ERCC Data Analysis Workshop

Use Case 2 Part 2: exRNA Discovery and Functional Analysis using the exRNA Atlas and Network Analysis Resources on the Genboree Workbench

Organized and Hosted by the Data Management and Resource Repository (DMRR)

Sunday 17 April, 2016 6-9pm

Data kindly provided by Kendall Jensen, Translational Genomics Research Institute

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

tgen

ERCC Data Analysis Workshop

Topics covered in Use Case 2 Part 2

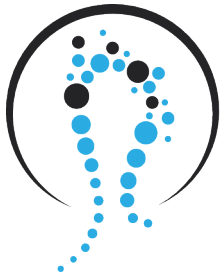
- Accessing samples in the exRNA Atlas
- Comparative analysis of exRNA samples using DESeq / exceRpt pipeline results and tools in the Genboree Workbench
- Finding information about exRNAs of interest
  - on Exocarta and Vesiclepedia
  - on GeneWiki and Wikidata
- Pathway analysis using Cytoscape & WikiPathways in the Genboree Workbench

Use Case 2: miRNA Changes in Alzheimer's and Parkinson's Disease

One goal of this use case is to show that the Genboree Workbench and the exceRpt small RNA-seq analysis pipeline can replicate the results of Burgos et al.

We have developed these pipelines because as the number of datasets in the exRNA Atlas grows, it is vital that they be analyzed in a reproducible and comparable way.

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.



Use Case 2: miRNA Changes in Alzheimer's and Parkinson's Disease

tgen

Biological Question of Interest

Alzheimer's and Parkinson's are two neurodegenerative diseases that are difficult to assess by biopsy, since the affected tissue is inaccessible.

In their study, Burgos et al. assessed the miRNA content in cerebrospinal fluid (CSF) and serum from postmortem subjects with full neuropathology evaluations. The goal of the study was to identify extracellular miRNA biomarkers that correlate with disease status and progression.

In this use case, we focus on biomarkers that correlate with disease status by replicating the differential expression analysis in Burgos et al.

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

ERCC Data Analysis Workshop

Topics covered in Use Case 2 Part 2

- **Accessing samples in the exRNA Atlas**
- Comparative analysis of exRNA samples using DESeq / exceRpt pipeline results and tools in the Genboree Workbench
- Finding information about exRNAs of interest
  - on Exocarta and Vesiclepedia
  - on GeneWiki and Wikidata
- Pathway analysis using Cytoscape & WikiPathways in the Genboree Workbench

Accessing samples in the exRNA Atlas for discovery and analysis

Sai Lakshmi Subramanian

ERC Consortium Data Management & Resource Repository (DMRR)

Baylor College of Medicine, Houston, TX

Outline

- Introduction to the exRNA Atlas
- Overview of exRNA profiling data flow
- Faceted sub-selection of biosamples
- Biosample partition grids
- Linear Tree drill-down sub-selection of samples
- Summary grid with exRNA profiling studies
- Informational bar charts – Atlas Statistics

Introduction to the exRNA Atlas

Data repository of the Extracellular RNA Communication Consortium (ERCC)

Developed and maintained by the Data Management and Resource Repository (DMRR)

Contains the exRNA profiles from various biofluids, conditions

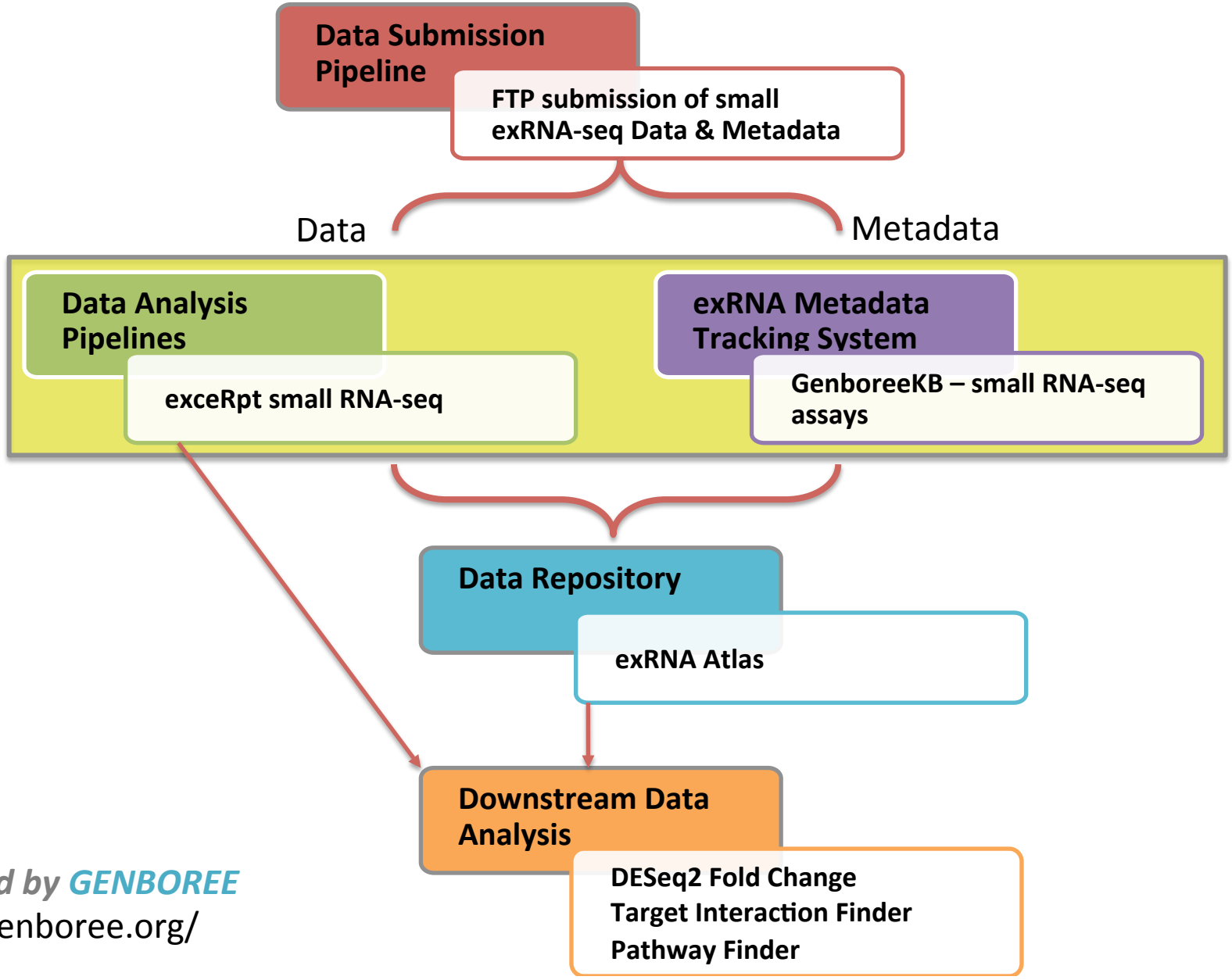
Faceted sub-selection and data navigation tools are available in the Atlas

Currently, stores samples profiled using small RNA-sequencing assays

All datasets are uniformly processed using the exceRpt small RNA-seq pipeline

As of today – **751** exRNA profiles are available in the **Public Atlas** and **1658** profiles are available in the **Consortium Atlas**

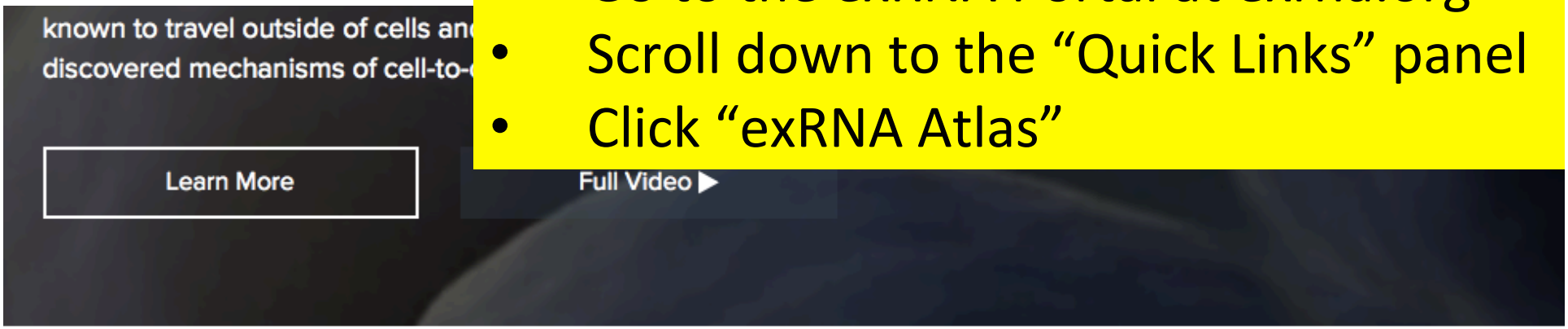
Overview of exRNA Profiling Data Flow



Powered by GENBOREE
http://genboree.org/

exRNA Atlas

- Go to the exRNA Portal at exrna.org
- Scroll down to the “Quick Links” panel
- Click “exRNA Atlas”



Link to exRNA Atlas

01.27.16 by Leonora Balaj and Louise C Laurent

First CLIA-validated exosome-based clinical liquid biopsy test is launched

exosomedx

Exosome Diagnostics, Inc. has announced the launch of ExoDx Lung(ALK), the first ever CLIA-validated exosome based blood test. This test

Quick Links

ExRNA Atlas
ExRNA @ BioGPS
ExRNA @ WikiPathways
ExoCarta
Vesiclepedia
miRandola

NIH National Institutes of Health
Turning Discovery Into Health

Getting Started – Tutorials, Video

Open the exRNA Atlas page → Click the link "**Getting Started**" below the charts, to open the tutorial Wiki in a new tab.

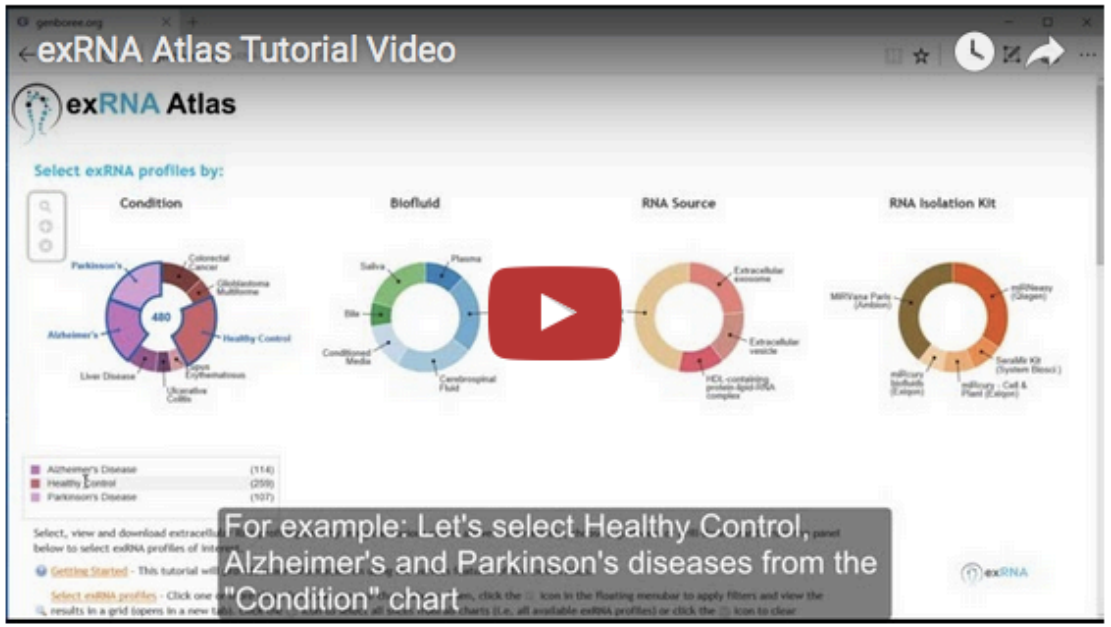
Select, view and download extracellular RNA profiling data by using the various charts above. Alternatively, choose a grid view or drill-down search from the panel below to select exRNA profiles of interest.

Getting Started - This tutorial will provide more information on using the various features of the exRNA Atlas.

Select exRNA profiles - Click one or more slices from one or
results in a grid (opens in a new tab). Click the icon to se
from all slices.

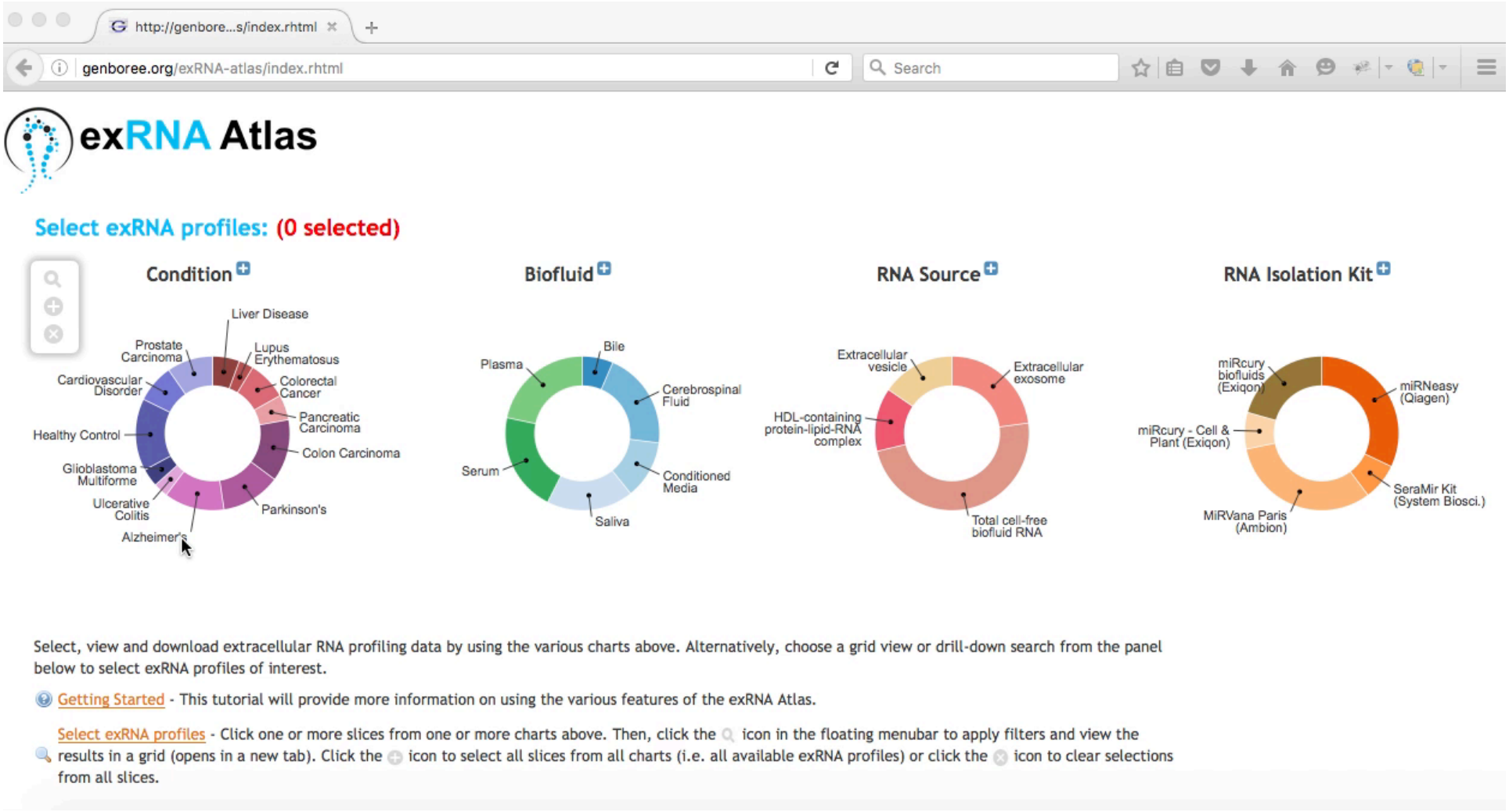
Introduction to the exRNA Atlas

Watch Video Tutorial on all of the available features in the exRNA Atlas.

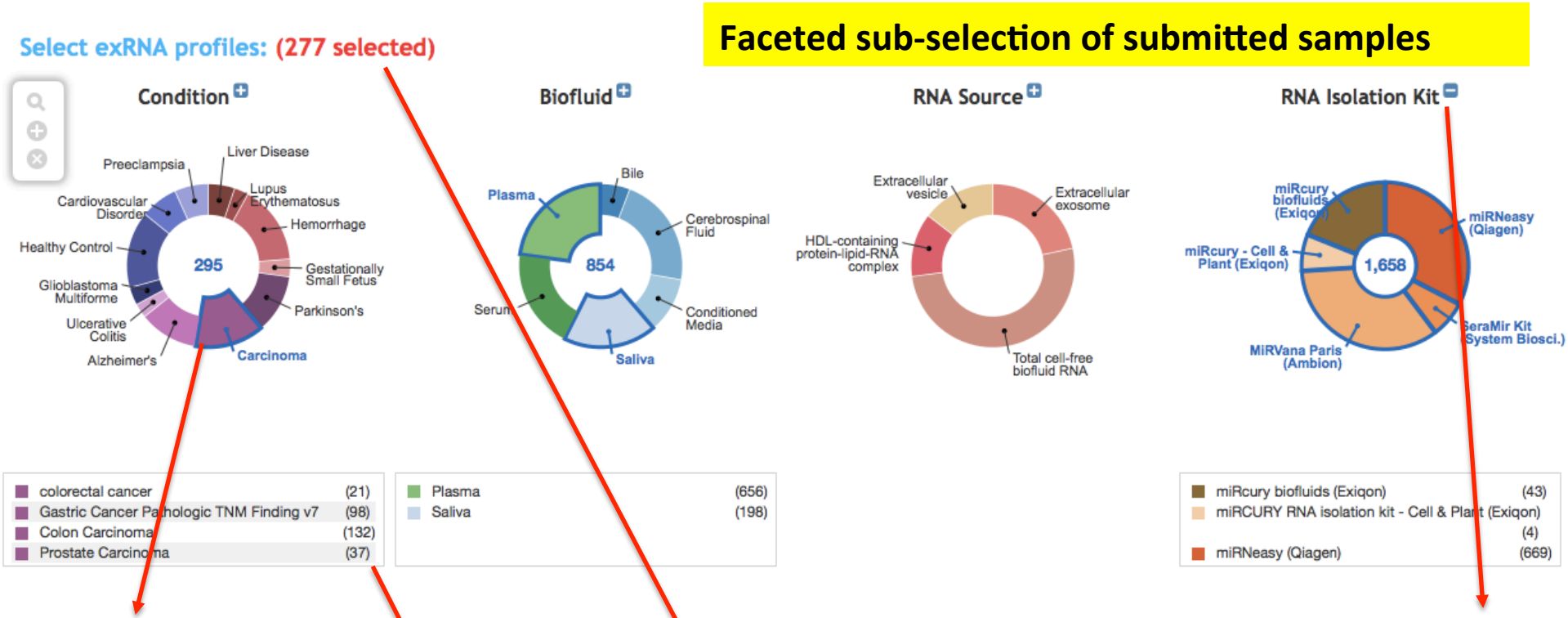


View tutorial video to learn more about the features in the Atlas

New Features in Atlas



Faceted sub-selection of samples



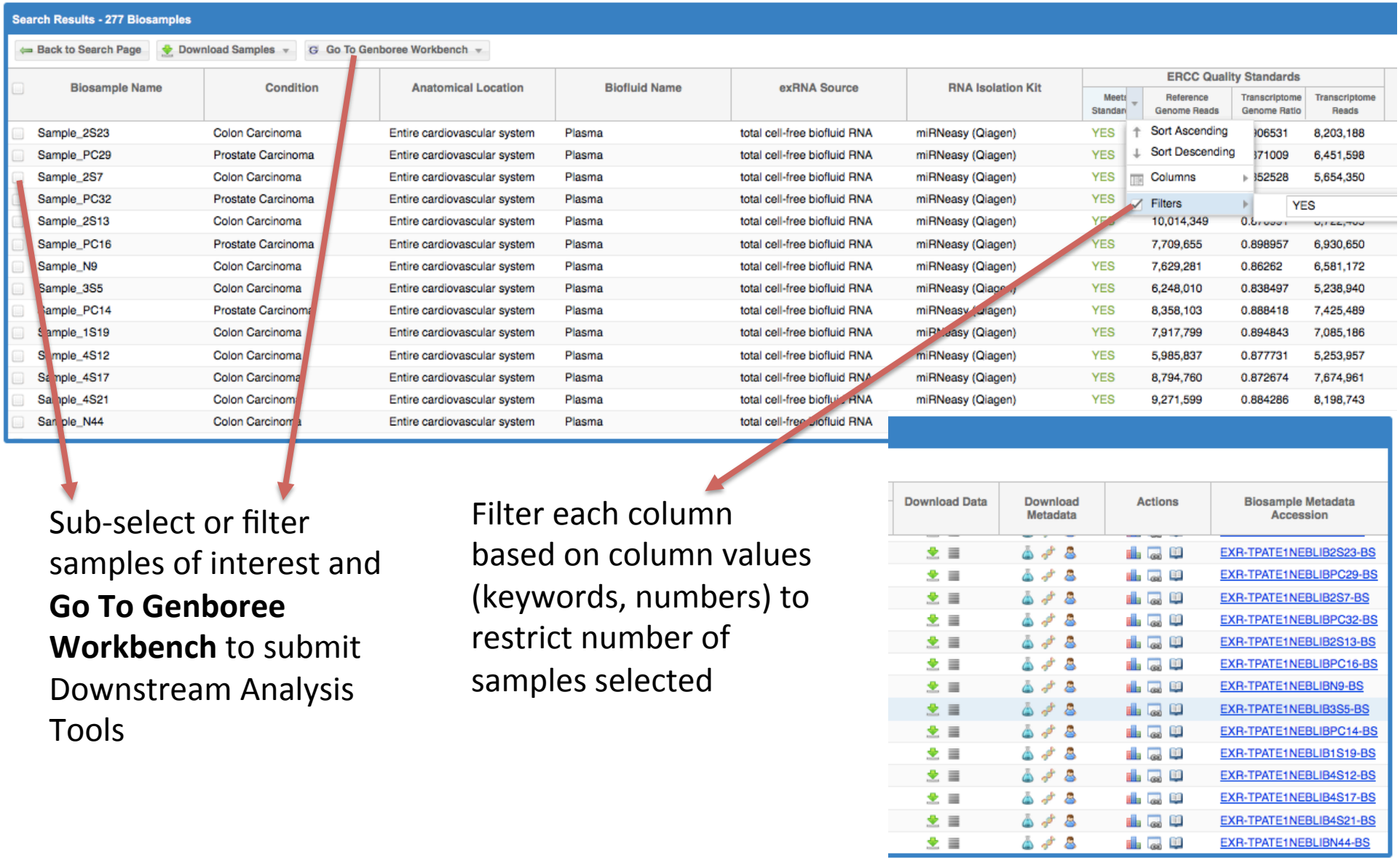
Grouped slice representing a category of conditions

Actual labels with number of samples for each condition

Number of samples selected

Select all or Clear all from each donut

Sample Sub-selection in exRNA Atlas

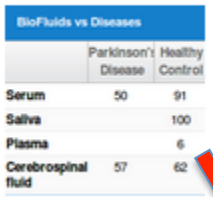


Sub-select or filter samples of interest and **Go To Genboree Workbench** to submit Downstream Analysis Tools

Filter each column based on column values (keywords, numbers) to restrict number of samples selected

Partition Grids in exRNA Atlas

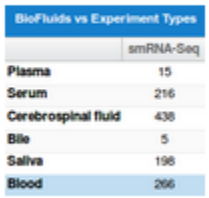
Biofluid vs Disease



BioFluids vs Diseases

	Parkinson's Disease	Healthy Control
Serum	50	91
Saliva		100
Plasma		6
Cerebrospinal fluid	57	62

Biofluid vs Experiment Type



BioFluids vs Experiment Types

	smRNA-Seq
Plasma	15
Serum	216
Cerebrospinal fluid	438
Bile	5
Saliva	198
Blood	266

BioFluids vs Experiment Types

	smRNA-Seq	mRNA-Seq	qRT-PCR
Plasma	15		
Serum	216		
Cerebrospinal fluid	438		
Bile	5		
Saliva	198		
Blood	266		

BioFluids vs Diseases

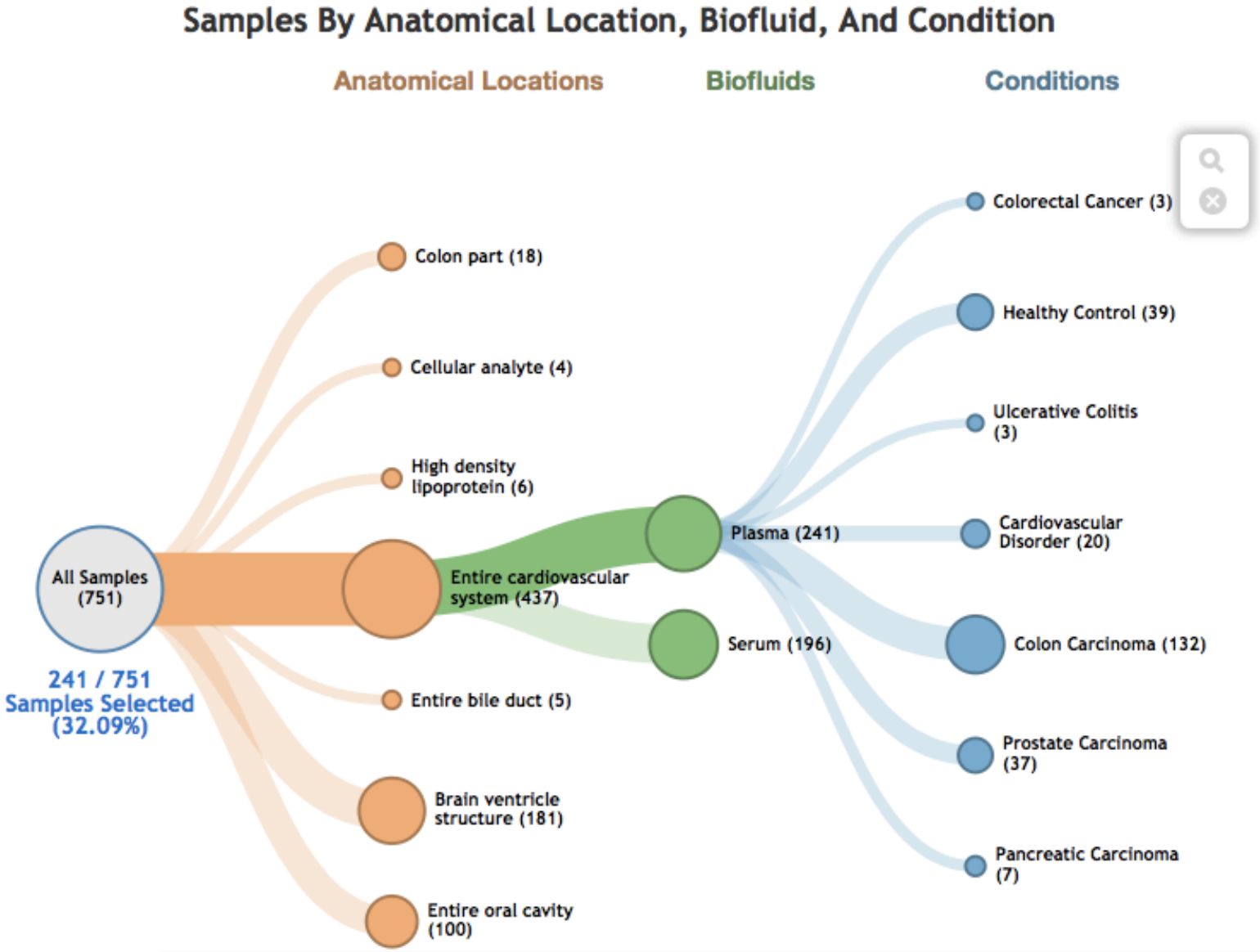
	Alzheimer's Disease	Chronic Maternal Hypertension with Superimposed Preeclampsia	Fetus Small for Gestational Age	Subarachnoid Hemorrhage	Healthy Control
Plasma					6
Serum	52	2	4		91
Cerebrospinal fluid	62			257	62
Bile					
Saliva					100
Blood				266	

Metadata about Biosamples:
smRNA-Seq » Bile

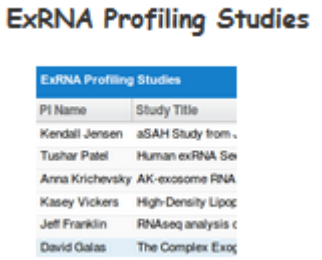
Back to Search Page | Download Samples | Go To Genboree Workbench

Biosample Name	Anatomical Location	exRNA Source	ERCC Quality Standards				Download Data	Download Metadata	Actions
			Meets Standard	Reference Genome Reads	Transcriptome Genome Ratio	Transcriptom Reads			
IYB2	Entire bile duct	extracellular vesicle	NO	5,168,243	0.434522	2,245,...			
IYB4	Entire bile duct	extracellular vesicle	YES	1,620,149	0.585237	948,171			
IYB1	Entire bile duct	extracellular vesicle	YES	994,960	0.770116	766,235			
IYB3	Entire bile duct	extracellular vesicle	YES	6,400,885	0.732687	4,689,...			
IYB5	Entire bile duct	extracellular vesicle	YES	1,723,941	0.607476	1,047,...			

Drill-down search in exRNA Atlas



Submission Summaries in Atlas



Grid for exRNA Profiling Studies

Analysis Accession ID	Study Title	PI Name	Funding Source	Grant Name/Number	Organization
EXR-AKRIC1AKGBMexo-AN	AK-exosome RNA	Anna Krichevsky	NIH Common Fund	1U19CA179563-01	BWH
EXR-DGALA1GUTPLASM-...	The Complex Exogenous RNA Spectra i...	David Galas	NIH Common Fund	1U01HL126496-01	Pacific Northwest Diabetes Research Ins.
EXR-DWONG1TMDW78D-AN	GC_ExRNA	David Wong	NIH	1UH2TR000923-01	University of California-Los Angeles
EXR-JFRAN1CRCDLD00-AN	RNAseq analysis of colorectal cancer ce...	Jeff Franklin	Common Fund/NIH: U19 CA179514-02 (...	1U19CA179514-01	Vanderbilt University School of Medicine
EXR-KJENS1ADPD0000-AN	Profiles of Extracellular miRNA in Cerebr...	Kendall Jensen	Michael J Fox Foundation for Parkinsons...	Non-ERCC Funded Study	Translational Genomics Research Institute
EXR-KJENS1aSAHPR-AN	aSAH Study from Jensen lab	Kendall Jensen	NIH	1UH2TR000891-01	Translational Genomics Research Institute
EXR-KVICK1KCVSLE00-AN	High-Density Lipoproteins ? small RNA			19CA179514-01	Vanderbilt University School of Medicine
EXR-LLAUR1M4TD4M0N-AN	Sept2014_ExRNA			H2TR000906-01	University of California-San Diego
EXR-TPATE15bHLB4-AN	Human exRNA Sequencing Study			H2TR000884-01	Mayo Clinic
EXR-TPATE1SwLbjS-AN	Mouse Extracellular Small RNA Sequer			H2TR000884-01	Mayo Clinic

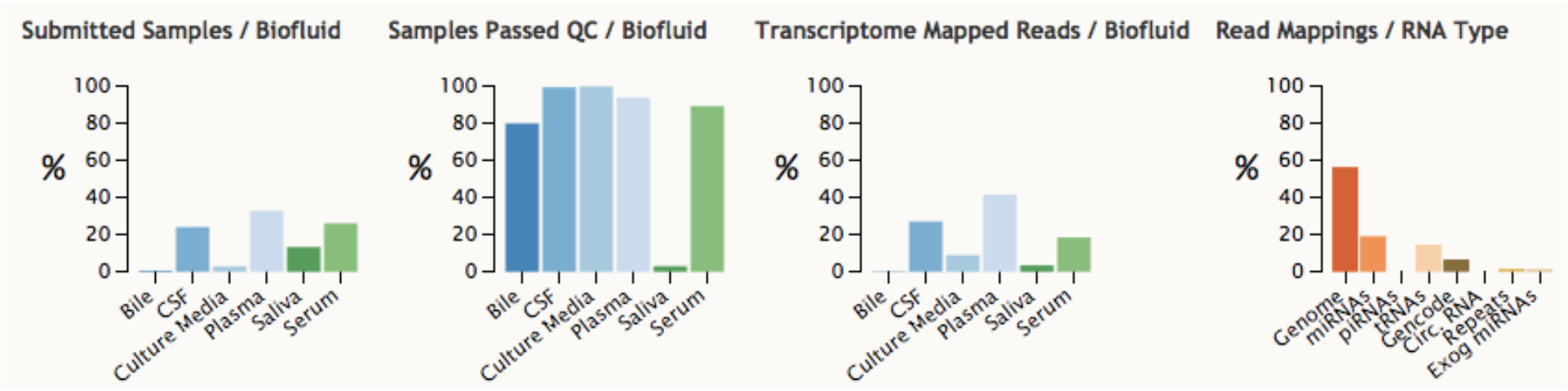
RNA PROFILE GRID

Property	Value
Analysis	EXR-DWONG1TMDW78D-AN
Genome Version	hg19
Type	Reference Alignment
Alignment Method	exceRpt smallRNA-seq Pipeline Version 2.2.8
Grid View	

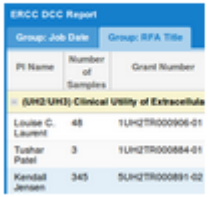
Grid with RNA Profile of Biosamples

Biosamples	Actions	Input Reads	After Clipping	Failed Quality Filter	Failed Homopolymer Filter	Calibrator	UniVec Contaminants	rRNAs	Reads Used for Alignment	Genome	miRNAs Sense	miRNAs Antisense	piRNAs Sense
EXR-DWONG1GCB22S5-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		26,351,419	22,840,990	966,719	16,730	29,734	352,126	1,474,434	20,001,247	12,236,321	2,365,823	237	69,437
EXR-DWONG1GCB12S4-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		21,336,449	19,440,864	936,622	49,707	1,123,315	451,420	2,776,712	14,103,088	6,527,116	397,875	2,152	339,072
EXR-DWONG1GCB16S8-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		30,127,548	28,309,474	2,919,653	34,181	3,627,535	590,215	489,461	20,648,429	7,934,985	106,331	1,010	67,747
EXR-DWONG1GCB09S3-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		18,811,513	15,330,513	712,469	17,901	1,283,739	414,625	605,702	12,296,077	4,760,247	31,594	870	26,709
EXR-DWONG1GCB20S3-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		27,327,328	25,037,737	1,636,895	19,692	2,064,483	549,676	1,717,042	19,049,949	7,415,962	69,261	1,122	54,075
EXR-DWONG1GCB07S3-BS **ExperimentType:** smRNA-Seq **Biofluids:** Saliva		33,396,244	30,418,227	2,701,076	22,045	4,561,878	1,315,529	390,196	21,427,503	7,359,546	62,495	1,283	53,539
EXR-DWONG1GCB05S4-BS **ExperimentType:** smRNA-Seq		30,164,451	27,685,268	2,137,689	9,486	2,781,277	344,879	1,892,810	20,519,127	7,818,525	172,231	2,165	43,874

Submission Summaries in Atlas



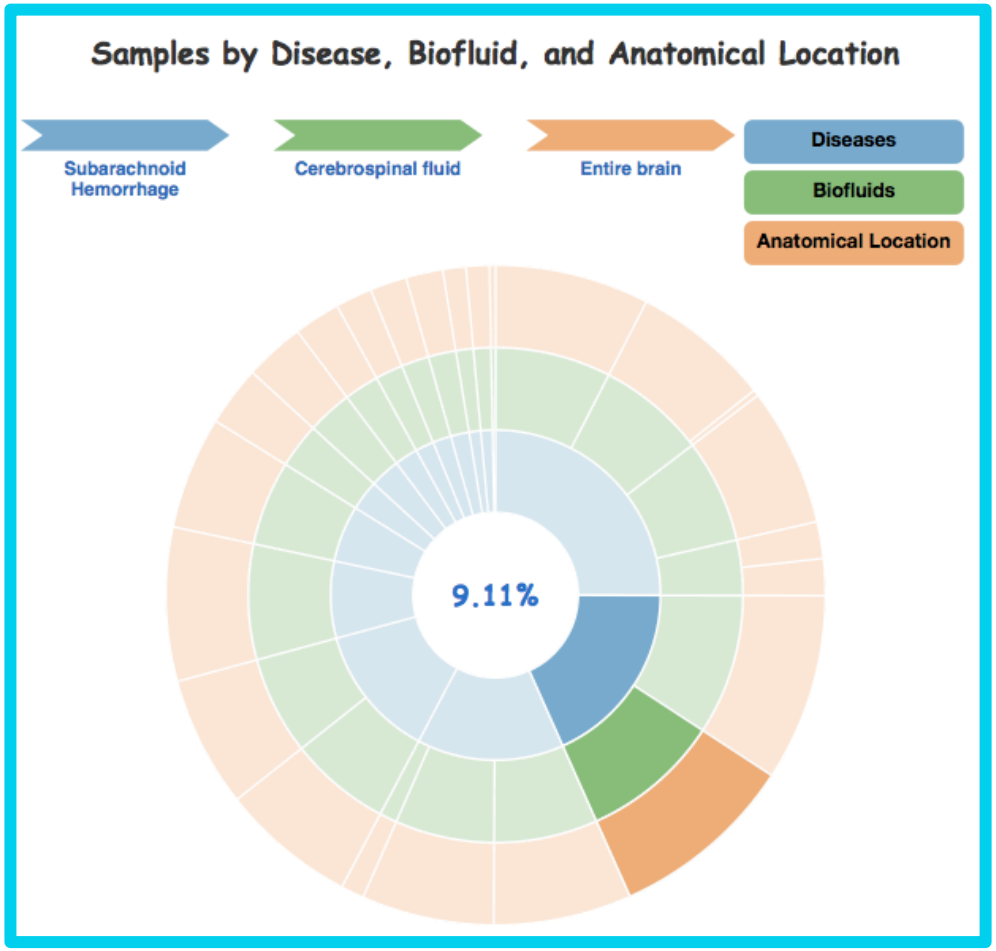
DCC Submission Summary



Group: Submission Month/Year | Group: RFA Title

Job Date	PI Name	Submitter's Name	Grant Number	Mode of Submissio	Organization of PI	Co PI Names	Processing Pipeline	Submission Category	Project Registered by PI with dbGaP?	Number of Submitted Samples
Group: Data Management and Resource Repository (DMRR) on Extracellular RNA (U54) RFA-RM-12-010										
Group: Defining A Comprehensive Reference Profile of Circulating Human Extracellular RNA (U01) RFA-RM-13-014										
2015-06	David J. Erle	Paula Godoy	1U01HL126493-01	Genboree Workbench	University of California San Francisco	[Not applicable]	exceRpt small RNA-seq	Samples Not Meant for Submission to DCC	Not Applicable	76
2015-07	David J. Erle	Paula Godoy	1U01HL126493-01	Genboree Workbench	University of California San Francisco	[Not applicable]	exceRpt small RNA-seq	Samples Not Meant for Submission to DCC	Not Applicable	4
2015-08	David J. Erle	Paula Godoy	1U01HL126493-01	Genboree Workbench	University of California San Francisco	[Not applicable]	exceRpt small RNA-seq	Samples Not Meant for Submission to DCC	Not Applicable	57
2015-09	Muneesh Tewari	Ryan Spengler	1U01HL126499-01	Genboree Workbench	University of Michigan at Ann Arbor	[Not applicable]	exceRpt small RNA-seq	Samples Not Meant for Submission to DCC	Not Applicable	22
Group: Extracellular RNA Biogenesis, Biodistribution, Uptake, and Effector Function (U19) RFA-RM-12-012										
Group: Non-ERCC Submission										
2015-06	Non-ERCC PI	Alex H	Non-ERCC Funded Study	Genboree Workbench		[Not applicable]	exceRpt small RNA-seq	Samples Not Meant for Submission to DCC	Not Applicable	22

Drill-down search in exRNA Atlas



- Use the circular partition diagram (or "sunburst" diagram) to interactively drill down into different subsets of biosamples.
- If you hover over a colored segment, you will see the **Disease » Biofluid » Anatomical Location** values for the biosamples in that subset.
- The percentage of samples falling into that subset will also be displayed.
- If you click a specific segment, you will **zoom** into that subset.
- This drill-down tactic is the best approach for low-population subsets that are hard to select when zoomed out.
- Clicking the **Search** icon in the floating menubar will open the tabular view of your biosample subset.
- Click the center circle to zoom out to the previous level.
- Your last hovered path is always visible. To clear it, click outside the circle.

Tools available at the DMRR

Data Analysis Pipelines & Tools

- exceRpt small RNA-seq Pipeline v3.3 – Genboree Workbench & FTP Submission
- RSEQtools long RNA-seq Pipeline – Genboree Workbench
- Target Interaction Finder – Genboree Workbench
- Pathway Finder – Genboree Workbench
- Fold Change Calculation using DESeq2 – Genboree Workbench
- KNIFE – Known and Novel Circular and Linear Isoform Explorer – Genboree Workbench

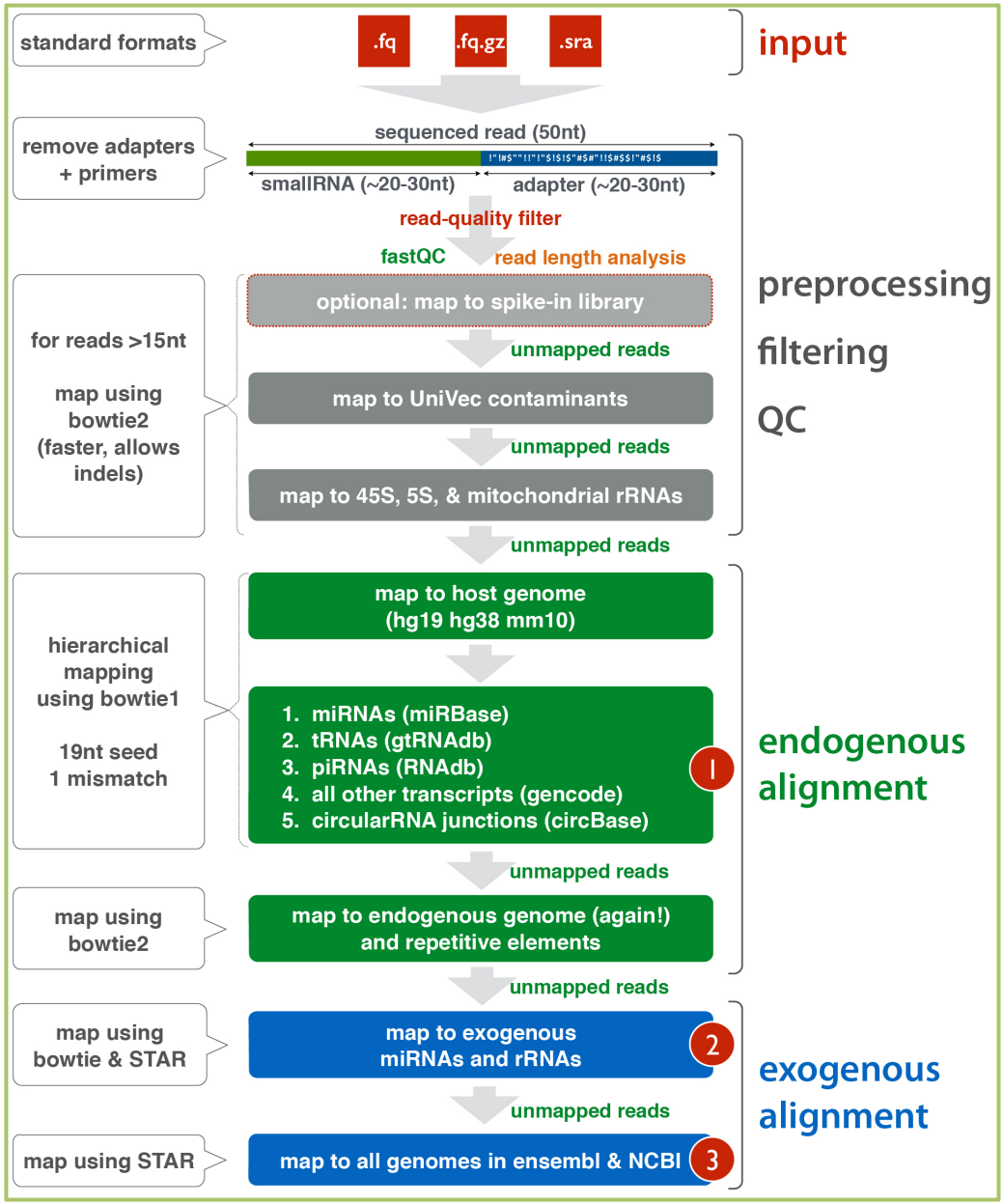
Data Submission Pipelines

- exRNA FTP data submission pipeline for small RNA profiling data

exRNA Metadata Tracking - GenboreeKB

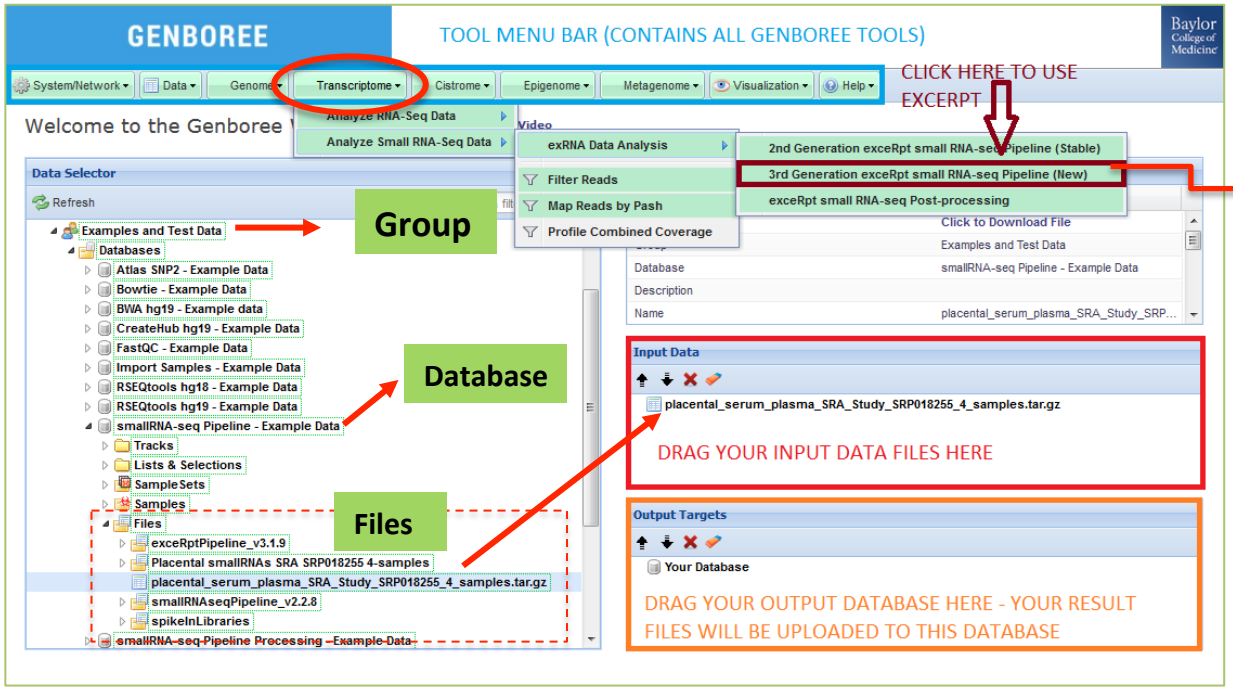
- Small RNA-Seq Assays
- Long RNA-Seq Assays

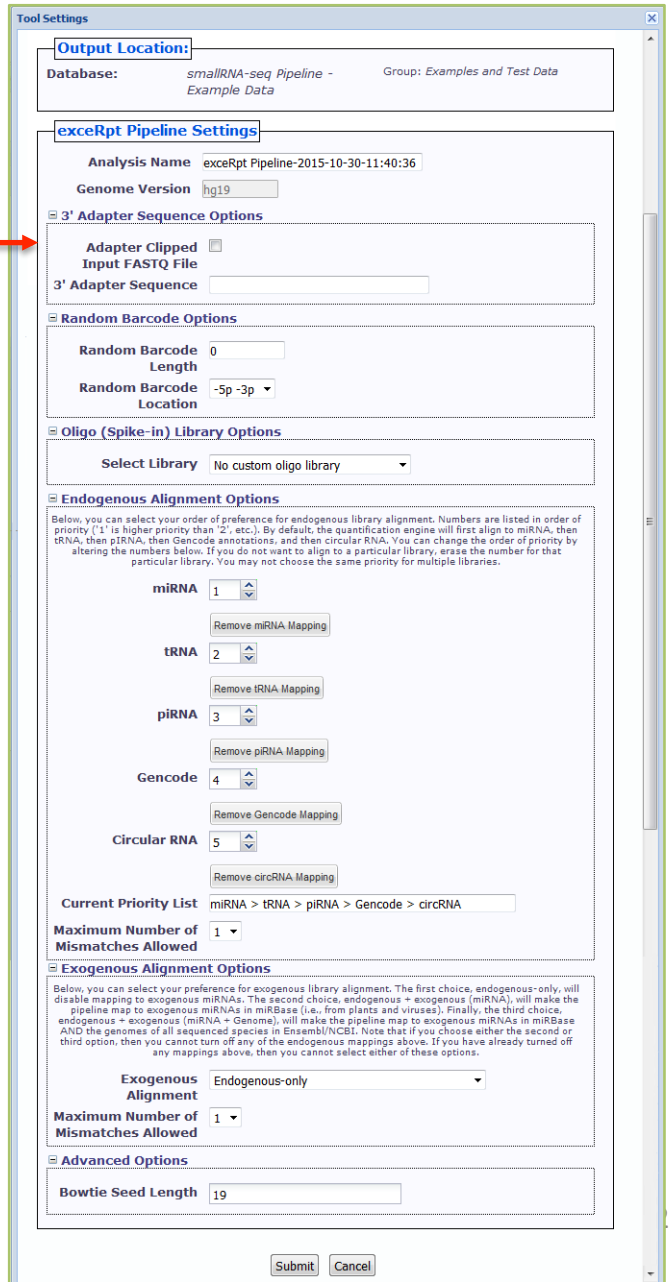
exceRpt v3.1.9 Workflow



Developed by Rob Kitchen at the Gerstein Lab, Yale University

exceRpt v3.1.9 in Genboree Workbench

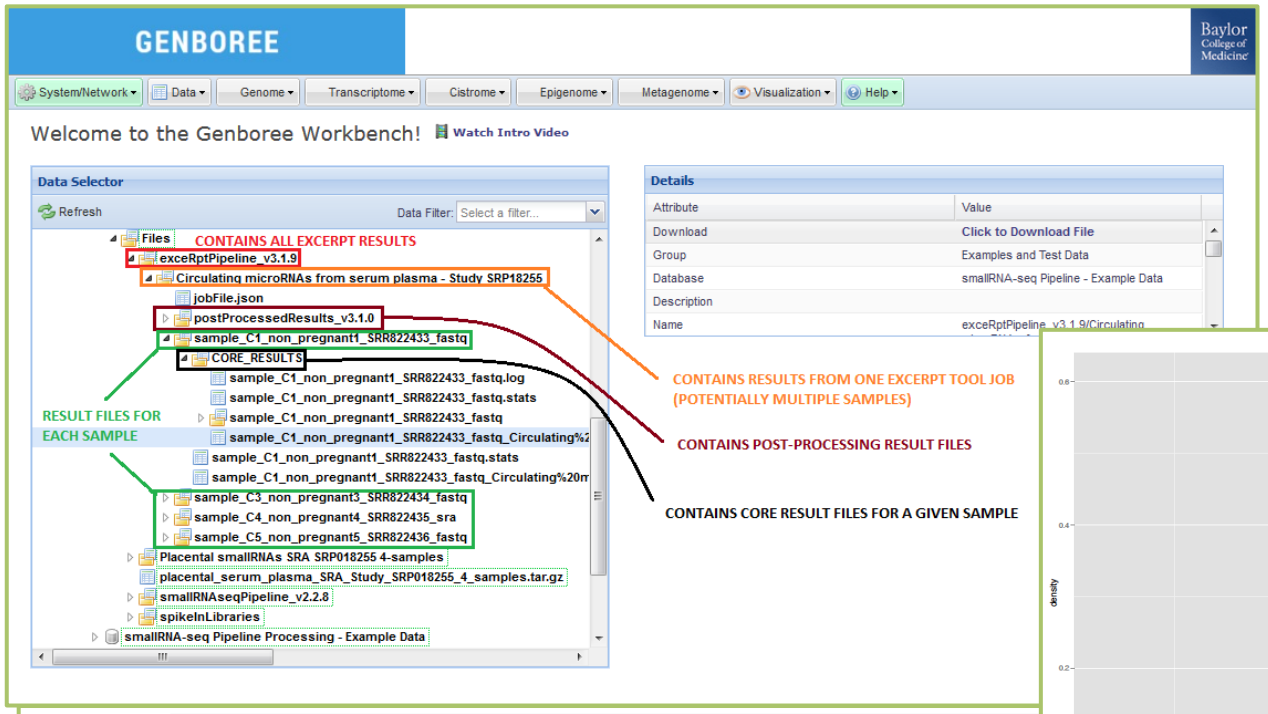


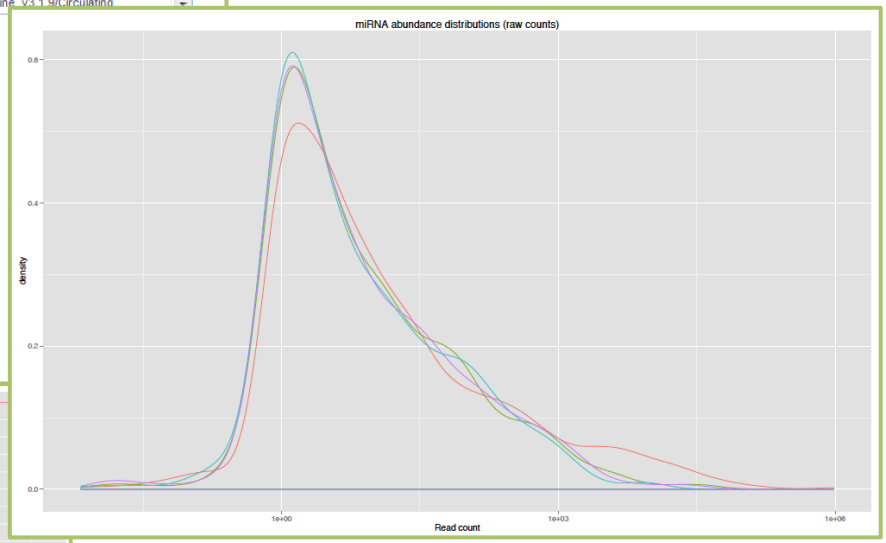


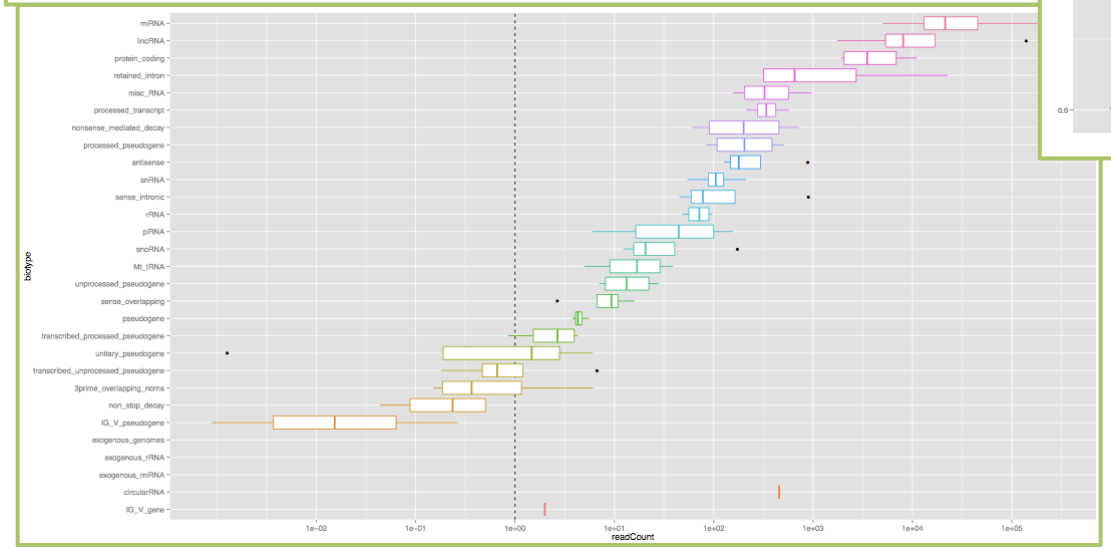
Tool Settings

- Provide 3’ adapter sequence, if known
- Set options for random barcodes – length and location
- Upload custom oligo sequences or use previously uploaded oligo sequences
- Select endogenous libraries for mapping
- Change order of endogenous libraries
- Set mapping options – mismatches, bowtie seed length
- Choose exogenous library alignments

exceRpt v3.1.9 in Genboree Workbench







ERCC Data Analysis Workshop

Topics covered in Use Case 2 Part 2

- Accessing samples in the exRNA Atlas
- **Comparative analysis of exRNA samples using DESeq / exceRpt pipeline results and tools in the Genboree Workbench**
- Finding information about exRNAs of interest
  - on Exocarta and Vesiclepedia
  - on GeneWiki and Wikidata
- Pathway analysis using Cytoscape & WikiPathways in the Genboree Workbench

Using the exRNA Atlas to Perform Comparative and Downstream Analysis of exRNA Samples in the Genboree Workbench

William Thistlethwaite

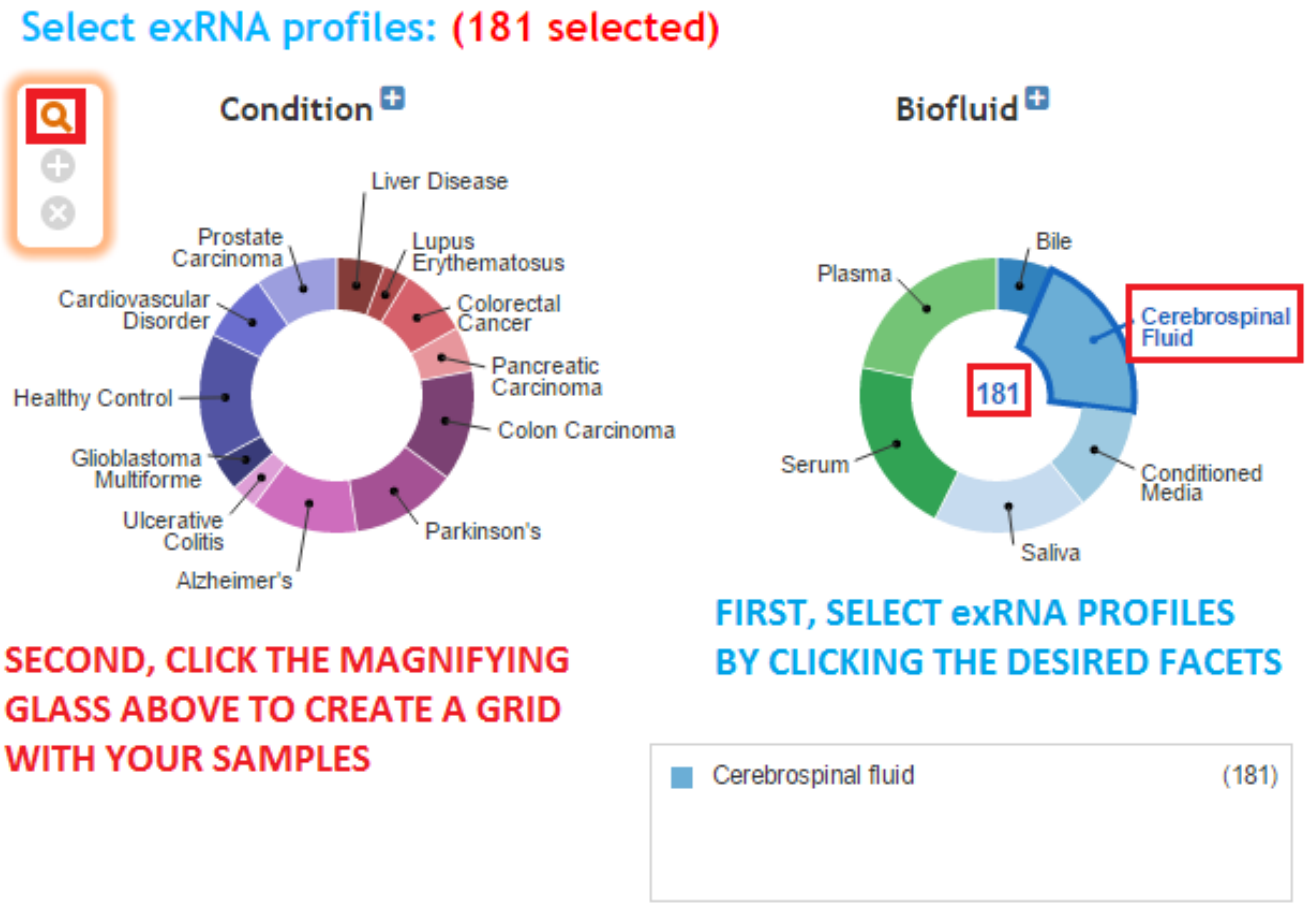
ERC Consortium Data Management & Resource Repository (DMRR)

Baylor College of Medicine, Houston, TX

Selecting Samples of Interest

- Go to the exRNA Atlas website
  - **Public:**
    - **http://genboree.org/exRNA-atlas/index.rhtml**
  - **Private (ERCC Only):**
    - **http://genboree.org/java-bin/exRNA-atlas/index.jsp**
- Use the faceted charts to select your samples of interest.
  - Click the appropriate facets and then click the magnifying glass icon to show corresponding samples in a grid.

Selecting Samples of Interest



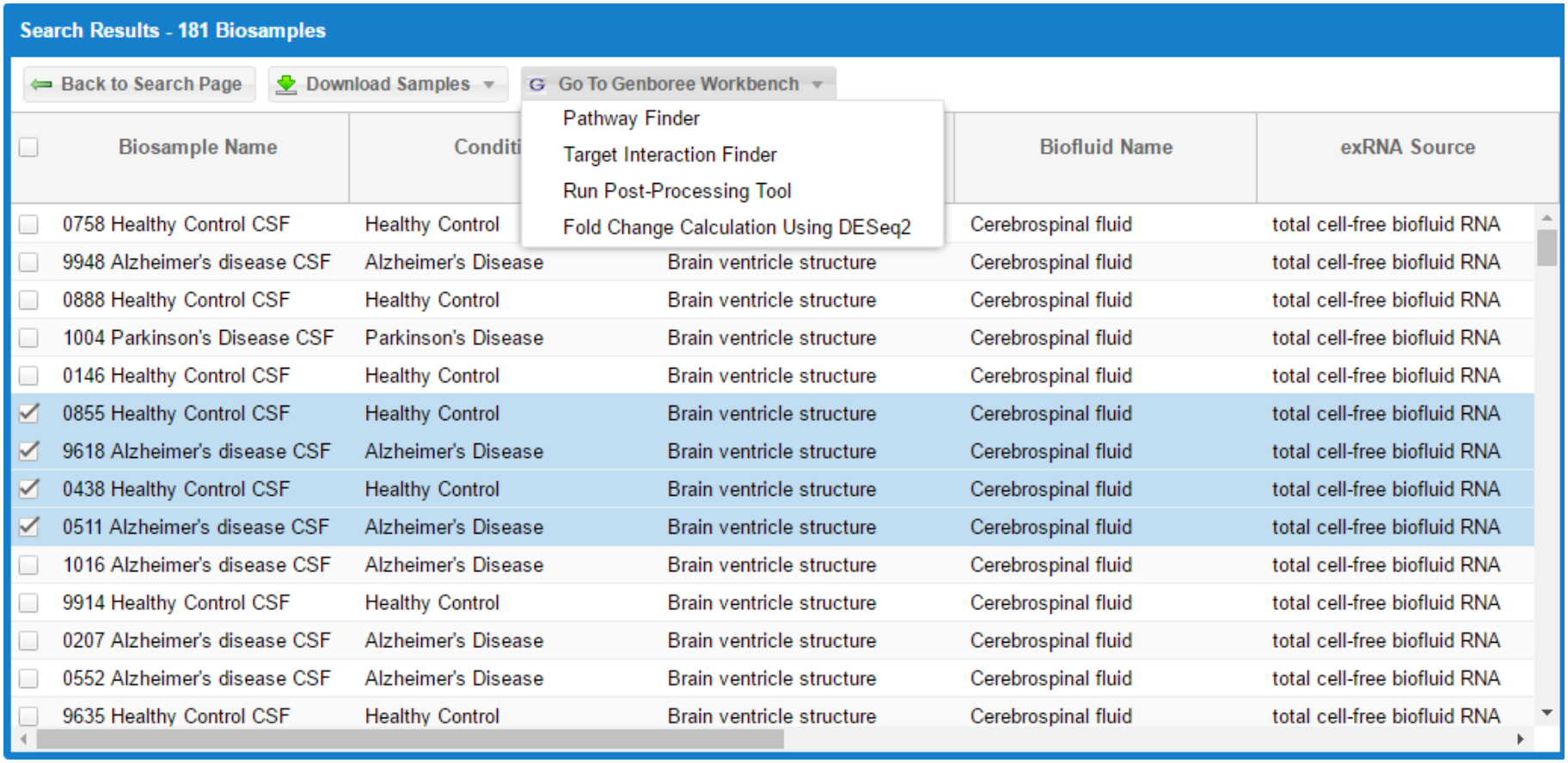
Picking Out Samples for Further Analysis

- Pick out the desired samples using the checkboxes to the left of each sample.
  - To select all samples, click the checkbox in the upper left corner of the grid.

- The different metadata columns (Condition, Anatomical Location, etc.) should help you figure out your samples of interest.

- Once you've picked out your samples, click the "**Go to Genboree Workbench**" button to see available tools.

Picking Out Samples for Further Analysis

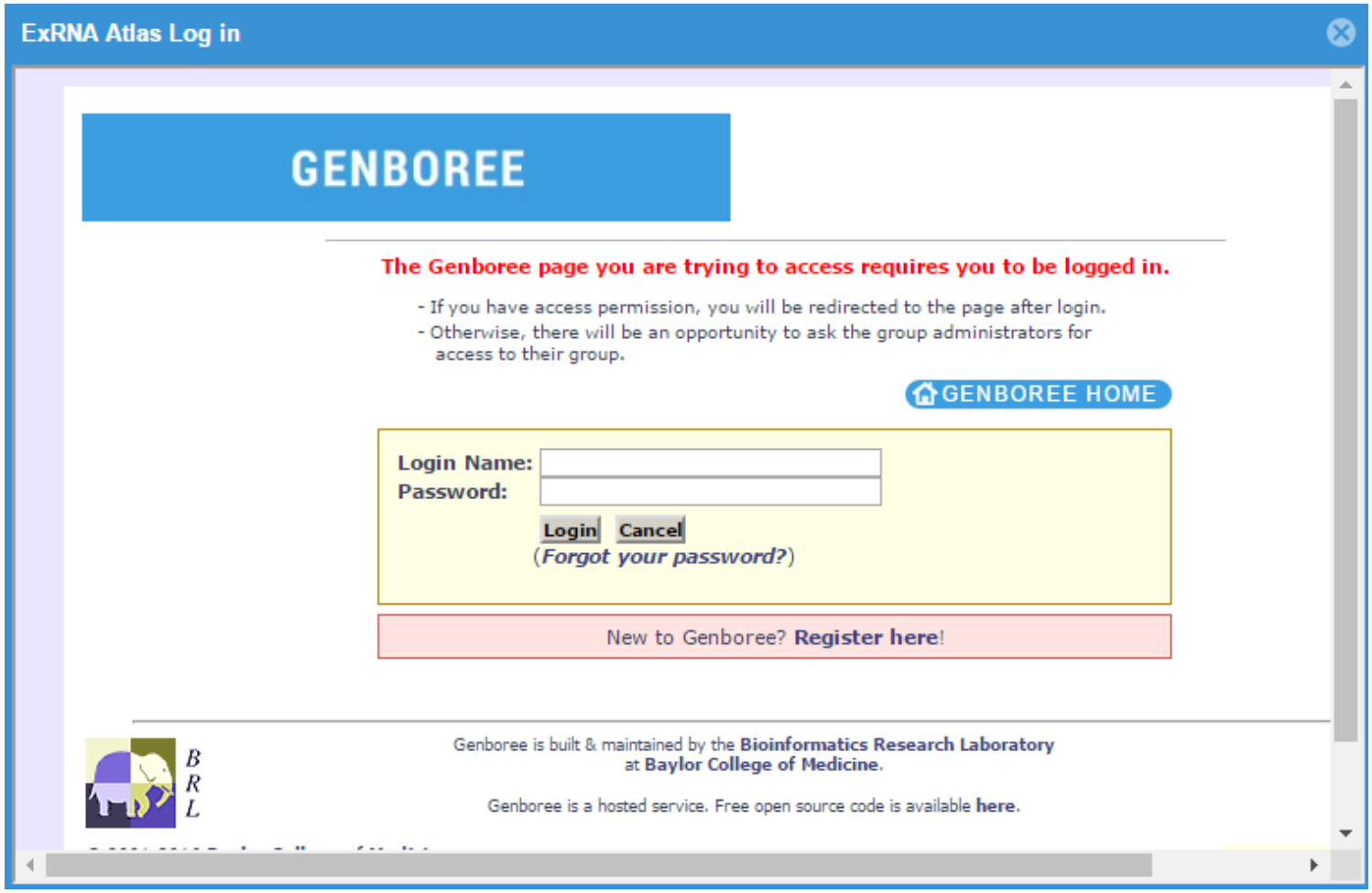


Going from Atlas to Workbench

- Once you've clicked the "Go to Genboree Workbench" button, you can choose a tool to run on your selected samples.

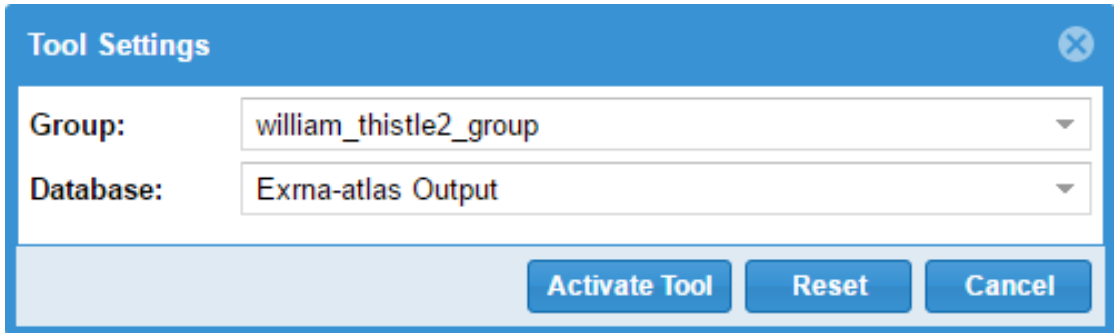
- You will be prompted to log into the Genboree Workbench once you choose a tool. This means that you must have a Genboree account to use the tools.
  - If you have an account already, you can fill in your login information and then click the "Login" button.
  - If you don't have an account, you can click the "Register here" link to create one.
  - Once you've logged in, you won't need to log in again for that Atlas session.

Going from Atlas to Workbench



Going from Atlas to Workbench

- After you've logged in, you'll be able to select the Group and Database which you want to use to store your output files for that tool run.
  - Each Genboree account starts out with a Group (named after your username), but you will need to create a Database in order to run any tools.
  - If the group you select doesn't have a Database, we will offer to create a Database for you (named "Exrna-atlas Output").
  - Pathway Finder does not require a Database to run.



Going from Atlas to Workbench

- Once you click "Activate Tool", you will be taken to the Genboree Workbench.
- Your Input Data panel and Output Targets panel will be filled out automatically by the Atlas.
- You can then select your tool of interest, fill out the appropriate settings, and then launch a tool job.
- We will now go into more depth on running
  - the exceRpt pipeline post-processing tool and
  - the DESeq2 differential expression tool

Run Post-Processing Tool

- The post-processing tool will take results from any number of exceRpt small RNA-seq pipeline runs and will condense valuable information into an easy-to-read format.
  - Instead of looking at read counts from 400 different files (each generated by a different sample), look at **1** file that contains all of the most important information!
  - The tool also generates useful plots and histograms for comparative analysis.

Run Post-Processing Tool

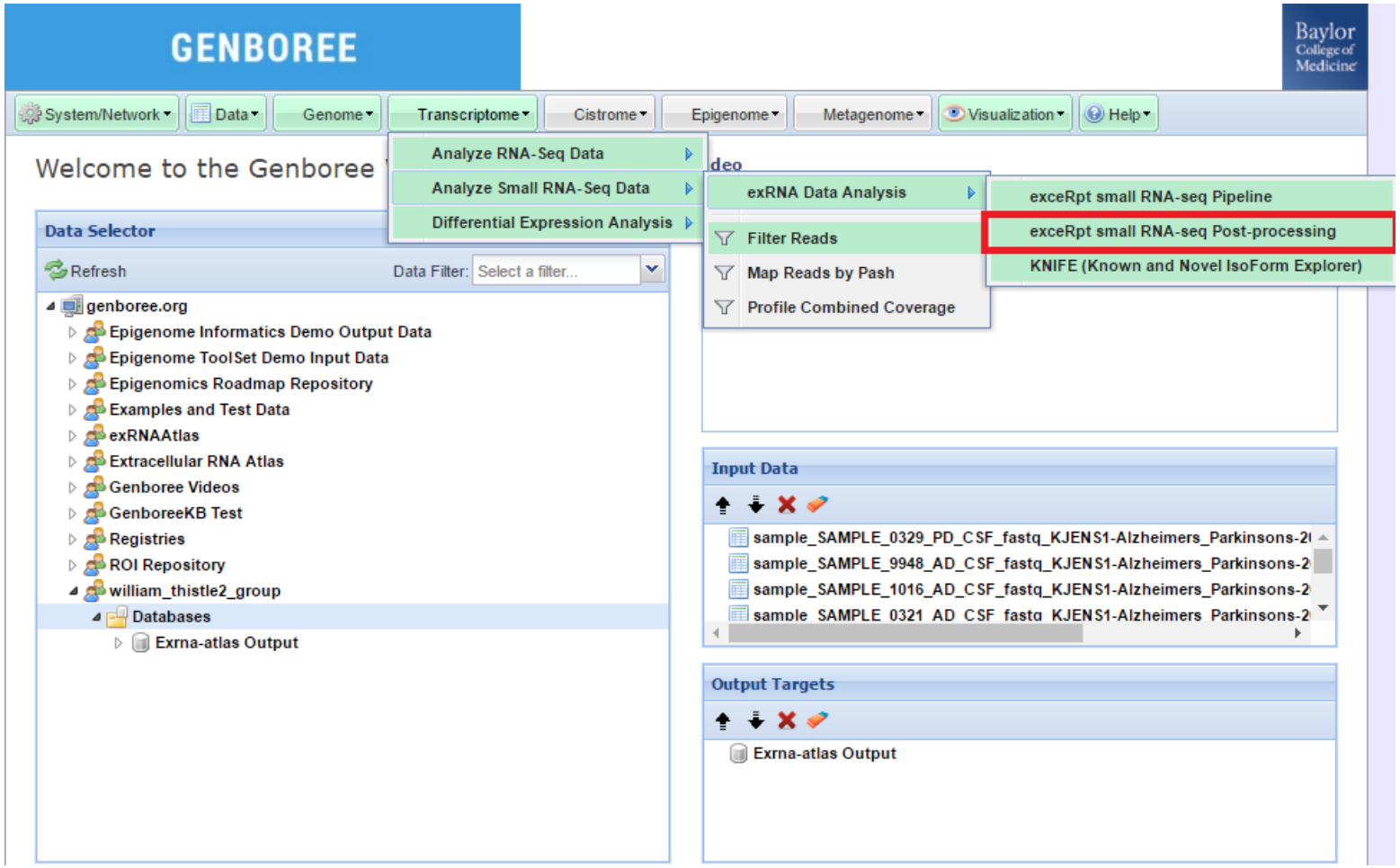
- In order to run the tool, select "Run Post-Processing Tool" from the Atlas and choose your Group and Database.

- Then, choose the post-processing tool in the tool menu:
  - Transcriptome -> Analyze Small RNA-Seq Data -> exRNA Data Analysis -> exceRpt small RNA-seq Post-processing

- Finally, fill out your Analysis Name (used for organizing your results on the Workbench) and click "Submit".

- You can follow the progress of your Job using the "Job Summary" tool (found under System/Network -> Jobs).

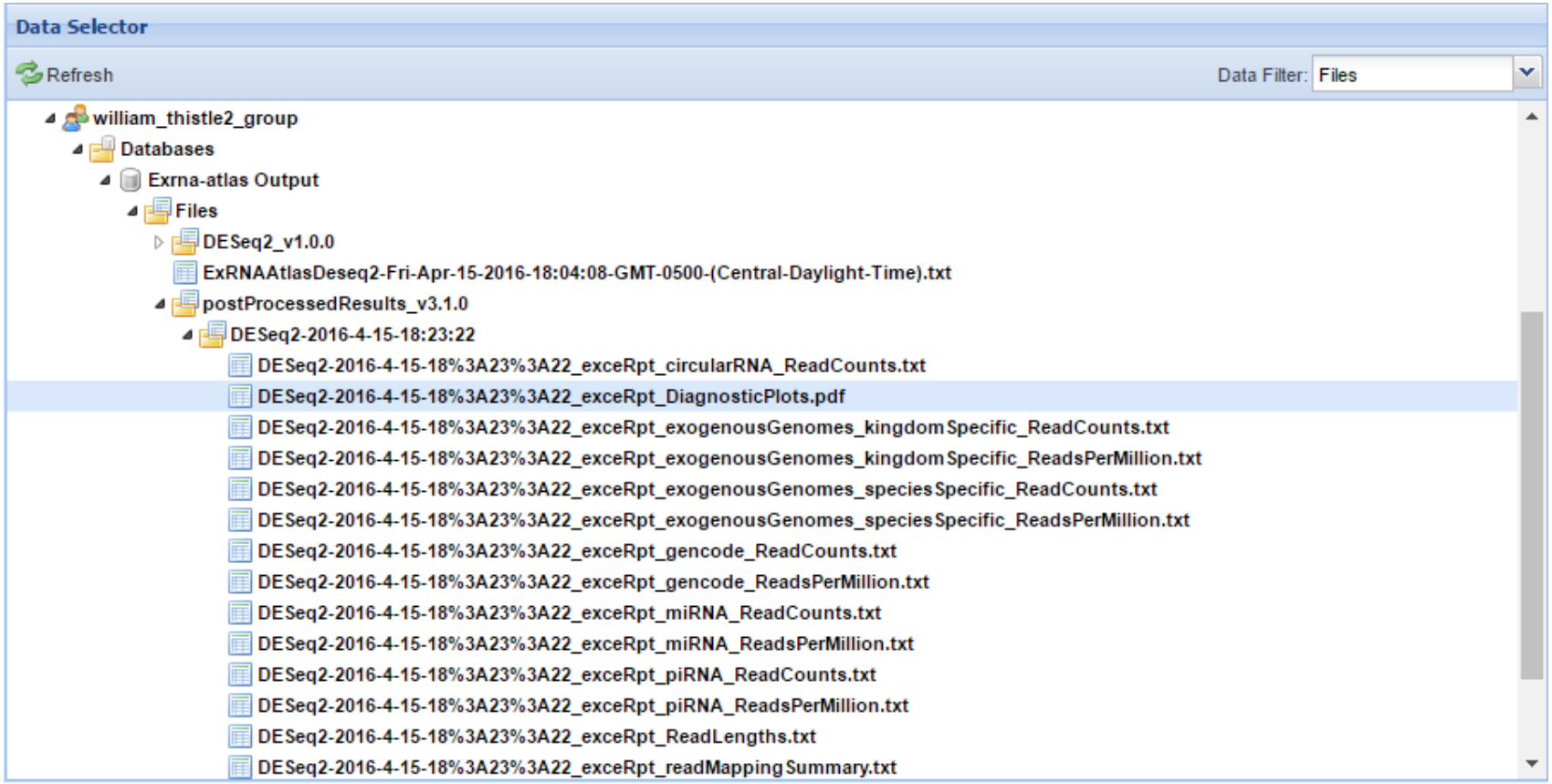
Run Post-Processing Tool



Outputs from Post-Processing Tool

- Once your job has completed, you can download the result files from the Workbench, using the Data Selector Panel.
- You should navigate to the Group and Database you chose earlier in the Atlas.
- Then, navigate to the following directory:
  - Files -> postProcessedResults_v3.1.0 -> [Your Analysis Name]
- In order to download a given file, click on it in the Data Selector panel and then click the "Click to Download File" link in the Details panel.

Outputs from Post-Processing Tool



Fold Change Calculation Using DESeq2

- This tool will test exRNA samples for differential expression of miRNAs using DESeq2 (version 1.6.3).

- Currently, the tool allows you to test a given factor (disease, for example) across two different factor levels (Alzheimer's disease versus control, for example).

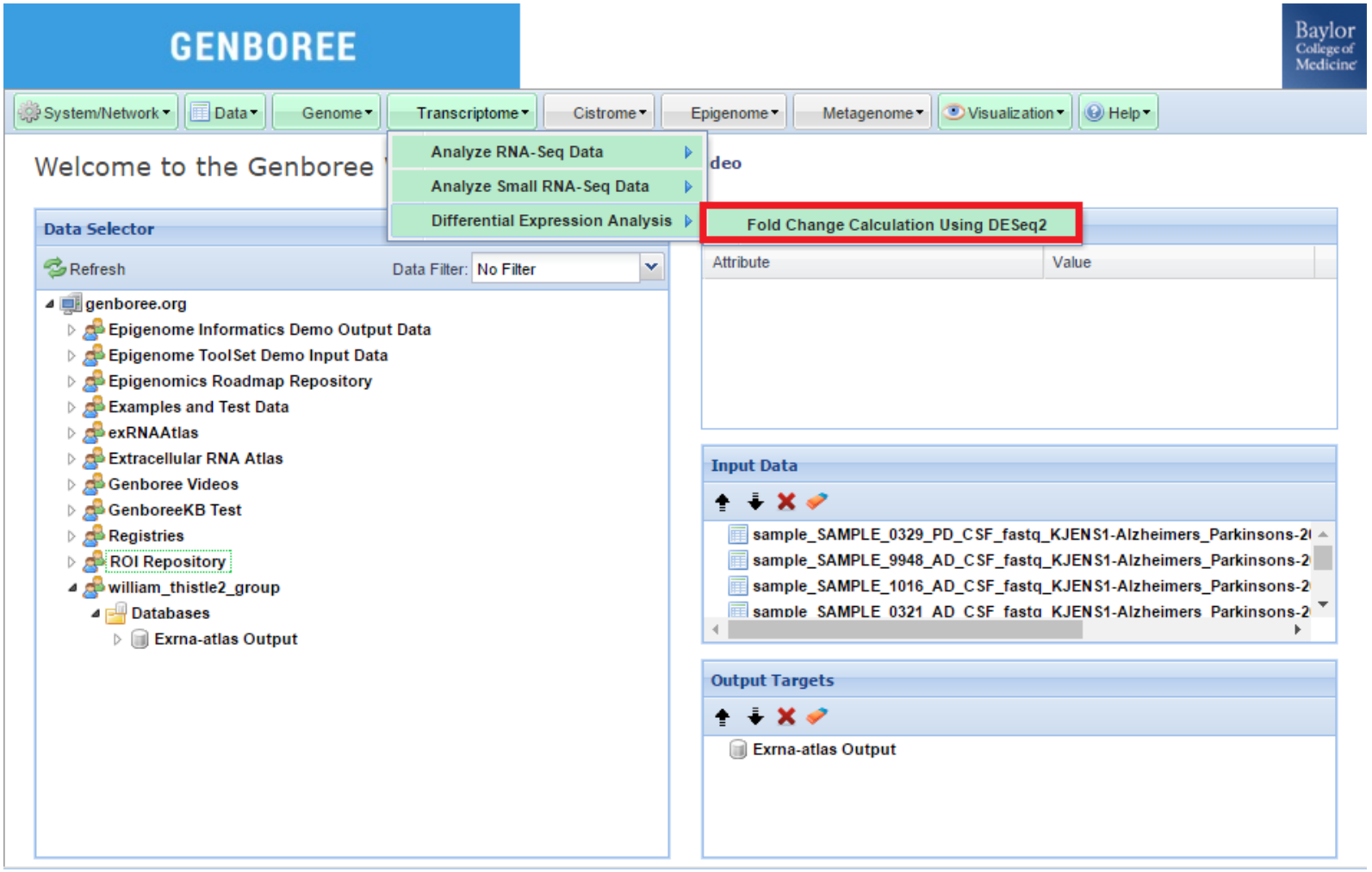
- We will continue to develop this tool and will add new features (like allowing analysis over multiple factors) in the coming months.

Fold Change Calculation Using DESeq2

- In order to run the tool, select "Fold Change Calculation Using DESeq2" from the Atlas and choose your Group and Database.

- Then, choose the DESeq2 tool in the tool menu:
  - Transcriptome -> Differential Expression Analysis -> Fold Change Calculation Using DESeq2

Fold Change Calculation Using DESeq2



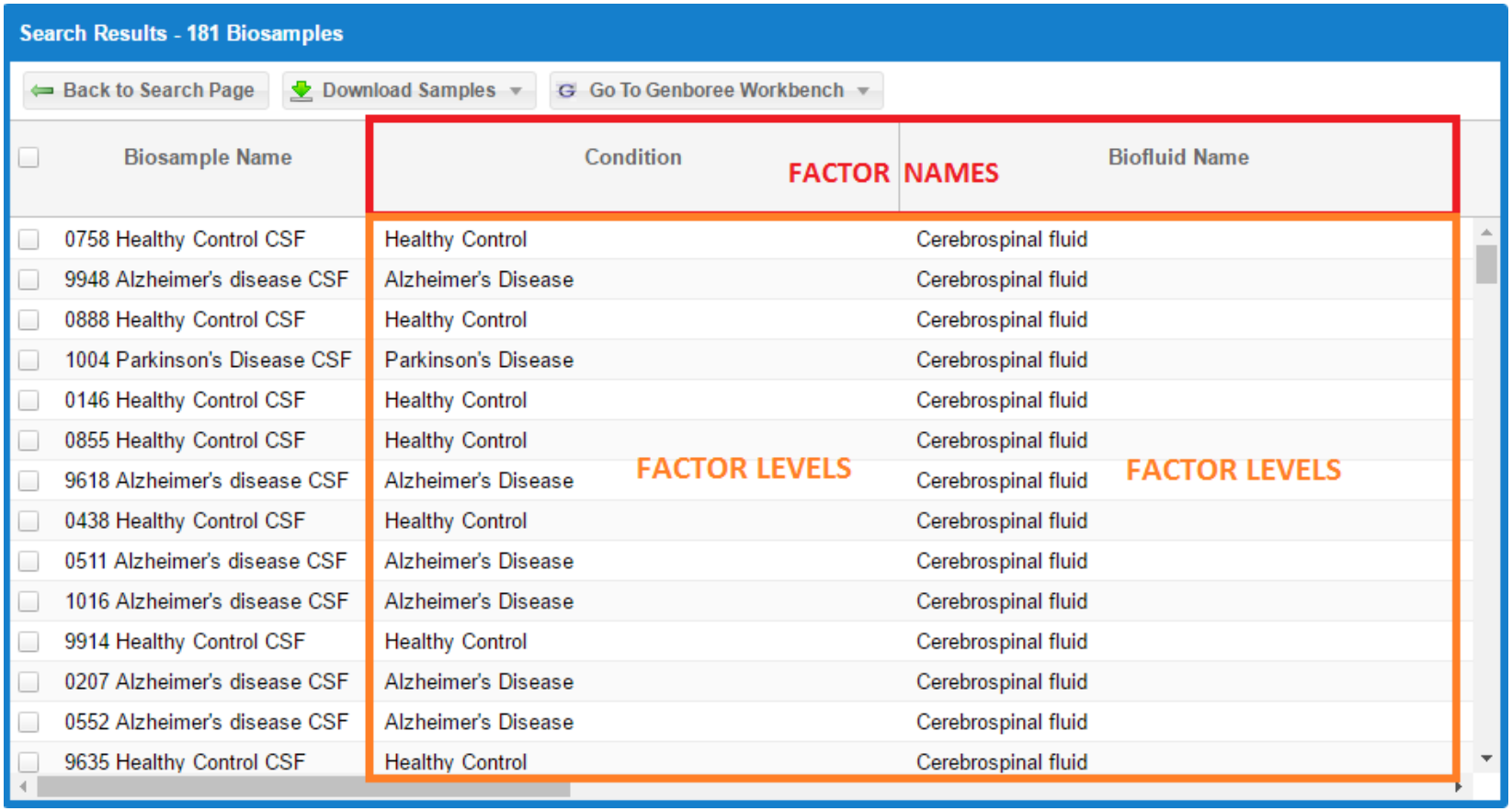
Fold Change Calculation Using DESeq2

- After choosing DESeq2, you will need to fill out your tool settings in the dialog box that pops up.

- You can use the Atlas grid to choose your factor name / factor levels.
  - Factor name is column name (Condition or Biofluid Name for now)
  - Factor levels can be found within those columns (Alzheimer's Disease, Healthy Control, etc.).

- Second factor level is used as base level (should probably be your control).

Fold Change Calculation Using DESeq2

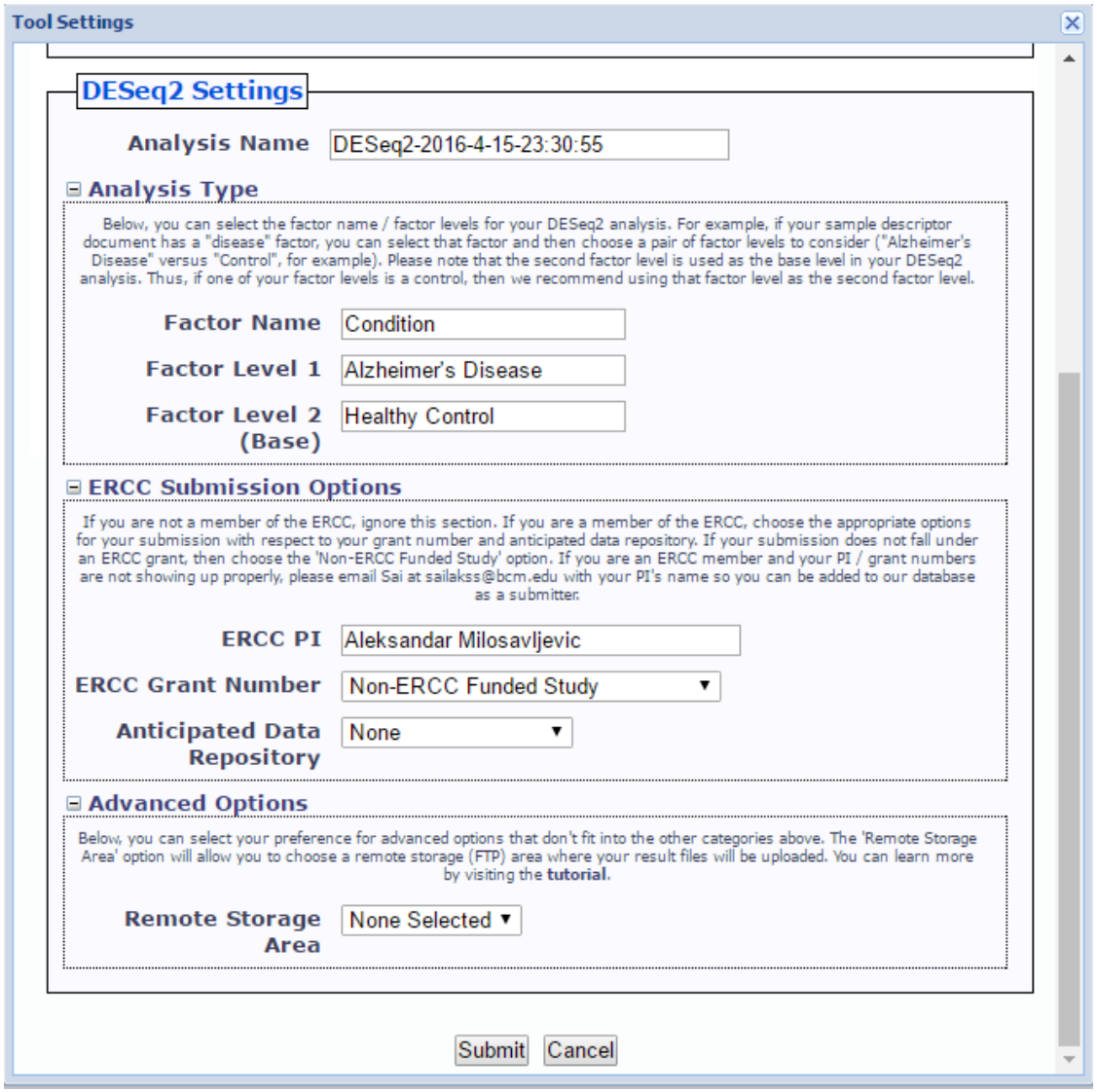


Fold Change Calculation Using DESeq2

- If you are an ERCC member, you should also fill out the ERCC Submission Options section.
  - This section helps us keep track of tool usage, and we can use the information to improve the tools and get valuable user feedback.

- Finally, you can choose to have your results uploaded to our FTP server via the "Remote Storage Area" option in the "Advanced Options" section. To learn more, follow this link:
  - http://genboree.org/theCommons/projects/exrna-tools-may2014/wiki/Using_Remote_(FTP)_Storage_for_exceRpt

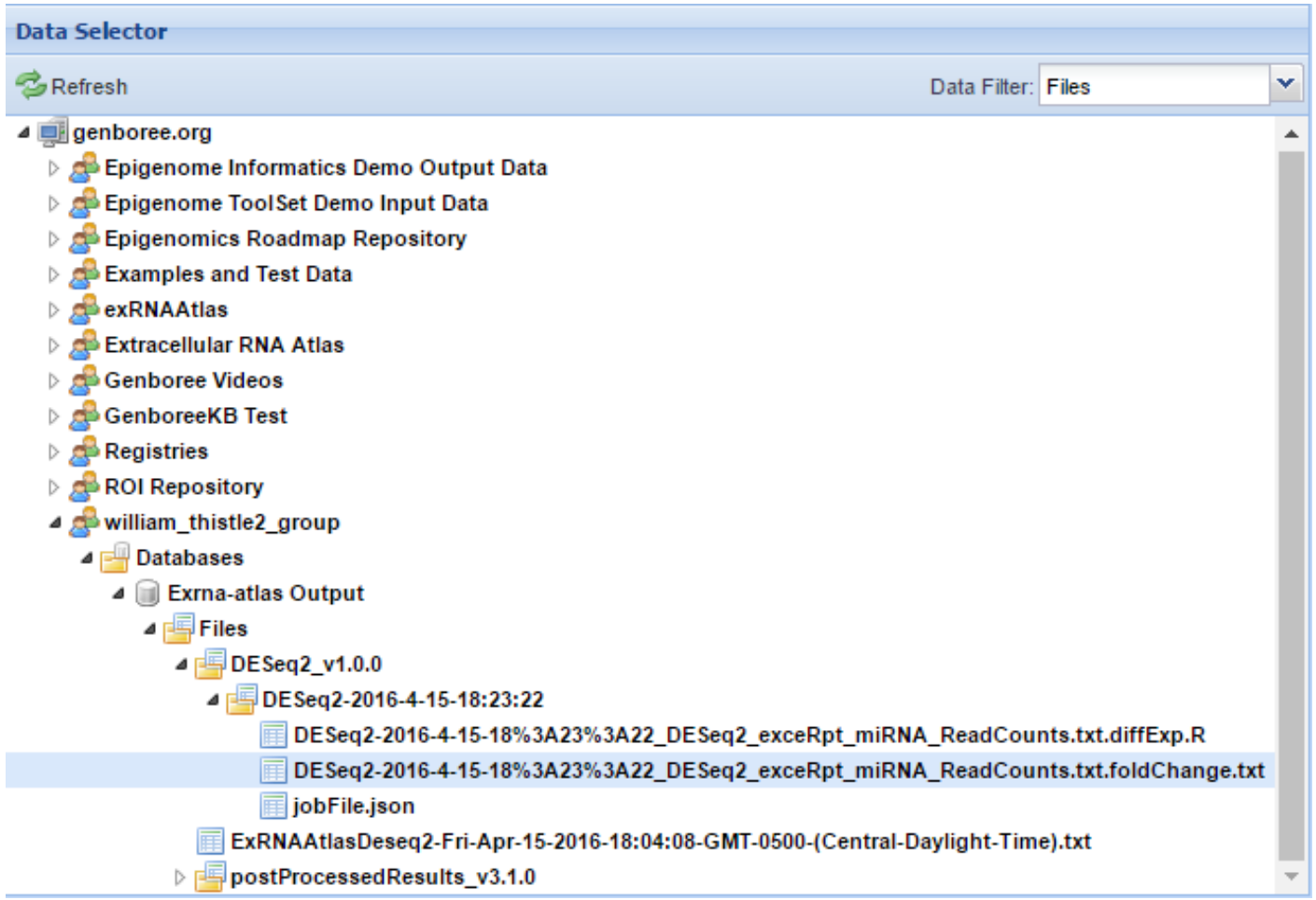
Fold Change Calculation Using DESeq2



Outputs from DESeq2

- Once your job has completed, you can download the result files from the Workbench, using the Data Selector Panel.
- You should navigate to the Group and Database you chose earlier in the Atlas.
- Then, navigate to the following directory:
  - Files -> DESeq2_v1.0.0 -> [Your Analysis Name]
- In order to download a given file, click on it in the Data Selector panel and then click the "Click to Download File" link in the Details panel.

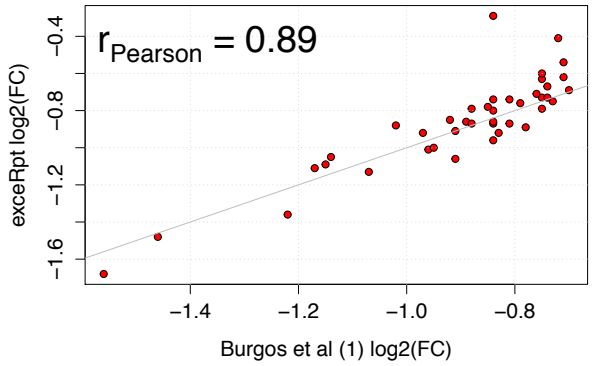
Outputs from DESeq2



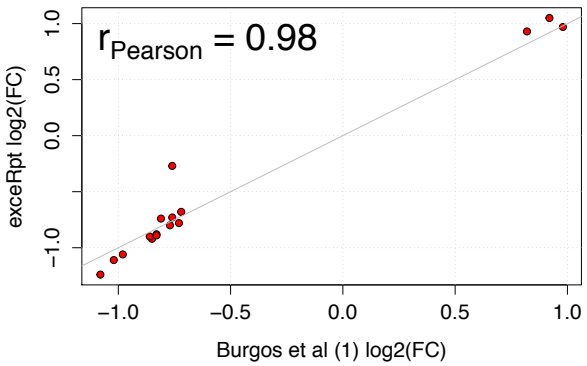
Use Case 2: miRNA Changes in Alzheimer's and Parkinson's Disease

Below is a comparison of the differential expression analysis results from Burgos et al. with the results from Genboree Workbench, namely running DESeq2 on the output of the exceRpt pipeline.

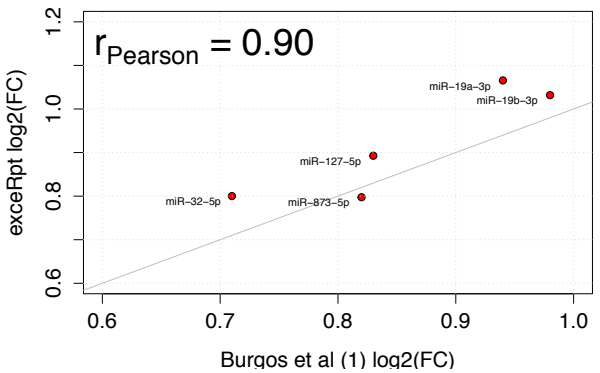
AD vs control in CSF



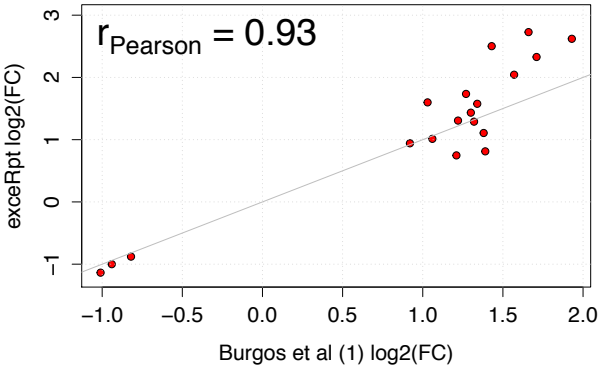
PD vs control in CSF



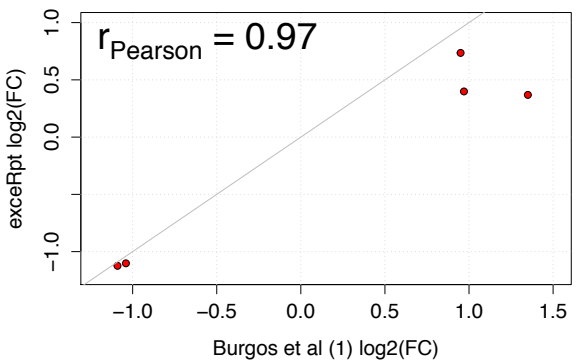
AD vs PD in CSF



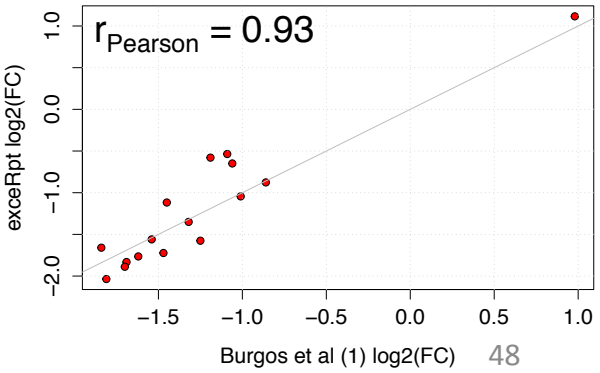
AD vs control in Serum

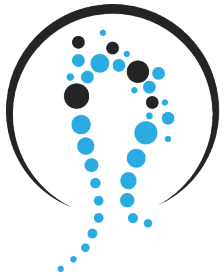


PD vs control in Serum



AD vs PD in Serum





ERCC Data Analysis Workshop

Topics covered in Use Case 2 Part 2

- Accessing samples in the exRNA Atlas
- Comparative analysis of exRNA samples using DESeq / exceRpt pipeline results and tools in the Genboree Workbench
- **Finding information about exRNAs of interest**
  - **on Exocarta and Vesiclepedia**
  - **on GeneWiki and Wikidata**
- Pathway analysis using Cytoscape & WikiPathways in the Genboree Workbench

Vesiclepedia and Exocarta

You can access both Vesiclepedia and Exocarta from the Quick Links sidebar at exRNA.org.

exRNA.org

Quick Links

ExRNA Atlas

ExRNA @ BioGPS

ExRNA @ WikiPathways

ExoCarta

Vesiclepedia

miRandola

Vesiclepedia and Exocarta

- a compendium of proteins, RNA and lipids found in exosomes
- manually curated from the scientific literature
- available since 2009

Mathivanan et al. *Proteomics* 2009
Keerthikumar et al. *J. Mol. Biol.* 2016

- a compendium of proteins, RNA, and lipids found in all types of EVs
- manually curated from the scientific literature
- focuses strongly on community annotation
- available since 2012

Kalra et al. *PLoS Biology* 2012

Vital Statistics

ExoCarta

STATISTICS	
Studies	286
Protein entries	41,860
Proteins	9,769
mRNA entries	4,946
mRNA	3,408
miRNA	2,838
Lipid entries	1,116

Vesiclepedia

STATISTICS	
Studies	538
Protein entries	92,897
mRNA entries	27,642
miRNA entries	4,934
Lipid entries	584
Species	33

	Exocarta	Vesiclepedia	In Common
All Publications	132	271	108
Human Publications	100	190	78

Exocarta


Credits | Contact | Vesiclepedia
ExoCarta
HOME
QUERY
BROWSE
DOWNLOAD
DATA SUBMISSION
HELP
EXOSOME PROTEIN, RNA AND LIPID DATABASE
Exosomes are 30-150 nm membrane vesicles of endocytic origin secreted by most cell types *in vitro*. ExoCarta, an exosome database, provides with the contents that were identified in exosomes in multiple organisms.
FunRich
Functional Enrichment Analysis Tool
Perform bioinformatics analysis of your extracellular vesicle data set using FunRich, a open access standalone tool.
Vesiclepedia
HOME
QUERY
BROWSE
DOWNLOAD
HELP
Vesiclepedia - Compendium on extracellular vesicles
STATISTICS
Studies 286
Protein entries 41,860
Proteins 9,769
mRNA entries 4,946
mRNA 3,408
miRNA 2,838
Lipid entries 1,116
EXOSOMAL MARKERS
Statistics of proteins that are identified more often in exosomes.
download ...

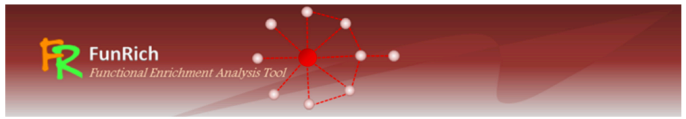
Vesiclepedia

Vesiclepedia

HOME | QUERY | BROWSE | DOWNLOAD | HELP

A community compendium for extracellular vesicles

Extracellular vesicles (EVs) are membraneous vesicles released by a variety of cells into the extracellular microenvironment. Based on the mode of biogenesis, EVs can be classified into three broad classes (i), ectosomes or shedding microvesicles (ii), exosomes and (iii), apoptotic bodies. Recent studies have ignited significant interest on EVs by elucidating their role in intercellular communication, pathogenesis, drug, vaccine and gene-vector delivery and as possible reservoirs of biomarkers. With such immense interest, the amount of data generated has increased exponentially. Here, we describe Vesiclepedia, a manually curated compendium of molecular data (lipid, RNA and protein) identified in different classes of EVs. Currently, Vesiclepedia comprises 35,264 protein, 18,718 mRNA, 1,772 miRNA and 342 lipid entries encompassed from 341 independent studies that were published over the past several years. Even though databases are indispensable resources for the scientific community, r ecent studies have shown that more than 50% of the databases are not updated for a long time. In addition, more than 20% of the database links are not active after its initial publication. To prevent such database decay and keep them updated, for the first time, we have initiated a continuous community annotation project with the active involvement of the EV researchers with long standing (> 10 years) and newly found reputation in the field. The principal investigators working on EVs have vowed to contribute data generated by their group in a regular and continuous fashion making this effort significantly unique. By undertaking such initiatives, we foresee the EV research community as trendsetters in data sharing. We expect, Vesiclepedia to evolve as a primary resource for EV research.



Perform bioinformatics analysis of your extracellular vesicle data set using FunRich, a open access standalone tool.

STATISTICS

Studies	538
Protein entries	92,897
mRNA entries	27,642
miRNA entries	4,934
Lipid entries	584
Species	33

LATEST NEWS

09/01/2015 - Vesiclepedia Version 3.1 released!!
09/01/2015 - Addition of new datasets to Vesiclepedia.

01/09/2013 - Vesiclepedia Version 2.1 released!!
01/09/2013 - Addition of new datasets to Vesiclepedia.

01/04/2013 - Vesiclepedia highlighted in Nature Methods
01/04/2013 - Manuscript describing Vesiclepedia was highlighted in the tool section of Nature Methods.
PubMed

Differential Expression of miRNAs in CSF

Control vs Alzheimer's

	Burgos et al		exceRpt + DESeq2	
miR Name	log2(FC)	P-value	log2(FC)	P-value
miR-124-3p	-1.56	1.00E-06	-1.68	2.00E-06
miR-138-5p	-1.46	1.00E-06	-1.48	7.00E-06
miR-127-3p	-1.17	1.90E-05	-1.11	2.55E-04
miR-132-3p	-0.89	1.90E-05	-0.86	1.29E-04
miR-127-5p	-1.15	3.10E-05	-1.09	3.07E-04
miR-136-3p	-1.02	4.00E-05	-0.88	1.16E-03
miR-381(-3p)*	-1.14	4.90E-05	-1.05	9.86E-04
miR-101-5p	-0.92	6.70E-05	-0.85	9.86E-04
miR-199b-5p	-1.22	6.70E-05	-1.36	1.29E-04
miR-136-5p	-0.91	1.91E-04	-0.91	7.73E-04

We will focus on the
top 10 most differentially expressed miRNAs
in CSF of Alzheimers' patients vs. healthy controls.

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

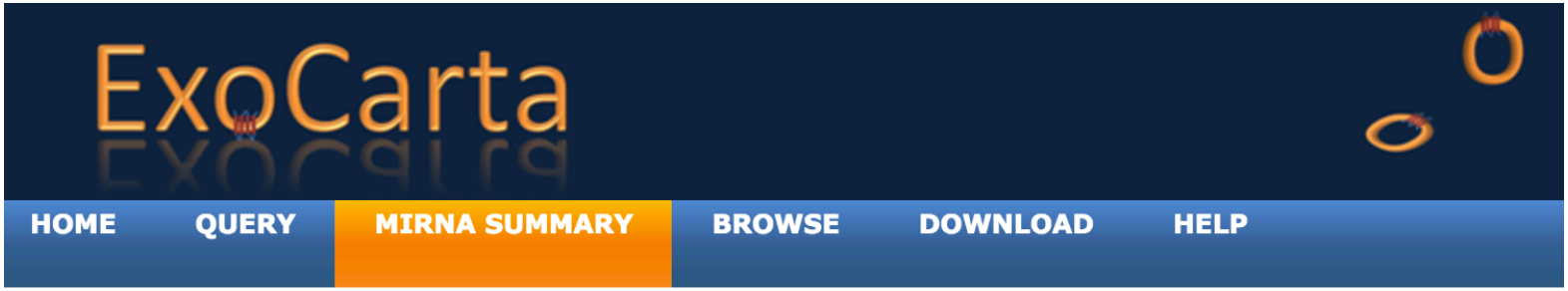
Querying Exocarta for miRNAs

http://exocarta.org/mirna_summary?species=Homo%20sapiens&mirna_id=miR-124-3p

Control vs Alzheimer's

miR Name

- miR-124-3p
- miR-138-5p
- miR-127-3p
- miR-132-3p
- miR-127-5p
- miR-136-3p
- miR-381(-3p)
- miR-101-5p
- miR-199b-5p
- miR-136-5p



miRNA description for miR-124-3p	
miRNA accession	**miR-124-3p**
Species	Homo sapiens
miR-124-3p identified in exosomes derived from the following tissue/cell type	
Colorectal cancer cells	Unpublished / Not applicable
Colorectal cancer cells	Unpublished / Not applicable
Melanoma cells	26176991 PubMed
Plasma	23663360 PubMed

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

Querying Exocarta for miRNAs

http://exocarta.org/mirna_summary?species=Homo%20sapiens&mirna_id=miR-124-3p

Control vs Alzheimer's

miR Name

- miR-124-3p
- miR-138-5p
- miR-127-3p
- miR-132-3p
- miR-127-5p
- miR-136-3p
- miR-381(-3p)
- miR-101-5p
- miR-199b-5p
- miR-136-5p

Experiment description of studies that identified miR-124-3p in exosomes

1	Experiment ID	218
	Identified molecule	miRNA miR
	Identification method	Human miRNA Microarray Kit
	PubMed ID	Unpublished / Not applicable
	Organism	Homo sapiens
	Experiment description	Characterization of colorectal cancer cell exosomal microRNA content in vitro
	Authors	-
	Journal name	**Not applicable**
	Publication year	0
	Sample	Colorectal cancer cells
	Sample name	HCT116 HT29
	Molecules identified in the study	miRNA
	Methods used in the study	miRCURY LNA microRNA Array 7th Gen
	Comments	NOTFOUND **NOTFOUND**

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

Querying Exocarta for miRNAs

http://exocarta.org/mirna_summary?species=Homo%20sapiens&mirna_id=miR-124-3p

Control vs Alzheimer's

miR Name

- miR-124-3p
- miR-138-5p
- miR-127-3p
- miR-132-3p
- miR-127-5p
- miR-136-3p
- miR-381(-3p)
- miR-101-5p
- miR-199b-5p
- miR-136-5p

3	Experiment ID	265
	Identified molecule	miRNA
	Identification method	RNA deep sequencing
	PubMed ID	26176991
	Organism	Homo sapiens
	Experiment description	Small RNA deep sequencing discriminates subsets of extracellular vesicles released by melanoma cells â€"evidence of unique microRNA cargos
	Authors	Lunavat TR, Cheng L, Kim DK, Bhadury J, Jang SC, Lasser C, Sharples RA, Lopez MD, Nilsson J, Gho YS, Hill AF, Lotvall J.
	Journal name	RNA Biology
	Publication year	2015
	Sample	Melanoma cells
	Sample name	MML-1
	Molecules identified in the study	Protein miRNA snRNA snoRNA mtRNA Ro associated Y-RNA MiscRNA
	Methods used in the study	Western blotting RNA deep sequencing
	Comments	NOTFOUND NOTFOUND

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

Querying Exocarta for miRNAs

http://exocarta.org/mirna_summary?species=Homo%20sapiens&mirna_id=miR-124-3p

Control vs Alzheimer's

miR Name

- miR-124-3p
- miR-138-5p
- miR-127-3p
- miR-132-3p
- miR-127-5p
- miR-136-3p
- miR-381(-3p)
- miR-101-5p
- miR-199b-5p
- miR-136-5p

4

Experiment ID	222
Identified molecule	miRNA
Identification method	RT-PCR
PubMed ID	23663360
Organism	Homo sapiens
Experiment description	Characterization of human plasma-derived exosomal RNAs by deep sequencing
Authors	Huang X, Yuan T, Tschannen M, Sun Z, Jacob H, Du M, Liang M, Dittmar RL, Liu Y, Liang M, Kohli M, Thibodeau SN, Boardman L, Wang L
Journal name	BMC Genomics
Publication year	2013
Sample	Plasma
Sample name	Plasma - Normal
Molecules identified in the study	miRNA tRNA snRNA snoRNA rRNA piRNA lncRNA
Methods used in the study	RT-PCR
Comments	NOTFOUND NOTFOUND

Burgos K., et al. (2014) Profiles of Extracellular miRNA in Cerebrospinal Fluid and Serum from Patients with Alzheimer's and Parkinson's Diseases Correlate with Disease Status and Features of Pathology. PLoS ONE 9: e94839.

Querying Vesiclepedia for miRNAs

http://microvesicles.org/mirna_summary?species=Homo%20sapiens&mirna_id=miR-124-3p

Control vs Alzheimer's

miR Name

- miR-124-3p
- miR-138-5p
- miR-127-3p
- miR-132-3p
- miR-127-5p
- miR-136-3p
- miR-381(-3p)
- miR-101-5p
- miR-199b-5p
- miR-136-5p

Vesiclepedia

QUERY | MIRNA SUMMARY | BROWSE | DOWNLOAD | HELP

miRNA description for miR-124-3p

miRNA accession	**miR-124-3p**
Species	Homo sapiens

miR-124-3p identified in exosomes derived from the following tissue/cell type

Urine [Exosomes]	24352158 PubMed

Experiment description of studies that identified miR-124-3p in exosomes

1	Experiment ID	357
	Identified molecule	miRNA miR
	Identification method	RNA deep sequencing
	PubMed ID	24352158 PubMed
	Organism	Homo sapiens
	Experiment description	Characterization and deep sequencing analysis of exosomal miRNA in human urine
	Authors	Lesley Cheng, Xin Sun, Bradley M. Coleman, Andrew F. Hill
	Journal name	Not applicable
	Publication year	0
	Sample	Urine
	Sample name	Urine - Normal
	Molecules identified in the study	miRNA
	Methods used in the study	RNA deep sequencing

tgen

Downloading Vesiclepedia and Exocarta

You can download both the Exocarta and Vesiclepedia databases as structured text files.

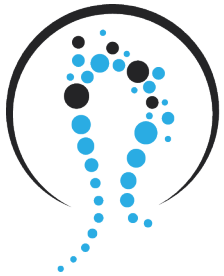
ExoCarta Download - 5 (Release date: 29 July 2015)	
Protein/mRNA data	ExoCarta_protein_mRNA_details_5.txt
miRNA data	ExoCarta_miRNA_details_5.txt
Lipid data	ExoCarta_lipid_details_5.txt
Exosome study details	ExoCarta_experiment_details_5.txt
Gene details	ExoCarta_gene_details_5.txt
Top 100 proteins	ExoCarta_top100_protein_details_5.txt

Vesiclepedia Download - Version 3 (Release date: 9 Jan 2015)	
Protein/mRNA data	Vesiclepedia_protein_mRNA_details.txt
miRNA data	Vesiclepedia_miRNA_details.txt
Lipid data	Vesiclepedia_lipid_details.txt
Experiment study details	Vesiclepedia_experiment_details.txt
Gene details	Vesiclepedia_gene_details.txt
PTM details	Vesiclepedia_PTM_details.txt

Downloading Vesiclepedia and Exocarta

The miRNA and Experiment structured text files have the following fields.

miRNA	Experiment
CONTENT ID	EXPERIMENT ID
CONTENT TYPE	PUBMED ID
MIRNA ID	SPECIES
SPECIES	EXPERIMENT DESCRIPTION
EXPERIMENT ID	SAMPLE
METHODS	SAMPLE SOURCE
ENTREZ GENE ID	SAMPLE NAME
COMMENTS	IDENTIFICATIONS
	METHODS
	YEAR
	ISOLATION METHOD
	VESICLE TYPE (Vesiclepedia only)



Downloading Vesiclepedia and Exocarta

```
10 input miRs
 0 miRs with no info in Exocarta
 7 miRs with no info in Vesiclepedia
```

Control vs Alzheimer's

miR Name
miR-124-3p
miR-138-5p
miR-127-3p
miR-132-3p
miR-127-5p
miR-136-3p
miR-381(-3p)
miR-101-5p
miR-199b-5p
miR-136-5p

miRNA	Experiments where found (E=Exocarta, V=Vesiclepedia)				
miR-124-3p	e218	e222	e265	v357	
miR-138-5p	e218	e222	v357		
miR-127-3p	e222				
miR-132-3p	e222	e223			
miR-127-5p	e222				
miR-136-3p	e222				
miR-381	e226				
miR-101-5p	e222				
miR-199b-5p	e117	e115	e116	e218	e222
	v117	v115	v116		
miR-136-5p	e218	e222			

After a bit of Perl scripting, we find the above associations between studies cataloged in Exocarta and Vesiclepedia and the top 10 differentially expressed miRNAs in the AD vs control comparison.

Downloading Vesiclepedia and Exocarta

Control vs Alzheimer's

miR Name
miR-124-3p
miR-138-5p
miR-127-3p
miR-132-3p
miR-127-5p
miR-136-3p
miR-381(-3p)
miR-101-5p
miR-199b-5p
miR-136-5p

Exp#	PMID	Cell Type	miRNAs found		
e115	21505438	T	miR-199b-5p		
e116	21505438	B	miR-199b-5p		
e117	21505438	dendritic	miR-199b-5p		
e218	--	colorectal cancer	miR-124-3p	miR-138-5p	
			miR-199b-5p	miR-136-5p	
e222	23663360	plasma	miR-124-3p	miR-138-5p	miR-127-3p
			miR-132-3p	miR-127-5p	miR-136-3p
			miR-101-5p	miR-199b-5p	miR-136-5p
e223	25330373	colon carcinoma	miR-132-3p		
e226	26027894	endothelial	miR-381		
e265	26176991	melanoma	miR-124-3p		
v115	21505438	T	miR-199b-5p		
v116	21505438	B	miR-199b-5p		
v117	21505438	dendritic	miR-199b-5p		
v357	24352158	urine	miR-124-3p	miR-138-5p	

Here we have listed the Pubmed IDs of each publication, along with the miRNAs associated with each one.

Results from Vesiclepedia and Exocarta

Control vs Alzheimer's

	Burgos et al		exceRpt + DESeq2	
miR Name	log2(FC)	P-value	log2(FC)	P-value
miR-199b-5p	-1.22	6.70E-05	-1.36	1.29E-04

PMID 21505438

Received 9 Aug 2010 | Accepted 23 Mar 2011 | Published 19 Apr 2011

DOI: 10.1038/ncomms1285

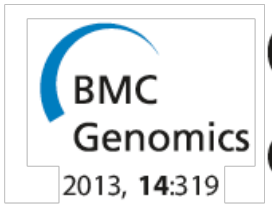
Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells

María Mittelbrunn[1,*], Cristina Gutiérrez-Vázquez[1,*], Carolina Villarroya-Beltri[1], Susana González[1], Fátima Sánchez-Cabo[1], Manuel Ángel González[1], Antonio Bernad[1] & Francisco Sánchez-Madrid[1,2]

miR-199b-5p

Comparison	Rank	FC(log2)	Adjusted p-value
Raji Cells vs Exosomes	42	-2.08	2.11E-02
DC Cells vs Exosomes	116	2.37	1.38E-02
J77 Cells vs Exosomes	166	1.79	1.49E-02

Results from Vesiclepedia and Exocarta



Characterization of human plasma-derived exosomal RNAs by deep sequencing

Xiaoyi Huang[1], Tiezheng Yuan[1], Michael Tschannen[2], Zhifu Sun[3], Howard Jacob[2], Meijun Du[1], Meihua Liang[4], Rachel L Dittmar[1], Yong Liu[5], Mingyu Liang[5], Manish Kohli[6], Stephen N Thibodeau[7], Lisa Boardman[6] and Liang Wang[1*]

Exp#	PMID	Cell Type	miRNAs found		
e222	23663360	plasma	**miR-124-3p**	miR-138-5p	**miR-127-3p**
			miR-132-3p	miR-127-5p	miR-136-3p
			miR-101-5p	miR-199b-5p	miR-136-5p

miR-124-3p and **miR-127-3p** were among the 20 most abundant RNAs found in plasma exosomes.

"The five most abundant miRNAs in the libraries were miR-99a-5p, miR-128, **miR-124-3p**, miR-22-3p, and miR-99b-5p, which together accounted for 48.99% of all detectable miRNAs."

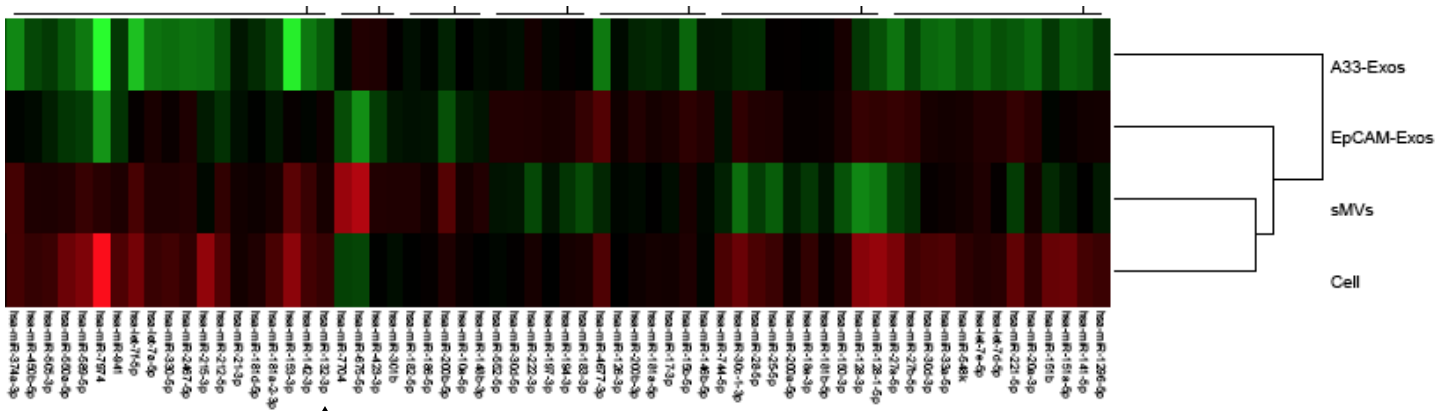
Results from Vesiclepedia and Exocarta

Exp#	PMID	Cell Type	miRNAs found
e223	25330373	colon carcinoma	miR-132-3p

PLOS ONE

October 2014 | Volume 9 | Issue 10 | e110314

Deep sequencing of RNA from three different EV subtypes released from the human LIM1863 colon cancer cell line uncovers distinct miRNA-enrichment signatures



miR-132-3p is depleted in immuno-affinity isolated A33 exosomes

Results from Vesiclepedia and Exocarta

Exp#	PMID	Cell Type	miRNAs found
e226	26027894	endothelial	miR-381

Table I. Top 15 miRNAs in cells

ID	Rank in cells	Rank in exosomes
miR-10B	1	1
miR-30A	2	3
miR-27B	3	2
miR-191	4	4
miR-411	5	7
miR-92B	6	16
miR-LET7I	7	5
miR-222	8	15
miR-100	9	10
miR-30E	10	17
miR-381	11	13

Journal of Extracellular Vesicles

Quantitative and qualitative analysis of small RNAs in human endothelial cells and exosomes provides insights into localized RNA processing, degradation and sorting

Bas W. M. van Balkom[1]*, Almut S. Eisele[1], D. Michiel Pegtel[2], Sander Bervoets[3] and Marianne C. Verhaar[1]

[1]Department of Nephrology and Hypertension, UMC Utrecht, Utrecht, the Netherlands; [2]Exosomes Research Group, VU University Medical Center, Amsterdam, the Netherlands; [3]ServiceXS B.V., Leiden, the Netherlands

Results from Vesiclepedia and Exocarta

Exp#	PMID	Cell Type	miRNAs found	
v357	24352158	urine	miR-124-3p	miR-138-5p

Characterization and deep sequencing analysis of exosomal and non-exosomal miRNA in human urine

Kidney International 2014 86: 433

In a technical study of methods for extracting miRNA from exosomes from urine, the authors found that **miR-124-3p** was only found when purified by a Norgen Biotek Urine Exosomal RNA kit, while **miR-138-5p** was not found by that kit but was found by ultracentrifugation.

FunRich

Finding relevant literature about small sets of miRNAs in Vesiclepedia is a piecemeal approach.

For a more integrative method, you can try FunRich. Currently a Windows application, it will be released as a tool on the Genboree Workbench this year.

Vesiclepedia enables community annotation

Membership on three conditions:

1) The laboratory head or group leader needs to sign up.

2) You must agree to submit datasets pertaining to extracellular vesicles continuously to Vesiclepedia, either before or after publication.

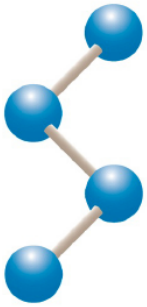
3) When reviewing articles, please mandate or request investigators to submit datasets on extracellular vesicles to Vesiclepedia.

Credit

All members were co-authors on the initial Vesiclepedia manuscript.

http://www.microvesicles.org

Kalra et al. PLoS Biology, 2012



THE SCRIPPS RESEARCH INSTITUTE®

Wikidata for Interpretation of miRNA RNA-seq data

Sebastian Burgstaller-Muehlbacher, PhD

@sebotic

https://commons.wikimedia.org/wiki/File:Wikidata-logo-en.svg

Contents

- Wikidata basics
  - Graph database
  - Document based
  - Semantic web integration
- Example
  - Data: Jensen Alzheimers and Parkinson disease data set.
  - Aim: Retrieve extracellular miRNA target genes and Gene Ontology terms.

WIKIDATA

Main page
Community portal
Project chat
Create a new item
Item by title
Recent changes
Random item
Nearby
Help
Donate

Print/export
Create a book
Download as PDF
Printable version

Tools
What links here
Related changes
Special pages
Permanent link
Page information
Concept URI
Cite this page

Nivolumab (Q7041828)

pharmaceutical drug
MDX-1106 | ONO-4538 | BMS-936558

In more languages

Language	Label	Description	Also known as
English	Nivolumab	pharmaceutical drug	MDX-1106 ONO-4538 BMS-936558
German	Nivolumab	monoklonaler PD-1 Antikörper	anti-PD-1
French	Nivolumab	No description defined	

Statements

CAS registry number
946414-94-4 edit
1 reference
+ add

UNII
31YO63LBSN edit
1 reference
+ add

instance of
chemical compound edit
1 reference
pharmaceutical drug edit
1 reference
biopharmaceutical edit
1 reference
monoclonal antibodies edit
1 reference
+ add

ChEMBL ID
CHEMBL2108738 edit
1 reference
+ add

Wikipedia (6 entries) edit
- ar نيفولوماب
- el Nivolumab
- en Nivolumab
- fr Nivolumab
- ja ニボルマブ
- pl Anti-PD-1

Wikibooks (0 entries) edit

Wikinews (0 entries) edit

Wikiquote (0 entries) edit

WIKIPEDIA
The Free Encyclopedia

Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia
Wikipedia store

Interaction
Help
About Wikipedia
Community portal
Recent changes
Contact page

Tools
What links here
Related changes
Upload file
Special pages
Permanent link
Page information
Wikidata item
Cite this page

Print/export
Create a book
Download as PDF
Printable version

Languages
العربية
Ελληνικά
Français
日本語
Polski
Edit links

Nivolumab

From Wikipedia, the free encyclopedia

Nivolumab (nye vol' ue mab; **ONO-4538**, **BMS-936558**, or **MDX1106**), marketed as **Opdivo**, is a human IgG4 anti-PD-1 monoclonal antibody developed by Ono Pharmaceutical and Medarex (later acquired by Bristol-Myers Squibb) for the treatment of cancer.[1][2] Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells.

Nivolumab is approved by the Food and Drug Administration for treatment of patients with unresectable or metastatic melanoma who no longer respond to other drugs.[3] In addition, it is approved for the treatment of squamous non-small cell lung cancer.[4]

Nivolumab

Monoclonal antibody	
Type	Whole antibody
Source	Human
Target	PD-1
Clinical data	
Trade names	Opdivo
Identifiers	
CAS Number	946414-94-4
ATC code	L01XC17
Chemical data	
Formula	$C_{6362}H_{9862}N_{1712}O_{1995}S_{42}$
Molecular mass	143.6 kDa

Contents [hide]

Mechanism of action [edit]

Nivolumab is an inhibitory ligand blocking antibody against the programmed death receptor. In contrast to traditional chemotherapies and targeted anti-cancer therapies, which exert their effects by direct cytotoxic or tumor growth inhibition, nivolumab acts by blocking a negative regulator of T-cell activation and response thus allowing the immune system to attack the tumor.[5][6] This is an example of immune checkpoint blockade.

PD-1 is a protein on the surface of activated T cells. If another molecule, called programmed cell death 1 ligand 1 or programmed cell death 1 ligand 2 (PD-L1 or PD-L2), binds to PD-1, the T cell becomes inactive. This is one way that the body regulates the immune system, to avoid an overreaction. Many cancer cells make PD-L1, which inhibits T cells from attacking the tumor. Nivolumab blocks PD-L1 from binding to PD-1, allowing the T cell to work.[5][6]

PD-1 blockade reinvigorates immune cells that are able to target cancer cells, which is speculated but not proven to reduce side effects.[5]

Clinical trials [edit]

Metastatic melanoma [edit]

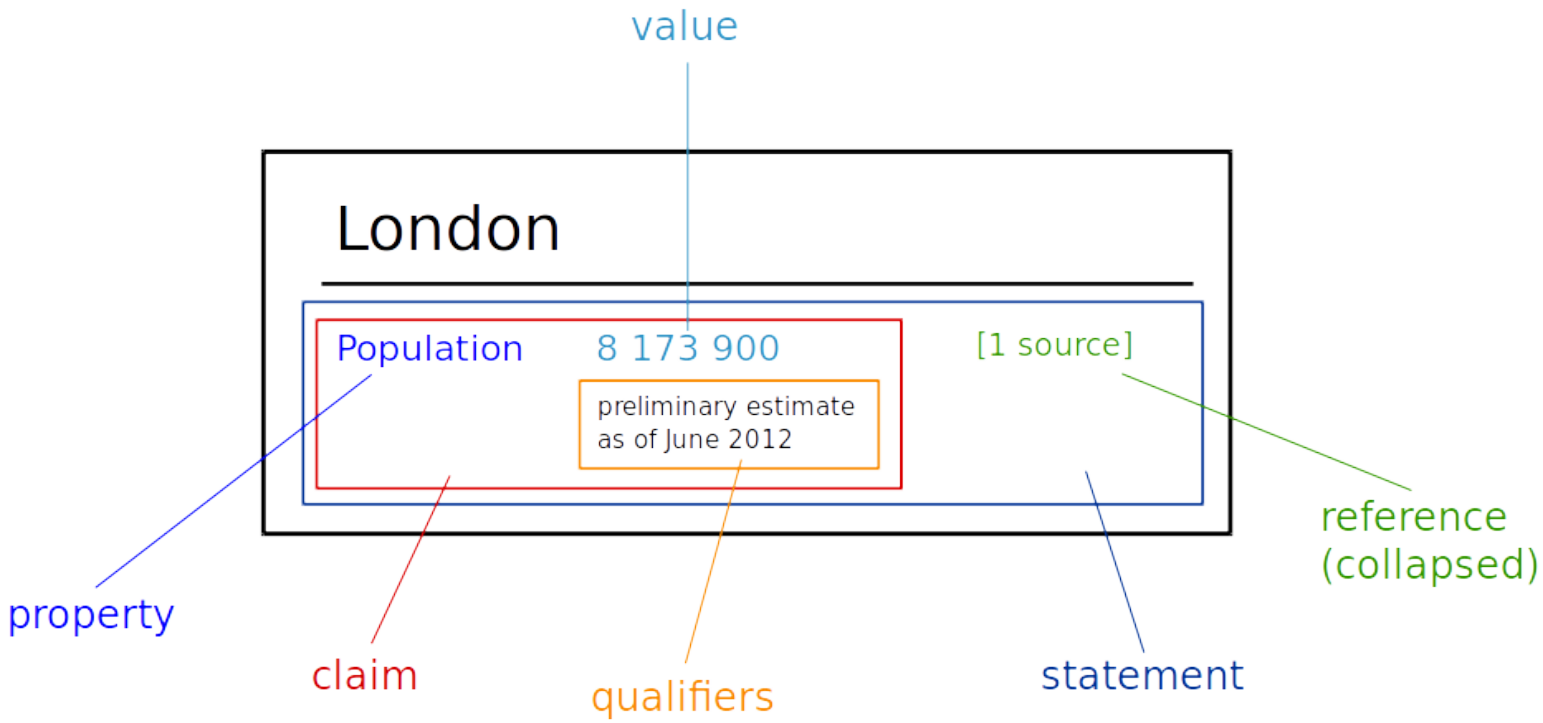
A phase 1 dose-optimization trial of nivolumab was performed in people with melanoma, lung cancer, kidney cancer and other cancers. Among the 107 melanoma patients in this trial, nivolumab demonstrated one-, two-year and three year survival rates of 62%, 48%, and 41%.

Toxicities, which were not cumulative and which mostly occurred during the first 6 months of therapy, included pneumonitis, low grade fatigue, diarrhea, pruritus, nausea, and decreased appetite. Pneumonitis was the most important adverse effect, leading to 3 deaths. Twenty-two percent of people in the trial experienced a treatment-related Grade 3 or Grade 4 toxicity.[7][8]

A second phase 1 trial examined combination treatment of metastatic melanoma with nivolumab and ipilimumab. Among 53 people treated concurrently with the highest dose (1 mg/kg nivolumab and 3 mg/kg ipilimumab), 53% had an objective response, all of whom saw their tumors shrink by 80% or more. An updated report from this trial, including an additional 41 people treated with the highest dose, stated that 79% were still alive after 2 years.[8][9]

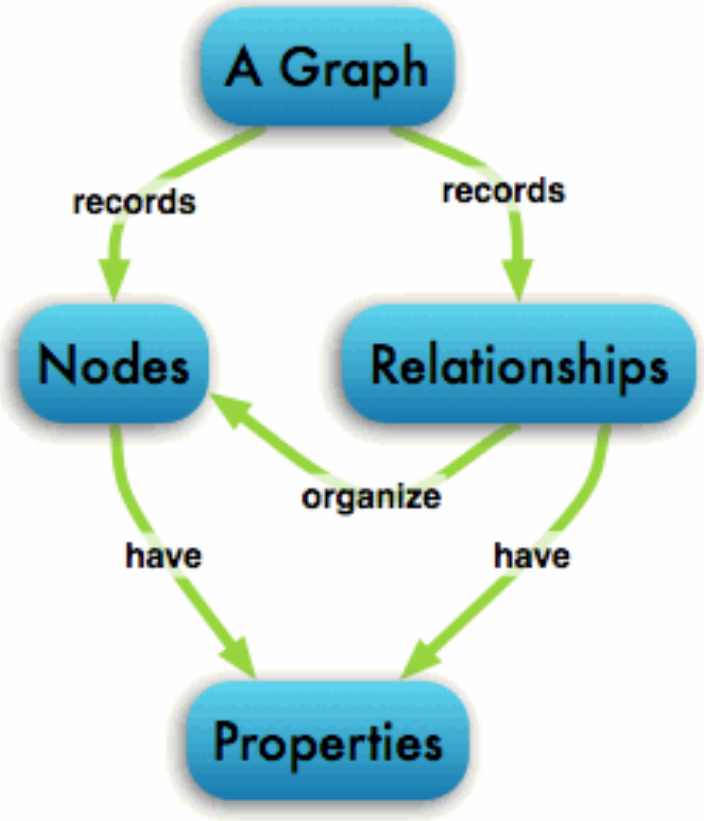
In a phase 3 trial comparing nivolumab monotherapy to treatment with traditional chemotherapy, nivolumab gave

A Wikidata Statement



https://commons.wikimedia.org/wiki/File:Wikidata_statement.svg

Wikidata is a Graph database



From neo4j.com

Wikidata API and query endpoints

- Three ways to access data:
  - Wikidata API allows read, write and full text search. (www.wikidata.org/w/api.php)
  - REST endpoint for fast, direct data access. (queryr.wmflabs.org/)
  - Wikidata query service (WDQS) as a SPARQL endpoint for complex queries.
  - (query.wikidata.org/)
-

Example

https://www.wikidata.org/wiki/Q23839066

http://query.wikidata.org

hsa-miR-127-3p (Q23839066)

mature human miRNA

No aliases defined

edit

In more languages

Language	Label	Description	Also known as
English	hsa-miR-127-3p	mature human miRNA	
German	No label defined	No description defined	
French	No label defined	No description defined	

Statements

subclass of	mature microRNA 0 references + add reference	edit
	Mir-127 0 references + add reference	edit
	+ add	

found in taxon	human 0 references + add reference	edit
	+ add	

regulates (molecular biology)	PR domain containing 1, with ZNF domain 0 references + add reference	edit
	X-box binding protein 1 0 references + add reference	edit
	B-cell CLL/lymphoma 6 0 references + add reference	edit
	SET domain containing (lysine methyltransferase) 8 0 references	edit

Wikidata Query Service

Examples | Prefixes | Tools | Help

```
PREFIX wd: <http://www.wikidata.org/entity/>
PREFIX wdt: <http://www.wikidata.org/prop/direct/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>

select distinct * where {
    ?qid rdfs:label 'hsa-miR-127-3p'@en .
    ?qid wdt:P128 ?gene .
    ?gene rdfs:label ?label filter (lang(?label) = "en") .
}
```

Press *[CTRL-SPACE]* to activate auto completion. Data last updated: 6:52:44 AM PDT, Apr 17, 2016

Execute | Clear | **23 Results in 147 ms** | Display | Download | Link

qid	gene	label
wd:Q23839066	wd:Q18028126	potassium voltage-gated channel, shaker-related subfamily, member 6
wd:Q23839066	wd:Q18030532	serpin peptidase inhibitor, clade B (ovalbumin), member 9
wd:Q23839066	wd:Q18030787	mitogen-activated protein kinase 4
wd:Q23839066	wd:Q18042716	repulsive guidance molecule family member a
wd:Q23839066	wd:Q18042959	ARP3 actin-related protein 3 homolog B (yeast)
wd:Q23839066	wd:Q18060686	ARP3 actin-related protein 3 homolog C (yeast)
wd:Q23839066	wd:Q17847411	B-cell CLL/lymphoma 6
wd:Q23839066	wd:Q17859718	septin 7
wd:Q23839066	wd:Q17916835	solute carrier family 29 (equilibrative nucleoside transporter), member 1
wd:Q23839066	wd:Q18029207	matrix metallopeptidase 13 (collagenase 3)
wd:Q23839066	wd:Q18036143	ZW10 interacting kinetochore protein

Wikidata Query Service | Examples | Prefixes | Tools | Help

```
PREFIX wd: <http://www.wikidata.org/entity/>
PREFIX wdt: <http://www.wikidata.org/prop/direct/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>

select distinct ?protein ?label ?go_id ?go_label ?go where {
    wd:Q23839066 wdt:P128 [wdt:P688 ?protein] .
    ?protein wdt:P681 ?go .
    ?protein rdfs:label ?label filter (lang(?label) = "en") .
    ?go wdt:P686 ?go_id .
    ?go rdfs:label ?go_label filter (lang(?go_label) = "en") .
} order by ?label
```

Press *[CTRL-SPACE]* to activate auto completion. Data last updated: 7:10:52 PM PDT, Apr 16, 2016

Execute | Clear | **154 Results in 191 ms** | Display | Download | Link

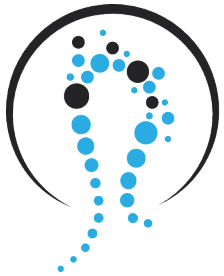
protein	label	go_id	go_label	go
wd:Q21130866	Actin-related protein 3B	GO:0005737	cytoplasm	wd:Q79899
wd:Q21130866	Actin-related protein 3B	GO:0005856	cytoskeleton	wd:Q154626
wd:Q21130866	Actin-related protein 3B	GO:0042995	cell projection	wd:Q14353100
wd:Q21130866	Actin-related protein 3B	GO:0070062	extracellular exosome	wd:Q14864178
wd:Q21130866	Actin-related protein 3B	GO:0005885	Arp2/3 protein complex	wd:Q21102007
wd:Q21140508	Actin-related protein 3C	GO:0005885	Arp2/3 protein complex	wd:Q21102007
wd:Q21108216	Actin-related protein 3C	GO:0070062	extracellular exosome	wd:Q14864178
wd:Q21108216	Actin-related protein 3C	GO:0005885	Arp2/3 protein complex	wd:Q21102007
wd:Q21116345	B-cell lymphoma 6 protein	GO:0005657	replication fork	wd:Q14817957
wd:Q21116345	B-cell lymphoma 6 protein	GO:0005634	nucleus	wd:Q21541775
wd:Q21111733	BolA-like protein 1	GO:0005739	mitochondrion	wd:Q39572

Statistics

WD items added	
Human genes	59,727
Mouse genes	73,352
Human proteins	27,194
Mouse proteins	16,172
Gene Ontology terms	42,281
Human miRNAs	2,619
Human diseases	6,782
FDA approved drugs	2,079

# of Properties	
Biology	34
Molecular biology	35
Medicine	28
Drugs/Chemistry	34

In total, our bots maintain ~220,000 items with each typically >10 statements. This results in a current extent of ~2,200,000 values being maintained on Wikidata by our bots.

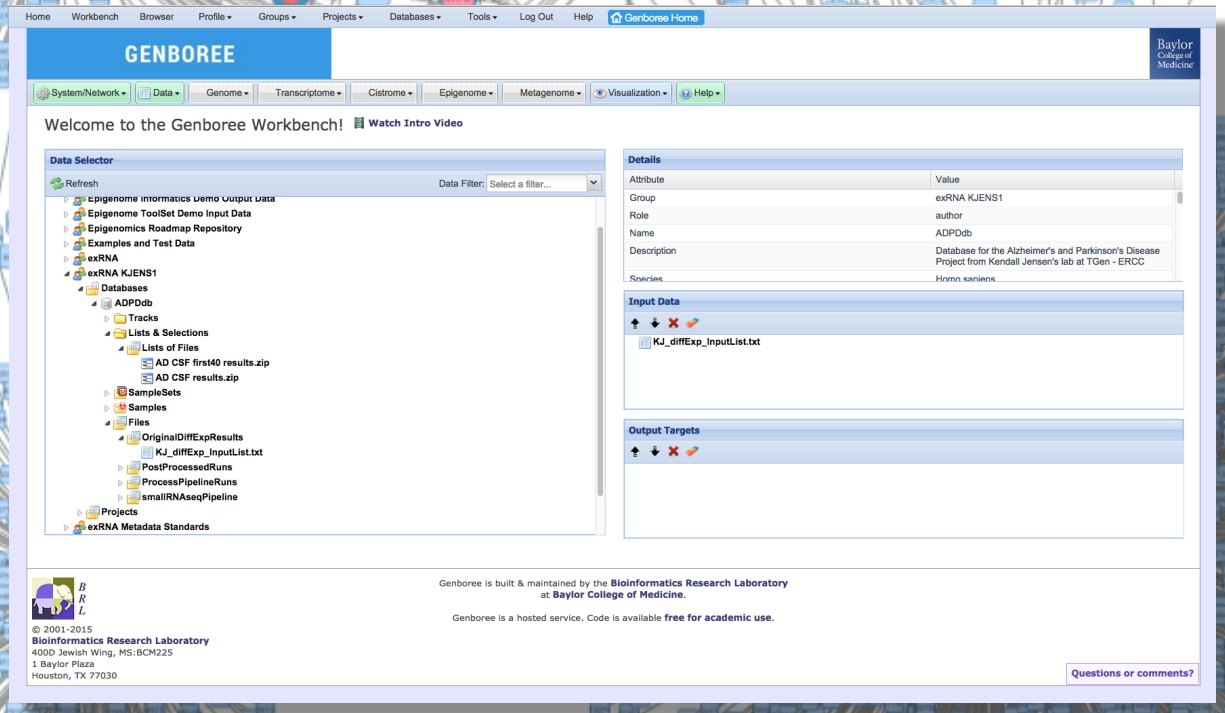


ERCC Data Analysis Workshop

Topics covered in Use Case 2 Part 2

- Accessing samples in the exRNA Atlas
- Comparative analysis of exRNA samples using DESeq / exceRpt pipeline results and tools in the Genboree Workbench
- Finding information about exRNAs of interest
  - on Exocarta and Vesiclepedia
  - on GeneWiki and Wikidata
- **Pathway analysis using Cytoscape & WikiPathways in the Genboree Workbench**

Pathway and Network Analysis
from the Genboree Workbench

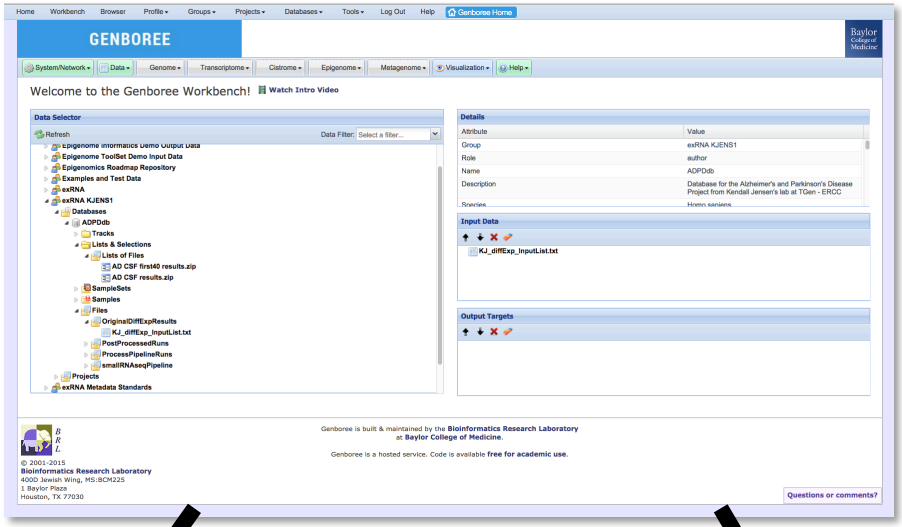


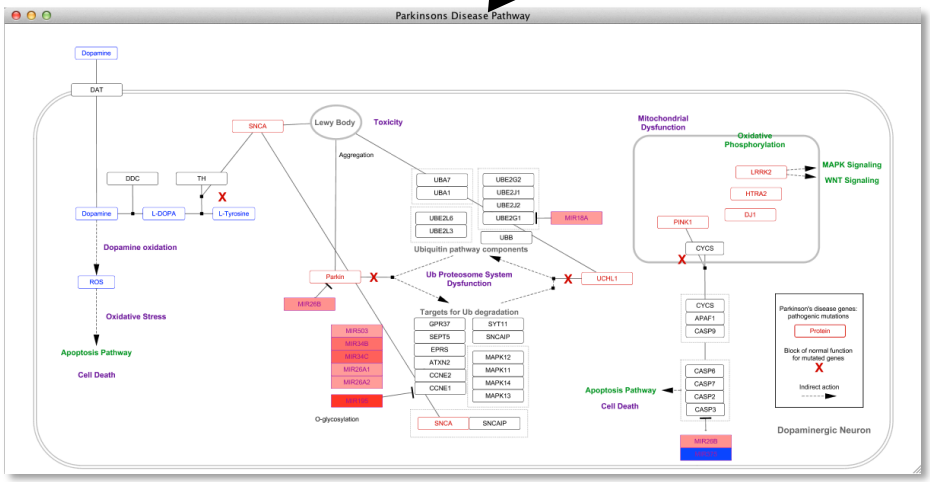
Alex Pico, PhD

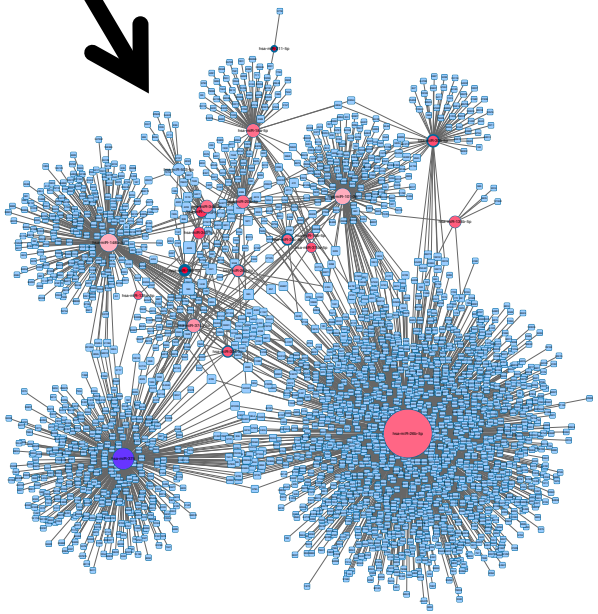
Gladstone Institutes, San Francisco

April 17, 2016

Pathway and Network Analysis







Pathway and Network Analysis

1. ***Why*** would you do this?
2. ***What*** would you do?
3. ***How*** would you do it?
4. ***Who*** can do this?

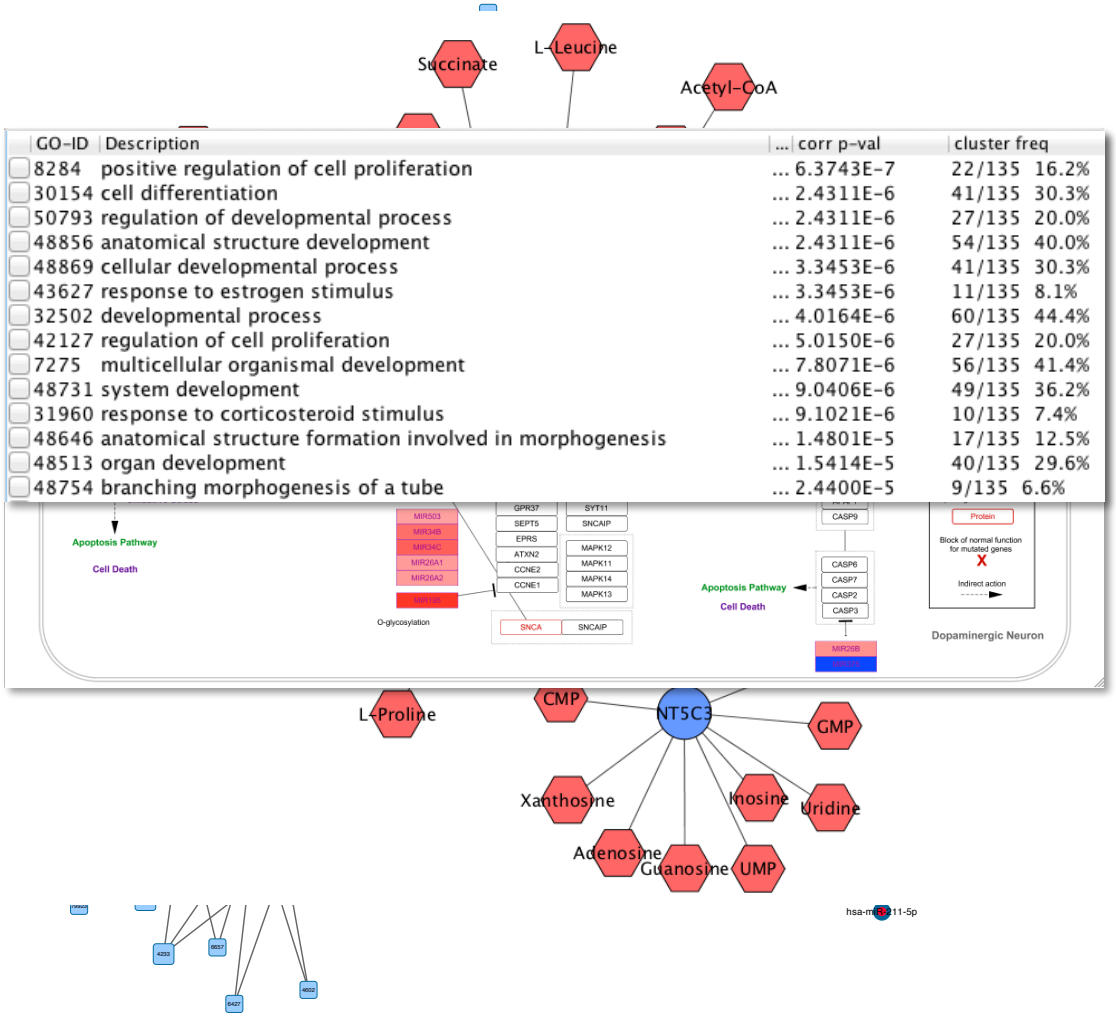
Pathway and Network Analysis: Why?

…a list of differentially expressed miRNA

identifier	baseMean	log2FoldChai	lfcSE	pvalue	padj
hsa-miR-195-5p	96.7700199	2.44841391	0.49366515	7.06E-07	0.00018136
hsa-miR-30e-3p	702.455493	2.02502471	0.41203155	8.89E-07	0.00018136
hsa-miR-211-5p	49.2191661	2.44930572	0.51596328	2.06E-06	0.00028071
hsa-miR-30b-5p	87.5770117	1.93973337	0.41974017	3.81E-06	0.00036691
hsa-miR-30c-5p	177.914843	1.7910964	0.39047141	4.50E-06	0.00036691
hsa-miR-30a-3p	727.311039	1.88682103	0.41998768	7.04E-06	0.00047852
hsa-miR-664-3p	9.70560333	2.35032438	0.53633997	1.18E-05	0.00068493
hsa-miR-26a-5p	4601.81791	1.69854746	0.40517223	2.76E-05	0.00140918
hsa-miR-34c-5p	635.267228	2.12361583	0.52355429	4.99E-05	0.00226158
hsa-miR-582-3p	32.7961329	1.8613787	0.46851513	7.10E-05	0.00289653
hsa-miR-26b-5p	755.55888	1.76395192	0.4495387	8.71E-05	0.00323141
hsa-miR-1298	739.885163	2.05340959	0.54460665	0.00016296	0.00554052
hsa-let-7f-1-3p	4.75127804	1.89744027	0.51372912	0.00022122	0.00694289
hsa-miR-375	1005.63367	-1.610137	0.44283469	0.00027693	0.00807049
hsa-miR-1247-5p	10.2790818	-1.8194525	0.51240356	0.00038403	0.00921681
hsa-miR-1911-5p	99.7237089	1.98039539	0.55768118	0.00038359	0.00921681
hsa-miR-374a-5p	10.8650312	1.89672368	0.53132051	0.00035721	0.00921681
hsa-miR-34b-5p	41.0116005	2.00714578	0.5692402	0.00042187	0.00956246
hsa-miR-152	77.4552781	1.35732907	0.3898756	0.00049872	0.01070941
hsa-miR-7-1-3p	2.63312729	1.67557636	0.49030805	0.00063223	0.01289758
hsa-miR-135a-5p	11.9855253	1.86274748	0.56392061	0.00095585	0.01695599
hsa-miR-18b-5p	8.77201213	1.78357817	0.53584358	0.00087302	0.01695599
hsa-miR-23c	103.658692	1.36705145	0.4124759	0.00091887	0.01695599
hsa-miR-135b-5p	8.74843581	1.82445524	0.55621122	0.00103753	0.01763794
hsa-miR-374a-3p	7.55916002	1.62705861	0.50745634	0.00134453	0.02194265
hsa-miR-148b-3p	812.441206	1.2714604	0.39939394	0.00145519	0.02204724
hsa-miR-18a-5p	10.7773676	1.70424536	0.53683176	0.00150025	0.02204724
hsa-miR-204-5p	65558.9447	1.71577961	0.54088519	0.00151305	0.02204724
hsa-miR-374b-5p	17.1285677	1.46507029	0.47932833	0.00223932	0.03150498
hsa-miR-3960	24.1059322	1.43616846	0.47370107	0.00243098	0.03306127
hsa-miR-3605-5p	33.4311818	-1.4371226	0.47567792	0.00251767	0.03313582
hsa-miR-101-3p	2484.00912	1.2855992	0.42889521	0.00272233	0.03470976
hsa-miR-34b-3p	33.7603604	1.70785085	0.57338237	0.00289611	0.03475334
hsa-miR-503	2.88157858	1.66640756	0.55795946	0.00282089	0.03475334

- **Identify expected hits**
- **Look up each one**
- **Prioritize for validation and further investigation**

Pathway and Network Analysis: Why?



GO-ID	Description	...	corr p-val	cluster freq
8284	positive regulation of cell proliferation	...	6.3743E-7	22/135 16.2%
30154	cell differentiation	...	2.4311E-6	41/135 30.3%
50793	regulation of developmental process	...	2.4311E-6	27/135 20.0%
48856	anatomical structure development	...	2.4311E-6	54/135 40.0%
48869	cellular developmental process	...	3.3453E-6	41/135 30.3%
43627	response to estrogen stimulus	...	3.3453E-6	11/135 8.1%
32502	developmental process	...	4.0164E-6	60/135 44.4%
42127	regulation of cell proliferation	...	5.0150E-6	27/135 20.0%
7275	multicellular organismal development	...	7.8071E-6	56/135 41.4%
48731	system development	...	9.0406E-6	49/135 36.2%
31960	response to corticosteroid stimulus	...	9.1021E-6	10/135 7.4%
48646	anatomical structure formation involved in morphogenesis	...	1.4801E-5	17/135 12.5%
48513	organ development	...	1.5414E-5	40/135 29.6%
48754	branching morphogenesis of a tube	...	2.4400E-5	9/135 6.6%

- **Networks**
  - **Target protein interactions**
  - **TF or drug interactions**
  - **Functional characterization**
- **Pathways**
  - **Known mechanism**
  - **New hypotheses**
- **Prioritize for validation and further investigation**

Pathway and Network Analysis: What?

Network Analysis

1. Find a database with miRNA-target protein interaction
2. Lookup each of your miRNA of interest
3. Merge binary interactions into a single network model
4. Apply layout algorithm on network
5. Visualize your data on network

Pathway Analysis

1. Find a database of pathway diagrams
2. Annotate pathways with miRNA based on target protein database
3. Lookup each of your miRNA of interest
4. Produce ranked list of relevant pathways
5. Load pathway into visualization tool
6. Visualize your data on network

Pathway and Network Analysis: What?

Network Analysis

1. ~~Find a data~~ ~~tein interaction~~
2. ~~Lookup eac~~
3. ~~Merge bina~~ ~~network model~~
4. Apply layout algorithm on network
5. Visualize your data on network

GENBOREE

Target Interaction Finder

Cytoscape

Pathway Analysis

1. Find a database of pathway diagrams
2. Annotate pathways with miRNA based on target protein database
3. Lookup each of your miRNA of interest
4. Produce ranked list of relevant pathways
5. Load pathway into visualization tool
6. Visualize your data on network

Pathway and Network Analysis: What?

Network Analysis

1. ~~Find a data~~ ~~tein interaction~~
2. ~~Lookup eac~~
3. ~~Merge bina~~ ~~network model~~
4. Apply layout algorithm on network
5. Visualize your data on network

GENBOREE

Target Interaction Finder

Cytoscape

Pathway Analysis

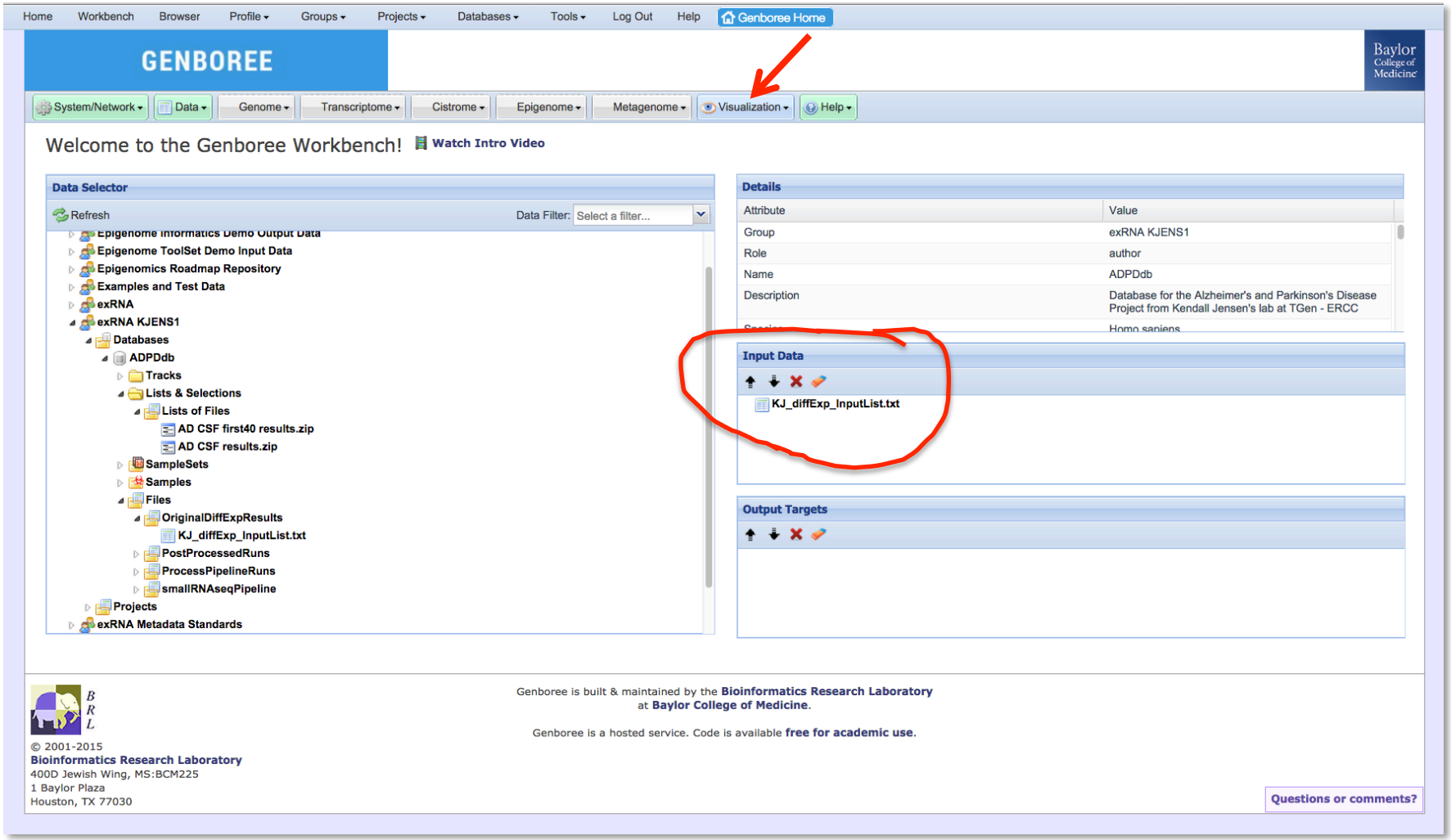
1. ~~Find a database of pathway diagrams~~
2. ~~Annotate path~~ ~~based on target protein database~~
3. ~~Lookup each o~~ ~~nterest~~
4. ~~Produce ranked list of relevant pathways~~
5. Load pathway into visualization tool
6. Visualize your data on network

GENBOREE

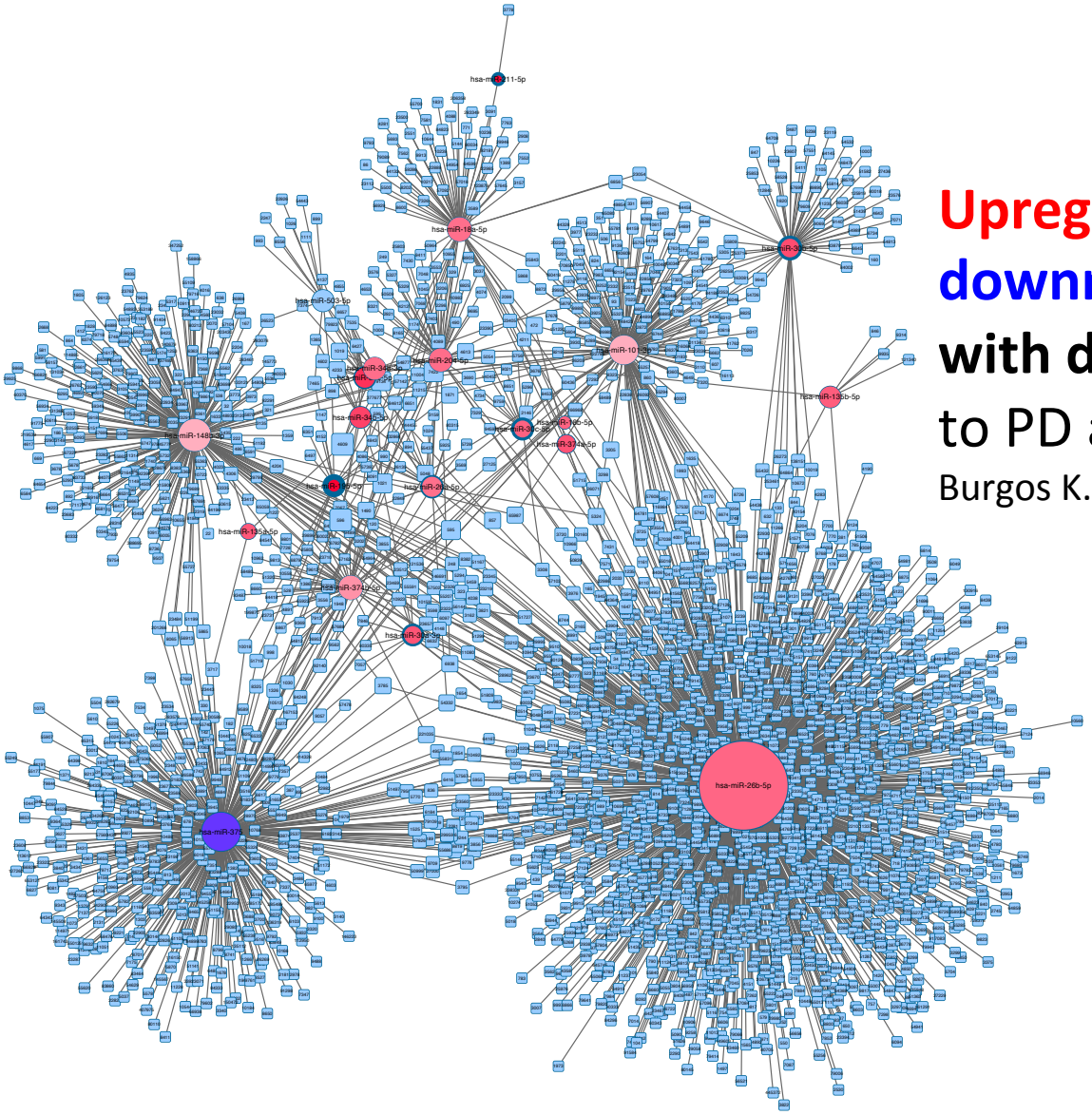
Pathway Finder

Cytoscape

Pathway and Network Analysis: How?



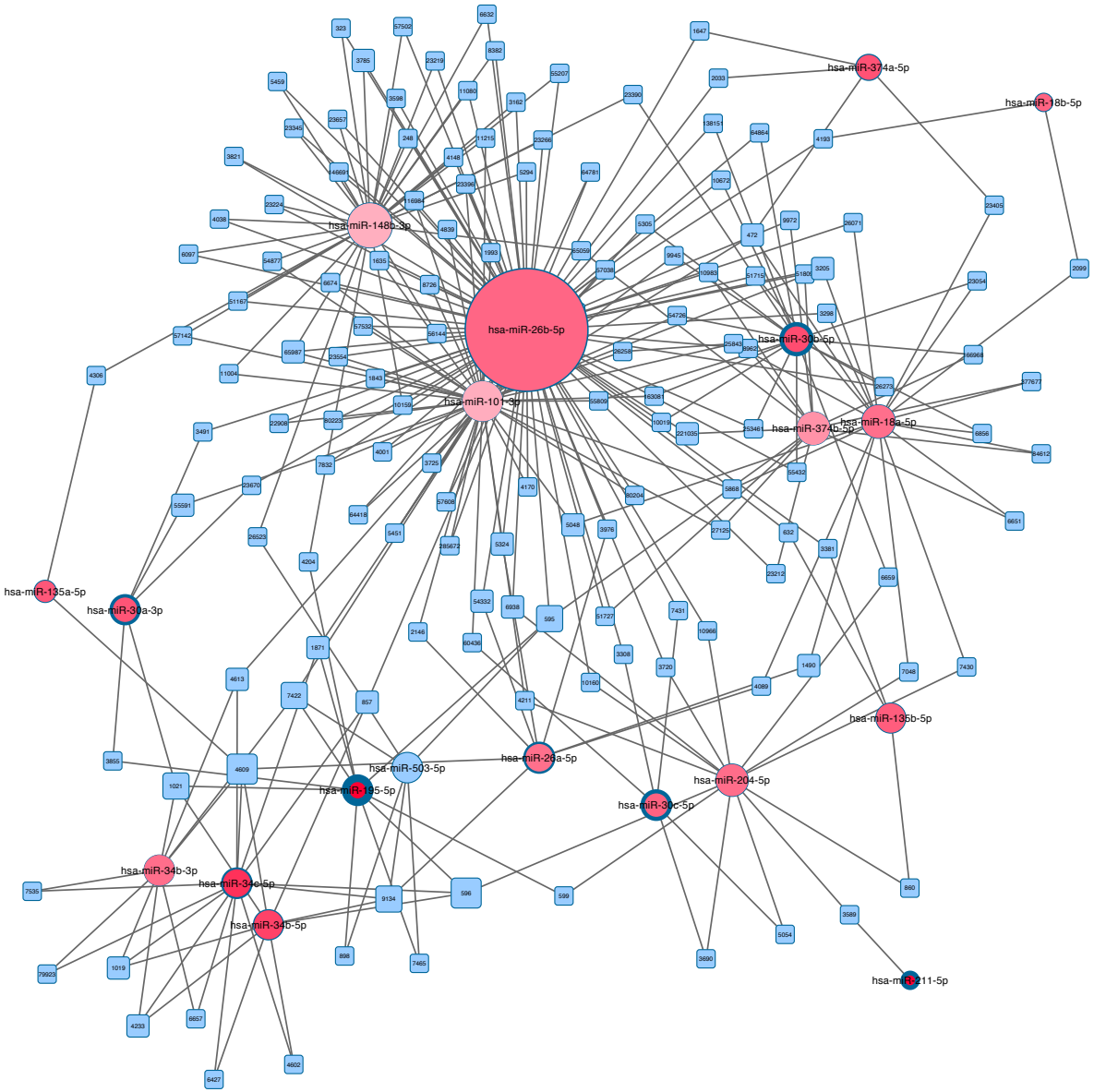
Pathway and Network Analysis: How?



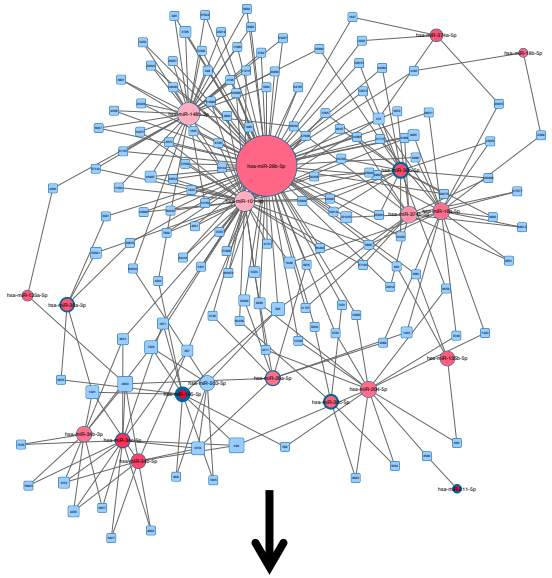
Upregulated and **downregulated** in **PD with dementia** relative to PD alone.

Burgos K., et al. (2014) PLoS ONE

Pathway and Network Analysis: How?



Pathway and Network Analysis: How?



BiNGO

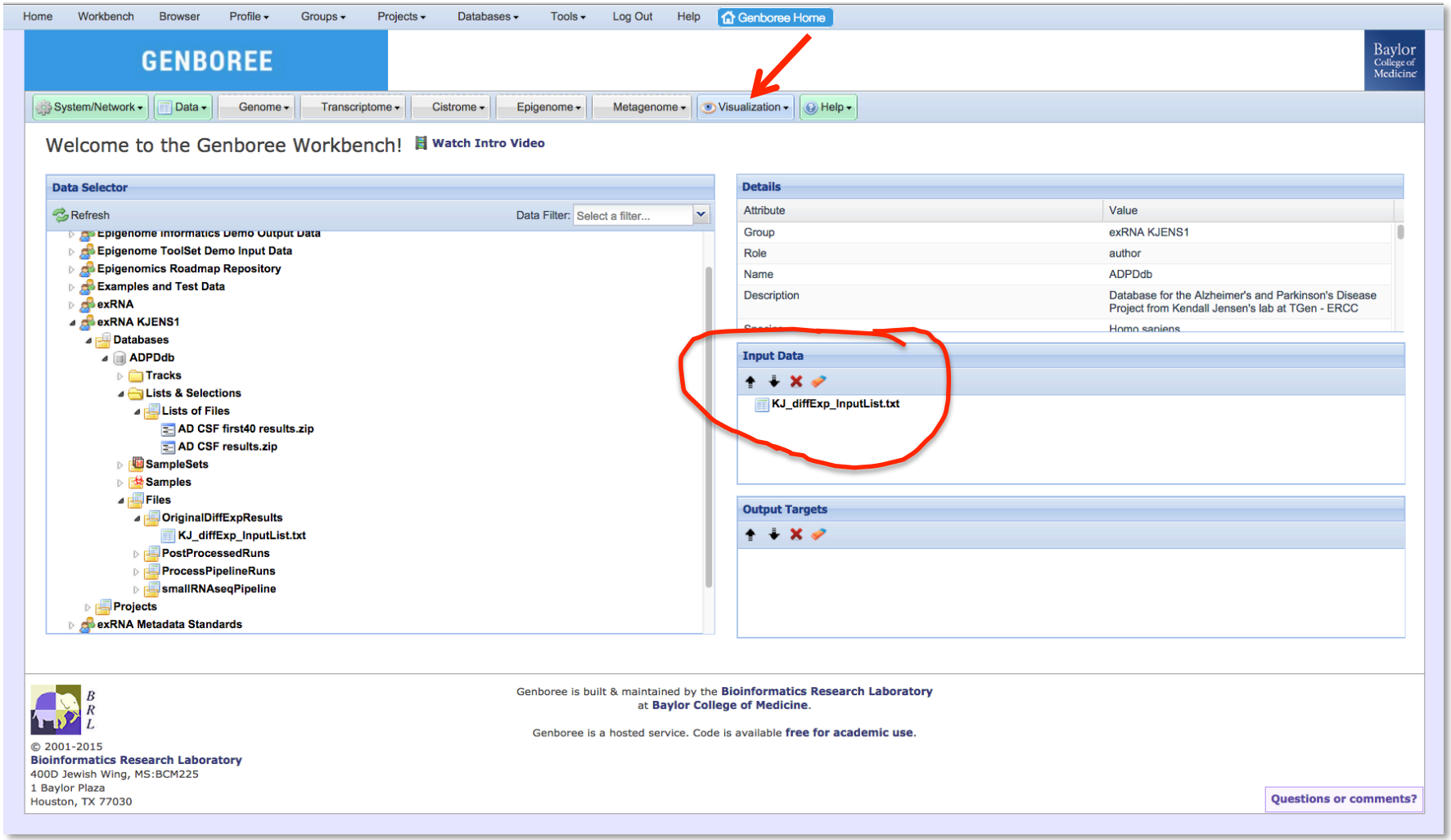
BiNGO 3.0+

Calculates overrepresented GO terms in the network and display them as a network of significant GO terms.

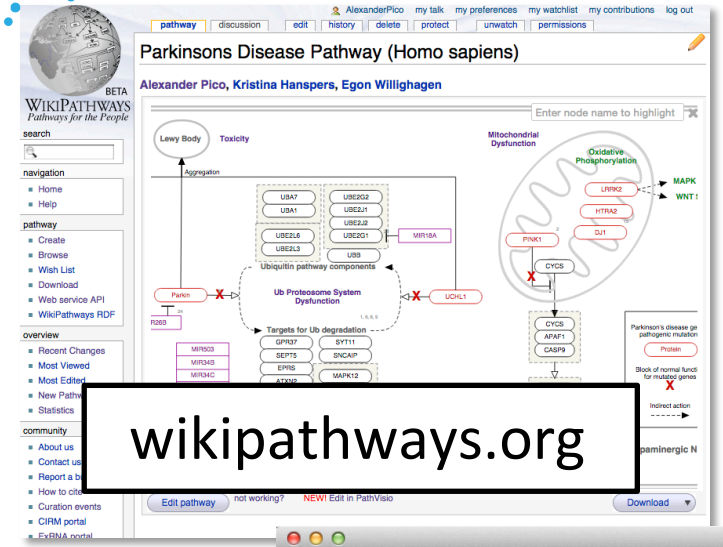
★★★★☆ (54) 19530 downloads

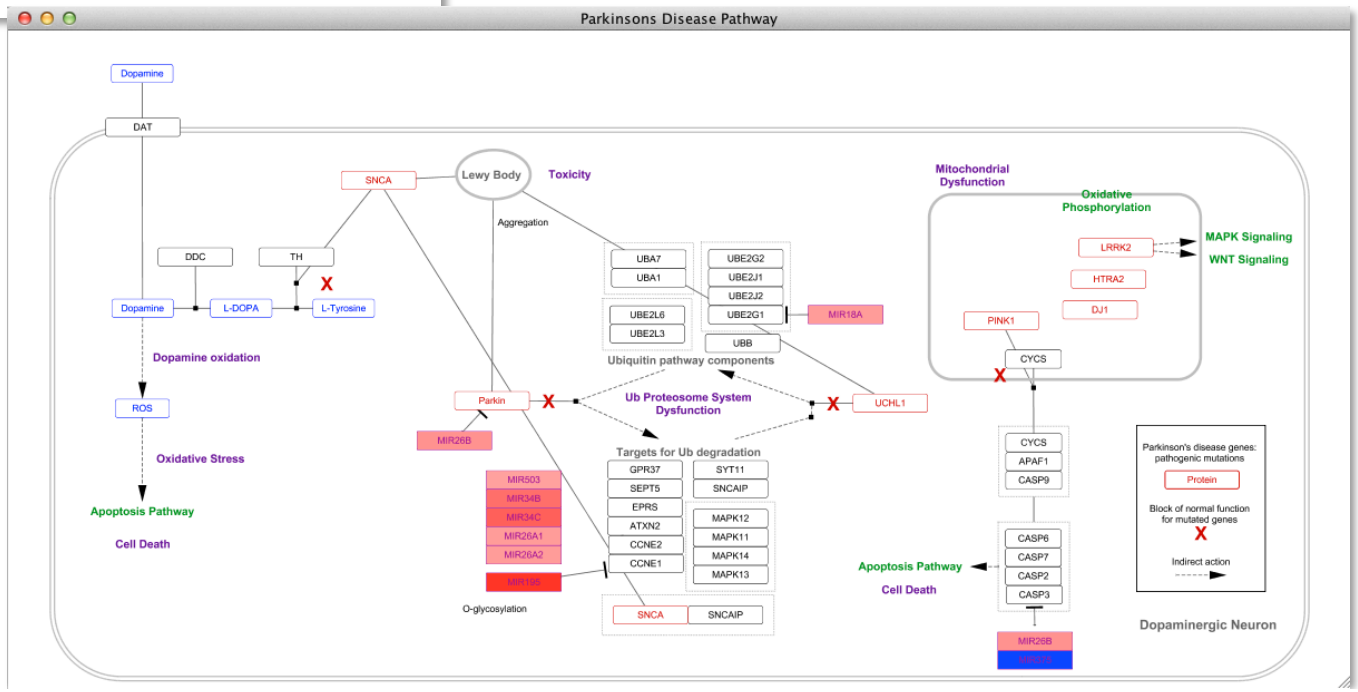
GO-ID	Description	...	corr p-val	cluster freq
8284	positive regulation of cell proliferation	...	6.3743E-7	22/135 16.2%
30154	cell differentiation	...	2.4311E-6	41/135 30.3%
50793	regulation of developmental process	...	2.4311E-6	27/135 20.0%
48856	anatomical structure development	...	2.4311E-6	54/135 40.0%
48869	cellular developmental process	...	3.3453E-6	41/135 30.3%
43627	response to estrogen stimulus	...	3.3453E-6	11/135 8.1%
32502	developmental process	...	4.0164E-6	60/135 44.4%
42127	regulation of cell proliferation	...	5.0150E-6	27/135 20.0%
7275	multicellular organismal development	...	7.8071E-6	56/135 41.4%
48731	system development	...	9.0406E-6	49/135 36.2%
31960	response to corticosteroid stimulus	...	9.1021E-6	10/135 7.4%
48646	anatomical structure formation involved in morphogenesis	...	1.4801E-5	17/135 12.5%
48513	organ development	...	1.5414E-5	40/135 29.6%
48754	branching morphogenesis of a tube	...	2.4400E-5	9/135 6.6%

Pathway and Network Analysis: How?



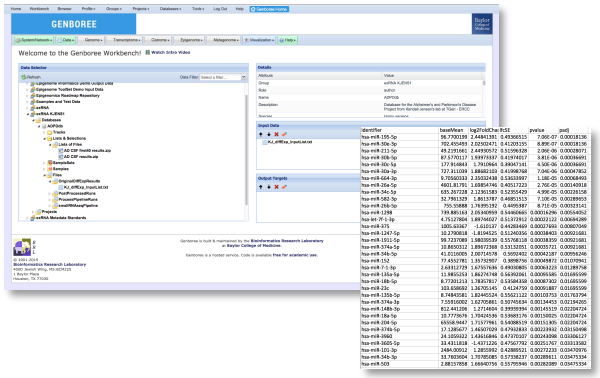
Pathway and Network Analysis: How?



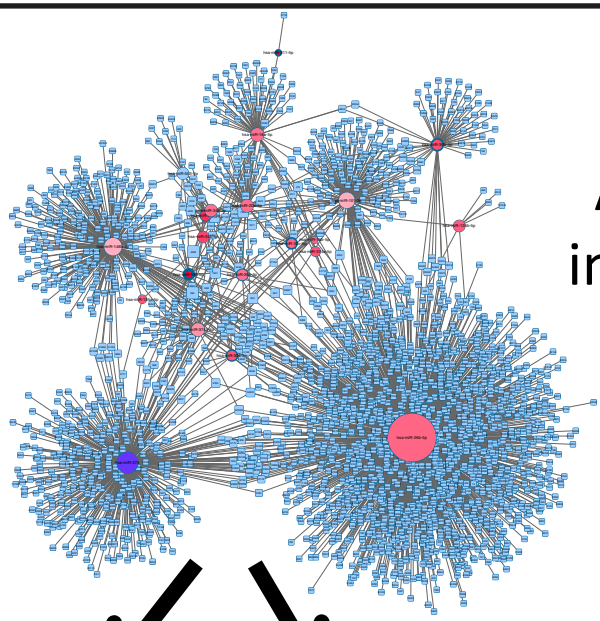


Pathway and Network Analysis: How?

Genboree

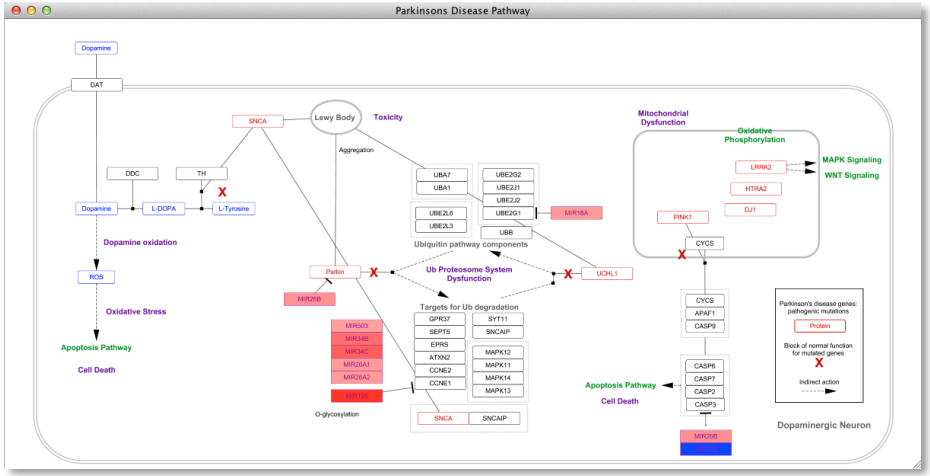


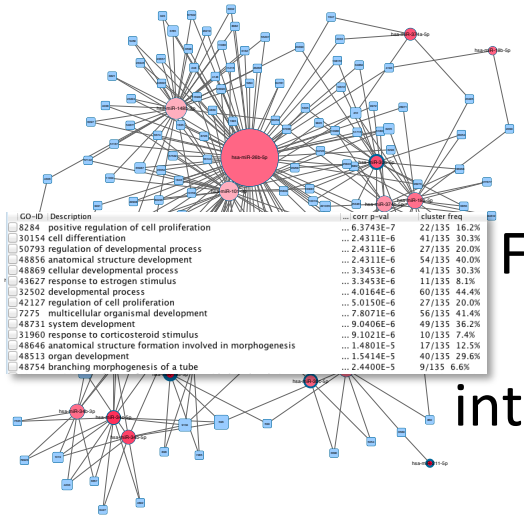
PD vs PDD diff exp
Burgos K., et al. (2014) PLoS ONE



All known interactions

Pathways





GO-ID	Description	corr p-val	cluster freq
8284	positive regulation of cell proliferation	6.3743E-7	22/135 16.2%
30154	cell differentiation	2.4311E-6	41/135 30.3%
50793	regulation of developmental process	2.4311E-6	27/135 20.0%
48856	anatomical structure development	2.4311E-6	54/135 40.0%
48869	cellular developmental process	3.3453E-6	41/135 30.3%
43627	response to estrogen stimulus	3.3453E-6	11/135 8.1%
32502	developmental process	4.0164E-6	60/135 44.4%
42127	regulation of cell proliferation	5.0150E-6	27/135 20.0%
7275	multicellular organismal development	7.8071E-6	56/135 41.4%
48731	system development	9.0406E-6	49/135 36.2%
31960	response to corticosteroid stimulus	9.1021E-6	10/135 7.4%
48646	anatomical structure formation involved in morphogenesis	1.4801E-5	17/135 12.5%
48513	organ development	1.5414E-5	40/135 29.6%
48754	branching morphogenesis of a tube	2.4400E-5	9/135 6.6%

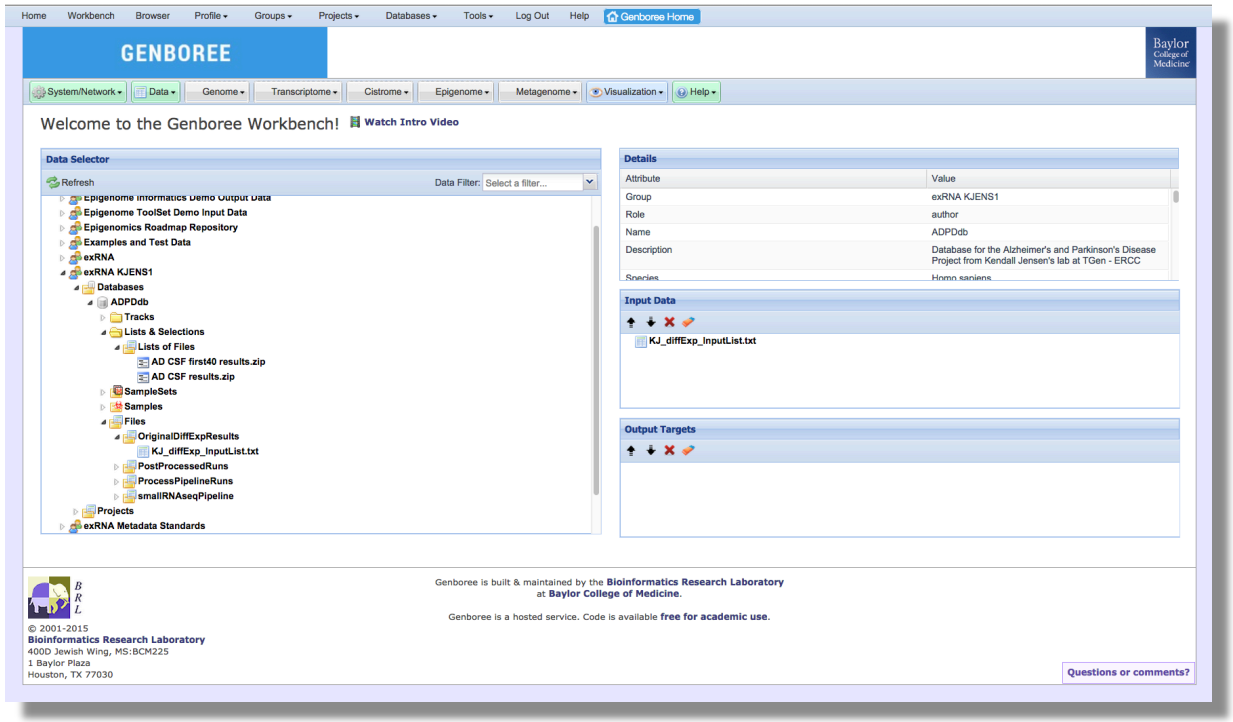
Focused set of interactions

Pathway and Network Analysis: Who?

1. ***Why*** would you do this?
2. ***What*** would you do?
3. ***How*** would you do it?
4. ***Who*** can do this?

Pathway and Network Analysis: Who?

Login:



Email: alex.pico@gladstone.ucsf.edu

Useful Links

exRNA Portal

- http://exrna.org
- **Portal Data & Software Resources**
  - http://exrna.org/resources/data/
  - http://exrna.org/resources/software

exRNA Atlas

- http://genboree.org/exRNA-atlas/
- **Atlas Tutorials**
  - http://genboree.org/theCommons/projects/exrna-mads/wiki/exRNA%20Atlas

ERCC Data Coordination Center Wiki

- http://genboree.org/theCommons/projects/exrna-mads/wiki

exRNA Data Analysis Tools Wiki

- http://genboree.org/theCommons/projects/exrna-tools-may2014/wiki

Presenters

exRNA Atlas
Sai Lakshmi Subramanian, Baylor College of Medicine, Houston, TX

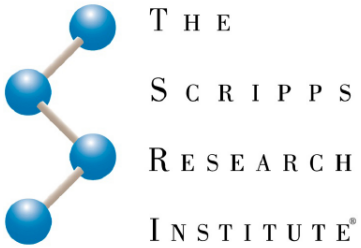
DESeq / exceRpt pipelines
William Thistlethwaite, Baylor College of Medicine, Houston, TX

Exocarta and Vesiclepedia
Roger P. Alexander, Pacific NW Diabetes Research Institute, Seattle, WA

GeneWiki and Wikidata
Sebastian Burgstaller-Muehlbacher, Scripps Research Inst., San Diego, CA

Pathway analysis
Alex Pico, Gladstone Institutes, San Francisco, CA

Acknowledgments

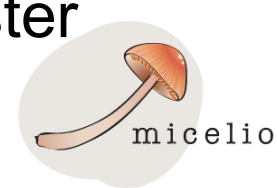


Andrew Su
Benjamin Good
Julia Turner
Tim Putman
(TSRI)

Elvira Mitraka
Lynn Schriml
(Disease Ontology, U Baltimore)

Gang Fu
(NIH, PubChem)

Andra Waagmeester
(Micelio.be)



Acknowledgements

La Trobe University, Melbourne, Australia

Suresh Mathivanan

Dr Shivakumar Keerthikumar

Mohashin Pathan

David Chisanga

Acknowledgements

All data submitters from the ERC Consortium

Baylor College of Medicine, Houston, TX
Aleksandar Milosavljevic, Director
Matthew Roth, Co-Director
Elke Norwig-Eastaugh

Genboree Dev Team at Baylor
Sai Lakshmi Subramanian
William Thistlethwaite
Andrew Jackson
Neethu Shah
Sameer Paithankar
Aaron Baker

Yale University, New Haven, CT
Mark Gerstein
Joel Rozowsky
Rob Kitchen
Fabio Navarro

Gladstone Institutes, San Francisco, CA
Alexander Pico
Anders Riutta
Kristina Hanspers

Pacific Northwest Diabetes Research Institute, Seattle, WA
David Galas
Roger Alexander

Stanford University, Stanford, CA
Julia Salzman
Linda Szabo

Sponsored by:
Grant ***1U54DA036134*** from the NIH Common Fund, through the Office of Strategic Coordination/Office of the NIH Director