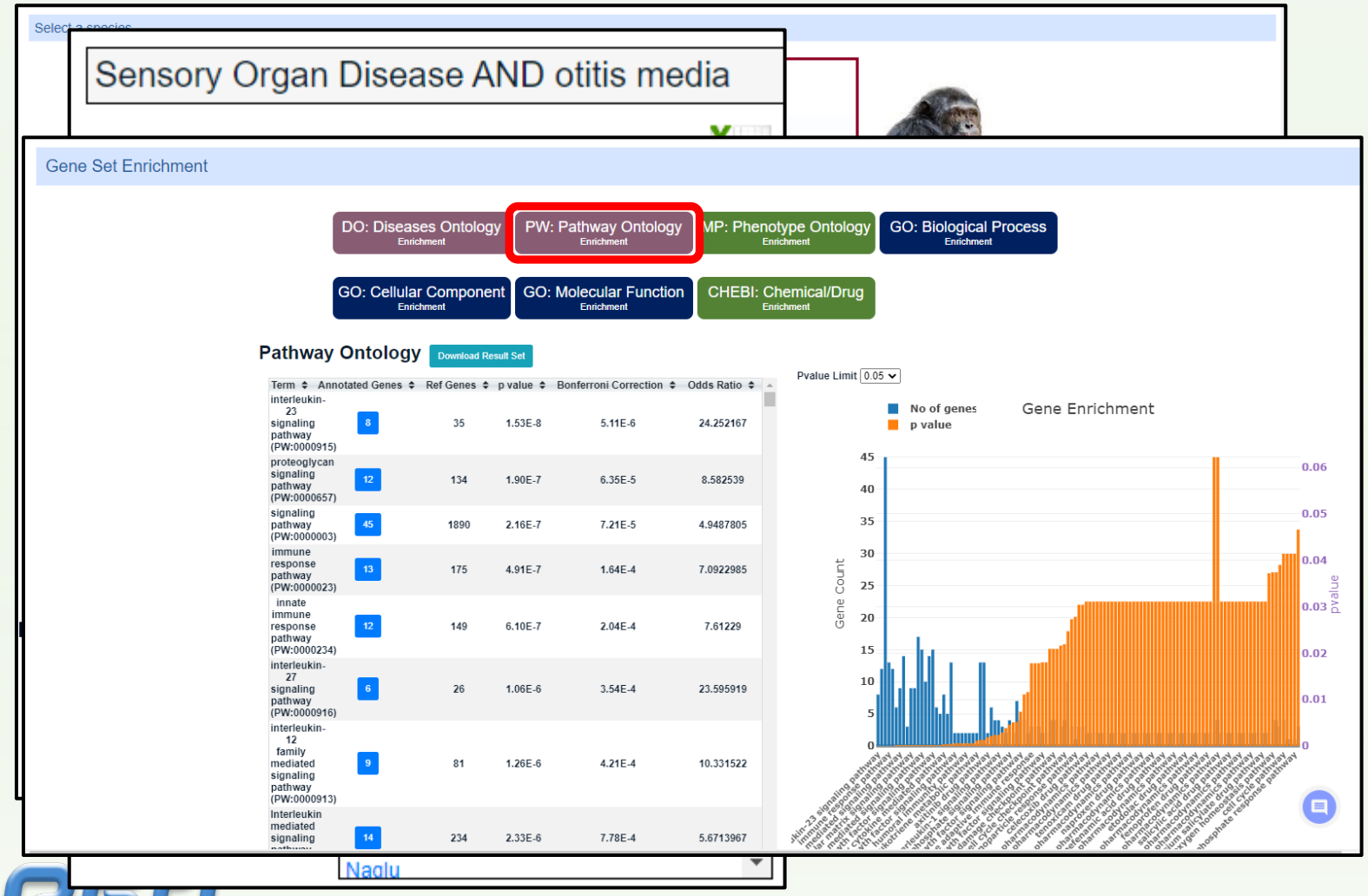
RGD's Disease Portals provide consolidated views of data related to 15 disease categories



- Going back up to the top of the page, we will select chinchilla as the species.
- When Chinchilla is chosen the list shows the 98 genes in chinchilla annotated to otitis media or any of its more specific children.
- When an ontology is selected in the "Gene Set Enrichment" section of the page, the list of genes is automatically submitted to the embedded MOET tool for enrichment analysis.
- Here RGD's Pathway Ontology has been selected.

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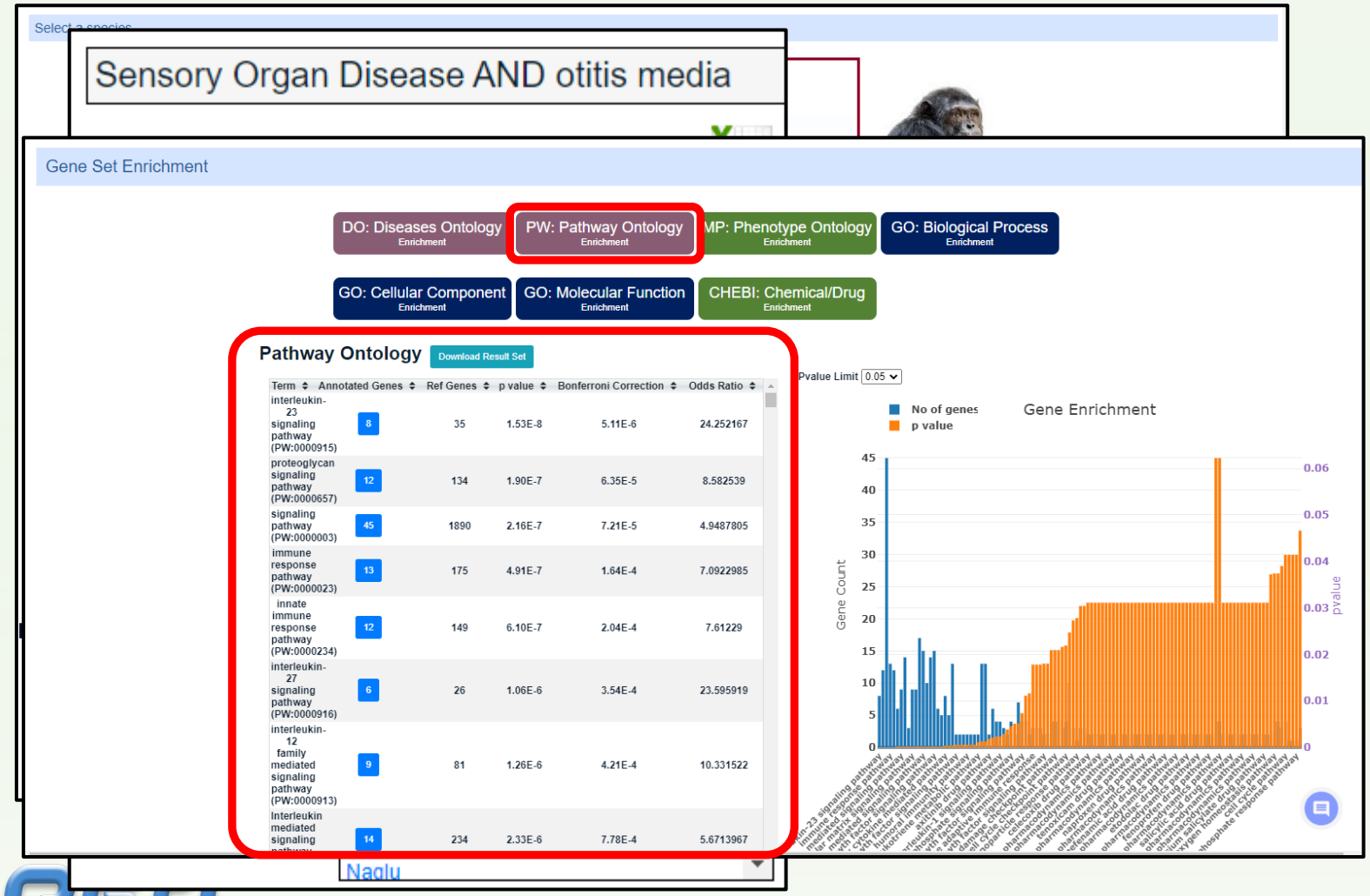
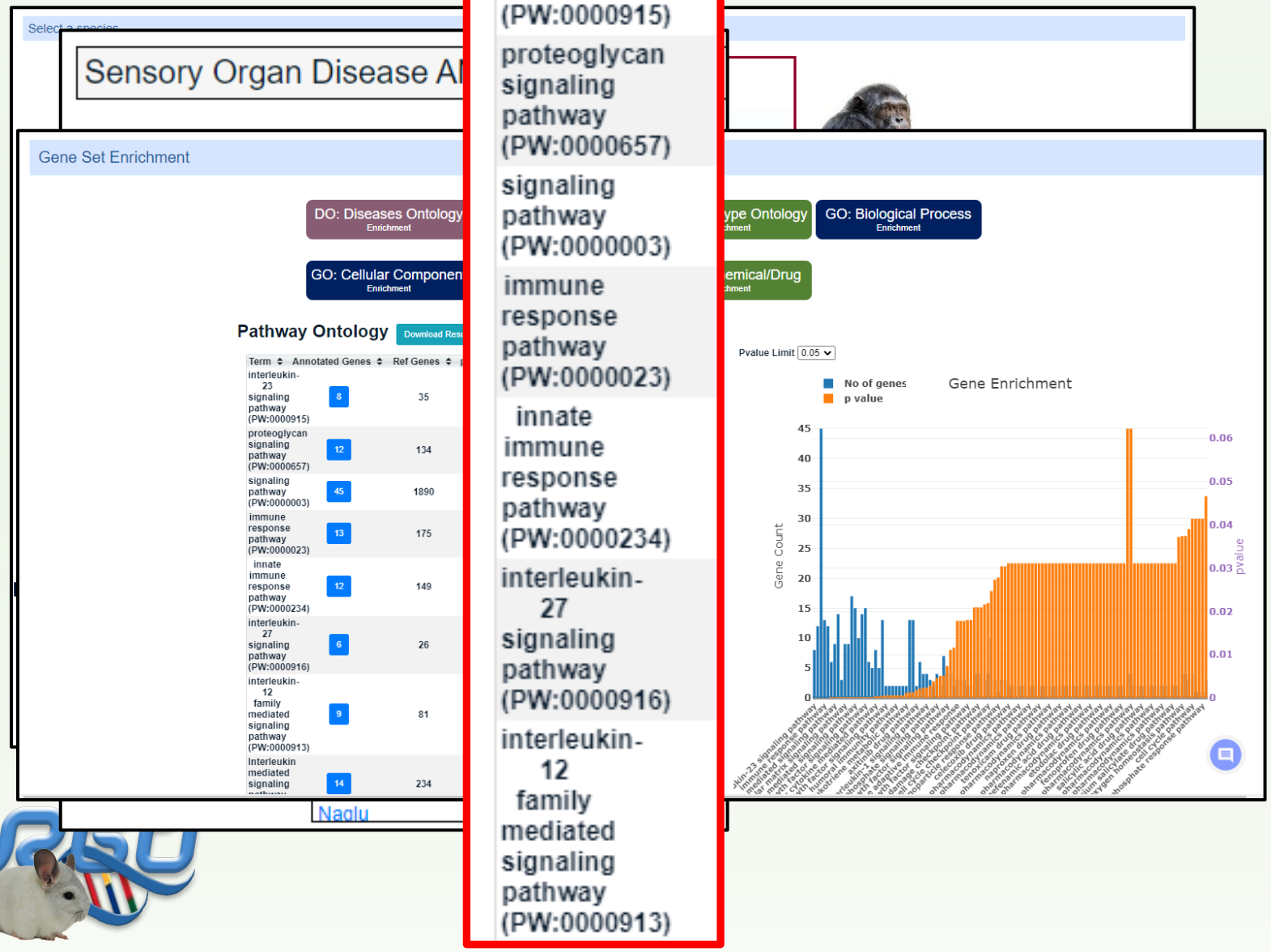
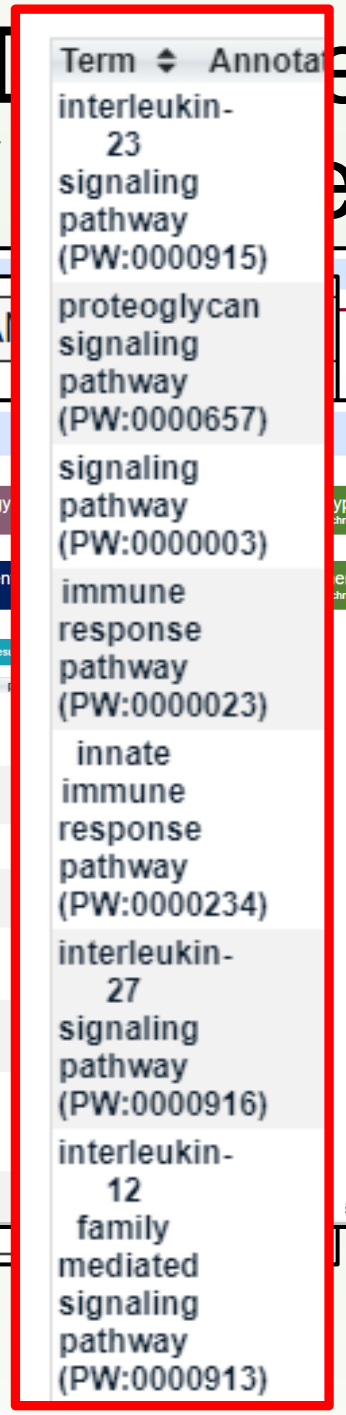
RGD's Disease Portals provide consolidated views of data related to 15 disease categories



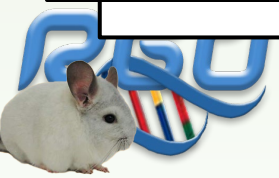
- The table in the enrichment results shows the list of terms over-represented in the annotations for the otitis media-related genes, the number of genes in the list annotated to that specific term or its children, uncorrected and Bonferroni-corrected p-values and odds ratios for each term.

RGD's D e Portals provide consolidated views of elated to 15 disease categories





- The table in the enrichment results shows the list of terms over-represented in the annotations for the otitis media-related genes, the number of genes in the list annotated to that specific term or its children, uncorrected and Bonferroni-corrected p-values and odds ratios for each term.
- Not surprisingly, the most enriched terms in the pathway ontology for the otitis media-related genes are interleukin signaling and immune-related pathways.



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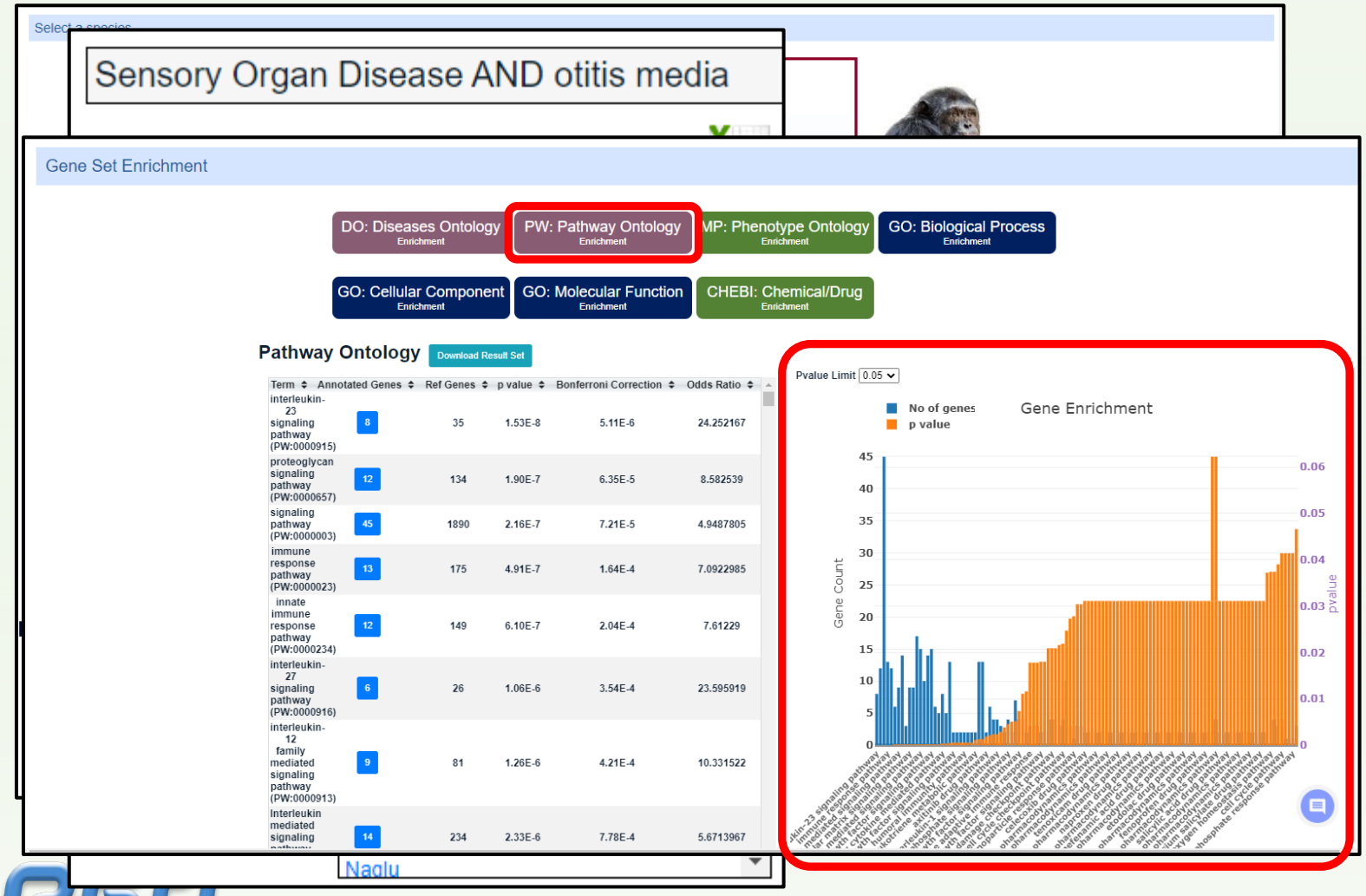

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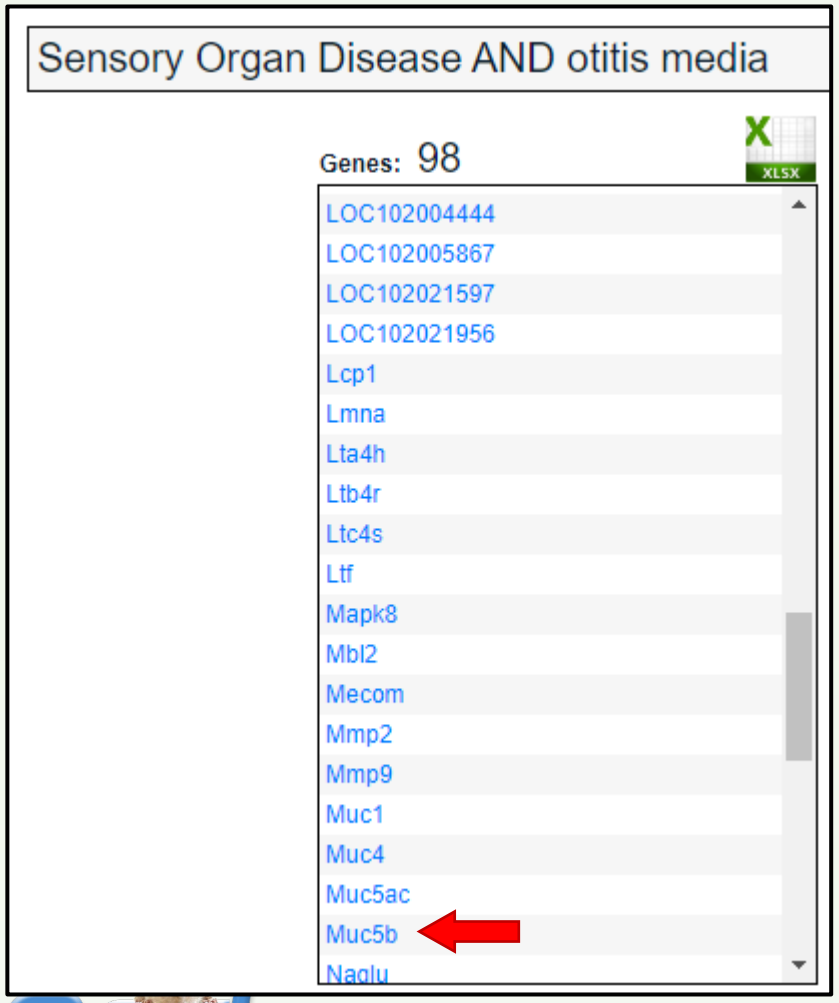
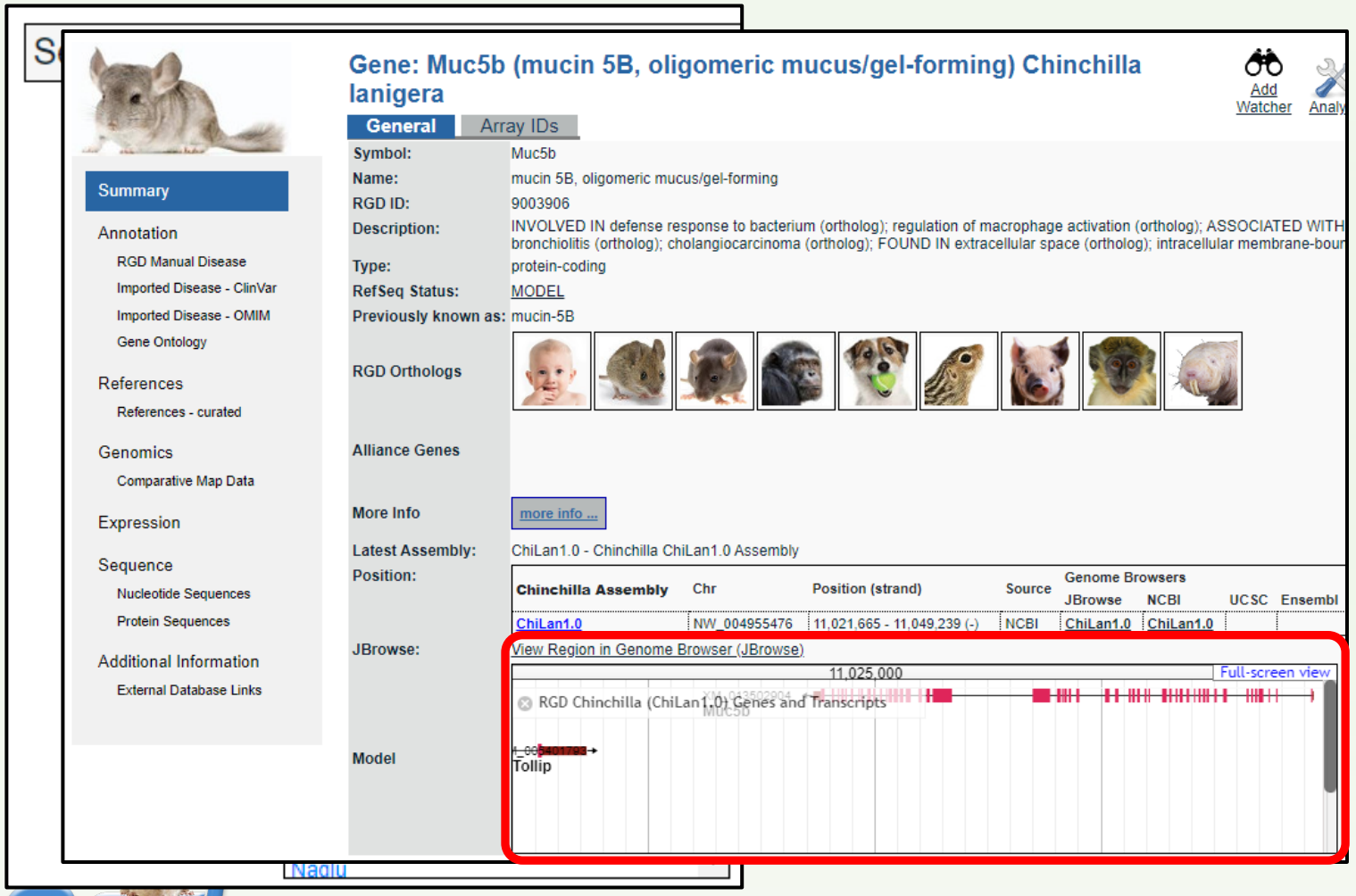
- Not surprisingly, the most enriched terms in the pathway ontology for the otitis media-related genes are interleukin signaling and immune-related pathways.
- The graph shows the number of genes in blue and p-values in orange for each term in the list.

RGD's JBrowse genome browser shows genes and RNA-Seq data in their genomic context



- Each gene in the disease portal list links to the respective gene report page, so clicking "Muc5b" takes you to the chinchilla mucin 5b gene page.

RGD's JBrowse genome browser shows genes and RNA-Seq data in their genomic context



- Each gene in the disease portal list links to the respective gene report page, so clicking "Muc5b" takes you to the chinchilla mucin 5b gene page.
- The Muc5b gene page in turn links to that gene's position in RGD's chinchilla JBrowse genome browser.

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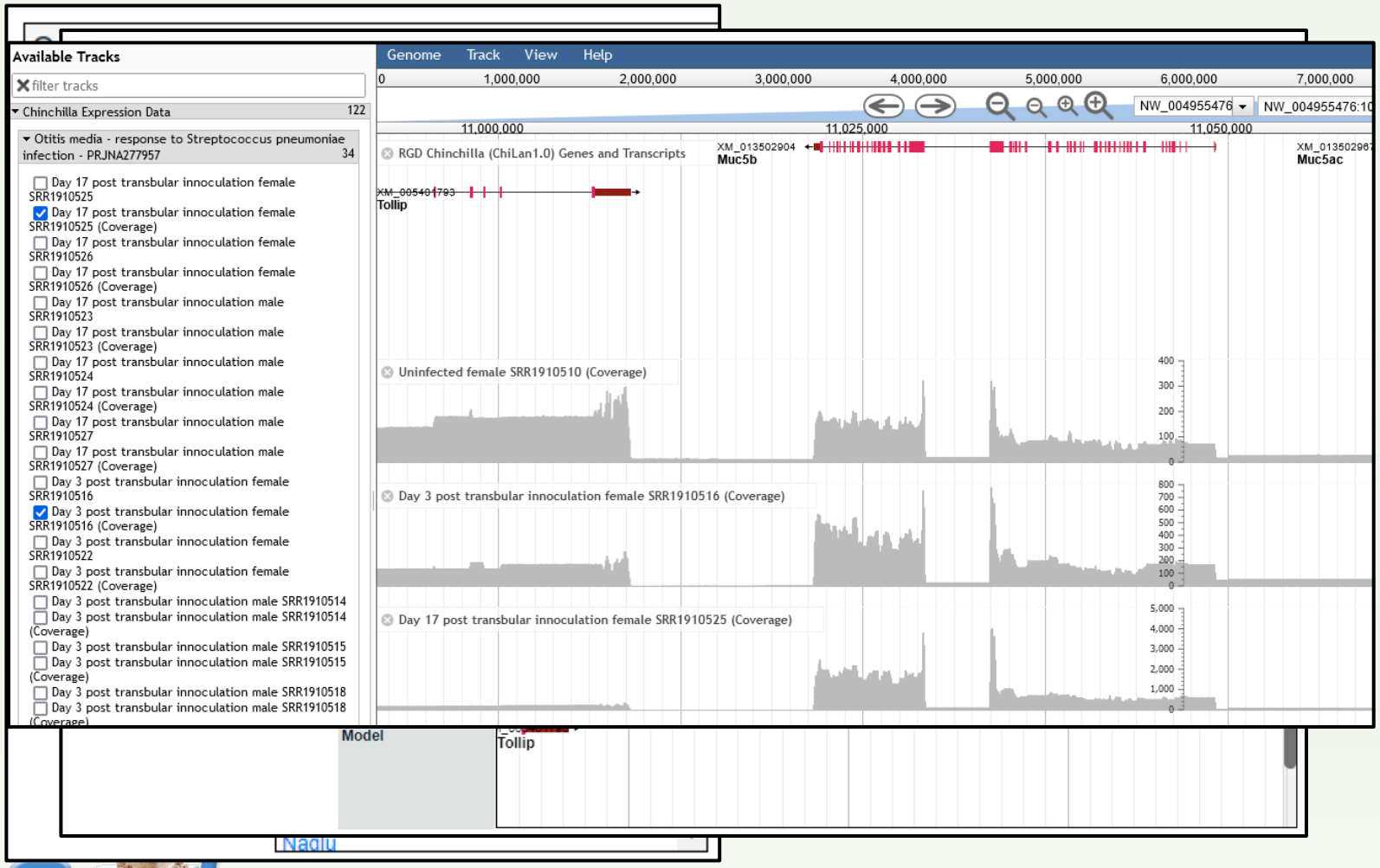
RGD's JBrowse genome browser shows genes and RNA-Seq data in their genomic context



- RGD has loaded genes from NCBI and Ensembl and RNA-Seq BAM alignments and coverage tracks from two projects:
  - Uninfected and infected middle ear mucosa from the Medical College of Wisconsin
  - 14 tissues from samples provided by Dr. Lauren Bakaletz's group at the Research Institute at Nationwide Children's Hospital

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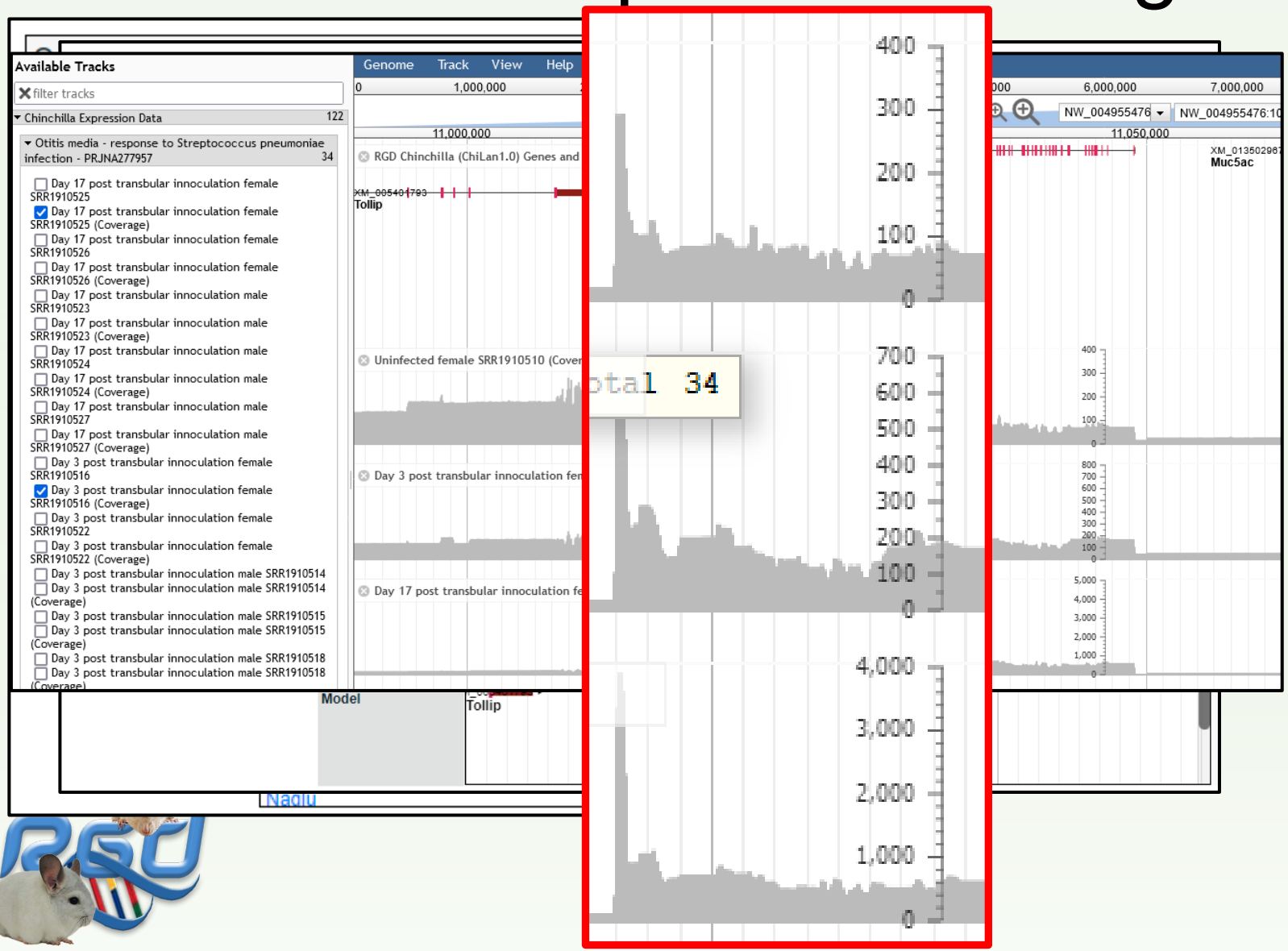
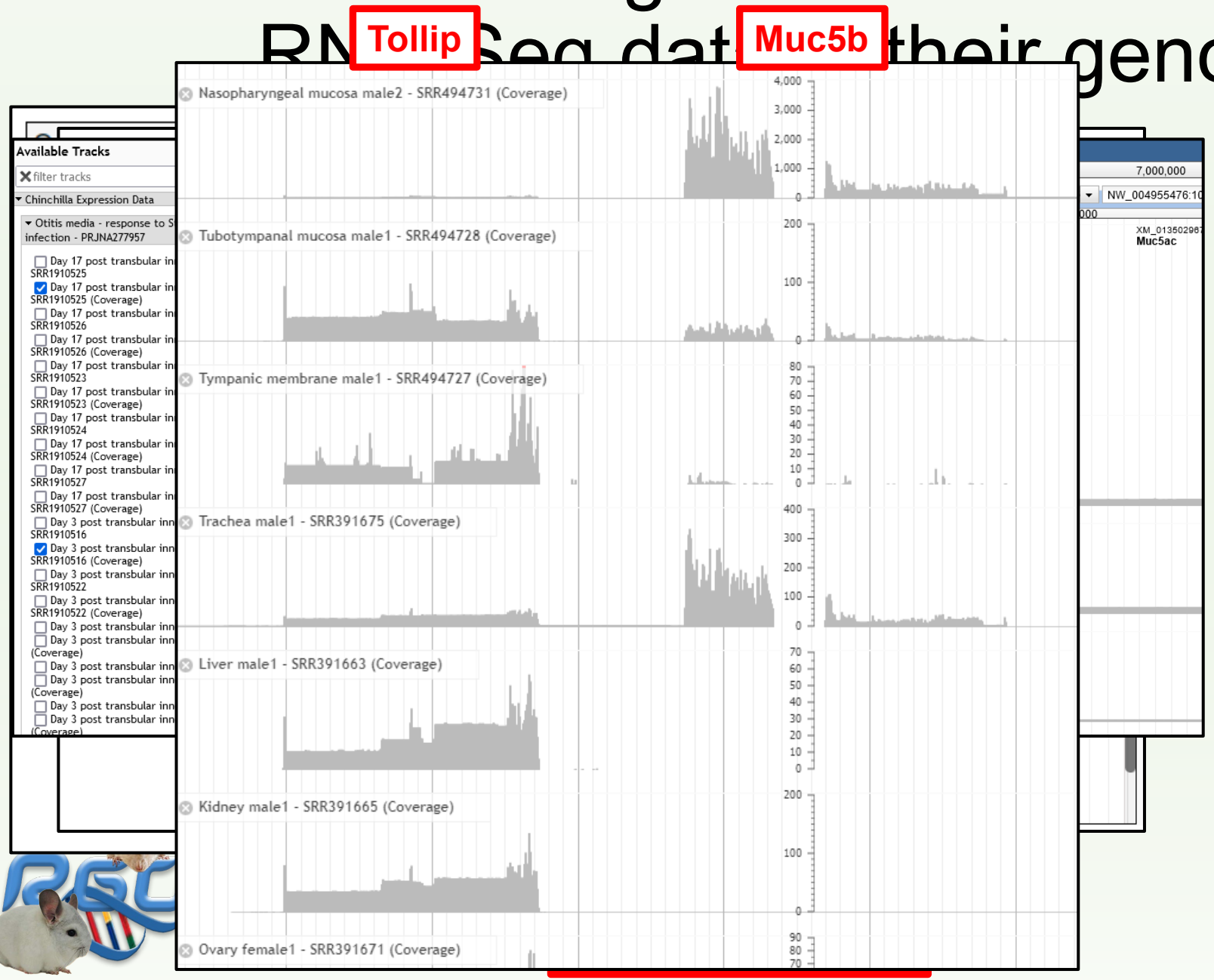


- RGD has loaded genes from NCBI and Ensembl and RNA-Seq BAM alignments and coverage tracks from two projects:
  - Uninfected and infected middle ear mucosa from the Medical College of Wisconsin
  - 14 tissues from samples provided by Dr. Lauren Bakaletz's group at the Research Institute at Nationwide Children's Hospital
- Muc5b increases in expression from uninfected (top graph) through 3 and 17 days of Strep infection.
- Note that although the patterns are similar, the scales are different.

RGD's JBrowse genome browser shows genes and RNA-Seq data in their genomic context



- Muc5b shows tissue-specific expression. As shown here, there is strong expression in the nasopharyngeal mucosa, lower expression in trachea, and little or none in tubotympanal mucosa, tympanic membrane, liver, kidney, ovaries or testes.
- Again, although the coverage patterns are similar, the levels are an order of magnitude different between nasopharyngeal mucosa and trachea

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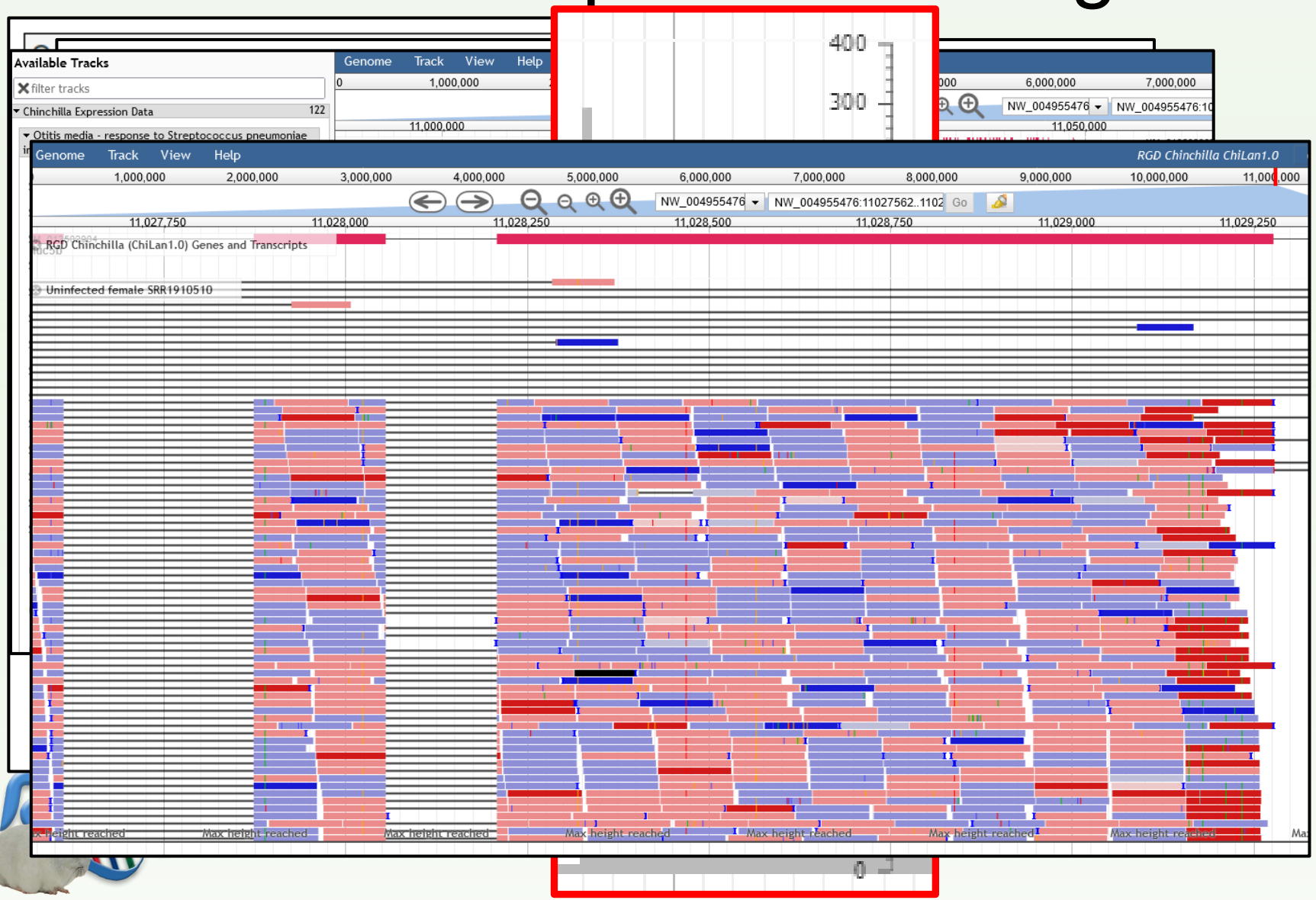
RGD's JBrowse genome browser shows genes and RNA-Seq data in their genomic context



- This display shows the RNA-Seq BAM alignments for two exons of Muc5b from one of the uninfected middle ear mucosa samples.
- The RNA-Seq data from these studies was used to improve the gene model predictions during the genome annotation process by NCBI and Ensembl.

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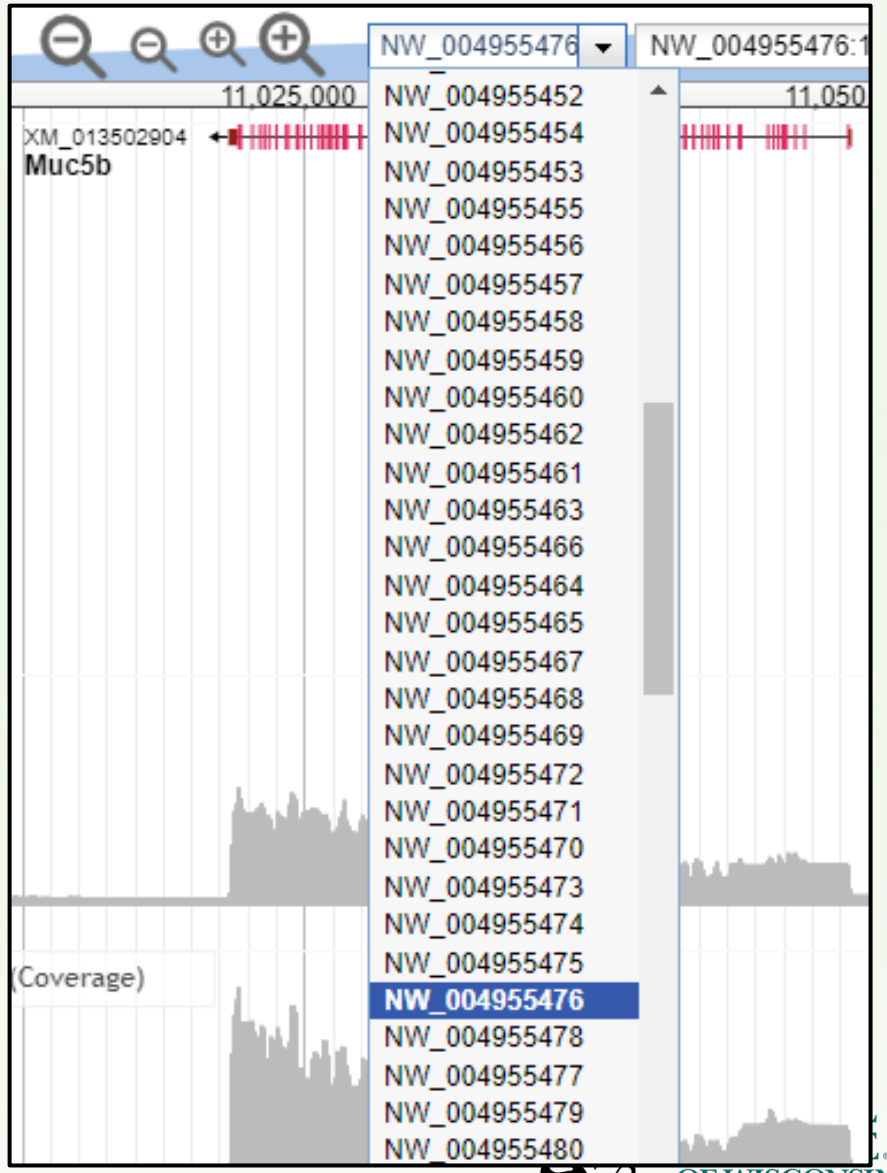
Conclusions and Questions for the research community

- This brief overview is only a subset of the rich set of data and tools that RGD provides for both clinical and translational researchers.
- If you have questions or are interested in more information, I am available to answer questions or give a more complete or targeted tour of what RGD has to offer.
- Contact me at jrsmith@mcw.edu, or through the "Contact" link at the top or the feedback link in the bottom right of most RGD pages.
- The Chinchilla genome is only assembled to the point of scaffolds. While this is sufficient for some applications, for true comparative genomics, phylogeny, etc. chromosome-level assembly would be required.

Is there interest in improving the chinchilla genome assembly?

Would groups be willing to do additional sequencing to support chromosome-level assembly?



Thank you!

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and the researchers who contribute data and who faithfully use our website and data!

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https://rgd.mcw.edu

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