	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

### BACKGROUND

The Allen Institute, a bioscience nonprofit founded in 2003, focuses on furthering knowledge and innovation specifically in cell, immune and brain science. Each separate sector of the institute has made its own important contributions to research, including an integrated 3D cell explorer and the Allen Brain Atlas.

The Allen Brain Atlas project began with the original goal of mapping gene expression in the mouse brain (Gilbert, 2018). Since mice are such a common model organism, especially when studying the nervous system and its associated disorders, understanding the mouse genome and its homology to humans is



Allen Brain Atlas P56 coronal slice of a mouse brain

extremely beneficial for research purposes. Since the dawn of its creation, the Allen Brain Atlas has expanded to include documentation of developing mice, the mouse spinal cord, adult and developing humans, and primate information (Gilbert, 2018).

The Allen Brain Atlas gives researchers many advantages when analyzing various aspects of the brain. The documentation of anatomy is important for biologists and neuroscientists who are just beginning to become familiar with nervous system structures. It provides detailed documentation of each structure on a brain slice and is a great resource to learn brain structures in a rostral to caudal order. *In situ* hybridization was utilized to create gene expression profiles for the most notable brain regions; the resulting values can be used for comparison of gene expression between animal models and humans, which will be the process explained in this procedure. It is also possible to utilize the gene expression values to determine the brain regions where the gene is most prevalent, which can assist in determining protein function. Understanding all of these components has implications in the study of the neurobiology and genetics of disease.

<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

# 1. PURPOSE

The purpose of this procedure is to become comfortable with the techniques used to compare gene expression between mouse and human models using the Allen Brain Atlas.

# 2. SCOPE

This procedure applies to qualified skills center users.

### 3. **RESPONSIBILITY**

- 3.1. It is the responsibility of the user to understand and perform the procedure described in this document.
- 3.2. It is the responsibility of the user performing the procedure to fully document any deviations from the written procedure.
- 3.3. It is the responsibility of the user to become trained on the procedure.

# 4. **DEFINITIONS**

- 4.1. Allen Institute A nonprofit, bioscience focused institute founded by Paul Allen in 2003 that emphasizes research in brain and cellular science.
- 4.2. Brain atlas A series of various brain slices from either human or animal brains that provides anatomical information in addition to other details about specific brain sections.
- 4.3. Rostral Towards the nose or beak, towards the front, anterior.
- 4.4. Caudal Towards the tail, towards the back, posterior.
- 4.5. Sagittal A longitudinal plane that divides the body into right and left sections.
- 4.6. Coronal A vertical plane that divides the body into front and back sections.
- 4.7. Fold change value The value that represents the average log2(intensity) of all samples in the target structure minus the average values in the contrast structure. It measures the degree of quantity change between final and original value.
- 4.8. *In situ* hybridization An assay that utilizes nucleotide probes that quantitatively measures the presence of mRNA in a cell.
- 4.9. Z-score The value that describes how many standard deviations the value falls from the mean. A positive z-score indicates a value higher than the mean, and a negative z-score indicates a value lower than the mean.

<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

### 5. MATERIALS/EQUIPMENT

5.1. Allen Brain Atlas – <u>https://portal.brain-map.org/</u>

### 6. PROCEDURE

#### 6.1. Installation of Brain Explorer

- 6.1.1. Go to the link to download the Brain Explorer 2 Software: <u>https://mouse.brain-map.org/static/brainexplorer</u>
- 6.1.2. Download the proper software for the specific computer being used and follow all of the sequential steps until the installation is complete.

#### 6.2. Becoming Comfortable with the Brain Explorer program

- 6.2.1. Go to the Allen Brain Atlas brain map website: https://portal.brain-map.org/
- 6.2.2. Hover over Atlases and Data and click on Mouse Brain Atlas. (Figure 1)

ALLEN BRAIN MAP Atlase	es and Data Browse Data Ex	xplore Technical Resources	Allen Institute 👻 Updates &
Cell Types Database	Mouse Brain Atlas	Human Brain Atlas	Aging, Dementia & TBI Study
Human and mouse brain data	te eitu hybridizetien (ISH) data	In situ hybridization (ISH) data	RNA-Seg data, human
Search cell feature data	Reference atlas, adult	Search RNA microarray data	Donor descriptions
RNA-Seg data	Reference histology	Reference atlases	Download RNA-Seg, clinical data
	Mouse strain diversity study	Download RNA-Seq, microarray	
Brain Observatory		Download MRI, DTI	Ivy Glioblastoma Atlas Project
Visual Coding - Neuropixels	Developing Mouse Brain		RNA-Seq data, human
Visual Coding - 2P Calcium	Atlas	Developing Human Brain Atlas	In situ hybridization (ISH) data
imaging	In situ hybridization (ISH) data	In situ hybridization (ISH) data	Donor descriptions
Software development toolkit	Reference atlases	RNA-Seq data	Download RNA-Seq, clinical data
Transgenic lines		RNA microarray data	
	Mouse Spinal Cord Atlas	Reference atlases	Schizophrenia Study: Gene
Mouse Brain Connectivity	In situ hybridization (ISH) data	Download RNA-Seq, microarray	expression
Atlas	Reference atlases (adult,	Download MRI, DTI	In situ hybridization (ISH) data, humar
Neuron projection maps	juvenile)		
Allen Brain Explorer		Developing Non-human primate (NHP)	Autism study: Gene expression
Transgenic lines	Gene Expression	Atlas	In situ hybridization (ISH) data, huma
	Navigators	In situ hybridization (ISH) data	
	Adult mouse	RNA microarray data	Sleep Study: Gene expression
	Developing mouse	Reference histology	In situ hybridization (ISH) data, mous

- 6.2.3. After selecting Differential Search, select the target brain structure of interest and search. (Figure 2)
  - The dentate gyrus will be used in this example.
  - Ensure that the Contrast Structure setting is marked as grey.
  - Select the coronal data only box.

	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

- 6.2.4. Scroll through the gene profiles and click on the gene name of the gene of interest. This will bring up a window to the right of the screen that showcases the Brain Explorer view. (Figure 2)
  - For this example, the *Cdh9* gene will be used.

Figure 2					70015					Search
	ISH D/	ATA R	EFERENCE	ATLAS	AGEA BRAIN EXPLORER REI	LATED STUDIES	V DC	CUMENT	ATION HELP	
	0									
		Differential	Search		DG x				Φ ?	
	C	Fine Struct	lure Search	0	Contrast Structure(s) grey x				Search	
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		Piuman Di	letential Seat	n	Coronal data only.	Expression arrest	iona (1).			
							Showi	ng page 3 of	129 14 44 85 81	
		Fold Cha	Experiment	Gene Symbol	Gene Name	Probe Name	Orientat	Plane	Expression Su	Correlation Cdh9
		Fold Cha 9.348	Experiment 71249055	Gene Symbol Faxo1	Gene Name forkhead box O1	Probe Name RP_050407_02	Orientat Antisense	Plane	Expression Su	Correlation Cdh9
		Fold Cha 9 348 9.100	Experiment 71249055 72472764	Gene Symbol Faxo1 Cdh9	Gene Name forkhead box O1 cadherin 9	Probe Name RP_050407_02 RP_051101_02	Orientat Antisense Antisense	Plane coronal coronal	Expression Su	Correlation Cdh9
		Fold Cha 9 348 9.100 8.802	Experiment 71249055 72472764 74363337	Gene Symbol Foxo1 Cdh9 Fam160a1	Gene Name forkhead box O1 cadherin 9 family with sequence similarity 160, member A1	Probe Name RP_050407_02 RP_051101_02 RP_051005_02	Orientat Antisense Antisense Antisense	Plane coronal coronal coronal	Expression Su	Correlation Cdt9 Coronal data only Basic cell groups and regions (grey)  Search
		Fold Cha 9 348 9.100 8.802 8.747	Experiment 71249055 72472764 74363337 73615793	Gene Symbol Foxo1 Cdh9 Fam160a1 Nr4a3	Gene Name forkhead box O1 cacherin 9 family with sequence similarity 160, member A1 nuclear receptor subfamily 4, group A, member 3	Probe Name RP_050407_02 RP_051101_02 RP_051005_02 RP_050810_04	Orientat Antisense Antisense Antisense Antisense	Plane coronal coronal coronal coronal	Expression Su	Correlation Cong Correlation Cong Basic cell groups and regions (grey) + Search
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		Fold Cha 9 348 9.100 8.802 8.747 8.426 8.136 8.002 7.417	Experiment 71249055 72472764 74363337 73615793 74272479 72081515 73520970 686	Gene Symbol Foxo1 Cdh9 Fam160a1 Nrt43 Nrtp1 Tanc1 Fam163b Ncor1	Gene Name Contreme 3 Contreme 3 Contreme 3 Family, with sequences similarity (50, promote A1 nuclear receptor as Johanny 4, group A, member 3 recerption 1 tetrastrooppose reports, annym neperal and cone family with sequences similarity (55, member 3 michael receptor compensator 1	Probe Name RP_050407_02 RP_051101_02 RP_051005_02 RP_050915_01 RP_050915_01 RP_051017_01 RP_Baytor_103014	Ortentat Antisense Antisense Antisense Antisense Antisense Antisense Antisense	Plane coronal coronal coronal coronal coronal coronal coronal	Expression Su	Correlation Cano Correlation org/ Basic cell groups and regions (are). • Search BrainExplorer View in 30
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6.2.5. Click on the View in 3D button on the Brain Explorer view tab. (Figure 2) 6.2.6. Open the image in the Brain Explorer 2 application. (Figure 3)



<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

- 6.2.7. Once in the Brain Explorer application, click the desired brain structures or regions in the A column of the structure toggle to add the reference atlas structure. (Figure 4)
  - The hippocampal formation was used in this example.
  - The structure can be rotated by clicking and dragging the model brain in various directions.
  - Make the reference atlas transparent via the Atlas and Transparent functions.



- 6.2.8. Moving the window of the density at the bottom makes the gene expression profile in the image more specific to dense regions if moved right, and broader to include less dense regions if moved left. (Figure 5)
- 6.2.9. Select a specific point on the gene expression map and make note of the gene expression annotation in the lower left-hand corner. It can be expanded into a new window to further evaluate gene expression if needed. (Figure 5)
  - Selecting the arrow in the top right corner of the gene expression annotation will open the experiment data for the gene. This page can be used according to the Allen Brain Atlas 1 SOP. (Figure 5)'







- Selecting either of the brain-shaped buttons in the lower left annotated map will bring up the reference atlas instead of a gene expression profile that can be used to evaluate the structures of interest anatomically. There are both coronal and sagittal visualizations. (Figure 6)



Figure 6

	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

### 6.3. Human Brain Atlas – Mouse Differential Gene Search

- 6.3.1. Go to the Allen Brain Atlas brain map website: https://portal.brain-map.org/
- 6.3.2. Select the Human Brain Atlas this time, and make sure that the page is on the Microarray setting. (Figure 7)



- 6.3.3. Select the Mouse Differential Search function and type in the brain region of interest, with the whole brain as the contrast structure. Press search. (Figure 7)
  - This will open a comparison of the differential search for various genes in the mouse and human brain atlases.
  - The human data will be viewed as a microarray with different probes, while the mouse data will pop up as a 3D visualization.
  - The fold change values can be compared between the mouse and human data for the specific genes.
- 6.3.4. Clicking on the Experiment tab for a specific gene will bring up the gene expression map in the Brain Explorer application. The data can then be analyzed as described in part 6.2. of this document. (Figure 7)
- 6.3.5. Clicking on one of the probes for the human gene will open a new page with a heat map as seen in the Allen Brain Atlas 1 SOP. (Figure 7)

<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

6.3.6. Select the probe of interest, click a corresponding point in the heat map and then click on the Brain Explorer tab to open the Brain Explorer application with the human data. (Figure 8)

Figure 8	ALLEN BRAIN ATLAS		
	HOME HUMAN BRAIN TOOLS		Search Q
	MICROARRAY ISH DATA MRI DOWNLOAD BRAIN EXPLORE	ER DOCUMENTATION HELP	
	Gene Search Enter Gene Name, Gene Symbol, NCBI     Differential Search CUST_441_Pix17507815     Gene Cassification     Musue Differential Search Search Store vact matches only	Accossion Number or Entrez Gene ID Search	
	Structure: programme(Ca)) descriptions(D)(D) butters region (CAR) accurite nucleus of the hypothalaenes (ARIs)	Serie Into: Symbol: Curvellan: conventioning promove Prode: CUR: 41(14(14)70715) Expression: - 4-core: no. logit benefity: no Related Osta: <u>Curvellan: Anno Anno Anno Anno Anno Anno Anno An</u>	Datab Fundor         ?         Hold Correlates           Click to         Jaunch BrainExplorer
	1 - 3 of 3	Donor H0301.2002 subthalamus (SbT)	
	Gens British         Probe bane           Ø         PACH         A.2 J.2 42723           U         PACH         CLIST_44_UVIT/PATHS           PRICH         CLIST_4_PH47781183		

- 6.3.7. Add coronal slices to the brain images by clicking the coronal brain button. (Figure 9)
  - Annotate the images with the same process as in section 6.2.
- 6.3.8. Click on a region in the region section of the heatmap on one of the images. This will bring up gene expression info in the top left corner of the screen. (Figure 9)



	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

### 6.4. Comparing Human and Mouse Gene Expression

6.4.1. Return to the Mouse Differential Search in the Human Brain Atlas using the previously specified search parameters. Locate the gene of interest from part 6.3. (Figure 10)

Figure 10	HOME HUMAN	BRAIN TOOLS				Search
	MICROARRAY ISH DA	TA MRI DOWNLOAD	BRAIN EXPLORER DO	CUMENTATION HELP		
	Gene Search Differential Search Gene Classification Mouse Differential Sear	Target Structure(s) Contrast Structure(	Hypothalamus (s) Brain	<ul><li>?</li><li>Search</li></ul>		
			Human Brain Mi			< 1 2 3 4 6 >
	Gene	Probe	Fold Change		Experiment	Fold Change
		CUST_441_PI417507815	101.042		55	1.687
	PMCH	A_23_P321223	90.749			
		CUST_6_PI417511553	76.682			

- 6.4.2. Comparing the Fold Change values can give some insight into variation in expression levels between the mouse and human brain. (Figure 10)
  - For reference, a fold change value of 3 indicates that the expression level in the structure of interest is about 3x higher than in the reference structure.
  - Note that human and mouse brain gene expression levels cannot be directly compared, as different probes and methodologies are used meaning that discrepancies exist. However, comparison can loosely be used as a tool to compare trends in the data.
- 6.4.3. Selecting a human probe from the differential search results will open a heat map. Click on a probe within the heat map and then Planar View to bring up the gene expression information. (Figure 11)
  - · Click within the heat map to choose the probe within a specific region.

Figure 11	Gene Search Enter Gene I     Differential Search CUST_441     Gene Classification     Mouse Differential Search Solve search	Name, Gene Symbol, NCBI Accession Number or Entrez Gene ID _PI417507815	
	Structure: gray matter (CM) termination (Tel) central contex (CA) limito lobe (LJ) hippocampa formation (HF) CK3 field (CAS)	Gen Info: Name: pro-metanin concentrating hormone Probe: / 23_P33/123 Expression = 2-score: -0.31933, log2 intensity: 2.42097 Related Data: gross encourses Done: H0351.2001, 24 yrs, M, Black or African American	Brain Explore     ?     Find Correlates       Planar View     In:     In:       Planar View     For:     [All Donors] ~       For this prote: A.22,P321223     For this prote: A.22,P321223
	1 - 3 of 3	Donor H0351.2001 CA3 field (CA3)	
	Gene Symbol Probe Name		
	PMCH         A_23_P321223           PMCH         CUST_441_P1417507815           PMCH         CUST_6_P1417511553		

<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

6.4.4. The planar view will open a new window that specifies gene expression level data in varying brain regions. (Figure 12)

Figure 12	H0351.2001	Probe PMCH: A_23_P321223 V Coronal S	Brain Explorer 🧇   Permalink   🛃
	R		L L
	= 1cm MNI Coordinate: -32, -2	28, -8 Structure: hippocampal formation CA3 field, left (CA3)	Expr. Level: 1.691 Z-Score: -0.685
	[0, 600]		[-2.5, 2.5]
	FL CgG HIF OL	.   PL   TL	Str.       DT.   MES. CbCx     PTg   MY
	4		×

- 6.4.5. Selecting a mouse brain experiment from the differential search results will open a new window specific to that experiment. (Figure 10)
- 6.4.6. Farther down on the page is a bar chart which can be used to analyze gene expression in the mouse brain. (Figure 13)
  - Note that in the example experiment, PMCH levels in the mouse brain are extremely low which is why there is a low expression value and no colored bar graphs are present.

	Specimen 1901		1 N N			
Figure 13	Organism	Mus musculus				
•	Strain	C57BL/6J				
	Age	56				
	Sex	м				
	Related Institute Da	ita -				
	MOUSE HUMAN					
	Brain Explorer	View in 3D				
		100			A	
		10	1304 microns	<pre>&lt; = &lt;</pre>	1.4.5	
	and the second s	1 C C C C C C C C C C C C C C C C C C C				
	•		12.3			
			4			+
	Structure: Hypoth	alamus (HY) raw expression value:	0.11: 1005: -3.20			
	4		52			- 4
	3					3
	2					2
	1					1
	Isocortex	OLF HPF CTXsp	STR PAL	TH HY	MB P MY	CB

<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

# 7. TROUBLE SHOOTING

**7.1.** The Brain Explorer view is grayed out when assessing via the human brain atlas: make sure to click directly on a probe within the green and red heat map to select a probe of interest (See step 6.4.3. for figure)

# 8. REFERENCES

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<b>F</b>	SKILLS CENTER STANDARD OPERATING PROCEDURE	A BIOFIZZ PRODUCTON
Allen Brain Atlas: Comparing Animal and Human Models Using the Brain Explorer	Effective Date: 03/01/2021	Revision # 1.0 A. Siclair Checked: M. Guzie

# 9. MODULE MASTERY TASK

This quiz will test your knowledge of gene expression analysis techniques using the Allen Brain Atlas.

- 1. Run a differential search in the Mouse Brain Atlas and choose a gene of interest. Write down your choice for both the gene and target structure.
- 2. Open the gene in the Brain Explorer application. Add brain regions or structures to the map and make them transparent. Submit the resulting image.
- 3. Select a specific point on the gene expression map and change the gene expression annotation window so that it shows the reference atlas for that point. Name the function of one of the structures or regions present in the atlas at that point.
- 4. Run a Mouse Differential Search using the Human Brain Atlas. Select a gene and write it down along with the target structure.
- 5. What are the fold change values for the a mouse experiment and a human probe for that gene? What conclusion can be drawn from this?
- 6. Select a specific probe in the human data for the gene and open it in the Brain Explorer. Add coronal slices along with 2 transparent brain structures/regions of interest. Submit the resulting image.
- 7. Utilizing section 6.4, what is the gene expression value for your chosen region in the human brain?
- 8. Utilizing section 6.4, what is the gene expression value for your chosen region in the mouse brain?
- 9. Why do you think it is important to compare gene expression levels of a gene of interest in the mouse brain compared to the human brain?