

Practical Applications of MRI in Toxicologic Pathology

Part of the Imaging Workshop of the International Academy of Toxicologic Pathology (IATP)

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In vivo Imaging- The Future is Now

Invited Review

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Toxicologic Pathology in the 21st Century

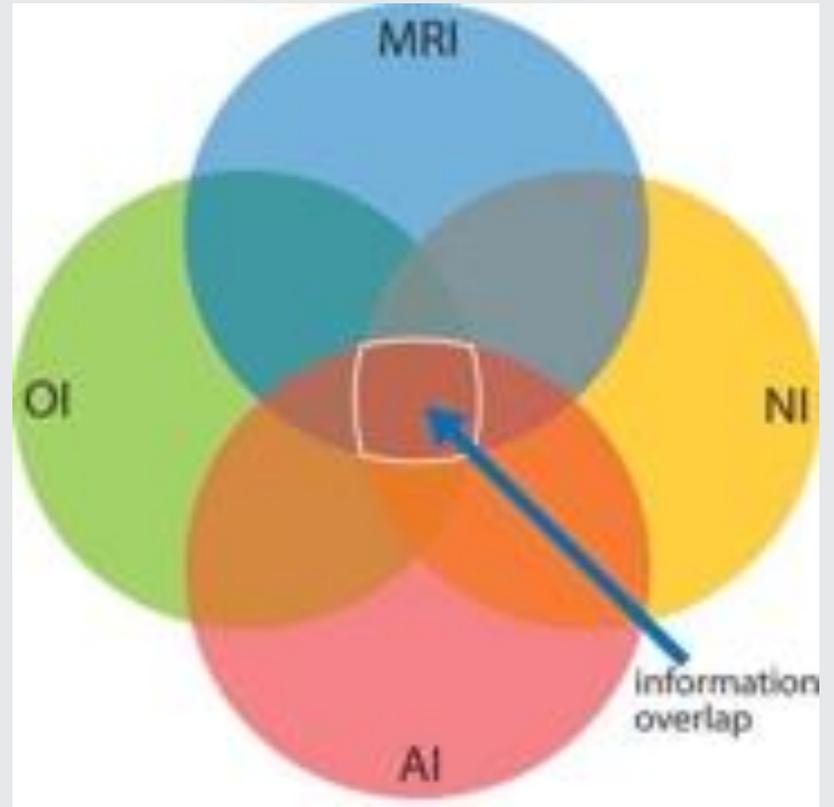
ROBERT A. ETTLIN

Ettlin Consulting Ltd., Muenchenstein, Switzerland

ABSTRACT

Toxicology is and will be heavily influenced by advances in many scientific disciplines. For toxicologic pathology, particularly relevant are the increasing array of molecular methods providing deeper insights into toxicity pathways, *in vivo* imaging techniques visualizing toxicodynamics and more powerful computers anticipated to allow (partly) automated morphological diagnoses. It appears unlikely that, in a foreseeable future, animal studies can be replaced by *in silico* and *in vitro* studies or longer term *in vivo* studies by investigations of biomarkers including toxicogenomics of shorter term studies, though the importance of such approaches will continue to increase. In addition to changes based on scientific progress, the work of toxicopathologists is and will be affected by social and financial factors, among them stagnating budgets, globalization, and outsourcing. The number of toxicopathologists in North America, Europe, and the Far East is not expected to grow. Many toxicopathologists will likely spend less time at the microscope but will be more heavily involved in early research activities, imaging, and as generalists with a broad biological understanding in evaluation and management of toxicity. Toxicologic pathology will remain important and is indispensable for validation of new methods, quality assurance of established methods, and for areas without good alternative methods.

In Vivo Imaging- Don't Choose, Fuse!



Advantages of MRI in Toxicology

- **Non invasive** - Permits longitudinal *in vivo* imaging to follow disease in the same animal (better statistics, less animals required)
- Can acquire numerous **digital slices** from whole fixed organs in **any plane** without destroying the specimen
- High **soft tissue contrast** as well as good bone visualization
- Provides a means to obtain **quantitative data**

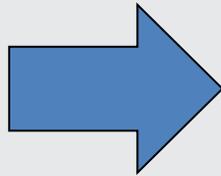


Provides complimentary information to conventional pathology- Better practice, safer drugs/products

MRI- A Psychological Barrier

- Expensive equipment
- Expensive maintenance
- Special facility required (shielded room)
- Safety issues (no metals around)
- Hard to operate
- For “MR gurus” only – High level of expertise required

Shift Happens – Compact MRI for **Everyone**



- Compact
- Quiet
- Affordable
- Easy to use
- Safe
- No special facility
- Maintenance-free

Complicated Software - No more

The screenshot displays the NRGConsole software interface, which is used for managing MRI sequences. The interface is divided into several panels:

- Left Panel (Sequence List):** A table listing various sequences with columns for Type, Sequence Name, Description, and Calib. The 'CALIBRATIONS' sequence is selected.
- Top Panel (Control Panel):** Contains buttons for 'Load Sequence', 'Check (F5)', 'Run (F3)', 'Debug', 'Stop (F8)', 'Break (F4)', and 'View Log'. The current sequence is 'seq_rev12'.
- Center Panel (Macro Editor):** A code editor showing the sequence design for 'seq_rev12'. The code includes comments and function calls such as `[MACRO] ASPECT`, `[FUNCTION] CreateReamination()`, `[LOG] 1`, `[FUNCTION] AddLogHeader()`, `[FUNCTION] OpenData-SEQ()`, `[FUNCTION] Message-SOG()`, `[FUNCTION] GetTabValue()`, and `[FUNCTION] CreateTabNumeric()`.
- Bottom Panel (Macro Archive):** A table listing macros with columns for Macro Name, Vars, Short Description, and Param 2 through Param 6. The 'seq_rev12' macro is highlighted.
- Right Panel (Tools):** A vertical toolbar with various editing and utility functions like 'Convert', 'Copy Rows', 'Cut Rows', 'Paste Rows', 'Del Rows', 'Add Rows', 'Undo', 'Mark', 'Unmark', 'Del Marked', 'Convert', 'Remove comment', 'Editor Help', 'Statements Syntax', 'Math Operators', 'Basic Functions', 'NTNMR Params', 'Sequence Params', 'System Params', 'Utilities', 'Export Macro', 'Import Macro', and 'Convert Matlab'.

The status bar at the bottom shows the date and time as 20/09/2015 6:20:45 PM, along with various system icons and a 'Config Items' dropdown menu.

Tons of Parameters to Optimize... No more

Protocol Details of Fast Spin Echo 2D (Amos Fast Spin Echo)

SAR (W/kg)	0	dB/dt (T/s)	0	dB/dt (% stimulation limit)	0	rms B1 (microT)	0	Scan time	00:01:03
------------	---	-------------	---	-----------------------------	---	-----------------	---	-----------	----------

Slice	
Scan type (2D/3D)	TwoDim
Max # slices for this TR	16
Number of slices	16
Slice thickness (mm)	1
Inter-slice gap (mm)	0.1
Center slice position	0
Slice orientation	Coronal
Advanced Parameters	

FOV/Resolution	
Force eq. FOV hor/ver	Yes
Hor. FOV (mm)	80
Vert. FOV (mm)	80
# phase encodings	192
# samples	200
FOV offset (vert, mm)	0
FOV offset (hor, mm)	0
Advanced Parameters	

Contrast (MRI)	
Time to repeat (TR, ms)	4000
Min TE	No
Time to echo (TE, ms)	77.854
Apply inversion pulse	No
Inversion time (TI, ms)	100.0
Flip angle (deg)	90
Apply diffusion-sensitizing gradients	No
Diffusion gradients	
Advanced Parameters	

Acquisition (k-space)	
# excitations	1
Phase enc. direction	Horizontal
Frequency direction	Vertical
Dwell time (microsec)	25
Partial Fourier	None
External (respiration) trigger	None
Advanced Parameters	

Reconstruction	
Scaling method	PerSeries
Advanced Parameters	

Perform calibrations	
Frequency calibration	No
Coil calibration	No
Shim calibration	No
RF calibration	No

Display calibration data	
Freq cal display mode	No
Coil cal display mode	No
Shim cal display mode	No
RF cal display mode	No

FSE parameters	
Echo train length (ETL)	16
Refocusing flip angle	180
FSE calibration	Retain
FSE cal display mode	No
Advanced Parameters	

One Touch MRI - Ask. Touch. Answer.



Login

please select your way to log-in **One Touch MRI** system

reader disconnected...	guest	manual access username _____ password _____ <input type="button" value="login"/>
register as a new user		

one touch MRI



Just Choose What You Need to Scan

The screenshot displays the 'one touch MRI' software interface. At the top, the user 'Yael Schiffenbauer' is logged in. The interface is divided into 'Ask' and 'Touch' sections. The 'Ask' section on the left contains a list of categories with checkboxes: Anatomy (Brain, Flank, Heart, Kidney, Liver, Peritoneum), Pathology (Fatty liver, Glyoma, Metastatic, Subcutaneous, Tumor), and Others (Bright blood, Physiology). The 'Touch' section on the right shows a grid of MRI scan thumbnails. Each thumbnail includes a timer, a mouse icon, and a list of labels. The labels for the thumbnails are: Row 1: Tumor Subcutaneous Flank; Tumor Metastatic Peritoneum; Brain; Tumor Brain Glyoma. Row 2: Heart; Heart Physiology Bright blood; Kidney; Liver Fatty liver. Row 3: (partially visible) Heart Physiology Bright blood. At the top right, there are options for 'Perspectives' (Default, AX, COR, SAG) and a 'Start' button. The bottom of the interface has a 'Clear' button.

Brain Protocols?

The screenshot displays the 'one touch MRI' software interface. At the top, the user is identified as 'Yael Schiffenbauer'. The interface includes navigation tabs for 'Ask-Touch' and 'Answers'. Below the header, there are options for 'Experiment: Free Experiment' and 'Untraced mouse', along with a 'Start' button and an 'Acquisition time: 0h 00m 00s' indicator.

The main area is divided into two sections: 'Ask' and 'Touch'. The 'Ask' section on the left contains three filter categories:

- Anatomy** (Show all):
 - Brain
 - Flank
 - Heart
 - Kidney
 - Liver
 - Peritoneum
- Pathology** (Show all):
 - Fatty liver
 - Glyoma
 - Metastatic
 - Subcutaneous
 - Tumor
- Others** (Show all):
 - Bright blood
 - Physiology

The 'Touch' section on the right shows two MRI scan thumbnails. The first thumbnail is labeled 'Brain' and has a timestamp of '08m52s'. The second thumbnail is labeled 'Tumor Brain Glyoma' and has a timestamp of '10m35s'. To the right of the thumbnails are perspective selection buttons for 'Default', 'AX', 'COR', and 'SAG'. A large, stylized fingerprint graphic is visible in the bottom right corner of the interface.

Heart protocols?

The screenshot displays the 'one touch MRI' software interface. At the top, the user 'Yael Schiftenbauer' is logged in. The main navigation bar includes 'Ask-Touch' and 'Answers'. Below this, the experiment type is set to 'Free Experiment' and 'Untraced mouse'. The acquisition time is '0h 00m 00s', and a 'Start' button is visible. The interface is divided into two main sections: 'Ask' and 'Touch'. The 'Ask' section on the left contains a list of anatomical and pathological categories with checkboxes. Under 'Anatomy', 'Heart' is selected. Under 'Pathology', 'Bright blood' is selected. The 'Touch' section on the right shows two MRI scan thumbnails. The first thumbnail is labeled 'Heart' and '04m30s'. The second thumbnail is labeled 'Heart', 'Physiology', and 'Bright blood' and '05m12s'. A 'Perspectives' menu at the top right shows 'Default', 'AX', 'COR', and 'SAG' views. A 'Clear' button is located at the bottom left of the 'Ask' section.

one touch MRI

Ask-Touch Answers

Yael Schiftenbauer

Experiment: Free Experiment Untraced mouse

Acquisition time: 0h 00m 00s Start

Ask

Anatomy Show all

- Brain
- Flank
- Heart
- Kidney
- Liver
- Peritoneum

Pathology Show all

- Fatty liver
- Glyoma
- Metastatic
- Subcutaneous
- Tumor

Others Show all

- Bright blood
- Physiology

Touch

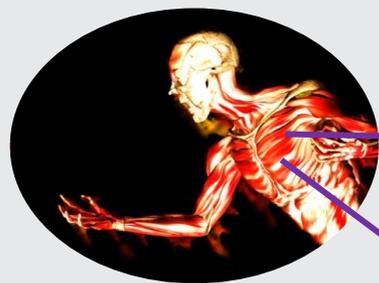
Perspectives: Default AX COR SAG

Heart 04m30s

Heart Physiology Bright blood 05m12s

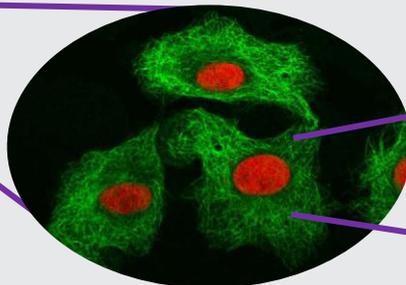
Clear

Source of Signal in MRI

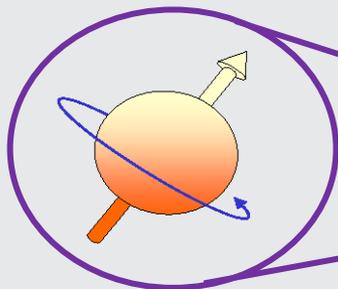
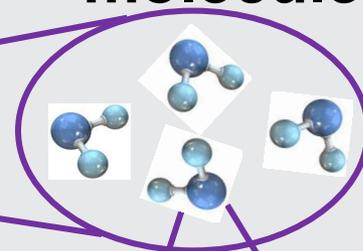


Tissue

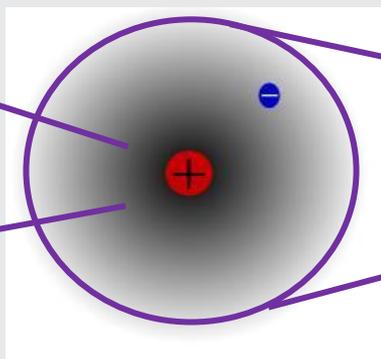
Cells



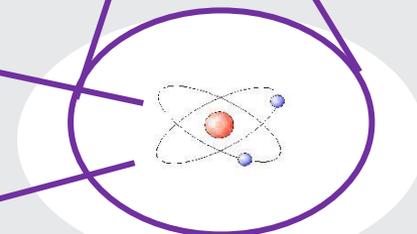
Water/fat molecules



Nuclear Spin



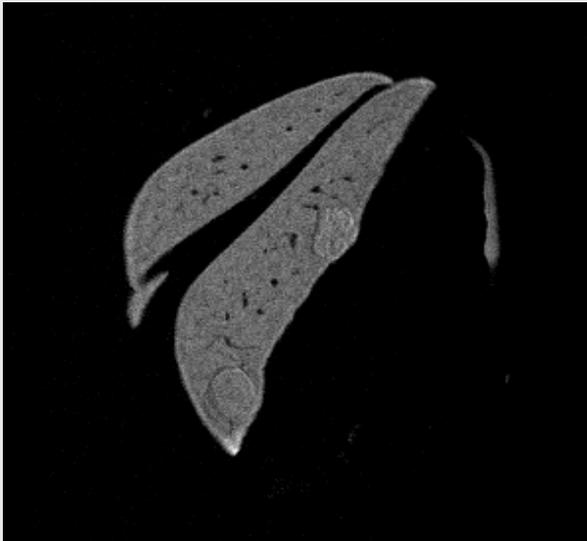
Hydrogen atom



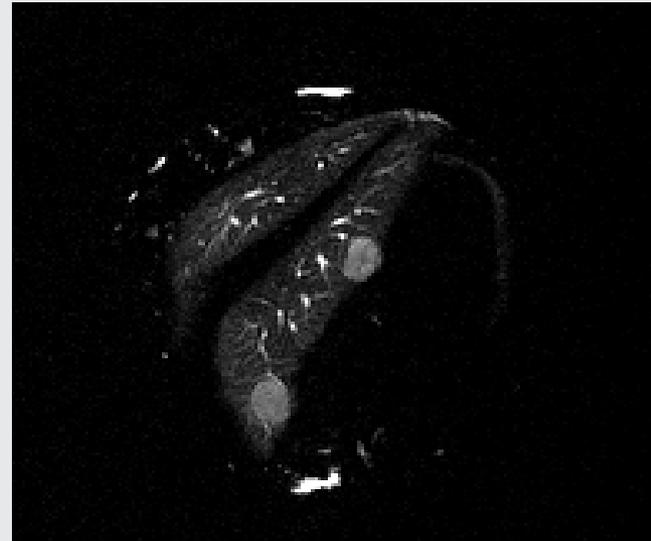
MRI Terminology

- By changing the frequency, duration and timing of applied magnetic fields and radio frequency (rf) pulses, MRI can provide what are basically “MRI stains”
- Most common “MRI stains” (Types of contrast) – T1 and T2

T1



T2



Any plane can be imaged



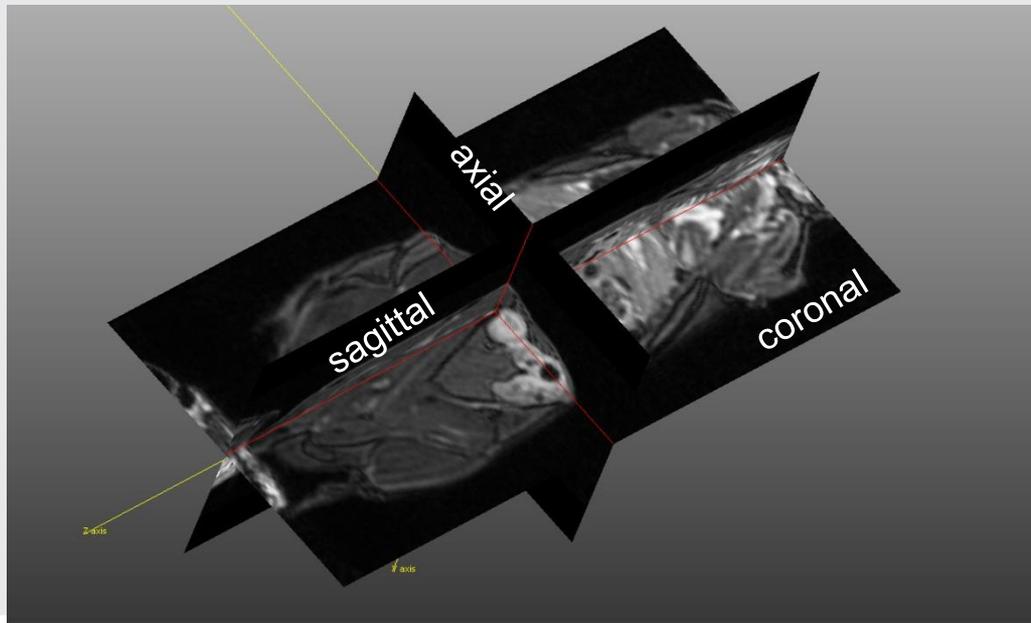
sagittal



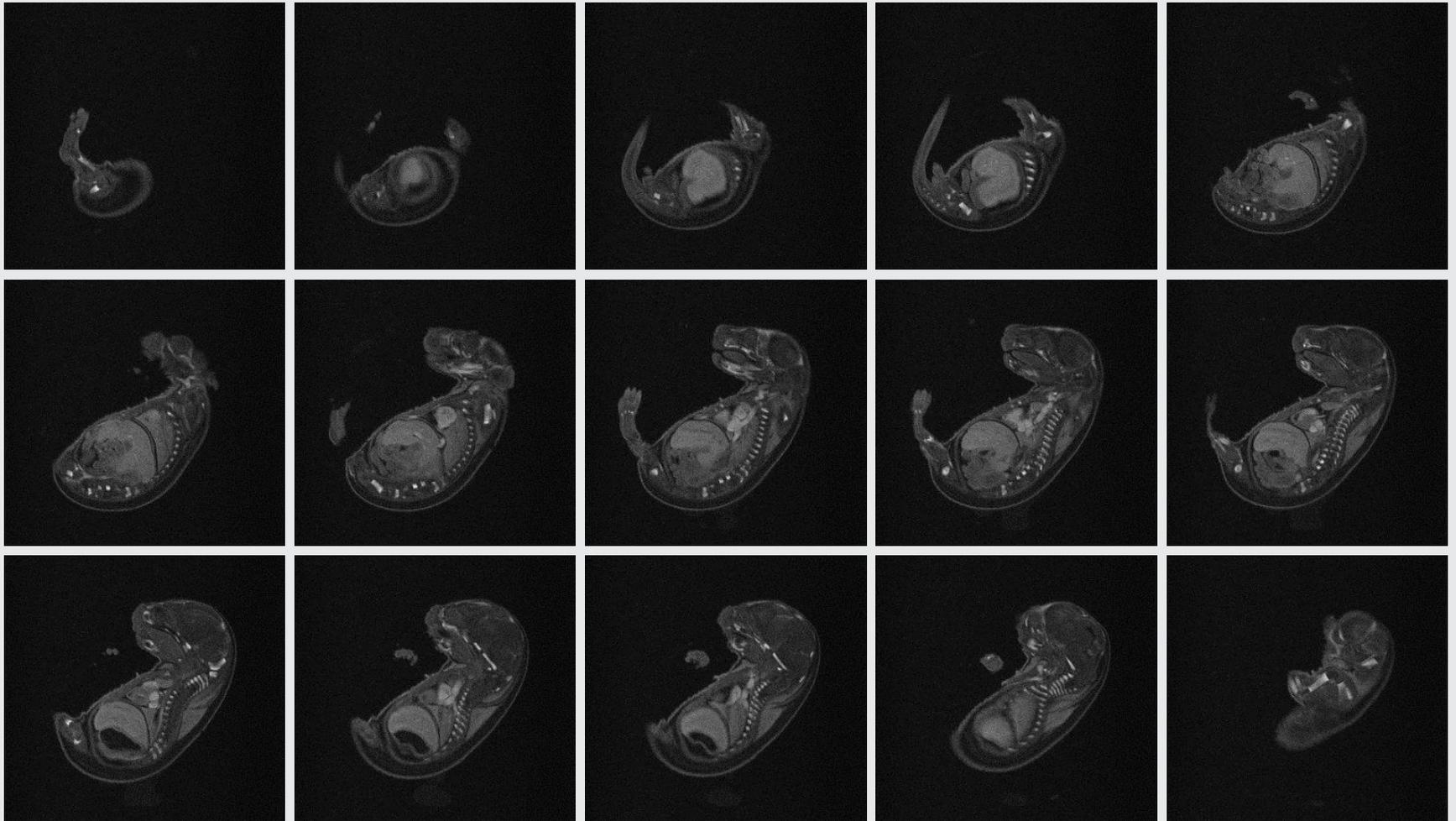
axial



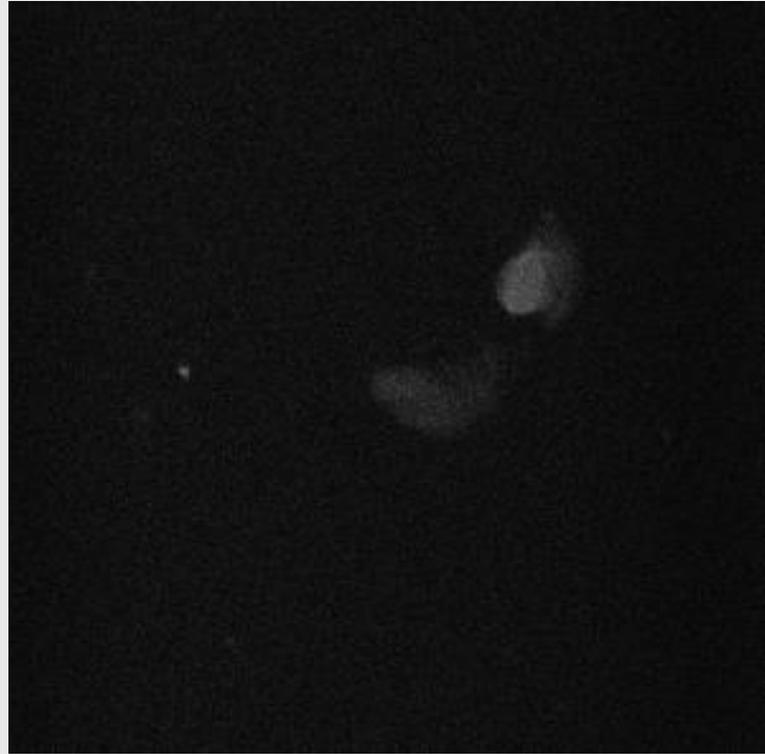
coronal



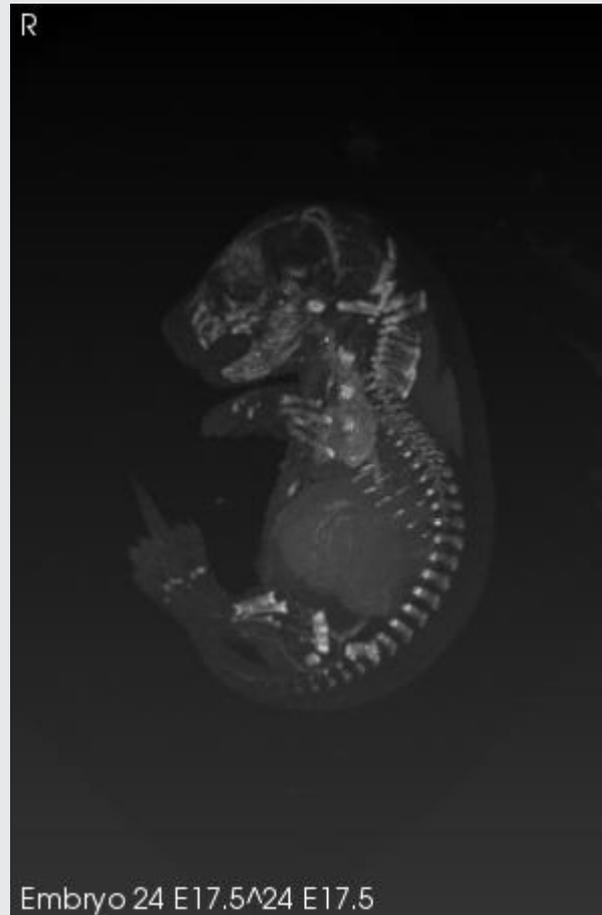
MRI Data Presentation- Individual Slices



MRI Data Presentation –Slice through Animation



MRI Data Presentation – See through 3D Rendering (MIP)

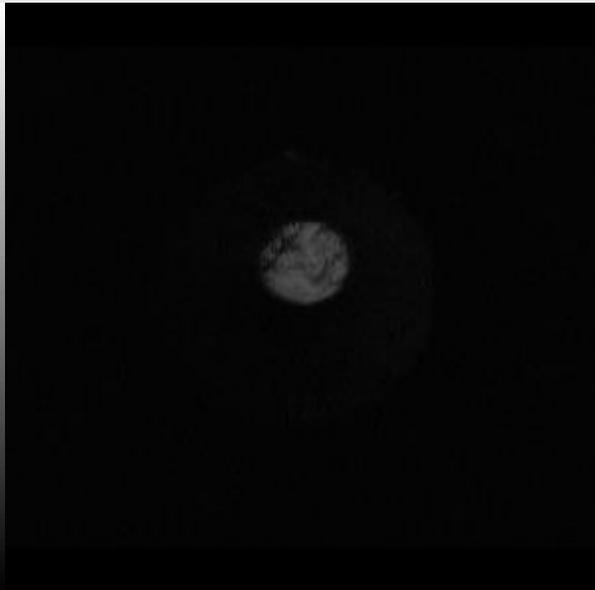


Segmentation – Volume Calculation

Sagittal



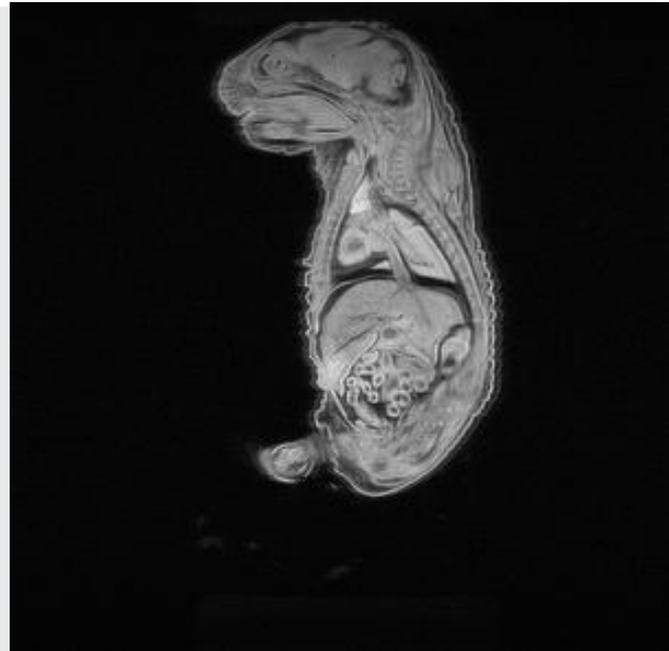
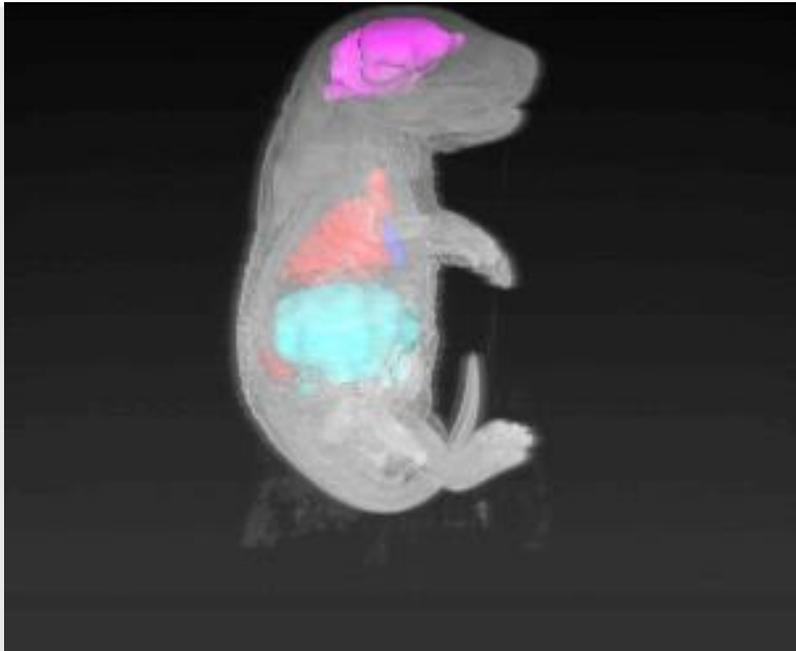
axial



coronal



Segmentation – Volume Calculation



ROI	Rat	Color	Voxels	Volume mm ³
Lungs	rat embryo control E20	red	28910	97.5713
Heart	rat embryo control E20	blue	8218	27.7358
Liver	rat embryo control E20	cyan	84566	285.41
Brain	rat embryo control E20	magenta	38770	130.849
Left Kidney	rat embryo control E20	dark red	3044	10.2735
Right Kidney	rat embryo control E20	dark cyan	2745	9.26438

Scientific Collaboration



National Institute of
Environmental Health Sciences



National Toxicology Program
U.S. Department of Health and Human Services



האוניברסיטה העברית בירושלים
The Hebrew University of Jerusalem



Methods

All scans performed on a M-series compact MRI by Aspect Imaging.

Animals:

- Anesthetized with isoflurane
- Heated
- Physiological monitoring

Fixed samples:

- In any fixative solution
- Fluorinert



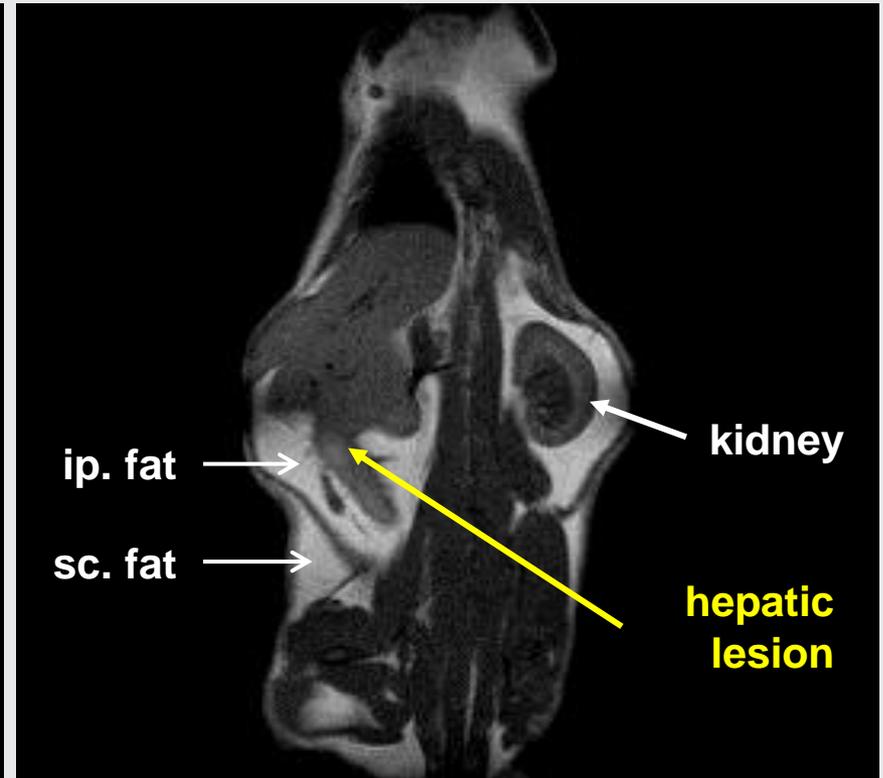
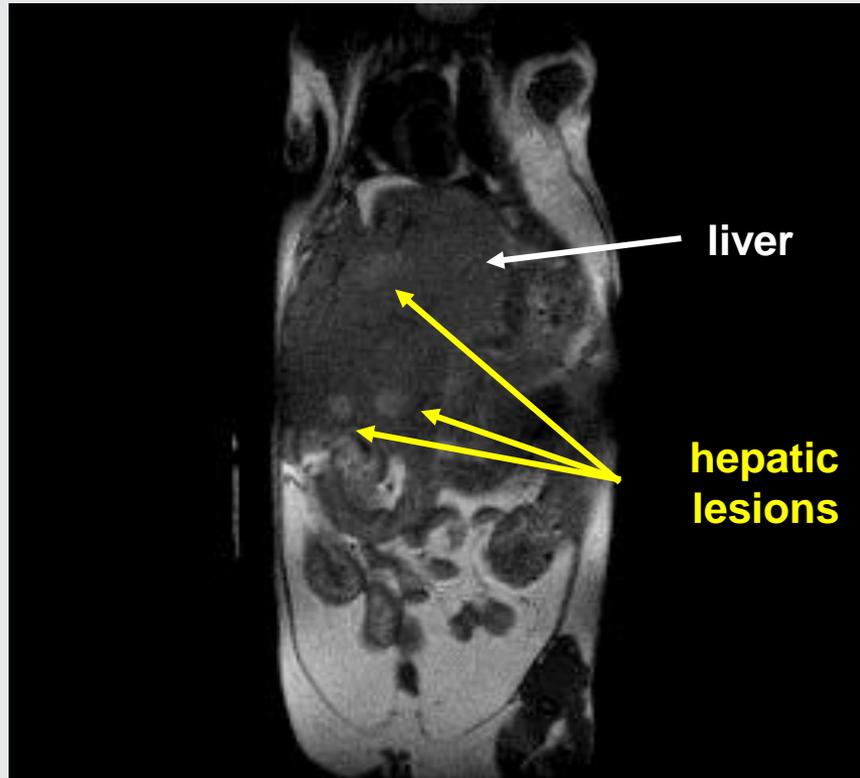
Models That Will be Presented

- [Focal liver lesions](#)
- [Acute kidney injury](#)
- [Local Safety of SC formulations](#)
- [Biodegradable implant](#)
- [Brain tumor growth](#)
- [Rat lung fibrosis](#)
- [Neurotoxicity](#)

Focal Hepatic Lesions

- **Model:** Mdr-/- mouse develops multiple focal hepatic lesions.
- **Objective:** Detect and measure volume of multiple focal lesions

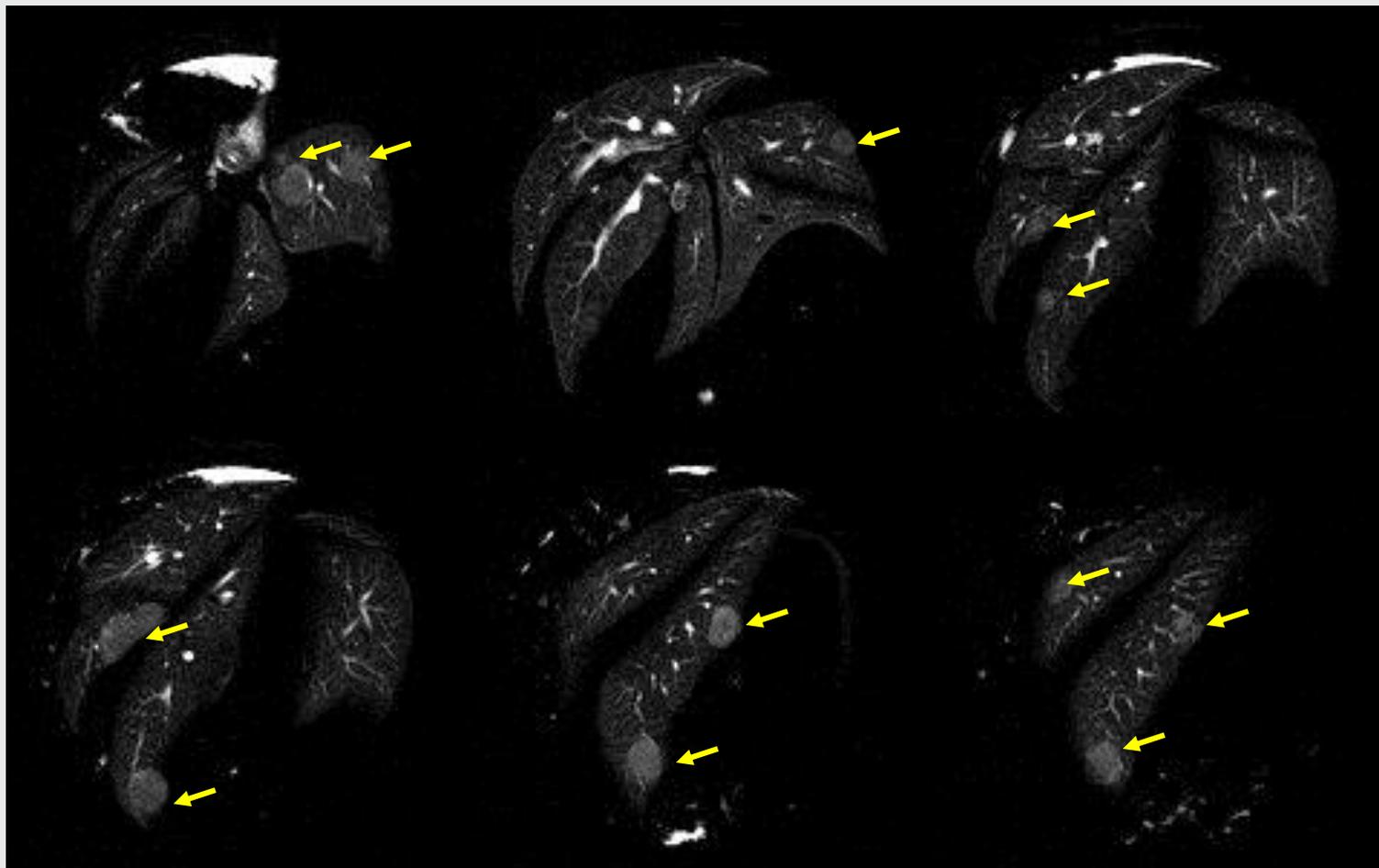
Detection of Multiple Focal Lesions in Mouse Liver – *In Vivo* MRI



resolution 270 μm ; slice thickness 1 mm; acquisition time 3.5 min

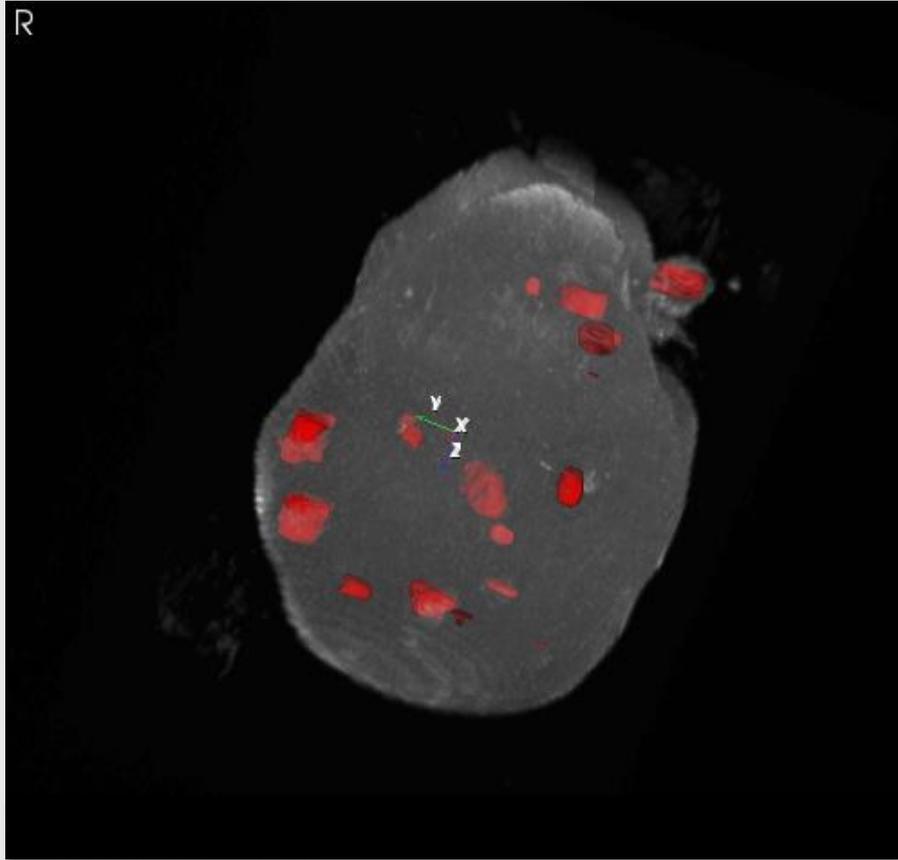
Multiple Focal Lesions in Mouse Liver

Ex vivo MRI



resolution 156 μ m; slice thickness 0.7 mm; acquisition time 35 min

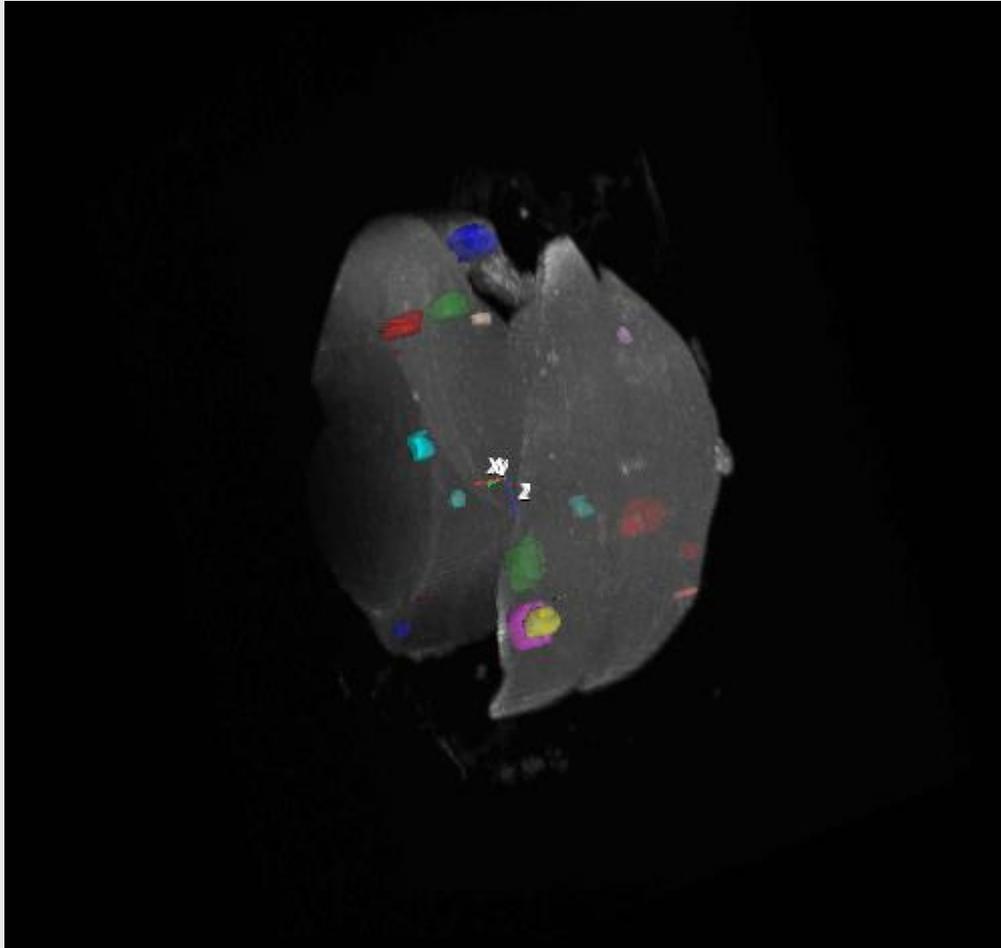
Segmentation of Lesions Based on *Ex Vivo* MRI



Quantification of Lesions Based on *Ex Vivo* MRI

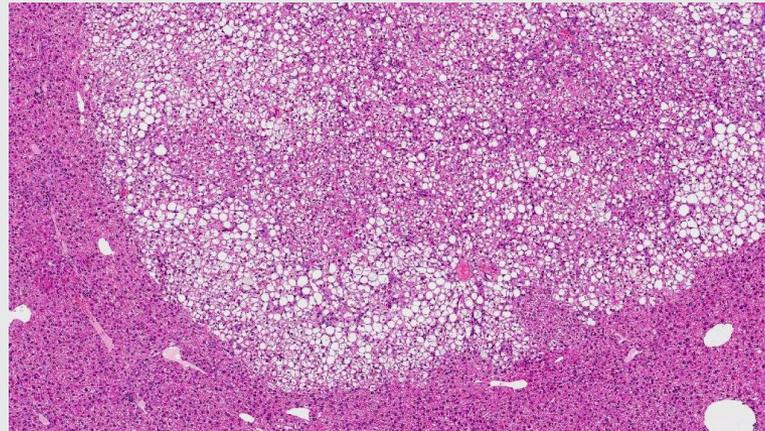
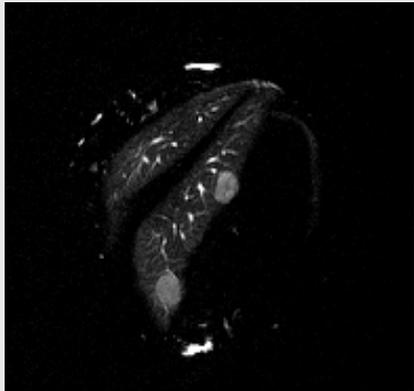
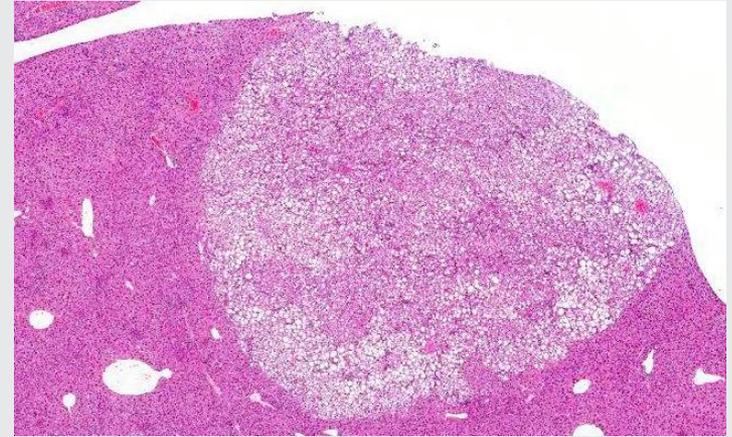
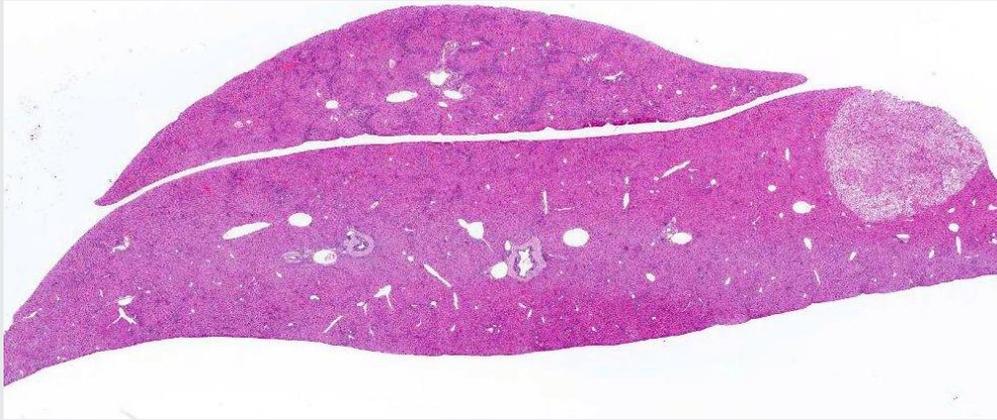
- **15** distinctive lesions were detected
- The smallest lesion detected had a diameter of **0.6 mm**
- The largest lesion had a diameter of **4.8 mm**
- Total liver mass **2593 mm³**
- Total lesion mass **60.3 mm³ (2.3%)**

Segmentation of Lesions Based on *Ex Vivo* MRI



ROI	Color	Voxels	Volume mm ³
1	red	701	2.6741
2	green	950	3.62396
3	blue	1123	4.28391
4	cyan	342	1.30463
5	magenta	2047	7.80869
6	yellow	831	3.17001
7	dark red	2271	8.66318
8	dark green	1961	7.48062
9	dark blue	204	0.778198
10	dark cyan	245	0.934601
11	tomato	201	0.766754
12	maroon	197	0.751495
13	orchid	99	0.377655
14	peach puff	143	0.545502
15	light sea green	152	0.579834

Classification of Liver Lesions as Focal Fatty Changes by Histopathology



Summary & Comment

- *In vivo* and *ex vivo* MRI evaluation were effective in identifying the location and measuring the volume of focal changes in the liver.
- This approach using *in vivo* MRI would allow for following lesion development over time
- In this study the MRI was done after lesions were fully developed, however, longitudinal studies using *in vivo* MRI would easily be feasible in this model

Rhabdomyolysis-Induced Acute Kidney Injury (AKI) in Mouse

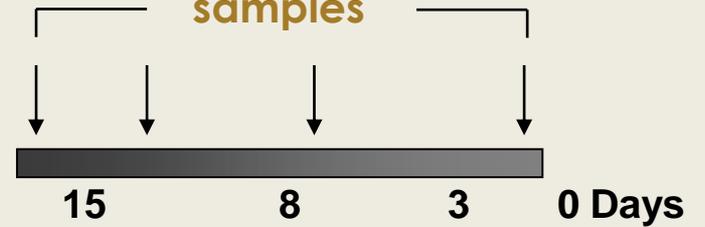
Mice Model of Glycerol-Induced AKI

CB6F1 Mice



IM 50% Glycerol

MRI + Blood samples

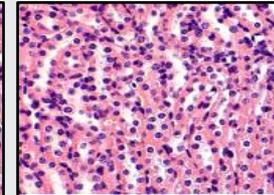
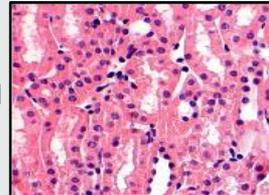


Histopathology – Day 3

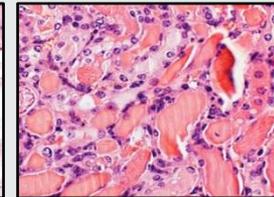
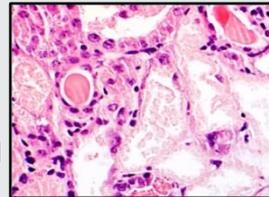
cortex

medulla

control



affected



Control vs Affected Kidney

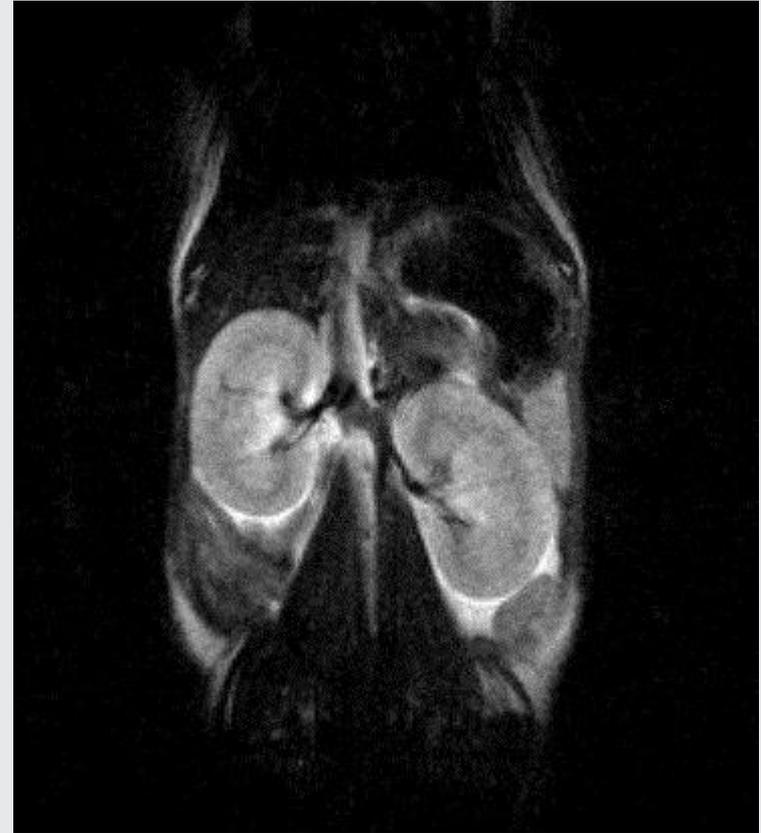
In Vivo MRI

Control

Affected

Day 3

cortex
medulla



resolution 234 μ m; slice thickness 1 mm; acquisition time 10 min

- **Loss of contrast**
- **Enlarged kidneys**

Following Disease Progression

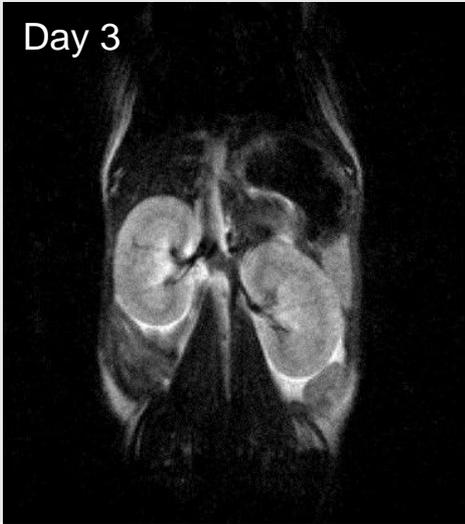
In Vivo MRI

Day 0

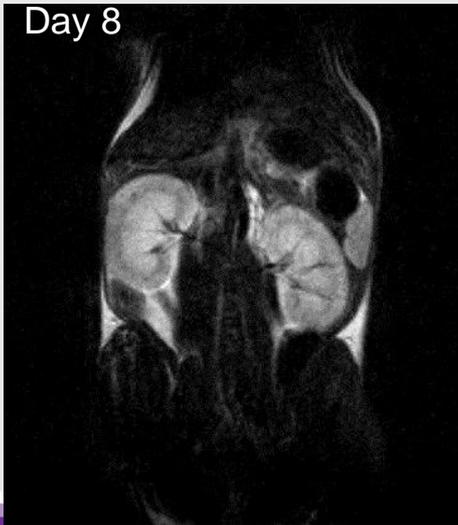


Contrast lost and kidney enlargement

Day 3

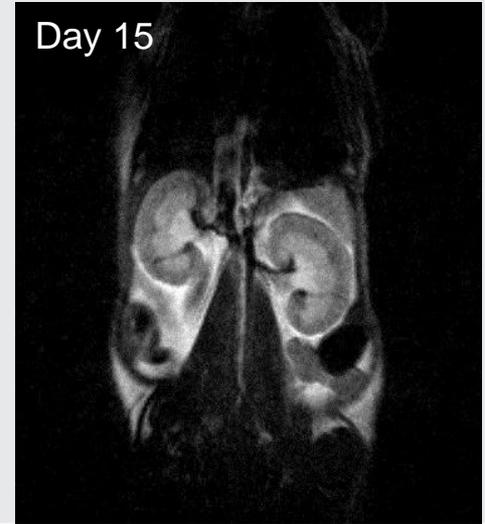


Day 8



Contrast and size recovered

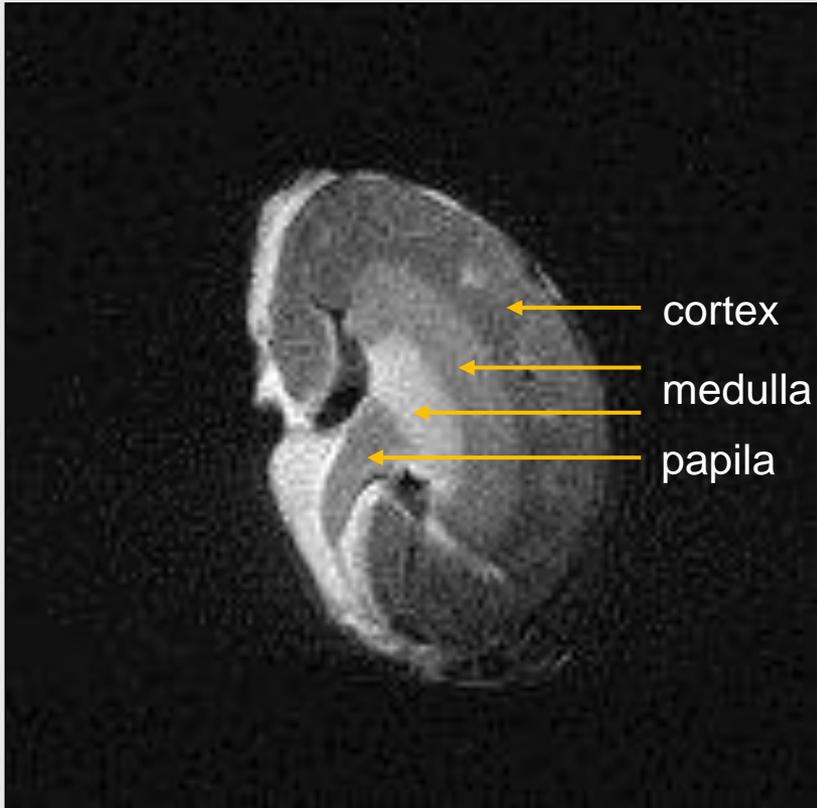
Day 15



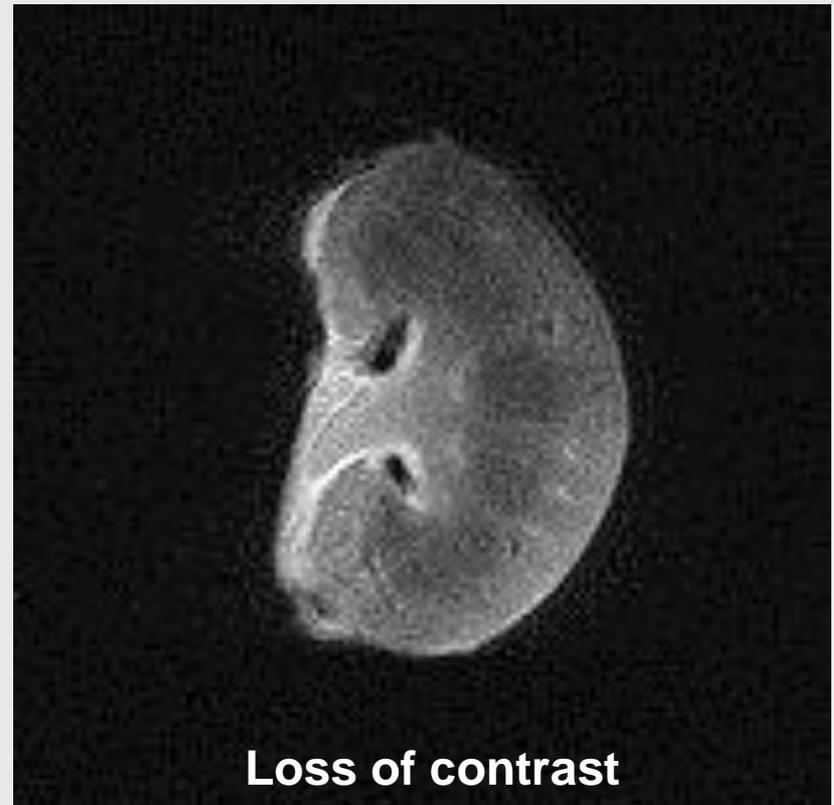
Control vs Affected Kidney

Ex Vivo MRI

Control



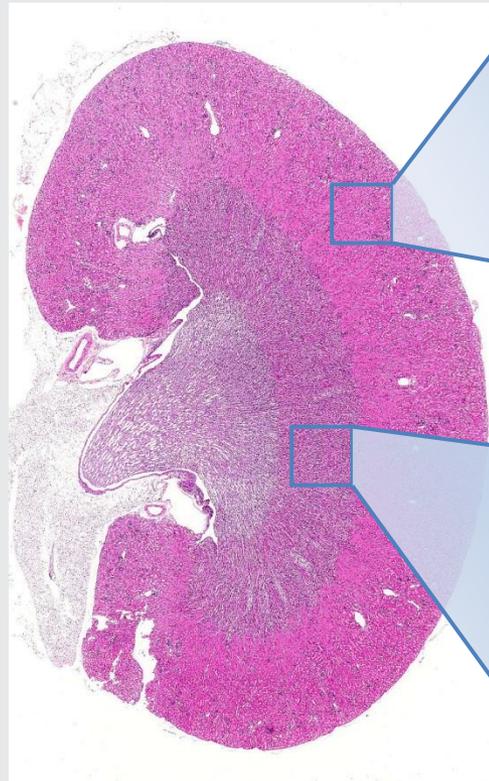
Affected



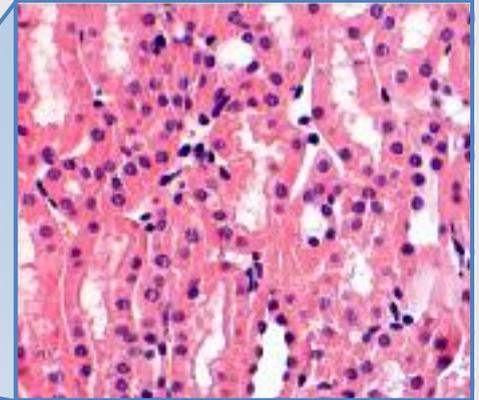
resolution 117 μm ; slice thickness 0.5 mm; acquisition time 56 min

MRI & Histology – Control Kidney

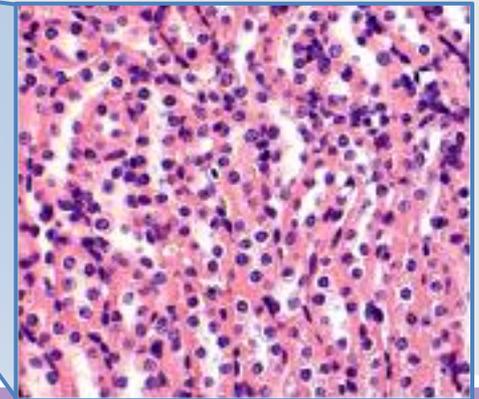
Ex Vivo



cortex X 200

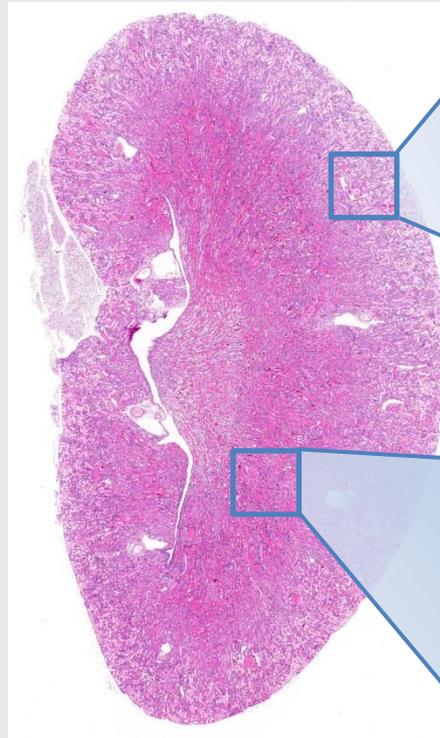


medulla X 200

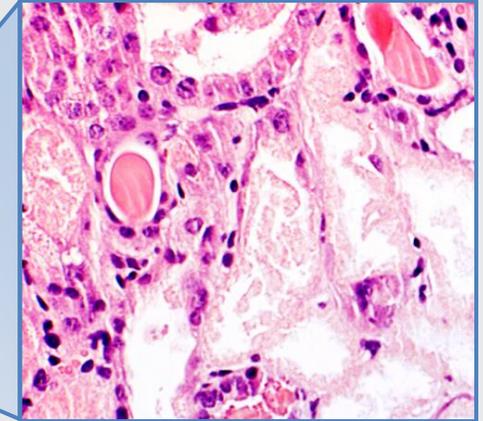


MRI & Histology – Affected Kidney

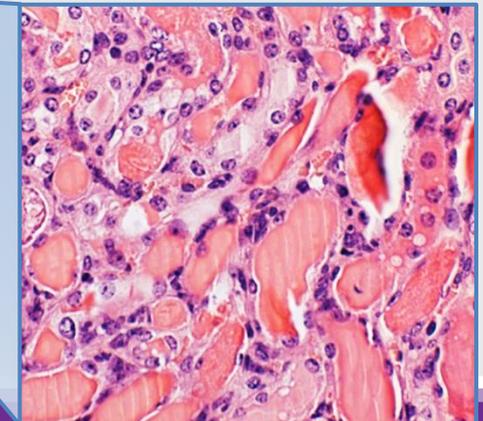
Ex Vivo



cortex X 200



medulla X 200



Summary of Findings & Comment

- *In-vivo* and *ex-vivo* MRI were effective in identifying alterations in the cortex and medulla
Histopathology: Maximal extent of cortical necrosis and medullary hyaline cast formation.
- *In-vivo* and *ex-vivo* MRI confirmed organ recovery.
Histopathology: The previously necrotic tubules were replaced by regeneration.

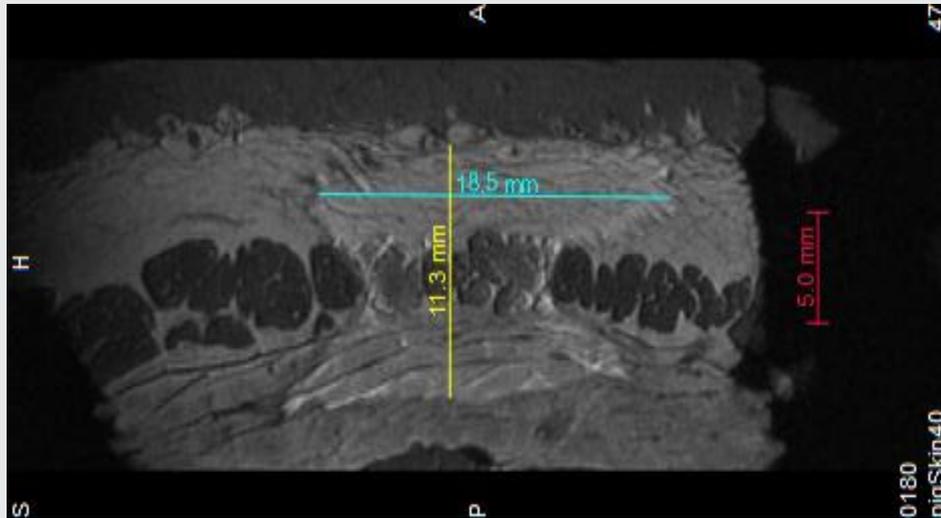
Local Safety of Subcutaneous Formulations

- **Model:** In this study, subcutaneous lesions were analyzed by MRI 2 weeks after a 24-hour continuous infusion of different formulations.
- **Objective of the experiment:** This was a feasibility study for application of the *Ex-Vivo MRI* in order to evaluate the subcutaneous toxic effects induced at the injection site of test compounds.

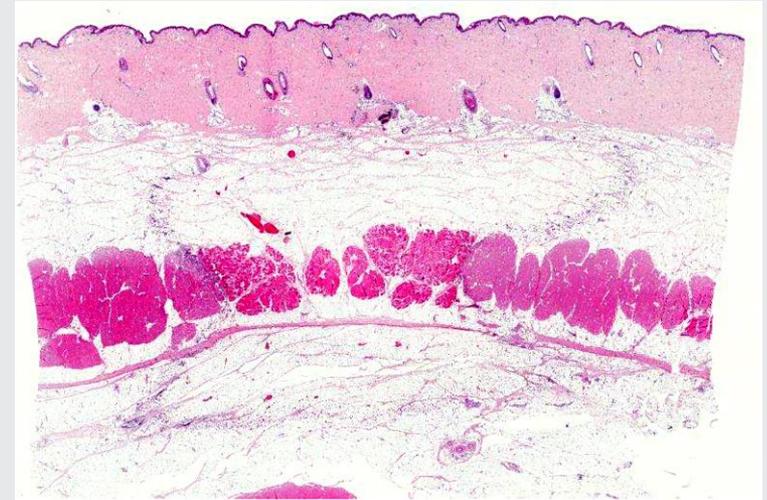
Subcutaneous Drug Injection Into Pig Skin

MRI vs. Histology

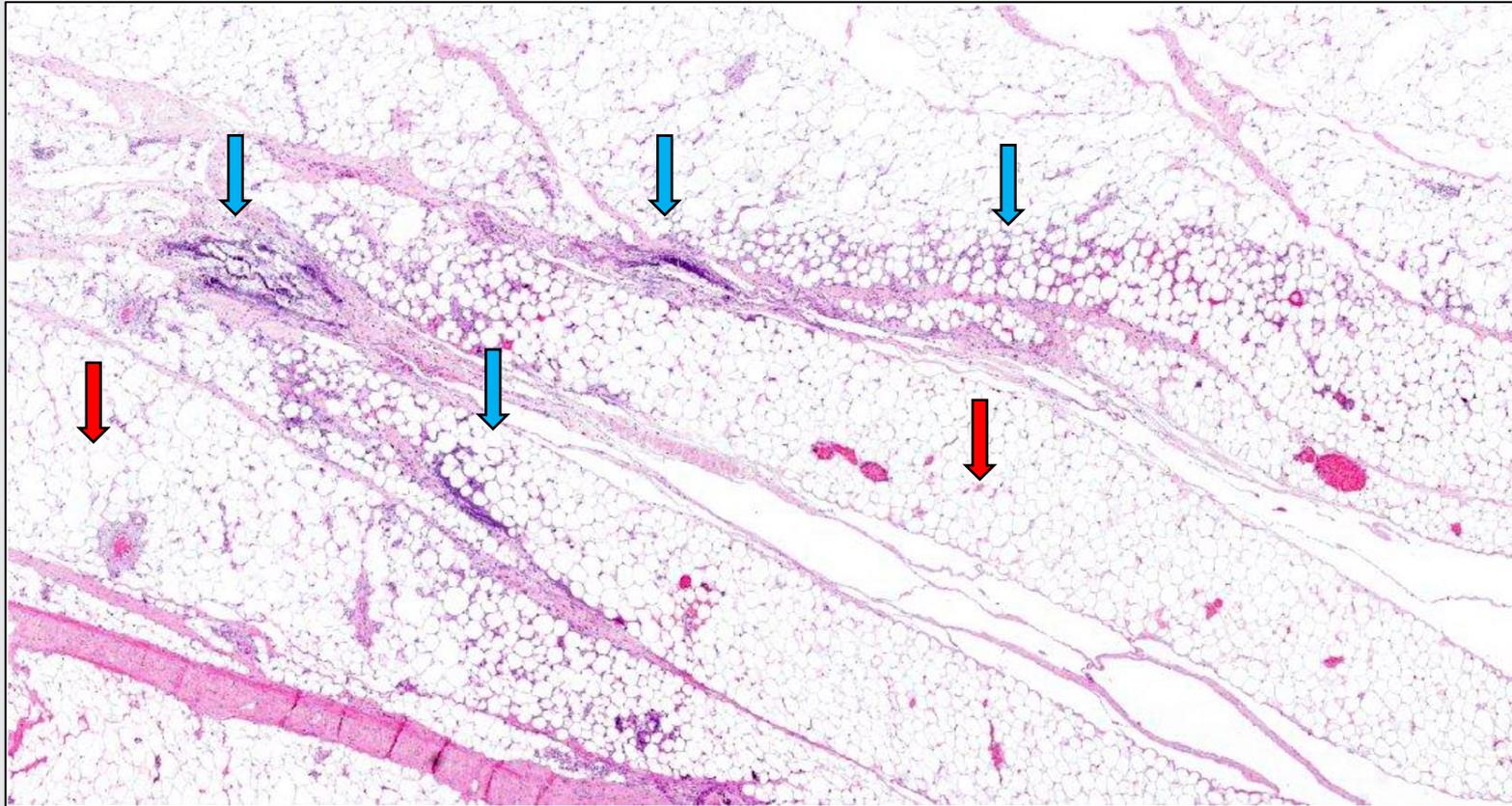
MRI (T1)



Histology

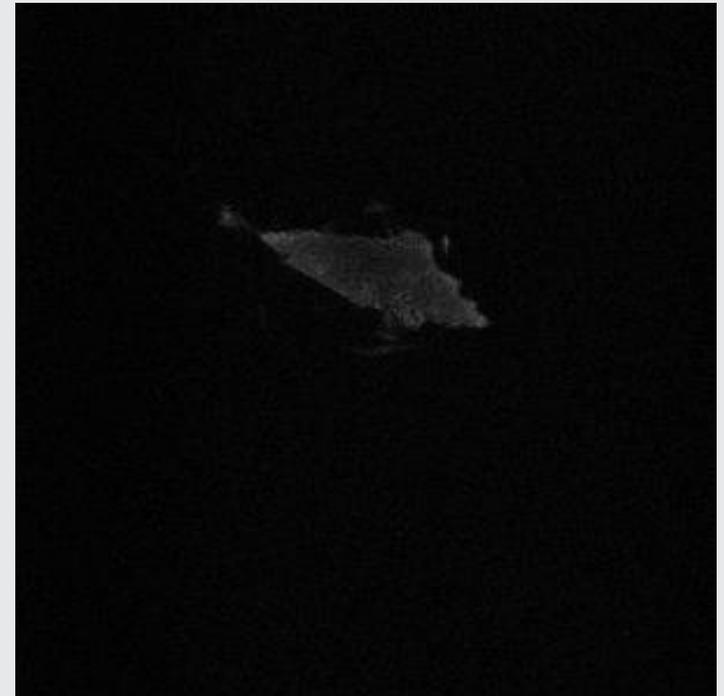
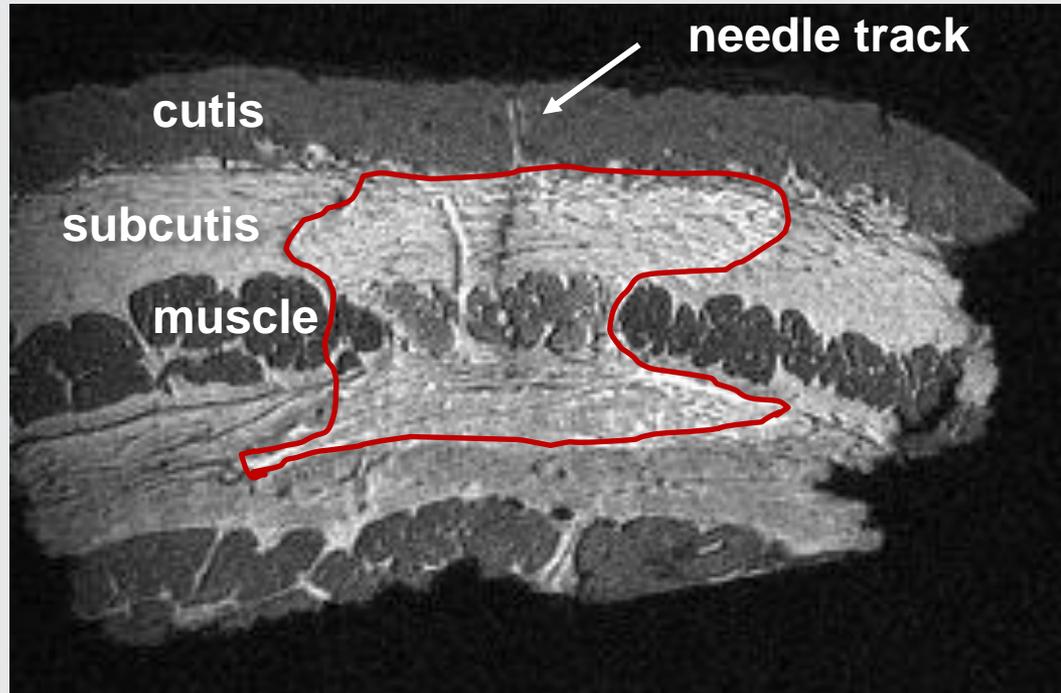


H&E Histopathology

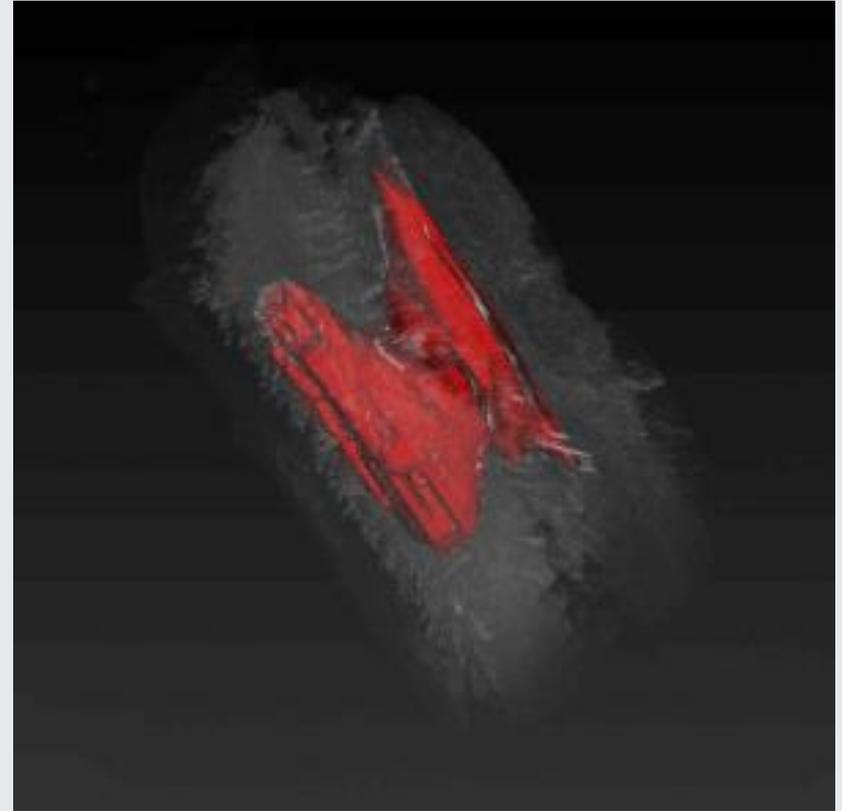
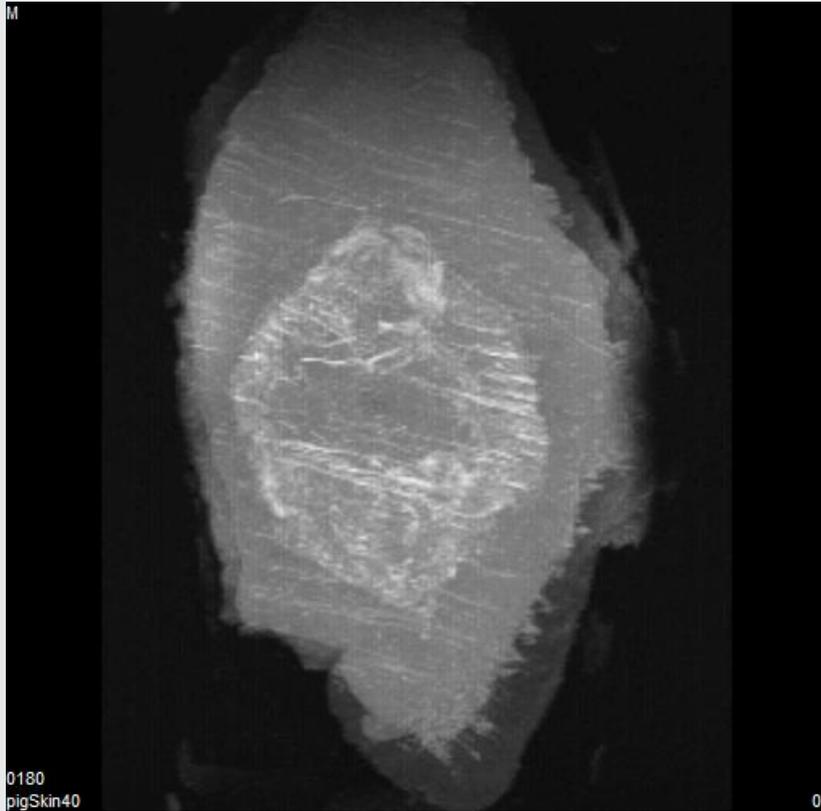


- ➡ Blue = Multifocal areas of fat necrosis & associated inflammation
- ➡ Red = Normal adipose tissue

Subcutaneous Drug Injection Into Pig Skin - *Ex Vivo* MRI



Segmentation and Quantification of Affected Volume - *Ex Vivo* MRI



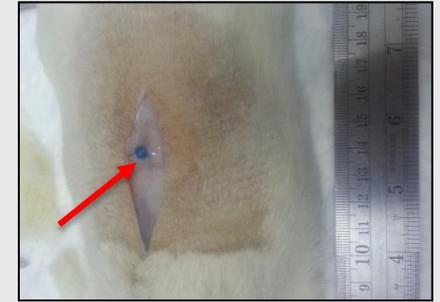
Affected Volume **2200 mm³**

Summary & Comment

- *Ex vivo MRI* was effective in identifying the location and quantifying the extent of subcutaneous necrosis and inflammation caused by different formulations.
- Applying this method on fixed tissues samples derived from different dose formulations provides a quantitative determination of relative irritancy of different injected formulations.

Biodegradable Implanted Device

- **Model:** A double layer of a 5x5 mm² device was implanted in the right paralumbar muscle of Sprague Dawley rats.



- A plastic bead was implanted subcutaneously just over the device to enable accurate localization and follow-up of the implantation site.
- **Objective:** Evaluation of *in vivo* MRI as a tool for assessment of degradation of a bio-degradable device.

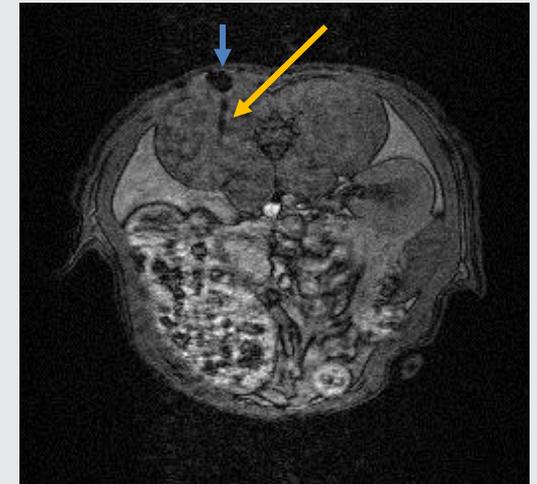
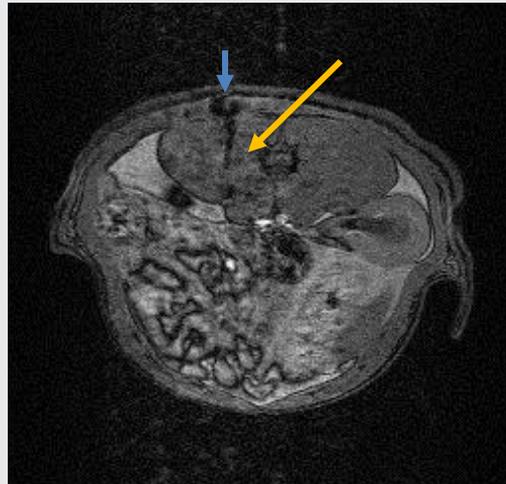
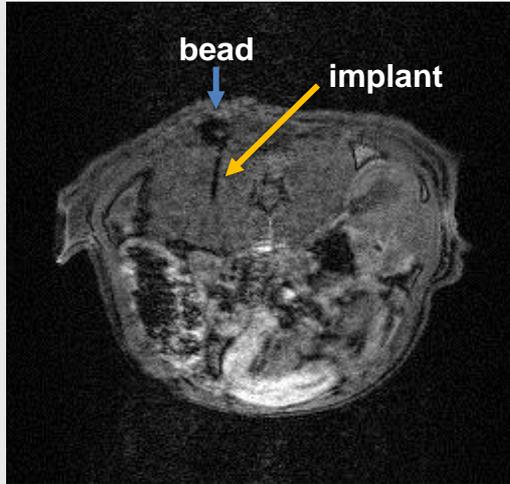
In Vivo MRI of Implanted Device

Day 5

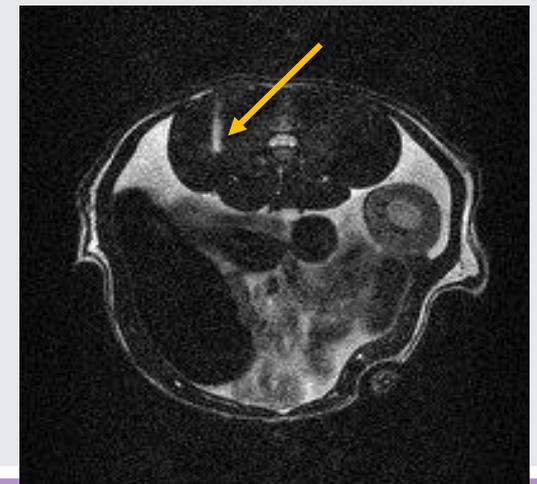
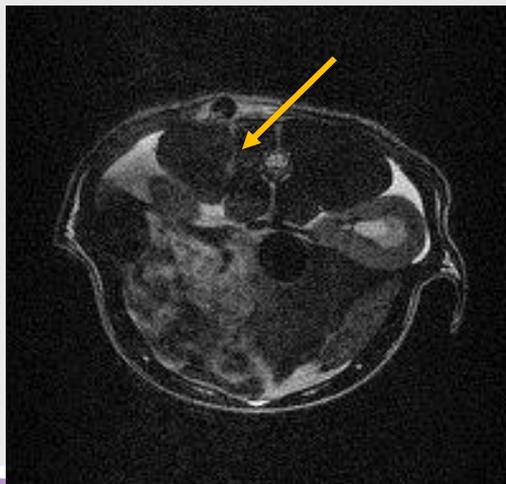
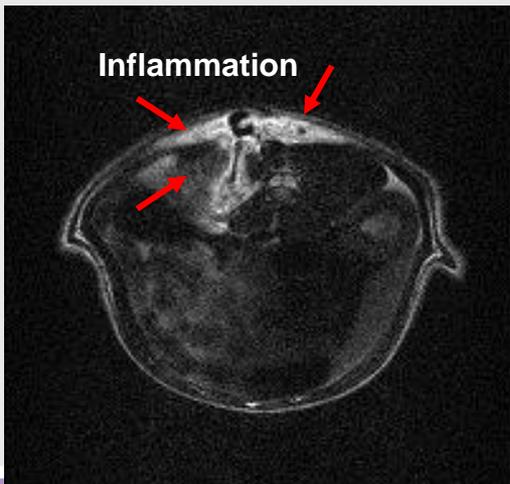
Day 30

Day 60

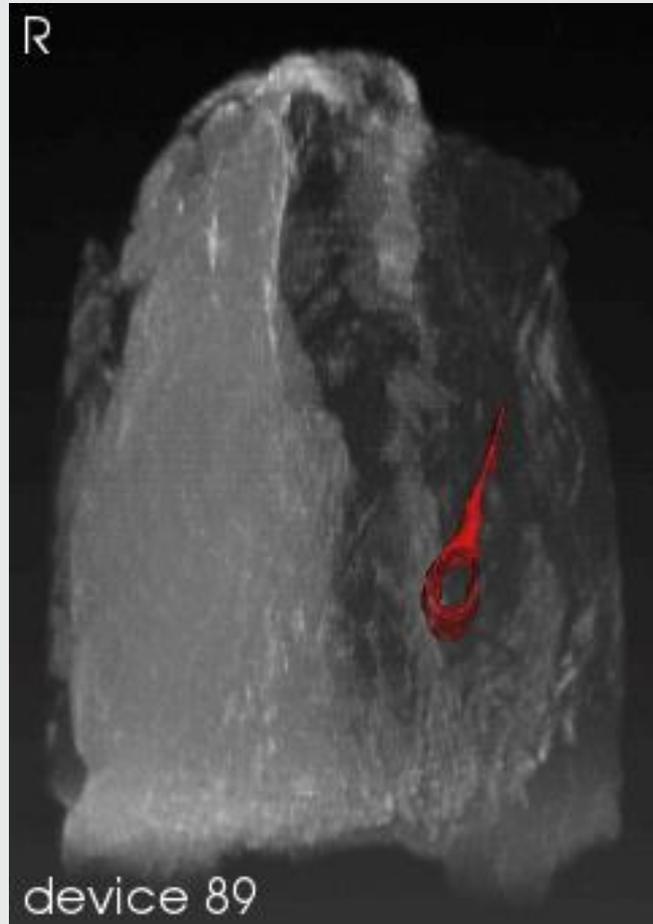
T1



T2

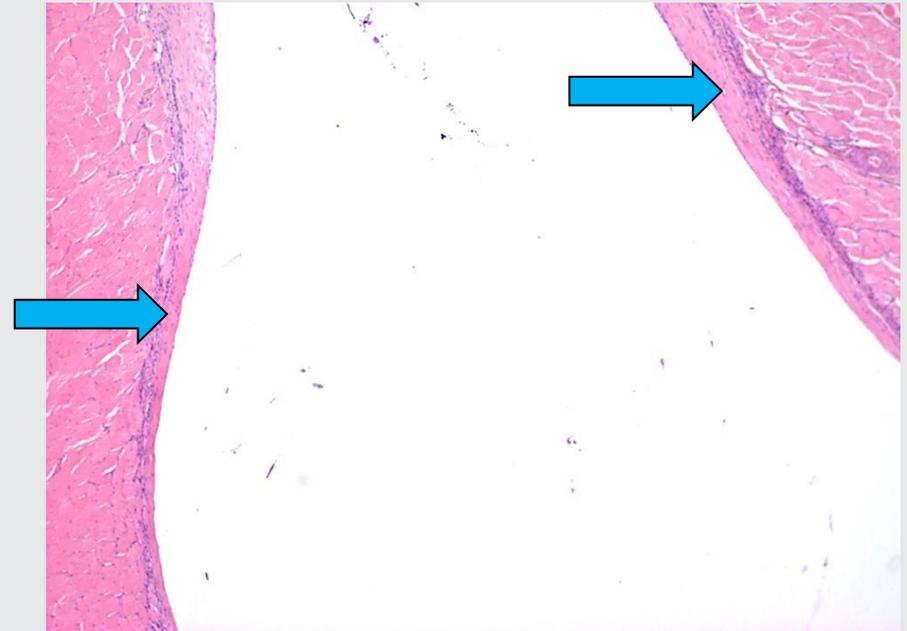


Ex Vivo MRI of Implanted Device Segmentation and Quantification



Volume of device: **32.2 mm³** at day 60

Histopathology of Implantation Site After 60 Days



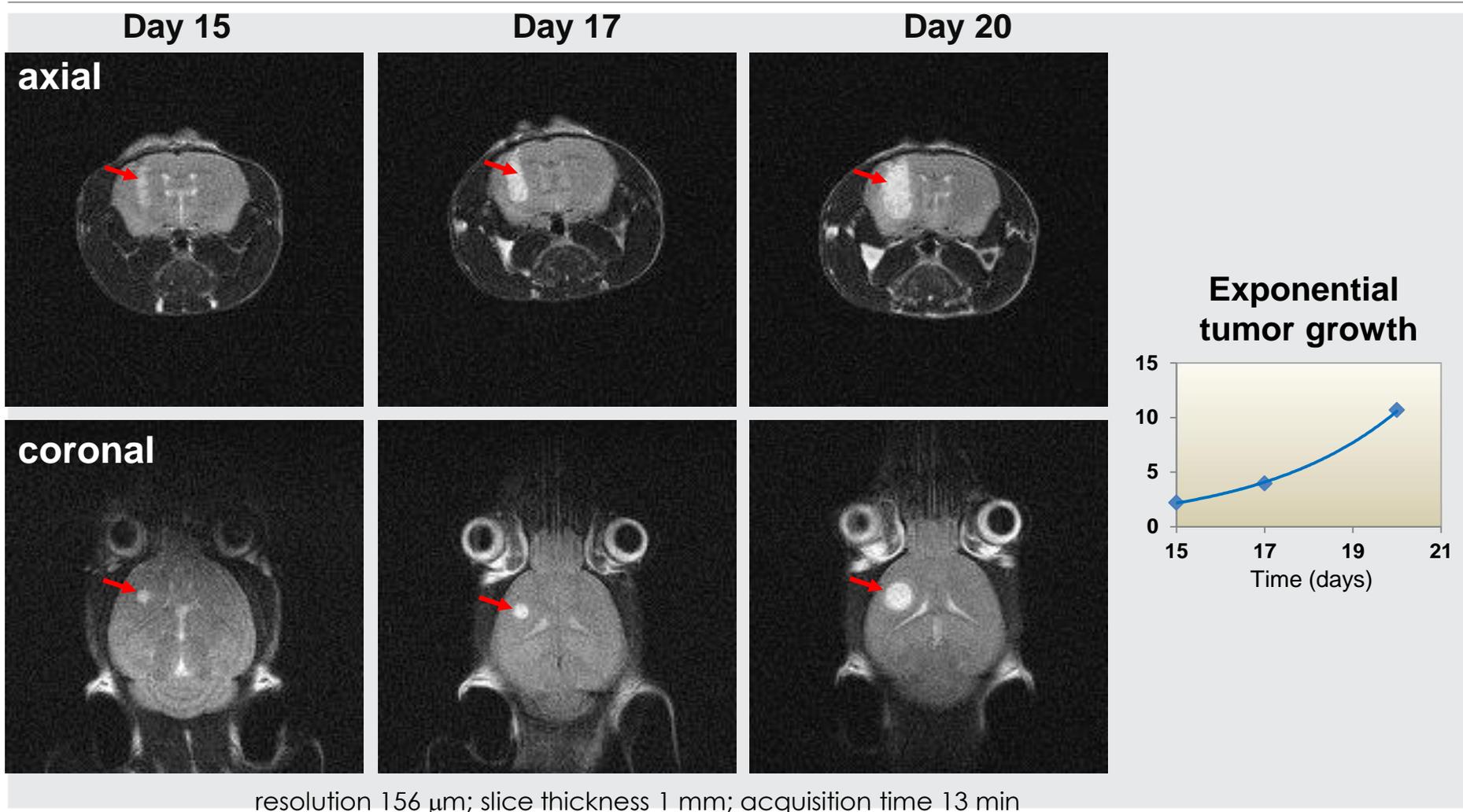
-  mature connective tissue capsule
-  cavity of device

Longitudinal Growth of a Brain Tumor

- **Model:** G1-261 glioma cells stereotactically injected into the right brain hemisphere of CB6F1 mice
- **Objective:** Longitudinal evaluation of tumor growth

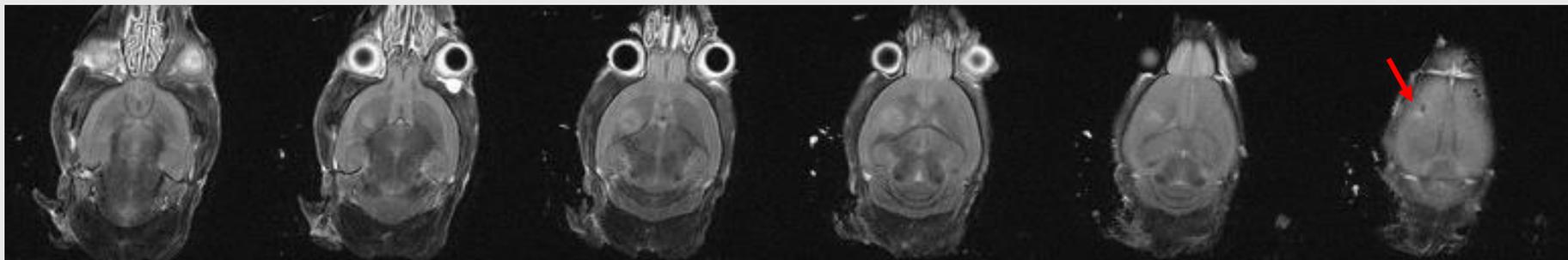
Longitudinal Evaluation of Tumor Growth

In Vivo MRI

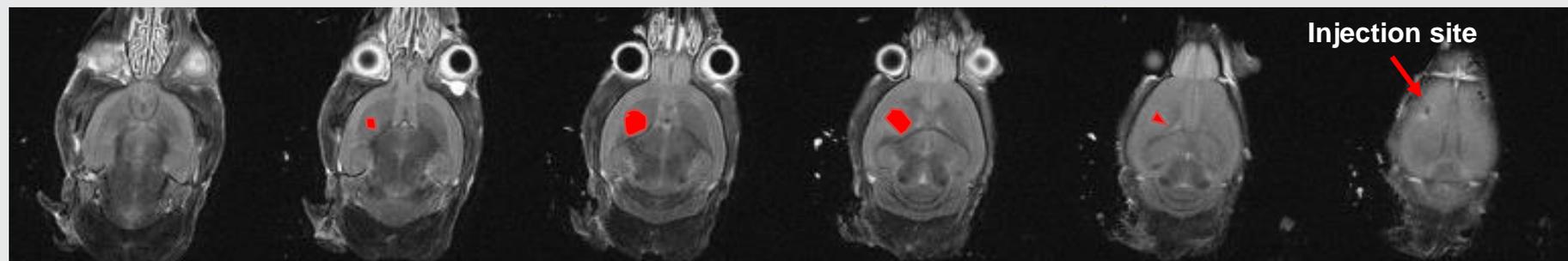


Tumor Segmentation – *Ex Vivo* MRI

Day 17 – coronal



Injection site

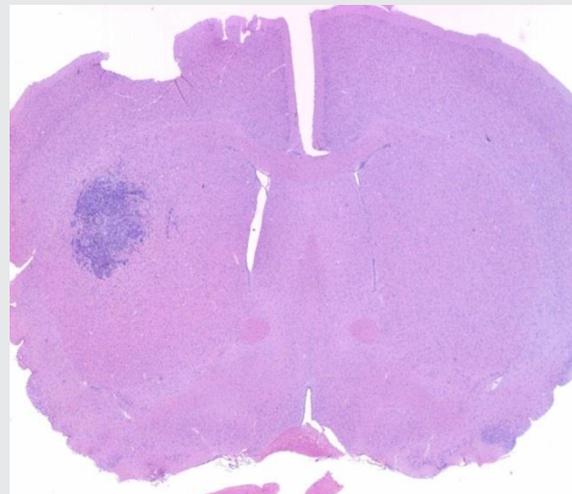
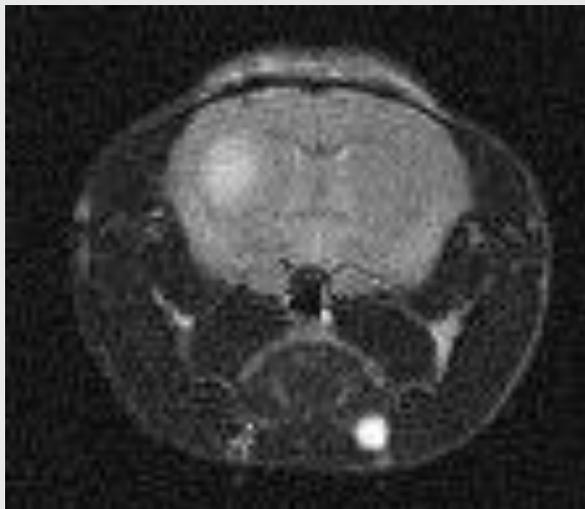


Injection site

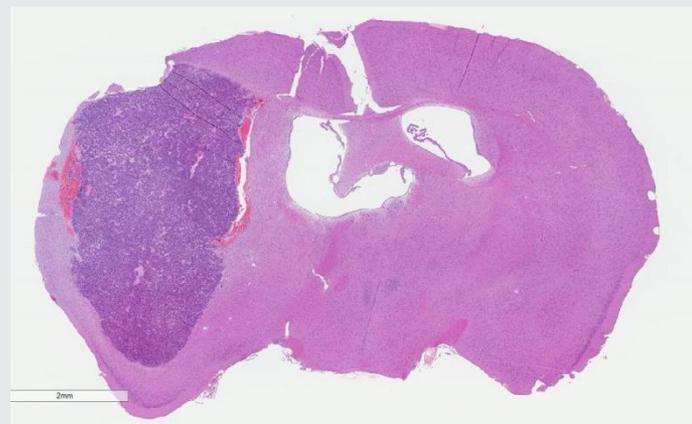
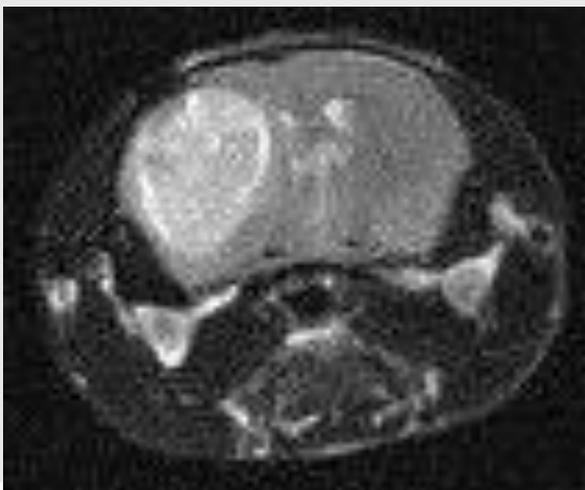
Tumor volume 6.6 mm³

Ex Vivo MRI vs Histology

Day 15



Day 20



Summary & Comment

- *In-vivo* and *ex-vivo* MRI evaluation provided a way to follow the time-related growth of an induced tumor in the brain and to determine the volume of the tumor.
- This model demonstrates the utility of using MRI for longitudinal studies and would be useful for testing the efficacy of anti-cancer drugs.

Rat Lung Fibrosis

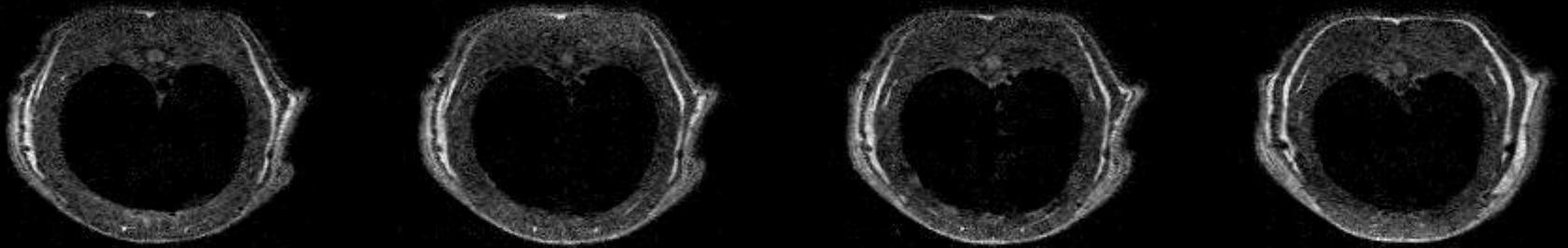
- **Model:** Single intratracheal instillation of bleomycin into 6 week-old Sprague Dawley rats
- **Objective:** Monitor lung fibrosis in rats using *in vivo* and *ex vivo* MRI as a tool for following temporal progression of the pathological process

Rat Lung Control vs. Fibrosis

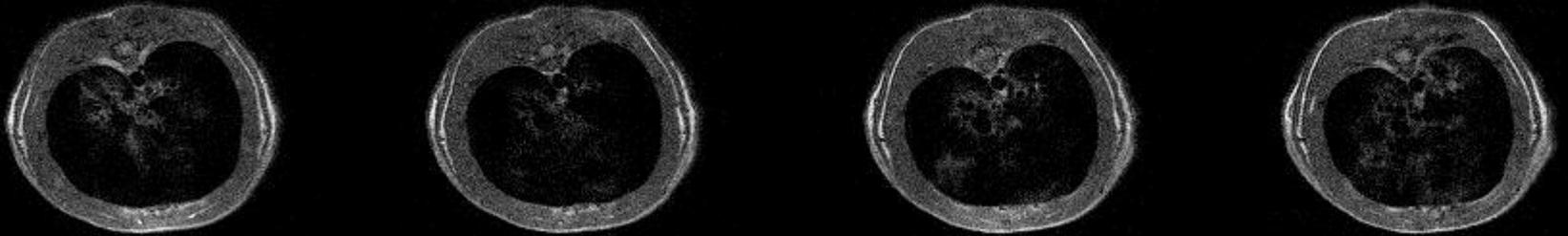
In Vivo MRI

Day 11 Post Instillation

control



fibrotic

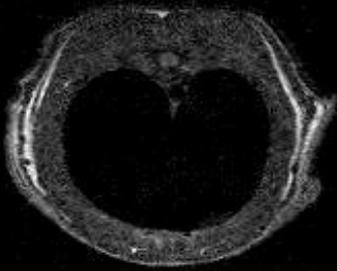


resolution 274 μm ; slice thickness 1.2 mm; acquisition time 4.5 min

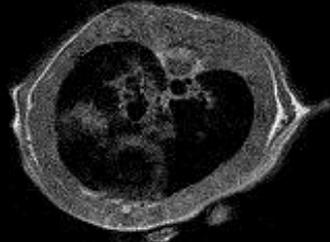
Time Course of Disease

In Vivo MRI

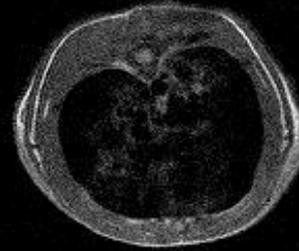
Day 0



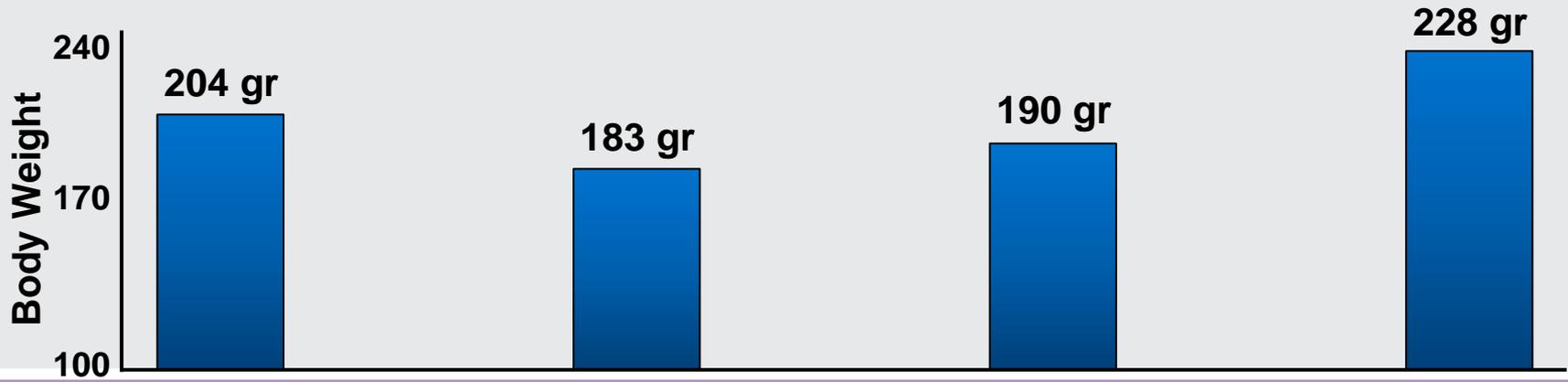
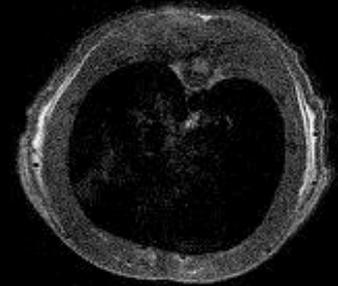
Day 8



Day 11

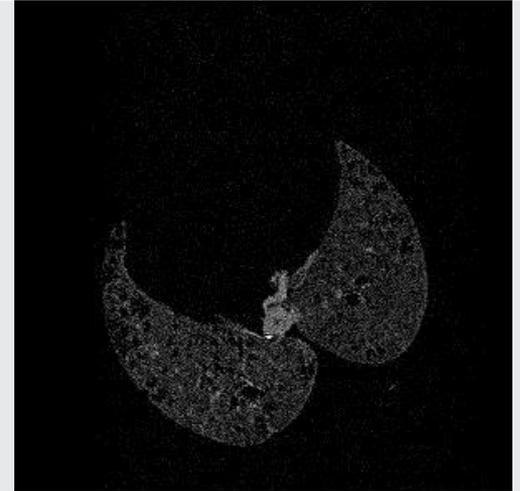
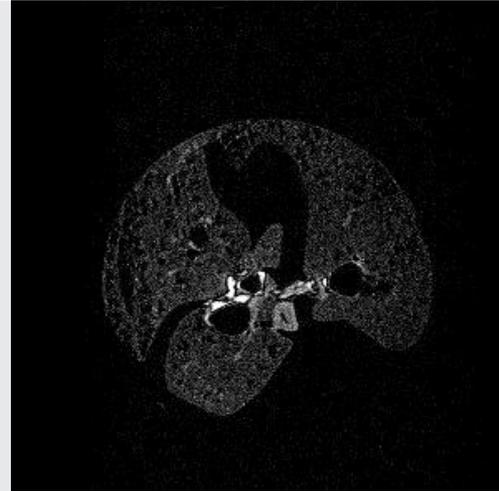
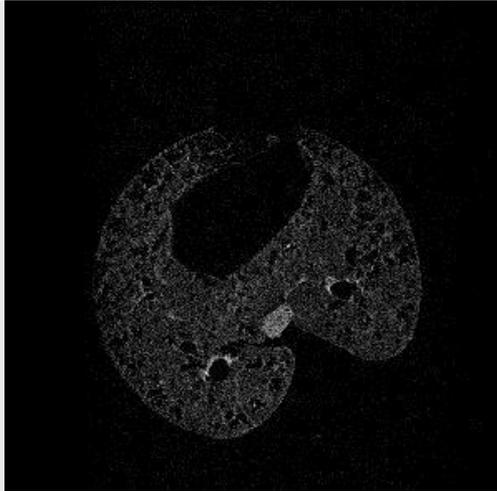


Day 14

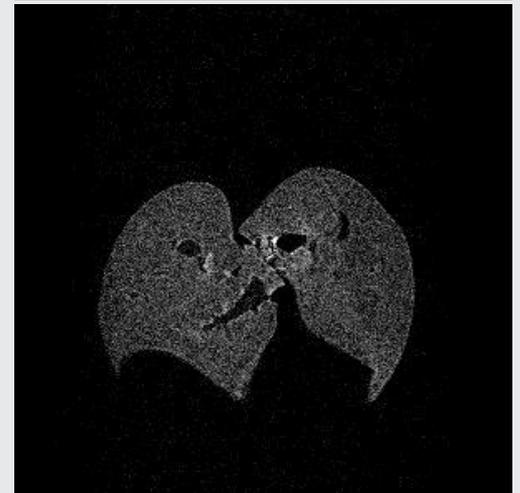
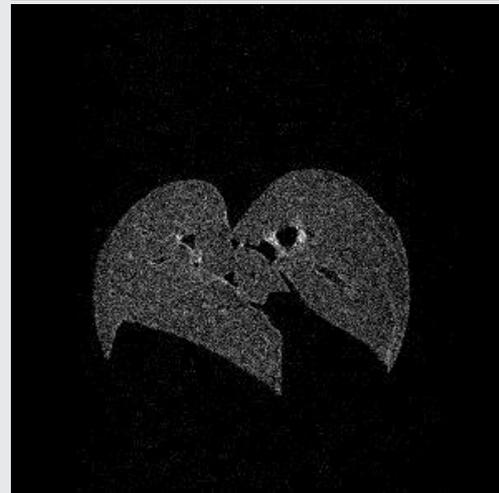
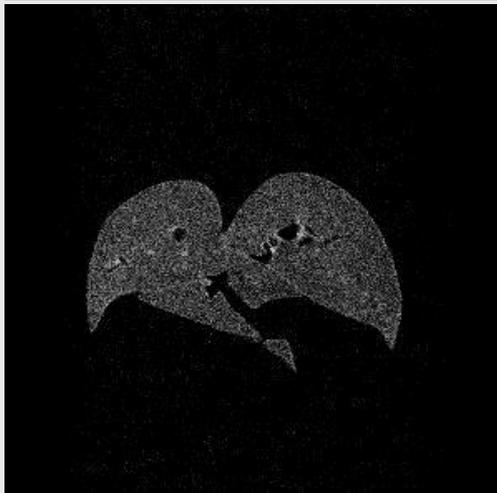


Control rat lungs inflated with air vs instilled in formalin (the ones instilled with formalin are a bit brighter)

control
air

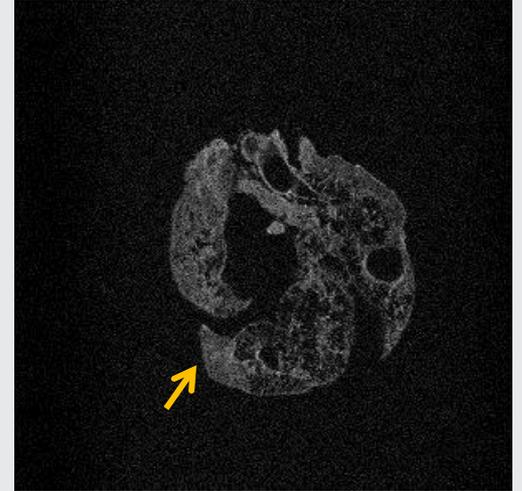
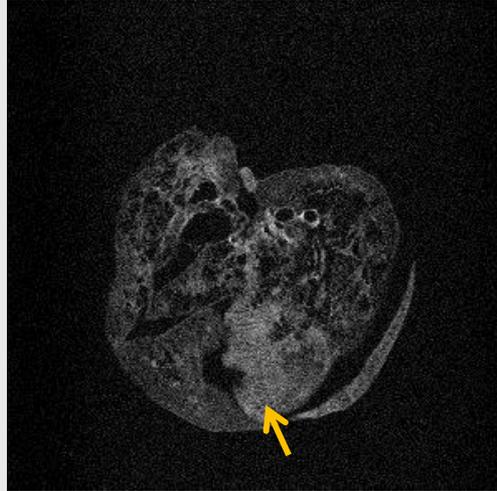
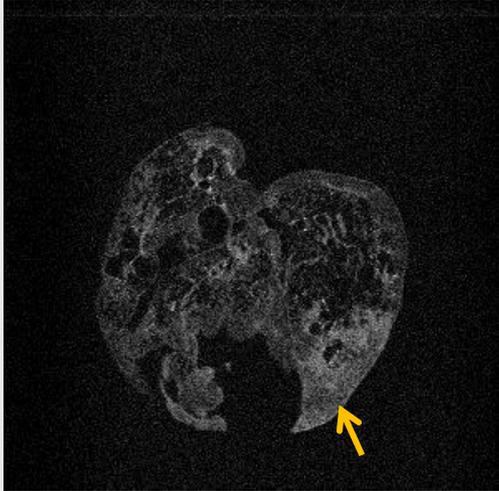


control
formalin

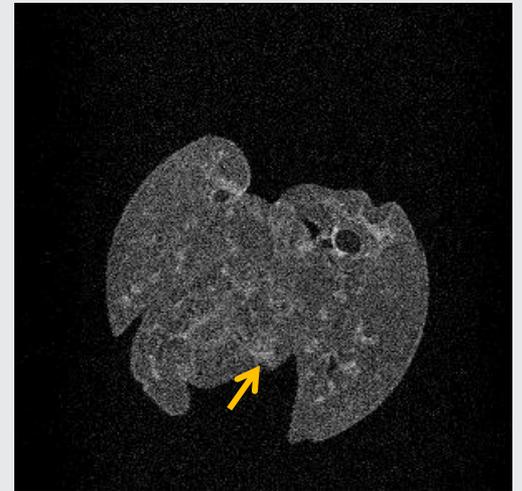
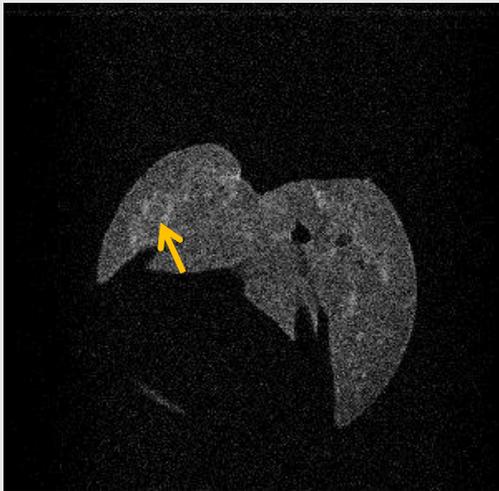


BLM rat lungs inflated with air vs instilled in formalin (fibrosis in “air” lungs is more visible on the darker background)

BLM
air



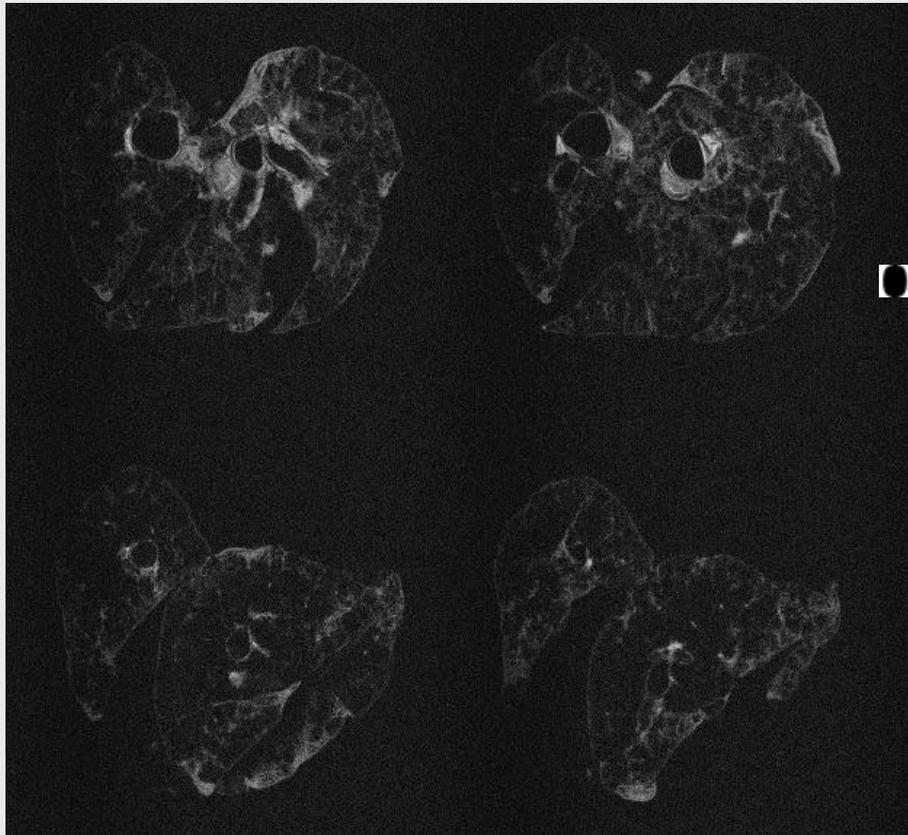
BLM
formalin



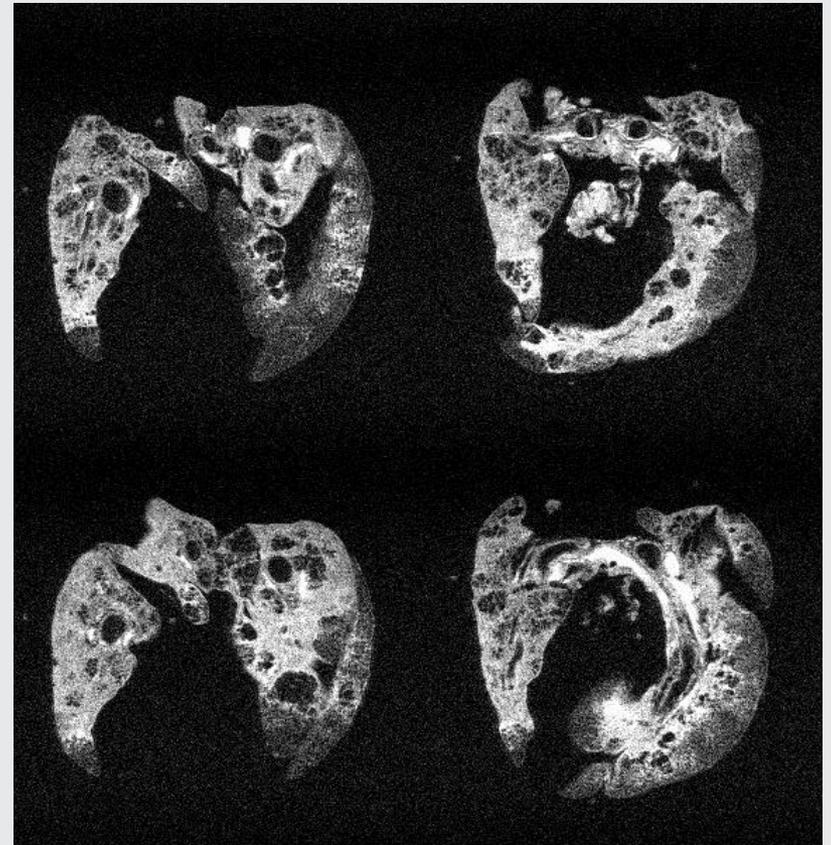
Control vs. Fibrosis – *Ex Vivo* MRI

Day 11 Post Instillation

Control



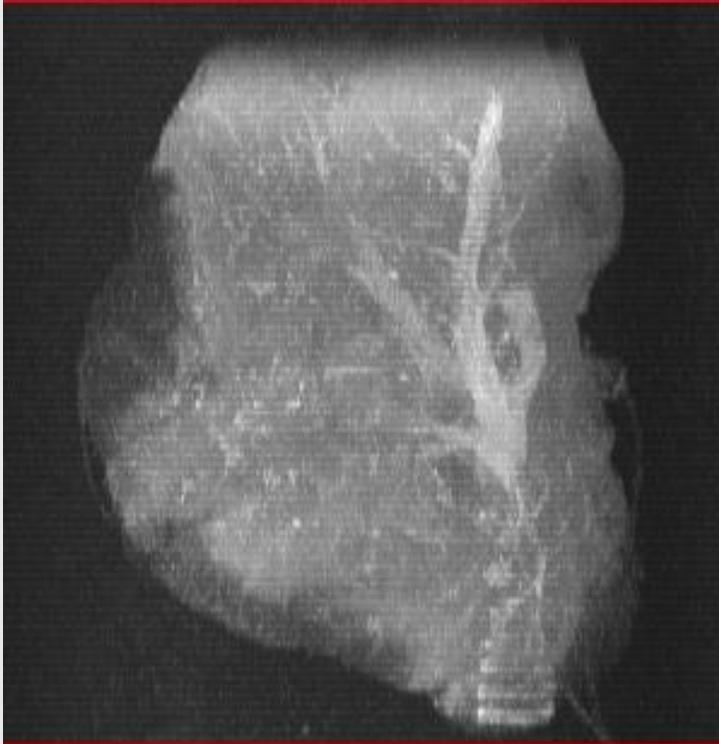
Fibrosis



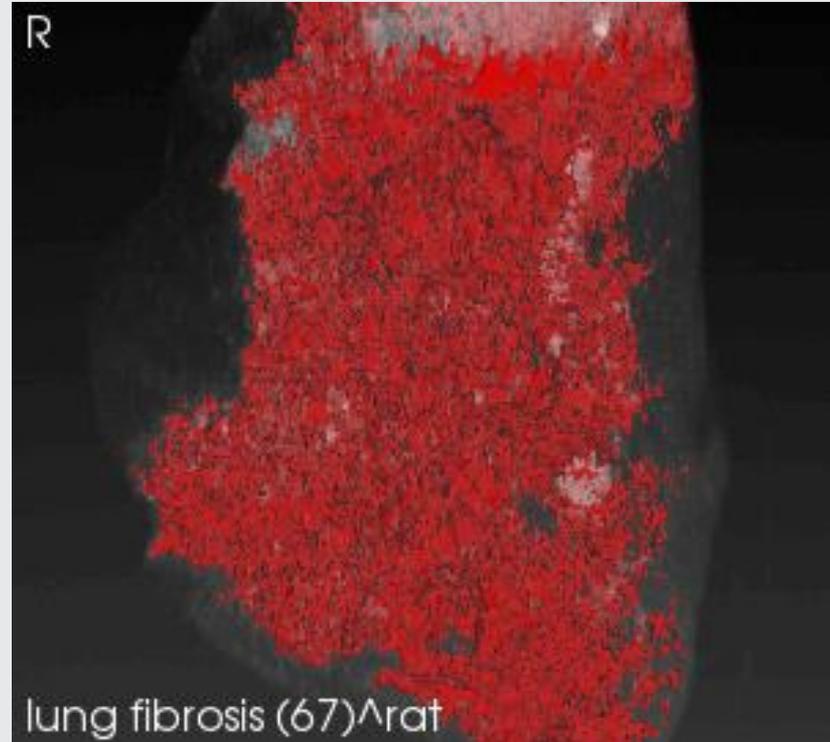
Fibrotic Rat Lung – Volume Quantification Based on *Ex Vivo* MRI

Day 11 Post Instillation

3D rendering



3D rendering + segmentation



Connective Tissue: **1267 mm³**

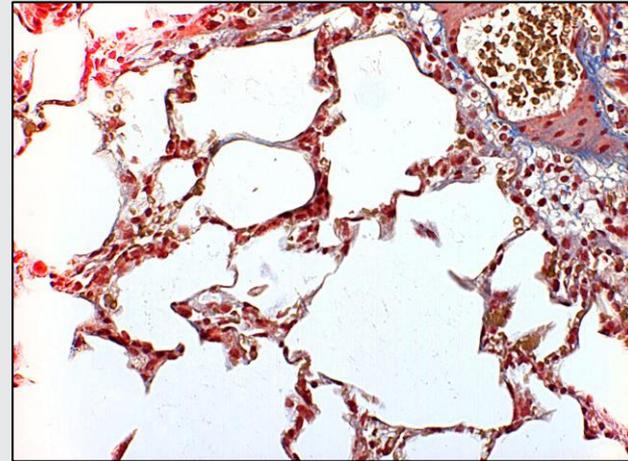
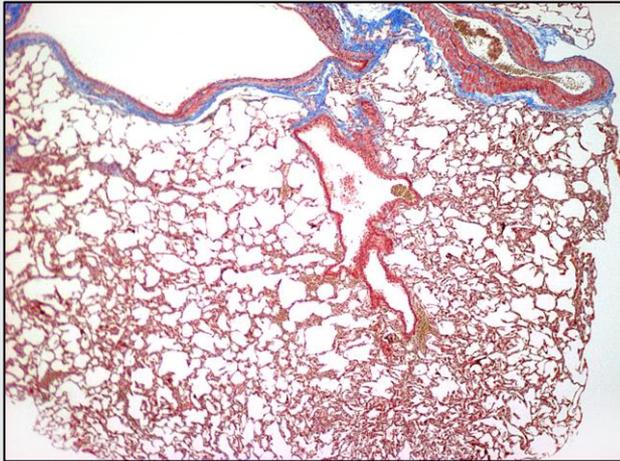
Normal Tissue: 1396 mm³

Histology – Masson's Trichrome

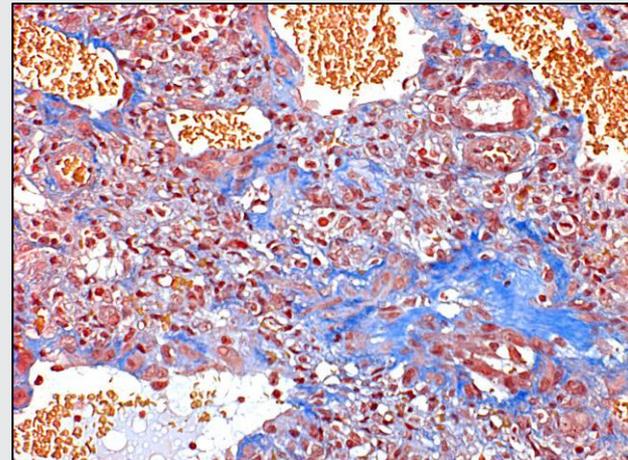
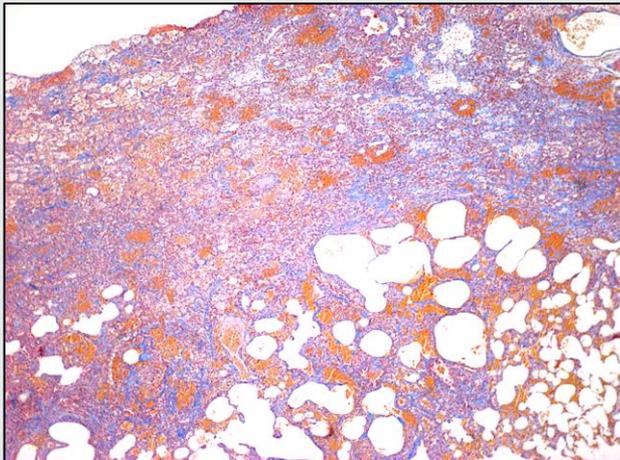
Low magnification

high magnification

control



fibrosis

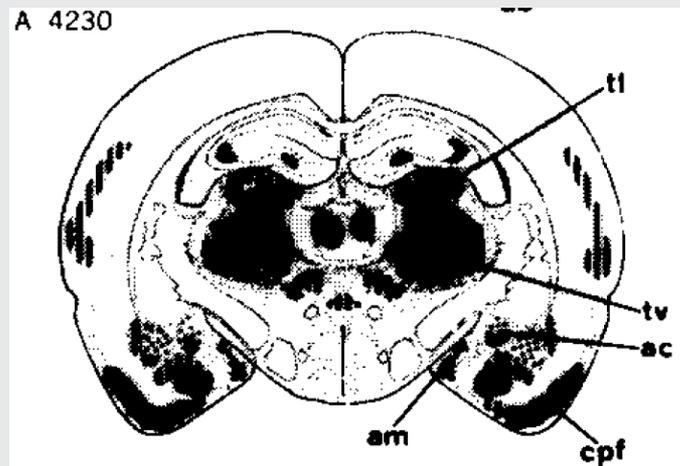


Summary & Comment

- *In vivo* MRI provides a longitudinal evaluation of pulmonary disease progression and regression
- *Ex vivo* MRI in combination with histology provides a quantitative assessment of the components of the interstitial thickening
- Based on the ability to quantify the extent of disease, different therapeutic modalities can be compared for their effectiveness

Pilocarpine- Induced Status Epilepticus

- **Model:** SD male rats treated with LiCl followed by Pilocarpine, a muscarinic cholinergic agonist and accepted model to induce status epilepticus and morphologic damage in rat brain.
- **Expected outcome:** Neuronal cell degeneration /necrosis

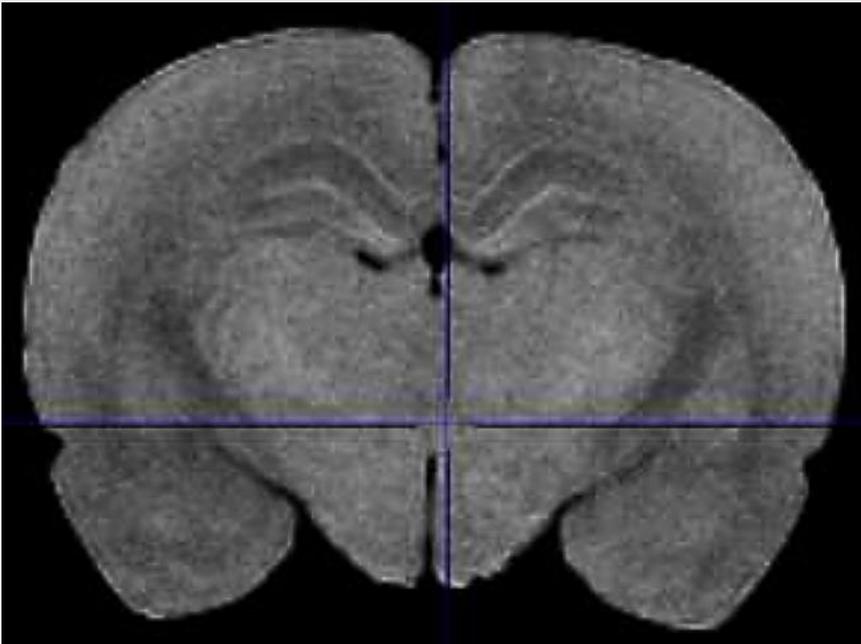


Dark areas : Severe
Hatched areas : Moderate
Dotted areas : Slight

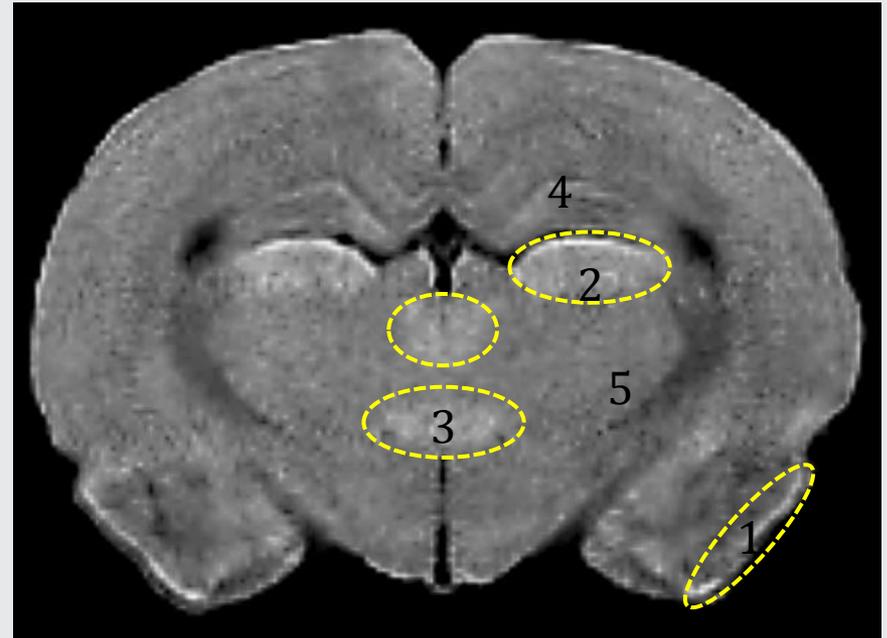
Control vs Pilocarpine

Ex vivo MRI (T1)

control



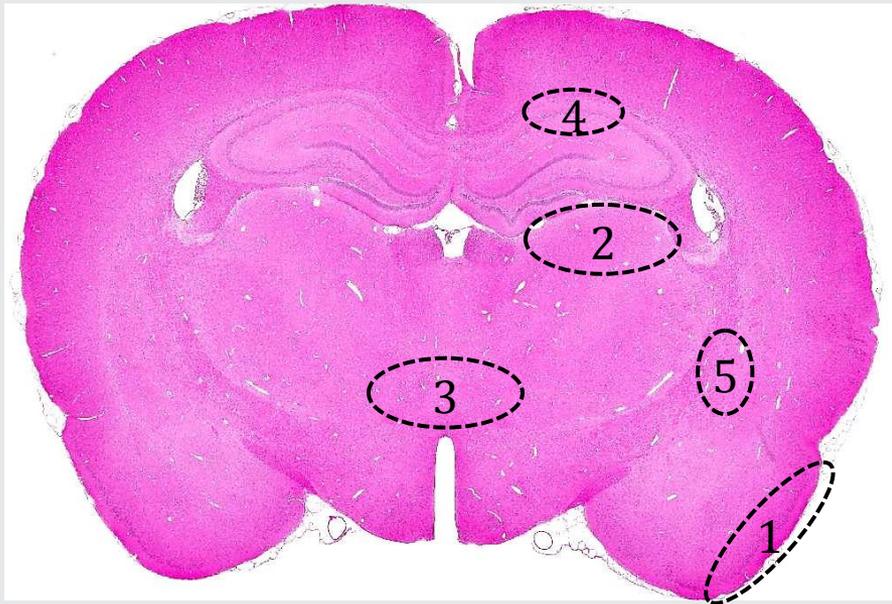
Pilocarpine



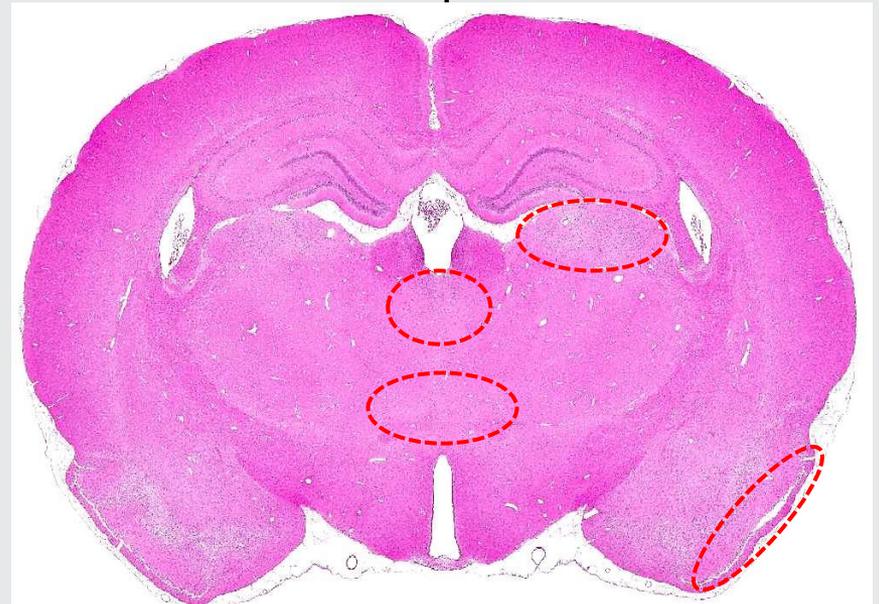
- 1: Piriform cortex
- 2: Lateral thalamic nucleus
- 3: Posterior hypothalamic nucleus
- 4: Hippocampus
- 5: Caudate putamen

Control vs Pilocarpine – H&E

control



Pilocarpine



- 1: Piriform cortex
- 2: Lateral thalamic nucleus
- 3: Posterior hypothalamic nucleus
- 4: Hippocampus
- 5: Caudate putamen

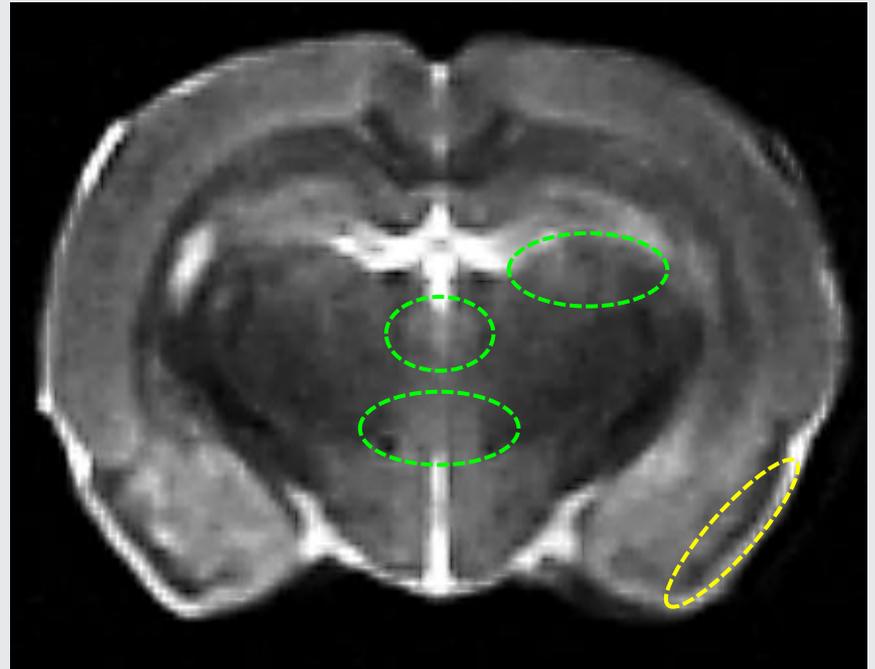
Control vs Pilocarpine

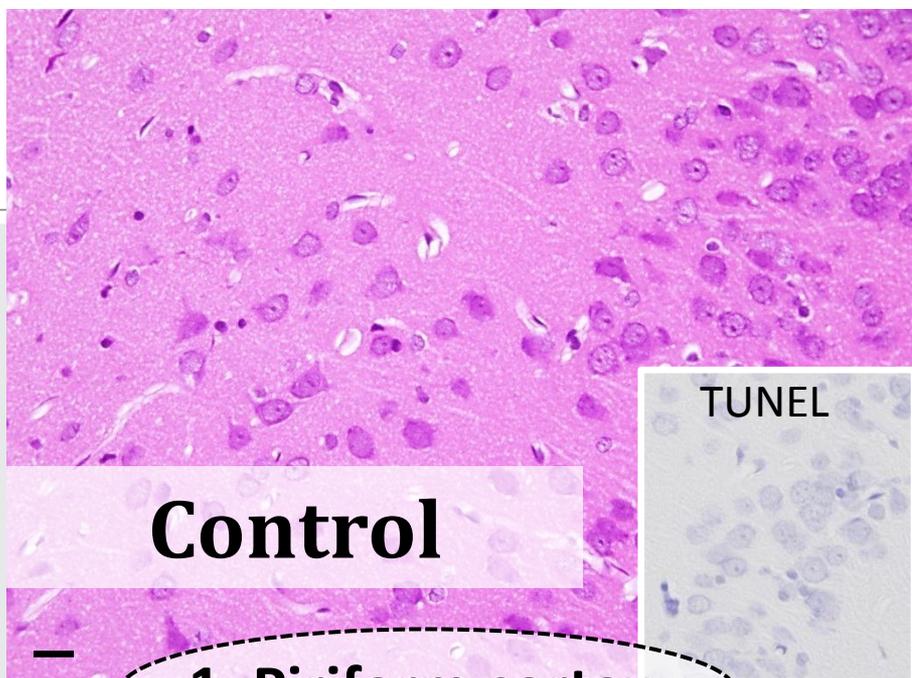
Ex vivo MRI (T2)

control

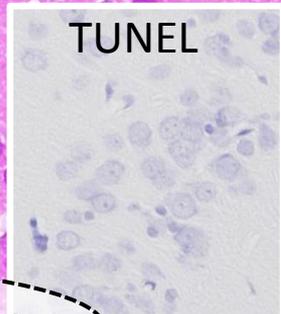


Pilocarpine

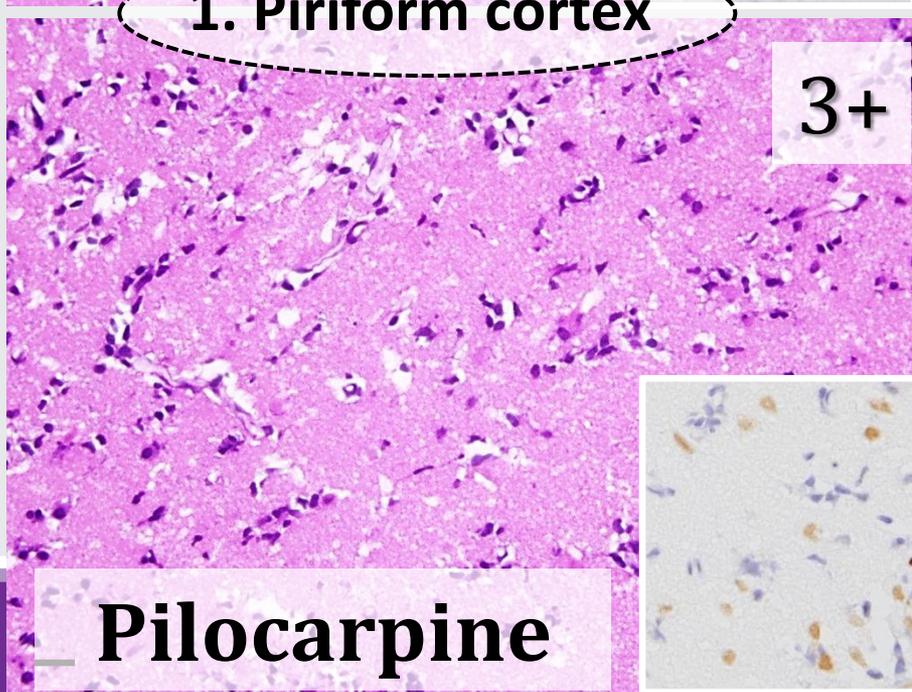




Control

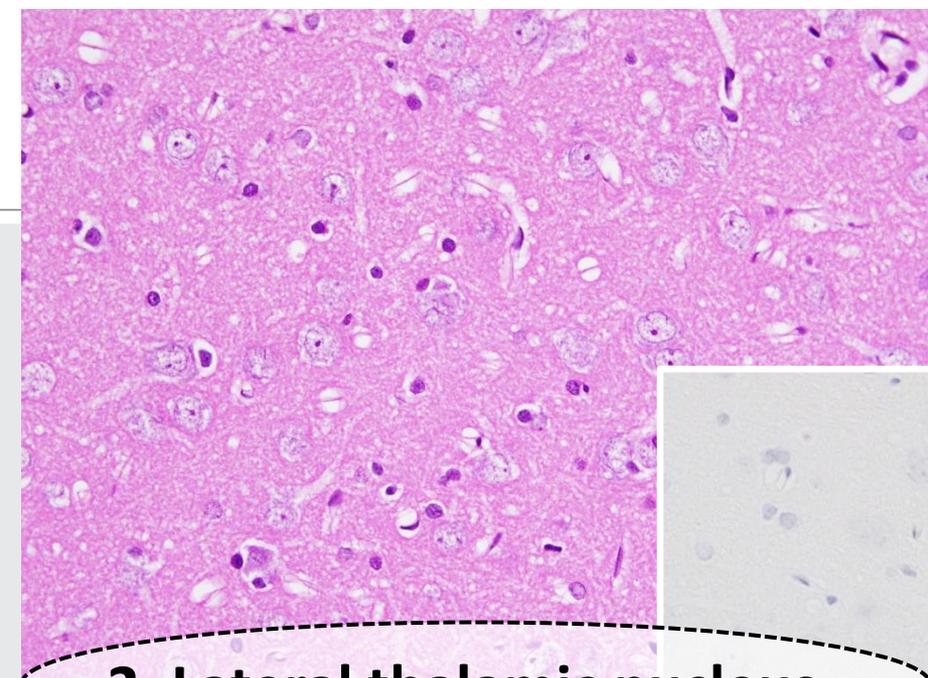
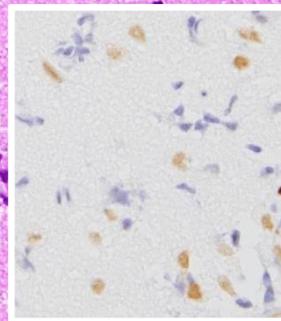


1. Piriform cortex

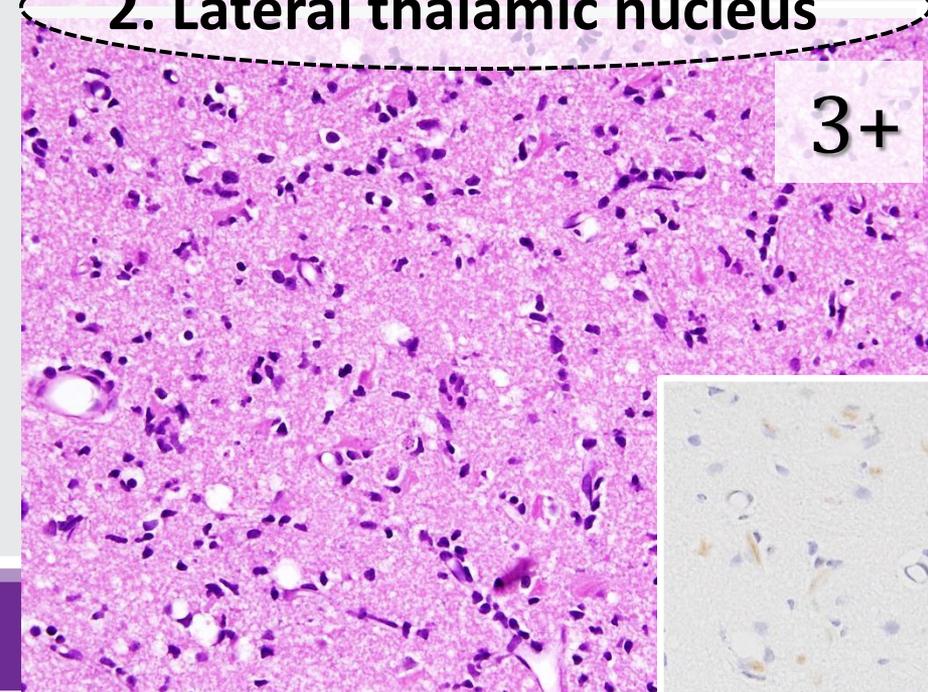


3+

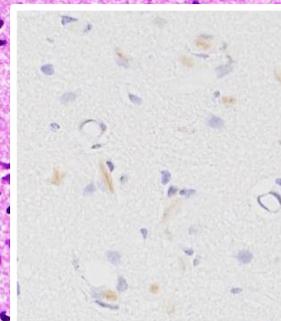
Pilocarpine



2. Lateral thalamic nucleus



3+



Control

Control

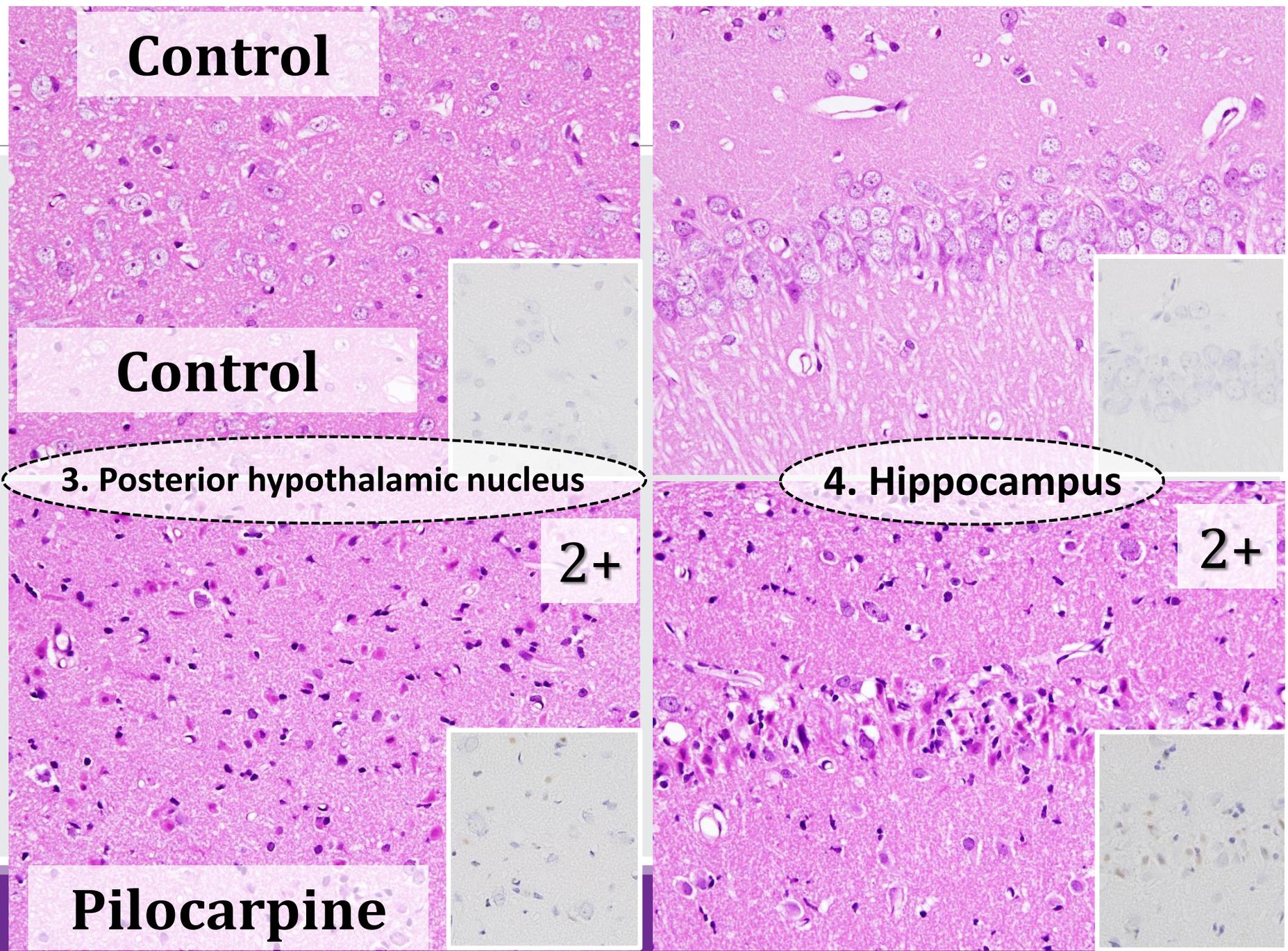
3. Posterior hypothalamic nucleus

2+

Pilocarpine

4. Hippocampus

2+

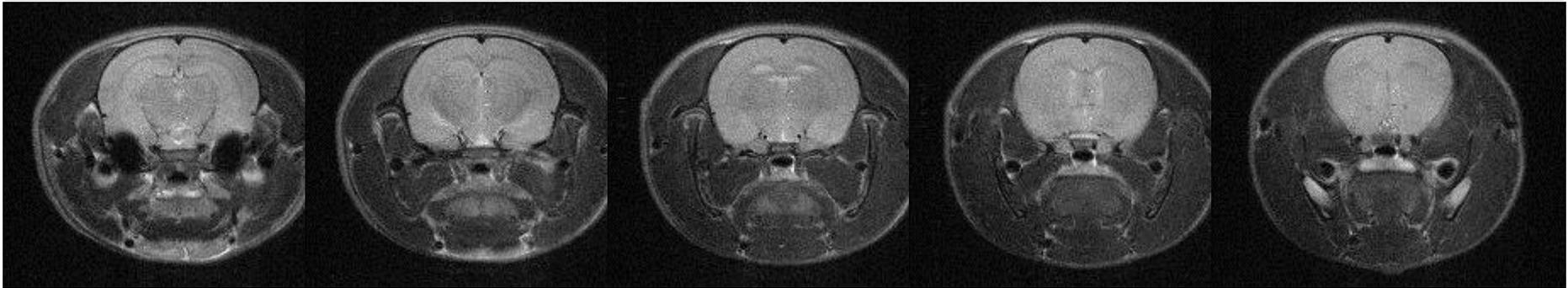


Summary

- MRI imaging demonstrated areas of high T1 and low T2 signals compared to controls in the piriform cortex, lateral thalamic nucleus, posterior paraventricular thalamic nucleus, and posterior hypothalamic nucleus of the cerebrum.
- Histopathology showed , neuronal cell degeneration and necrosis accompanied by gliosis in these areas.
- MRI analysis of fixed organs before routine slide preparation could provide useful information for histopathologic evaluation in preclinical toxicity studies

Neurotoxicity induced with Kainic acid

Base line

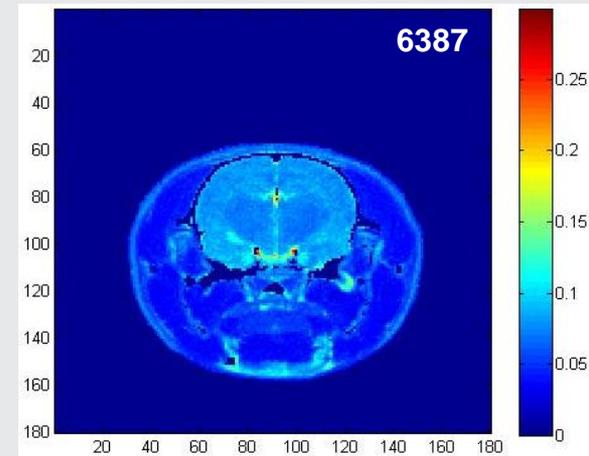
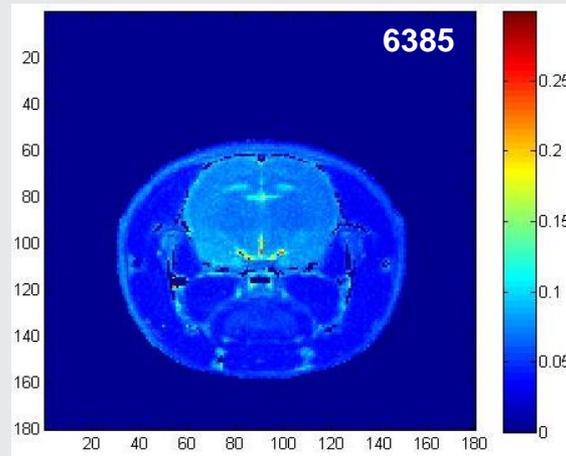


3rd day

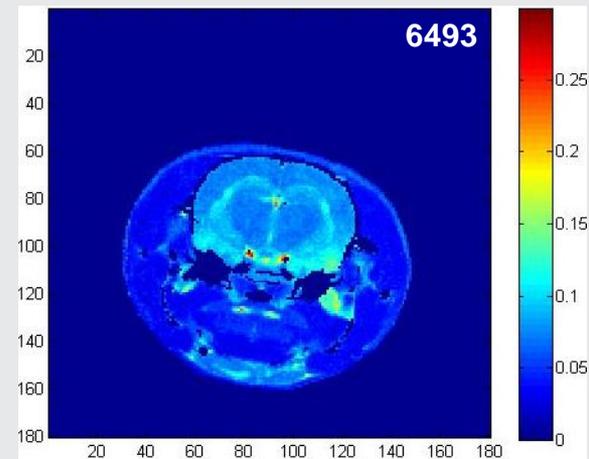
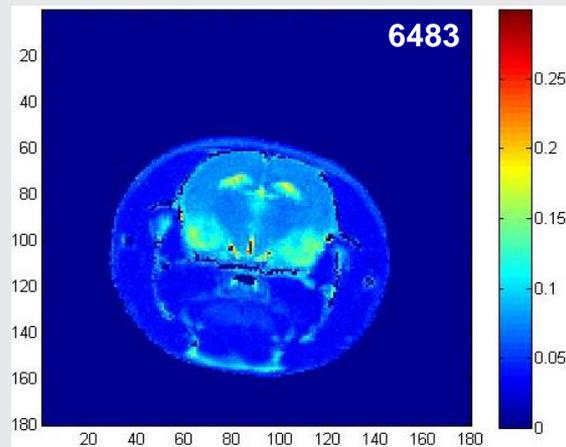


T2 maps following treatment with Kainic acid

Baseline:



3rd day



T2 maps following Kainic acid : 1T comparable with 7T

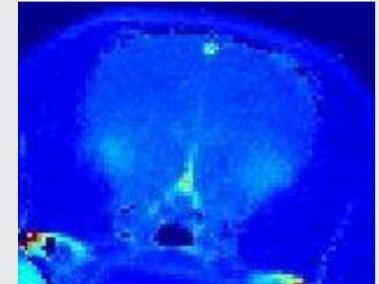
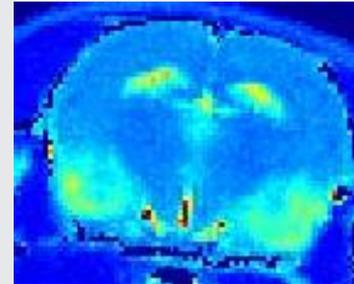
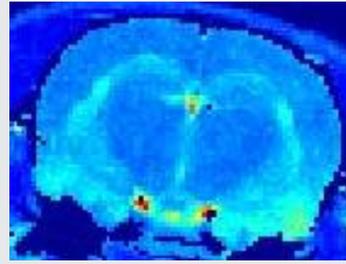
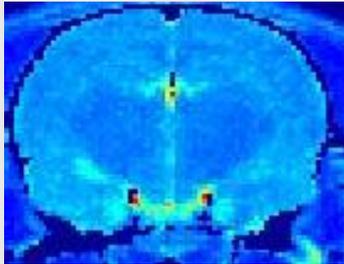
control

KA

KA

KA

1 Tesla



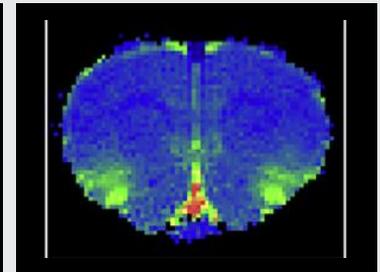
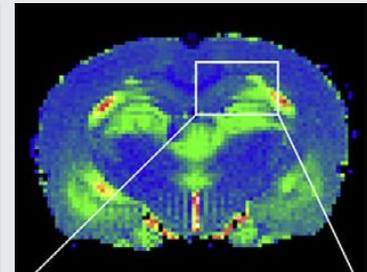
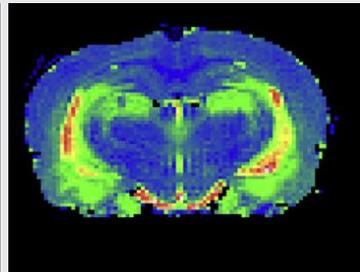
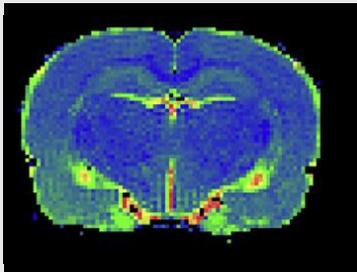
control

edema

neurodegeneration
In hippocampus

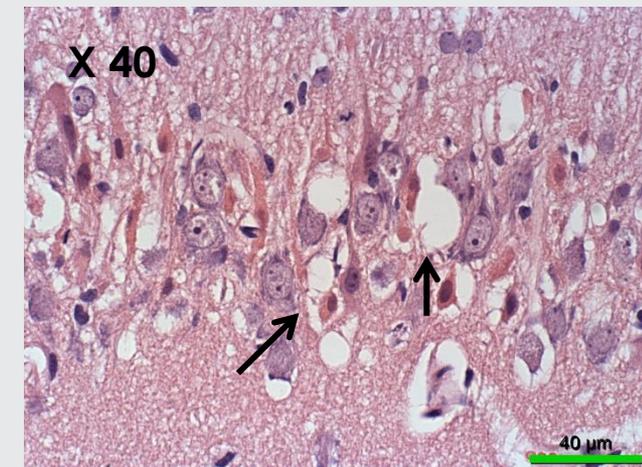
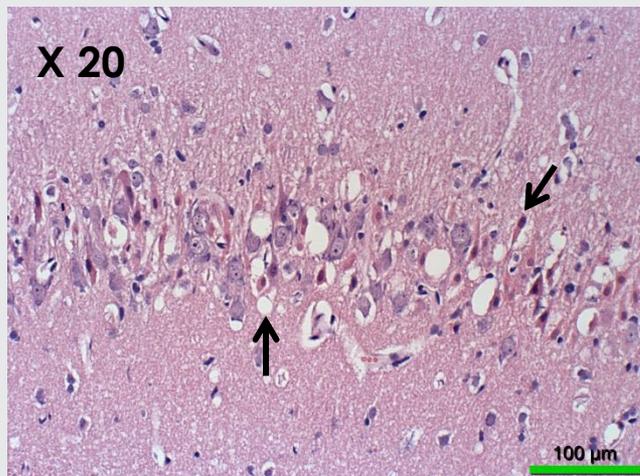
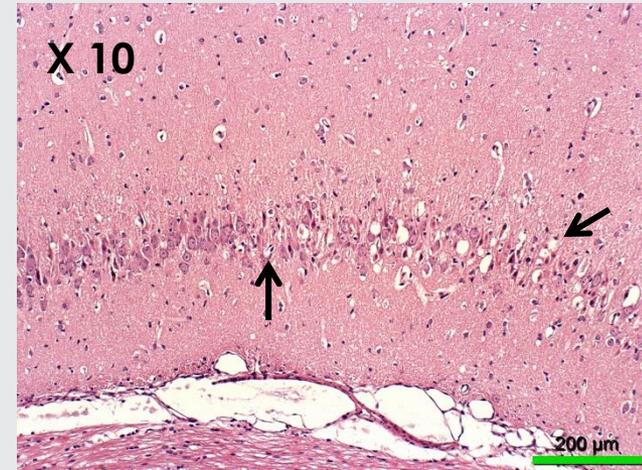
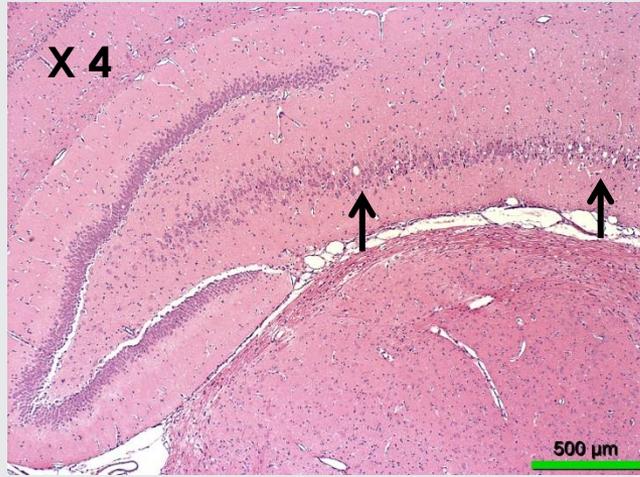
edema in
insular cortex

7 Tesla

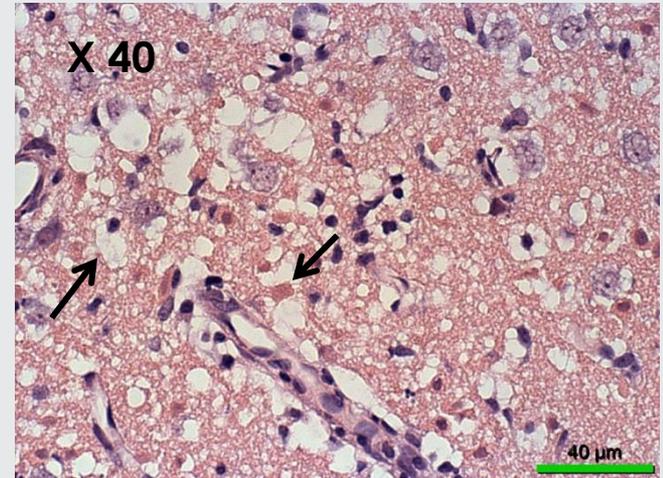
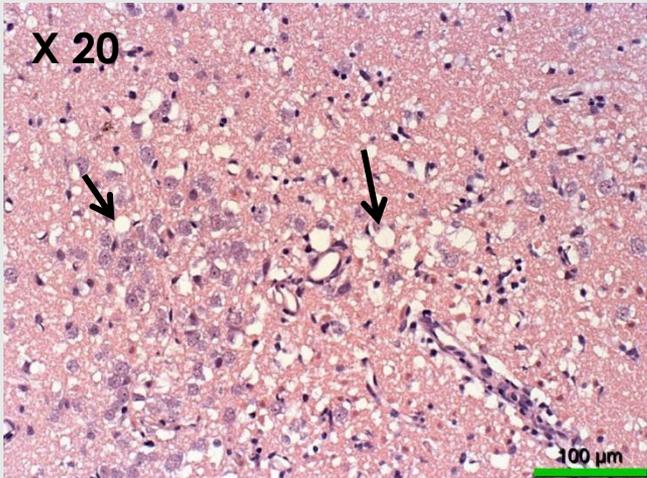
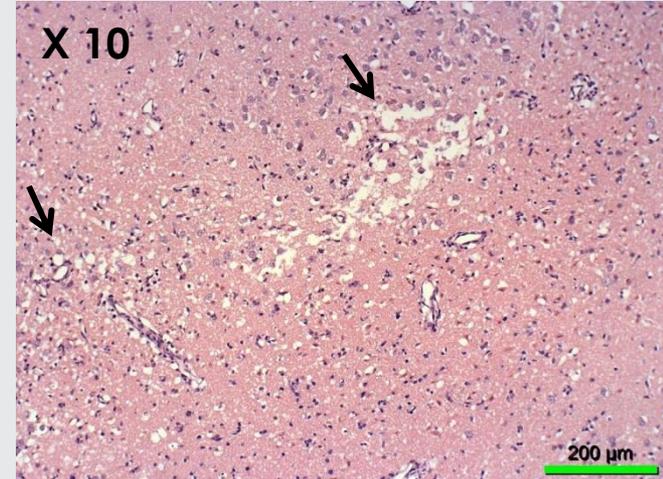
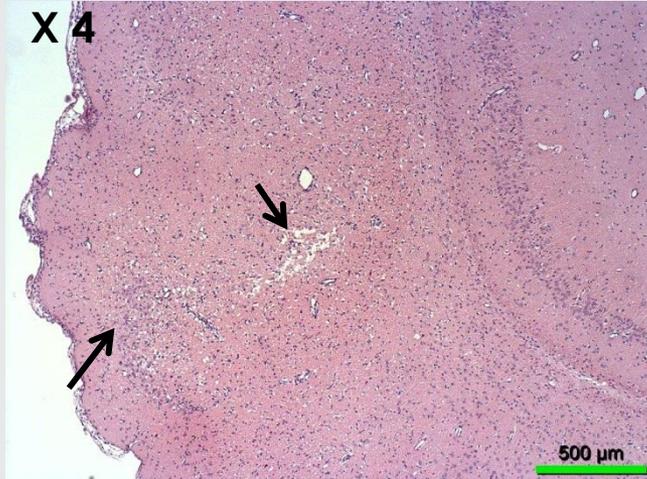


Note the disarrayed cellular layer in the CA3 region of the hippocampus, suggestive of neurodegeneration even in the absence of silver deposition.

Neuronal degeneration, necrosis and vacuolation in hippocampus



Intramyelinic edema, neuronal necrosis and gliosis in amygdaloid nuclei region



Validation study performed by the FDA regarding the use of MRI in neurotoxicity studies

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The use of MRI to assist the section selections for classical pathology assessment of neurotoxicity  CrossMark

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ARTICLE INFO ABSTRACT

Conclusions: “collect Smart sections...”. “..The application of full brain MRI imaging that informs neuropathology offers the potential to dramatically improve detection of neurotoxicity produced by new drugs and facilitate new drug development, review and approval processes, and to qualify an imaging biomarker of neuropathology.”

imaging biomarker of neuropathology.

MRI-based Histology- **Smart Sections** Added Value for Lesion Evaluation

- Localize the lesions
- Count the lesions
- Measure lesions volume
- Longitudinal in-vivo follow-up in the same animal
- Information about homogeneity of the lesions

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