Expanding your Histopathology Capabilities with MRI Technology

Dr. Yael Schiffenbauer and Dr. Abraham Nyska

International Academy of Toxicologic Pathology (IATP)

- Academy of learned scientists dedicated to establishing standards of excellence in education, training, and practice of toxicologic pathology
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Objective statement

- This presentation addresses the practical applications of compact MRI, and will demonstrate practical concept examples in the field of “smart histology”.
- The presentation will demonstrate how compact MRI technology can serve as an important adjunct to toxicologic pathology by nondestructively providing 3-dimensional (3-D) digital data sets, detailed morphological insights, and quantitative information.

In-vivo Imaging - The Future is Now!

Invited Review

Toxicologic Pathology, 41: 689-708, 2013

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623312466192

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.

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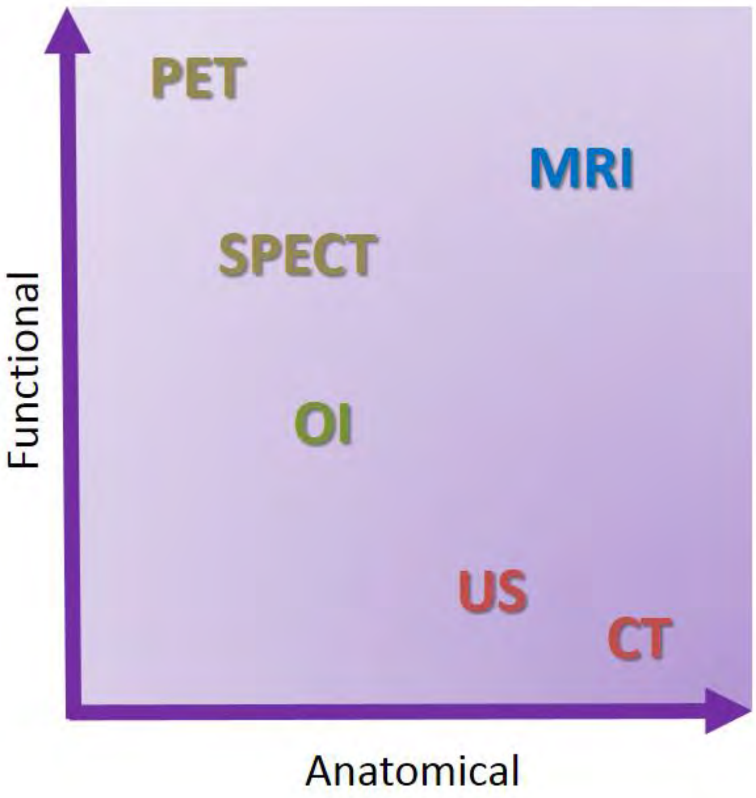
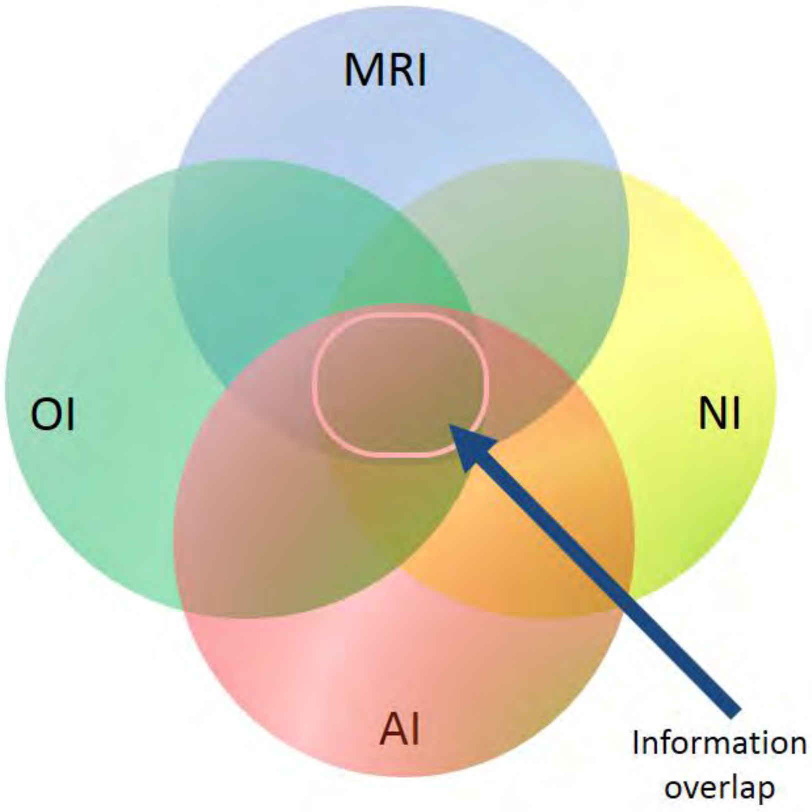
In-vivo Imaging - **Don't Choose, Fuse!**





Traditional 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

Evolution of MRI Technology

- MRI has come a long way
  - Smaller
  - Less expensive
  - Easier to use
- Non-clinical applications
  - Quantify tissue alterations
  - Monitor disease progression
  - Assess efficacy and response

Aspect Imaging
Preclinical MRI Solutions

M-Series Compact, High-Performance MRI Systems

aspectimaging

Shift Happens –
Compact MRI for Everyone, Anywhere

=

M-Series Compact MRI Systems - A Game Changer in the MRI Arena

Benefits:

- ✓ Quiet operation
- ✓ Low Cost
- ✓ No shielding required
- ✓ Normal Lab Safety
- ✓ 1-Day System Setup
- ✓ Maintenance-free design
- ✓ No special staffing requirements
- ✓ Negligible running costs

Placed anywhere in the facility:
next to other modalities, behind the barrier, bench-top, easily moved to different locations

Total Small-Animal Solution for *in vivo* Imaging

- Animal-specific beds
- Anesthesia delivery system
- Physiology monitoring
- Application-specific RF imaging coils
- Multi-modal Imaging

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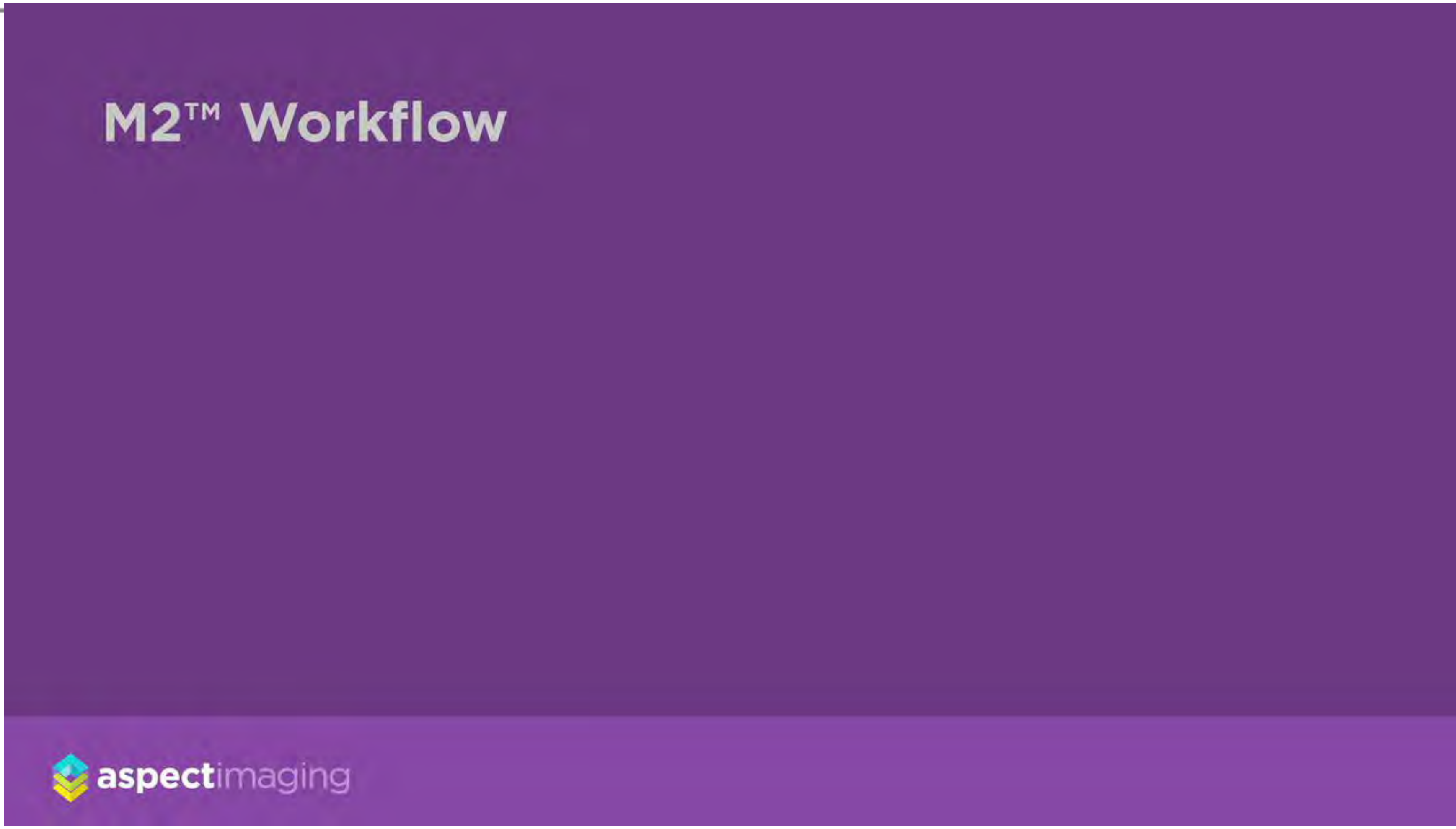
System Workflow - *in vivo*



MRI made easier

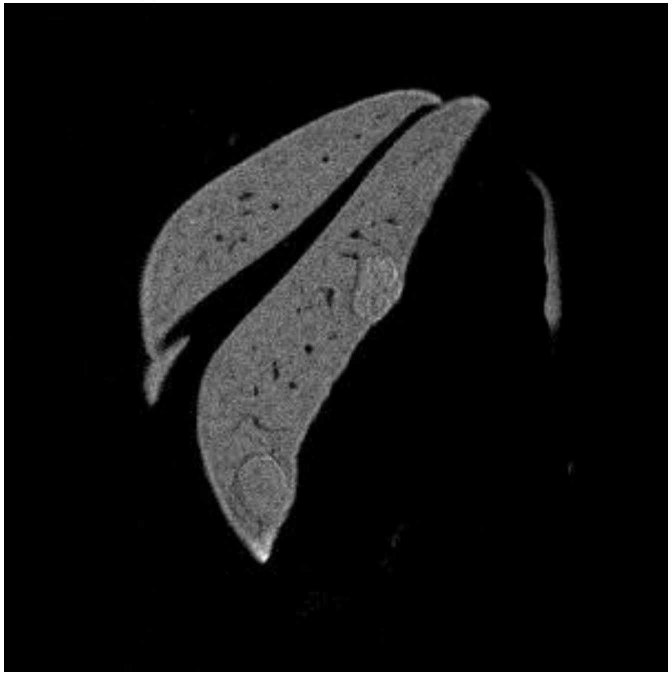
- No more complicated software…
- Ready-to-use automatic protocols
- One Touch MRI - Ask. Touch. Answer

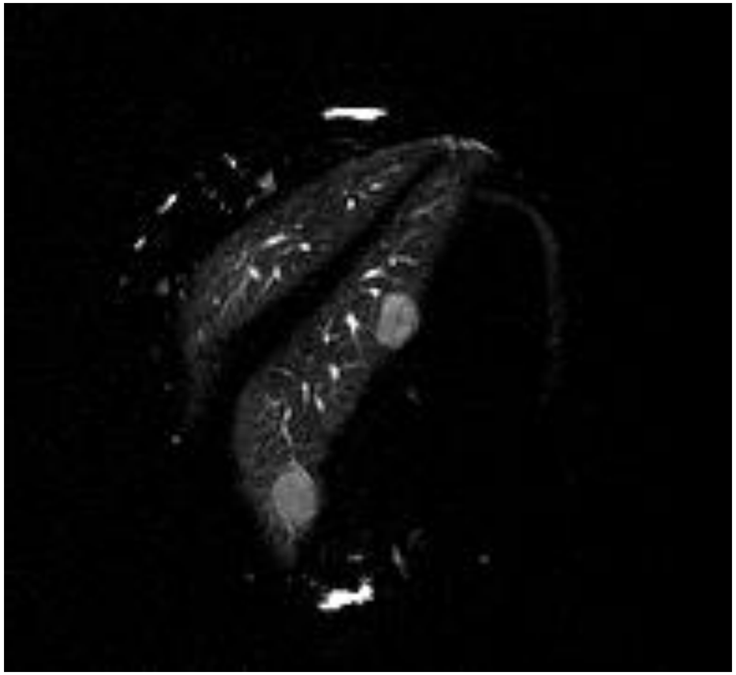
MRI terminology

- 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

MRI terminology

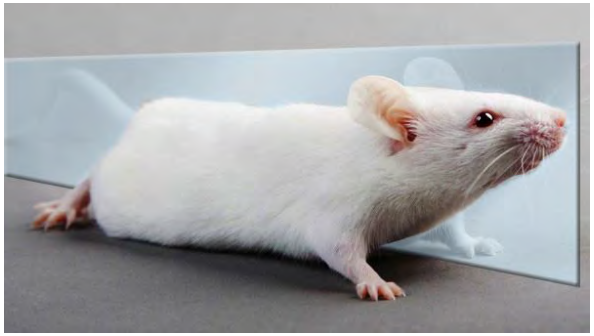
T1



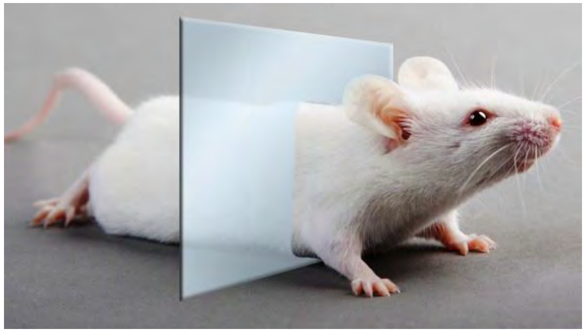


T2

Any Plane Can Be Imaged

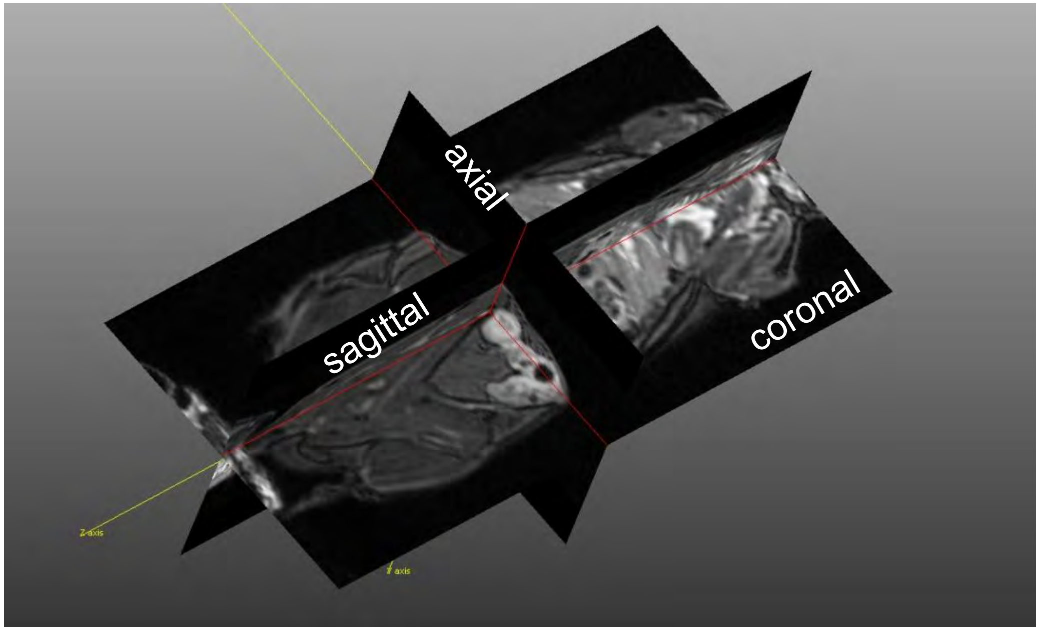


sagittal

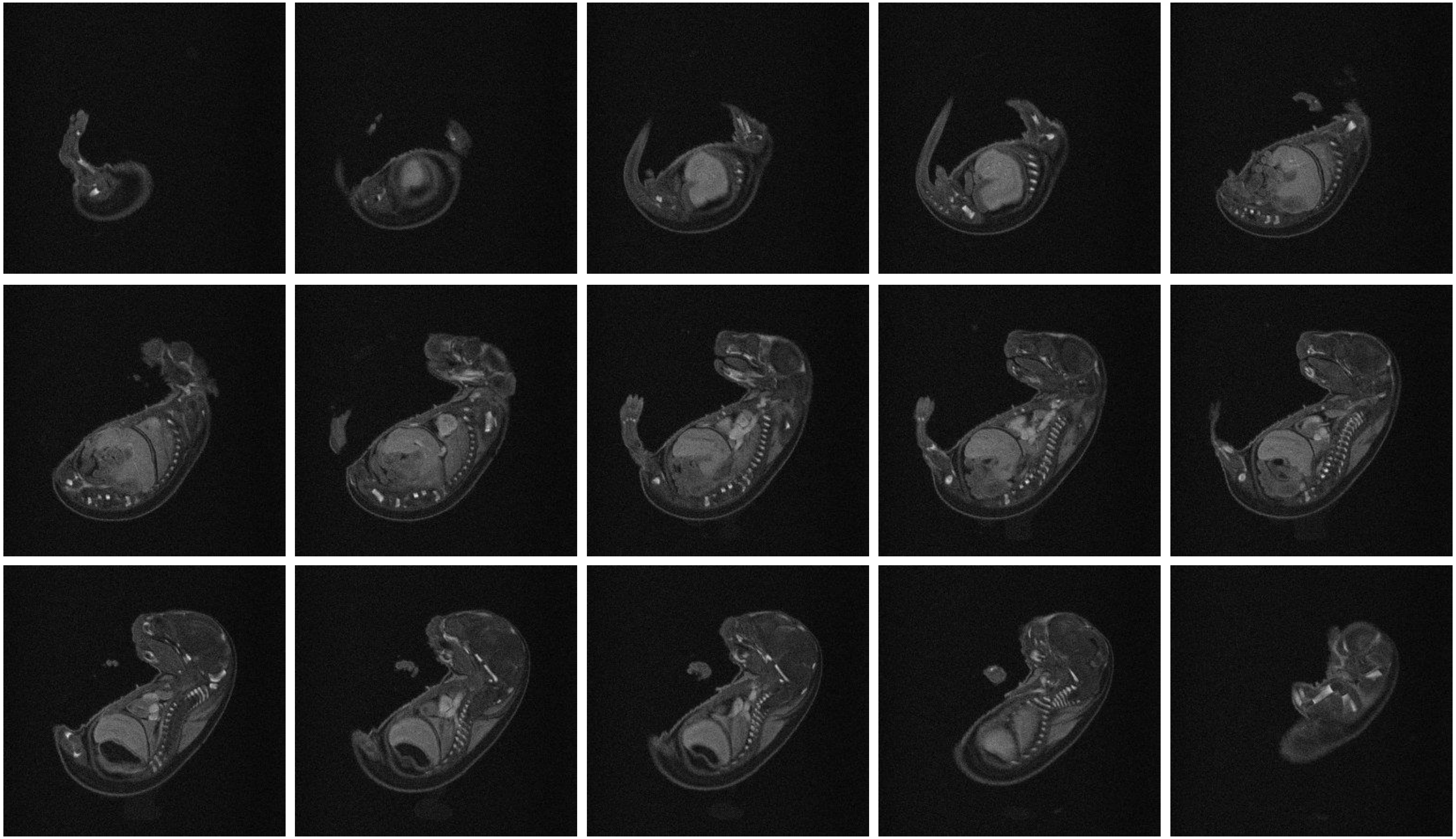


axial

coronal

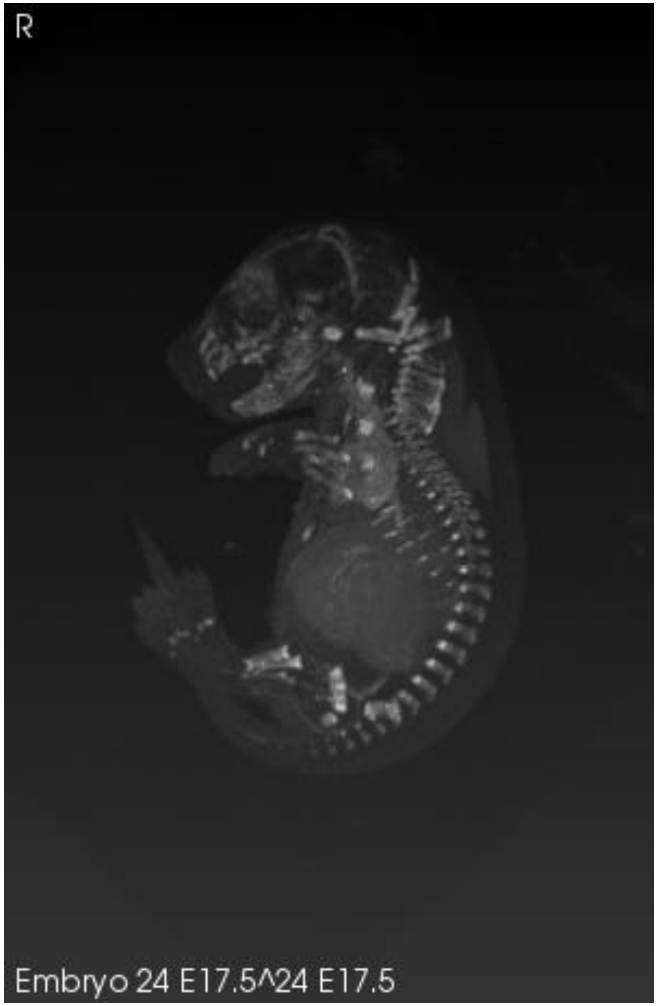


MRI Data Presentation - Individual Slices



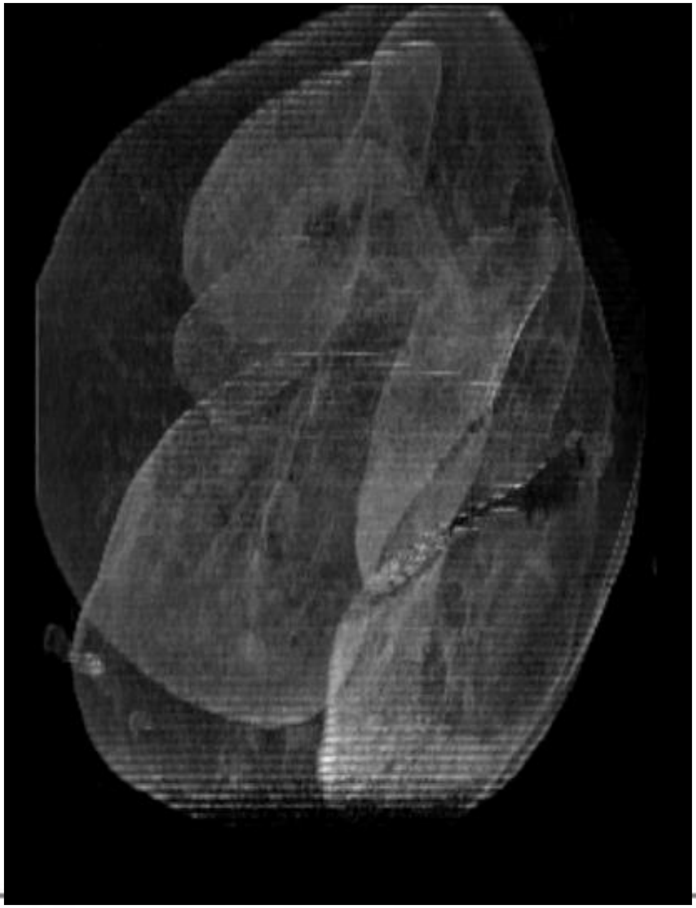
MRI Data Presentation - Slice Through Animation

MRI Data Presentation - See Through 3D Rendering (MIP)

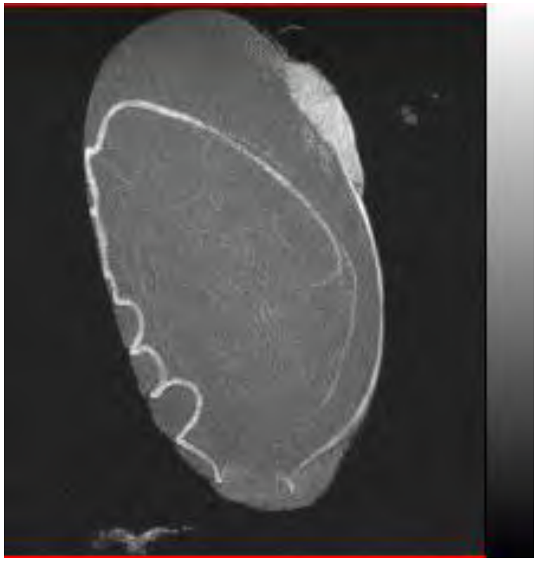


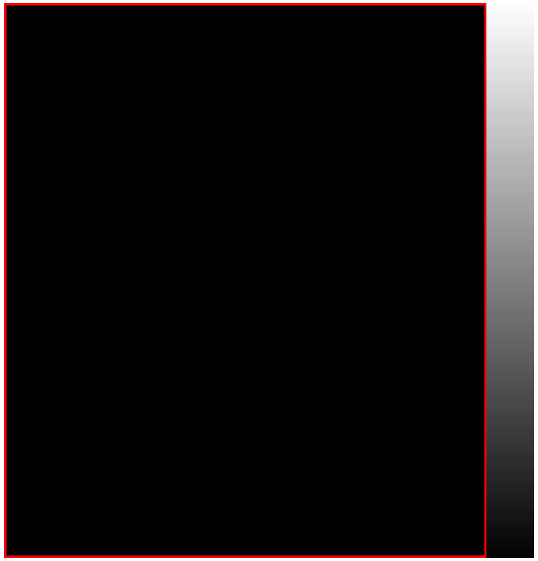
Hepatocellular Carcinoma (HCC) – *Ex Vivo* MRI

3D Rendering

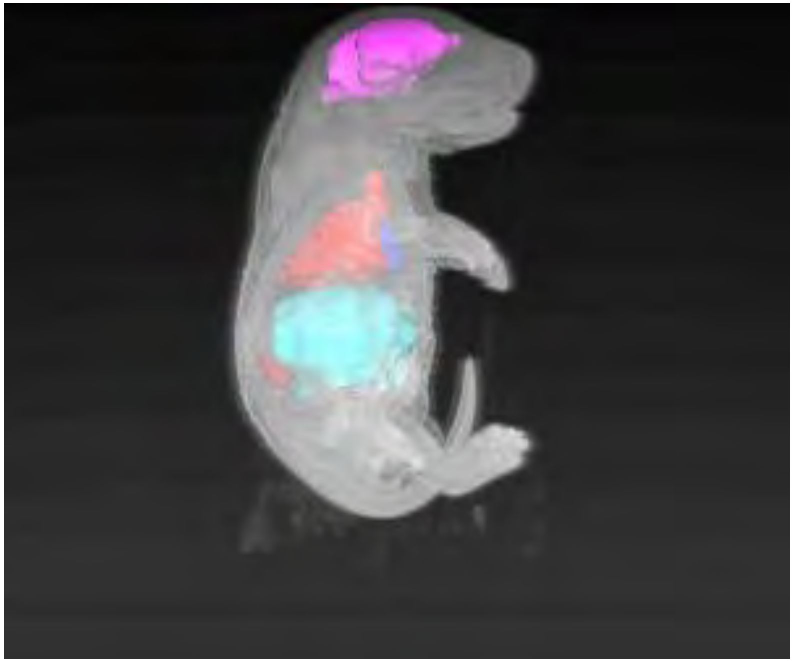


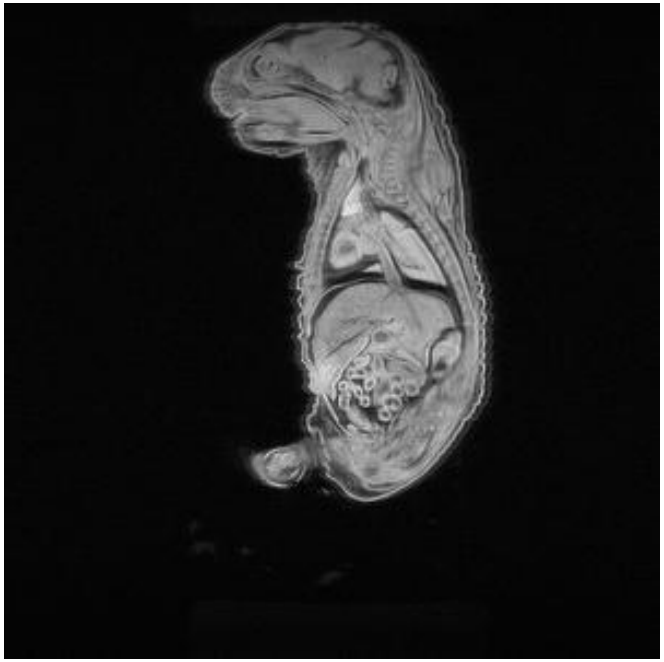
Rat testicle - 3D rendering and slice animation





Segmentation - Volume Calculation





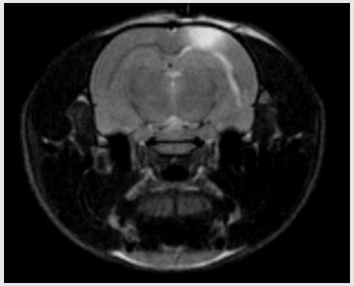
Segmentation - Volume Calculation

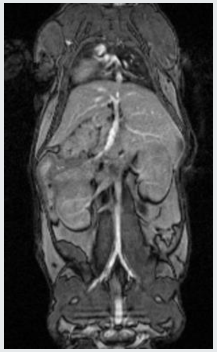
ROI	Rat	Colour	Voxels	Volume mm^3
Lungs	Rat embryo control E20	Red	28910	97.5713
Heart	Rat embryo control E20	Blue	8218	27.7358
Liver	Rat embryo control E20	Cyan	84566	285.41
Brain	Rat embryo control E20	Magenta	38770	130.849
Left kidney	Rat embryo control E20	Dark red	3044	10.2735
Right kidney	Rat embryo control E20	Dark cyan	2745	9.26438

Typical Acquisition time: In vivo/Ex vivo MRI of the brain

Typical acquisition time for in vivo: 3-8 minutes

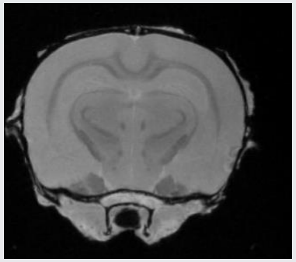
- In plane resolution 150-250 μm/ Slice thickness 1mm

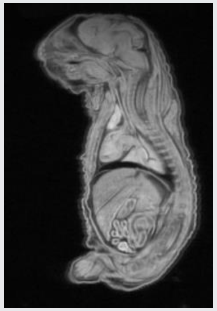


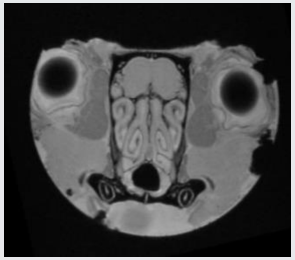


Typical acquisition time for ex vivo : 0.5-2 hours

- In plane resolution 60-150 μm/ Slice thickness 0.3mm







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MRI - HISTOLOGY

MRI-based histology **– "Smart sections"**

Or

"Smart histology"

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

Methods

- All scans performed on M-series Compact MRI by Aspect Imaging
- Animals
  - Anesthetized with isoflurane
  - Heated
  - Physiological monitoring
- Fixed samples
  - In any fixative solution
  - Fluorinert

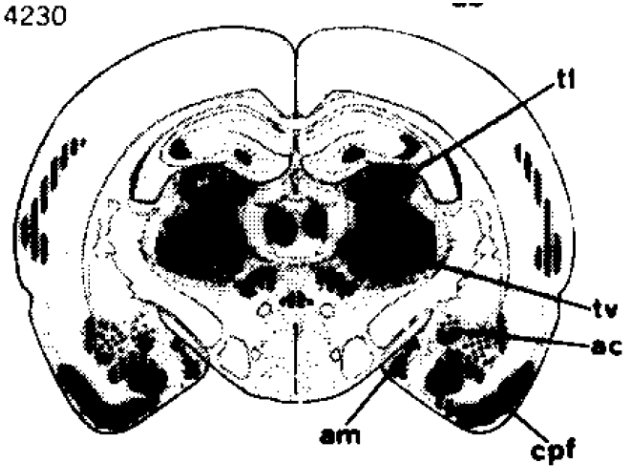
Concepts and Preclinical Models that will be Presented:

- MRI in Testing of Neurotoxic Potential
- MRI in Safety Evaluation of Stem Cells
- MRI in Evaluation of biodegradable implanted device
- MRI in Efficacy Testing of Anti-Cancer Drugs
- MRI in Testing of Carcinogenic Potential
- MRI in Toxicity Testing of Drugs
- MRI in Tolerability (Irritancy) Testing of Drugs
- MRI in Efficacy Testing of Anti-fibrotic Drugs

Concept: MRI in Preclinical Testing of Neurotoxic Potential: Model of 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.

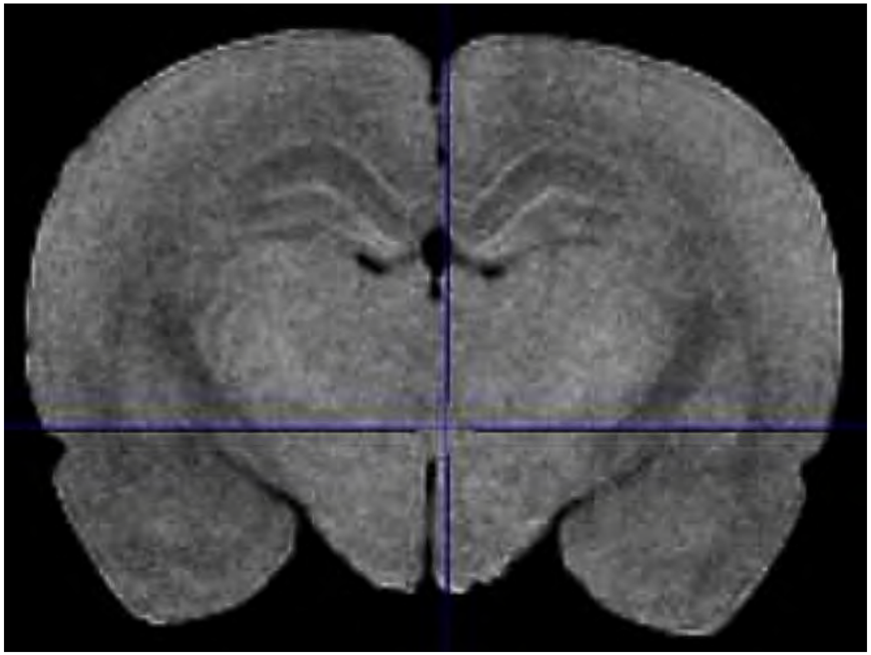
- Expected outcome: Neuronal cell degeneration /necrosis



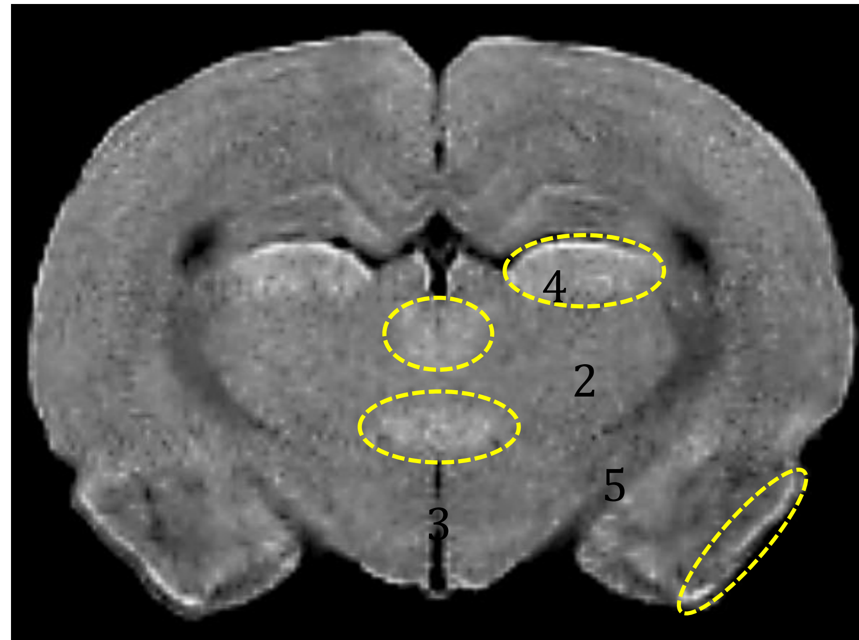
Dark areas : Severe
Hatched areas : Moderate
Dotted areas : Slight

Control vs. Pilocarpine
Ex vivo MRI (T1)

control



Pilocarpine



1: Piriform cortex

2: Lateral thalamic nucleus

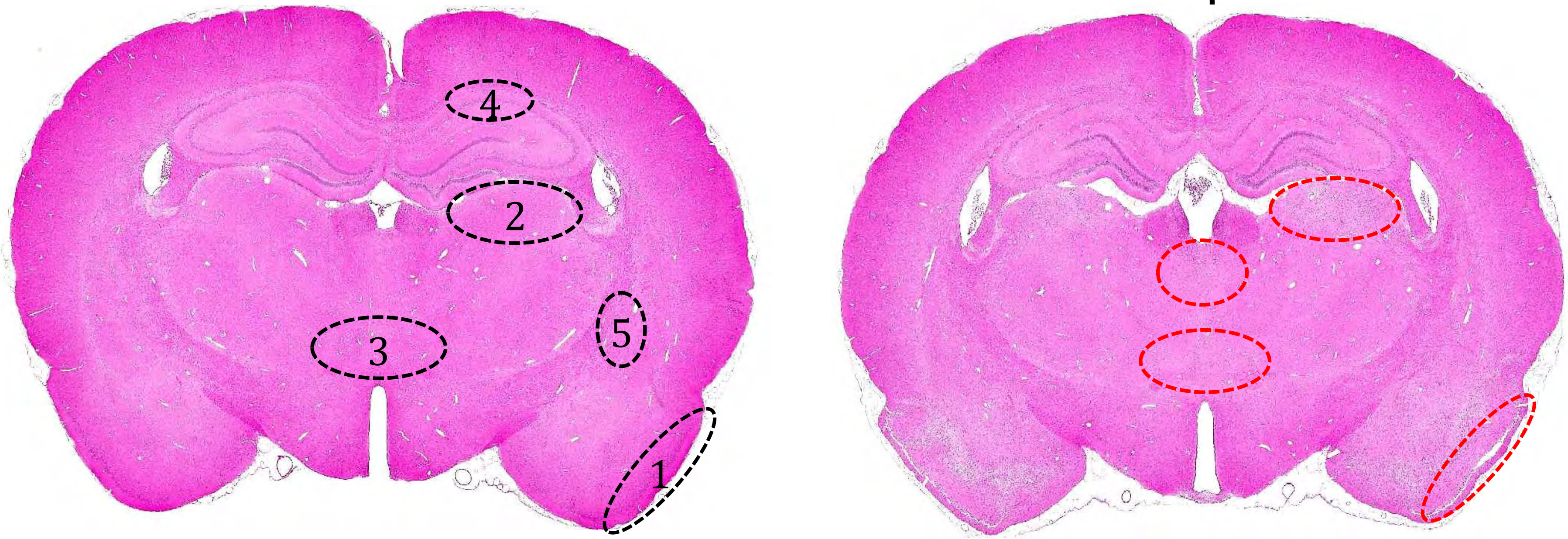
3: Posterior hypothalamic nucleus

4: Hippocampus

5: Caudate putamen

Control vs. Pilocarpine – H&E

control　　　　　　　　　　Pilocarpine



1: Piriform cortex

2: Lateral thalamic nucleus

3: Posterior hypothalamic nucleus

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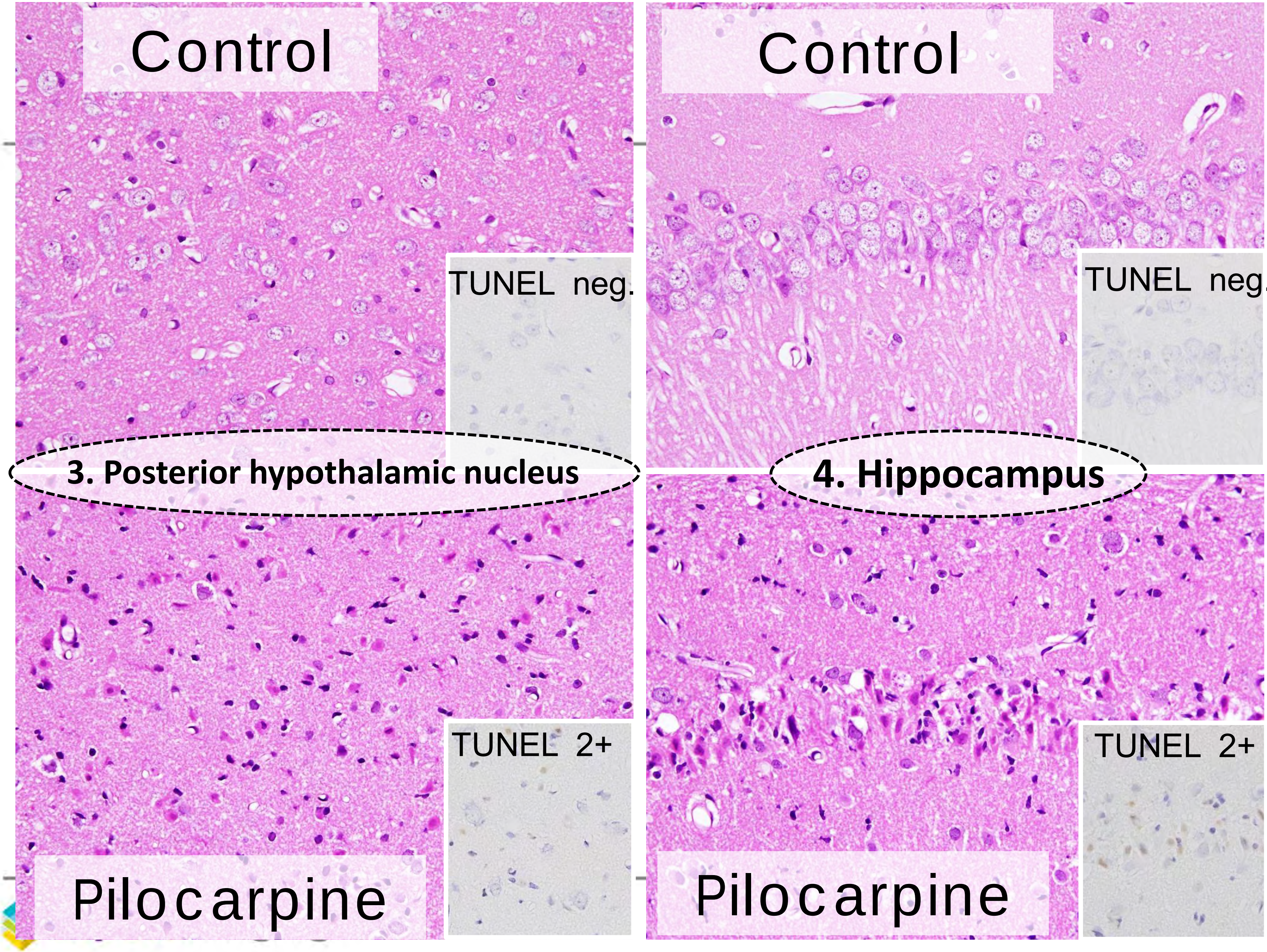
5: Caudate putamen


Control
TUNEL neg.
3. Posterior hypothalamic nucleus
TUNEL 2+
Pilocarpine
Control
TUNEL neg.
4. Hippocampus
TUNEL 2+
Pilocarpine

Summary and Conclusion

- 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

J Toxicol Pathol 2015; 28: 217–224

Original Article

Application of a compact magnetic resonance imaging system for toxicologic pathology: evaluation of lithium-pilocarpine-induced rat brain lesions

Yoshikazu Taketa[1*], Motohiro Shiotani[1], Yoshiharu Tsuru[2], Sadaharu Kotani[3], Yoshihide Osada[3], Tatsuto Fukushima[3], Akira Inomata[1], and Satoru Hosokawa[1]

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毒性病理評価におけるMagnetic Resonance Imaging（MRI）の有用性

-ラット脳固定臓器における神経病変のMRIによる検出-

JTP Scientific Awards

JTP Scientific Awards

The Board of Directors and the Publication Committee of the Japanese Society of Toxicologic Pathology (JSTP) annually confer the JTP Scientific Awards to individuals and organizations for their distinguished contributions to the society's official journal, the Journal of Toxicologic Pathology (JTP).

The JTP Scientific Awards consist of 4 awards, the JTP Paper Award, the JTP Incentive Award, the JTP Achievement Award and the JTP Distinguished Service Award. The JTP Paper Award includes the JTP Best-Paper-of-the-Year Award and the JTP Excellent-Paper-of-the-Year Award, which are self-explanatory. The JTP Incentive Award is selected from the papers which are the first experiences for their first authors to submit papers to JTP.

The JTP Achievement Award is given to the most frequently referred paper for the preceding 5 years. The JTP Distinguished Service Award is given to an organization from which 5 (Bronze), 10 (Silver), 25 (Gold), 50 (Platinum) or 100 (Diamond) papers have been submitted. It should be noted that these awards are principally conferred to the JSTP members.

JTP Scientific Awards 2015

JTP Best-Paper-of-the-Year Award	
Title	Application of a compact magnetic resonance imaging system for toxicologic pathology: evaluation of lithium-pilocarpine-induced rat brain lesions
Author	Yoshikazu Taketa, Motohiro Shiotani, Yoshiharu Tsuru, Sadaharu Kotani, Yoshihide Osada, Tatsuto Fukushima, Akira Inomata, Satoru Hosokawa
Journal	Journal of Toxicologic Pathology 28: 217-224, 2015

Validation Study Performed by the FDA Regarding the Use of MRI in Neurotoxicity Studies

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

ELSEVIER

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

CrossMark

Joseph Hanig[a,*], Merle G. Paule[b], Jaivijay Ramu[b], Larry Schmued[b], Tetyana Konak[b], Srinivasulu Chigurupati[b], William Slikker Jr.[c], Sumit Sarkar[b], Serguei Liachenko[b]

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ARTICLE INFO

ABSTRACT

<u>Conclusions:</u> "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."

Concept: MRI in Preclinical Safety Evaluation of Stem Cells:

Mouse Stem-Cell Teratoma Model

- **Objective:** Using the compact MRI for the Assessment of tumorigenicity following intrathecal Transplantation of Human Embryonic Stem Cells (hESC) in Mice

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

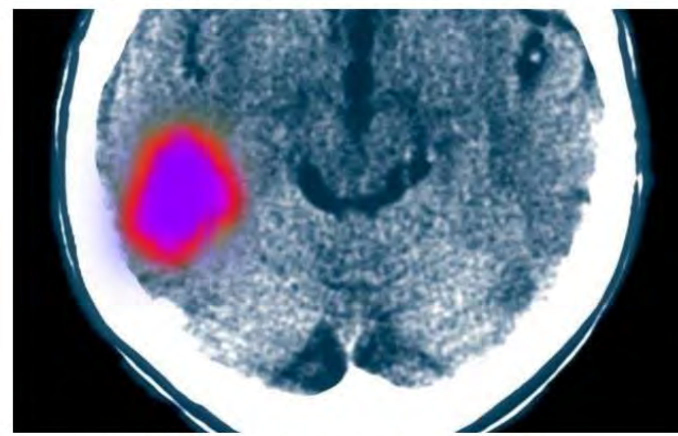
Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem-Cell Tourism"

This letter was published on June 22, 2016, at NEJM.org.

Science

Stroke survivors walk again after Stanford injects stem cells into brain

share



Stem cell injections have allowed stroke patients to walk again

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem-Cell Tourism"

This letter was published on June 22, 2016, at NEJM.org.

Such experimental treatments must be studied in a safe, regulated environment.

The NEW ENGLAND JOURNAL of MEDICINE

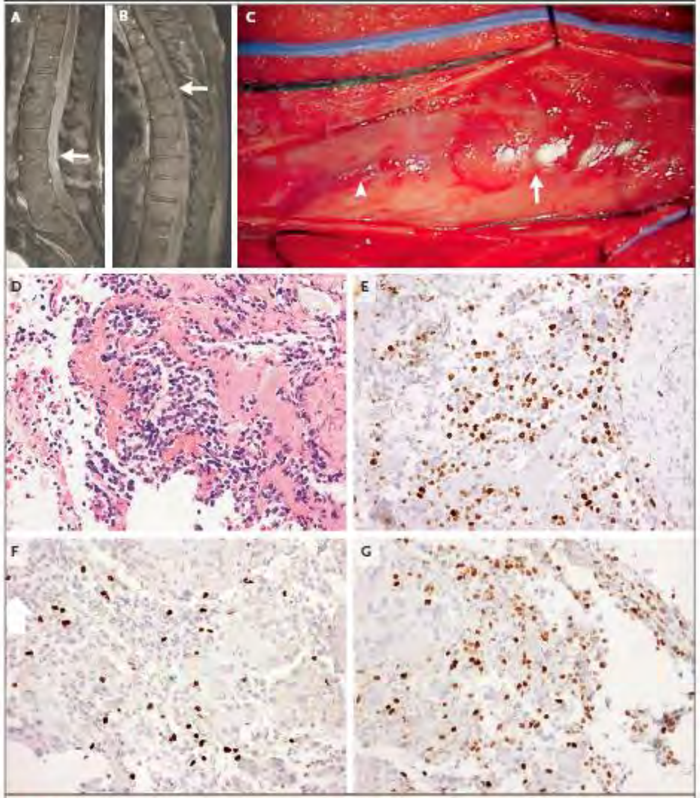


Figure 1. Findings Obtained on MRI, during Surgery, and after Biopsy.

Panels A and B show sagittal, T_1-weighted magnetic resonance imaging (MRI) scans of the spine obtained after the administration of contrast material. Panel A shows areas of enhancement in an intradural mass that extends throughout the lumbar spine (arrow), and Panel B shows the rostral extent of enhancement in the thoracic spine (arrow). Panel C shows abnormal arachnoid mater (arrow) and an engorged vein (arrowhead) during surgery after a dural incision was made. Panels D through G show histopathological specimens of lesional cells. Panel D shows intradural primitive atypical cells after staining with hematoxylin and eosin. Panels E, F, and G show the results of immunohistochemical testing for MIB-1 (MKI67), a marker of cellular proliferation, for OLIG2, a glial marker, and for SOX2, a glial stem-cell marker, respectively.

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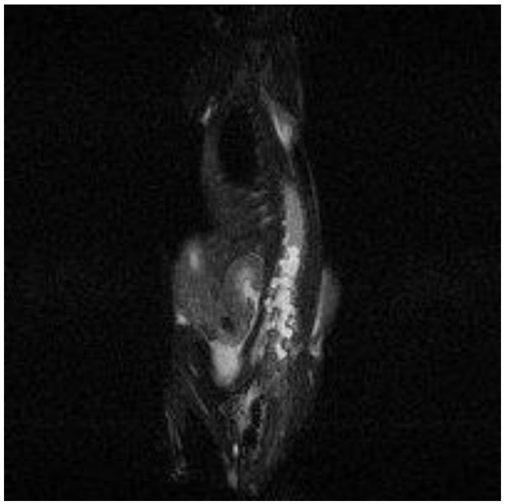
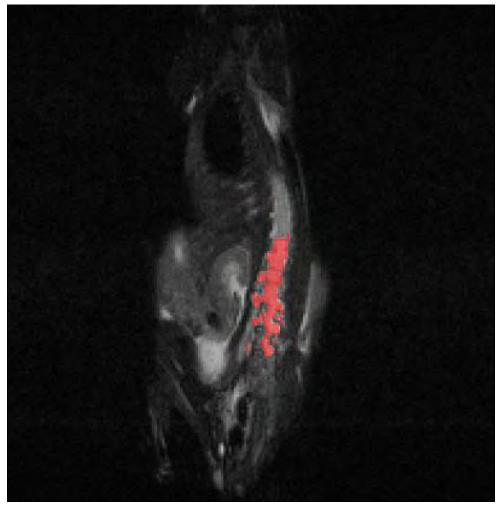
Materials and Methods

- Two mice injected with the vehicle control and 3 injected with hESC
- Injection within the inter-vertebral (L5 to L6) grove.
- Daily clinical evaluation
- *In vivo* MRI on 2 occasions (days 25 & 48)
- Sacrifice on day 55, followed by formalin fixation, *ex vivo* MRI, and histopathology

Spinal teratoma – Segmented

In vivo

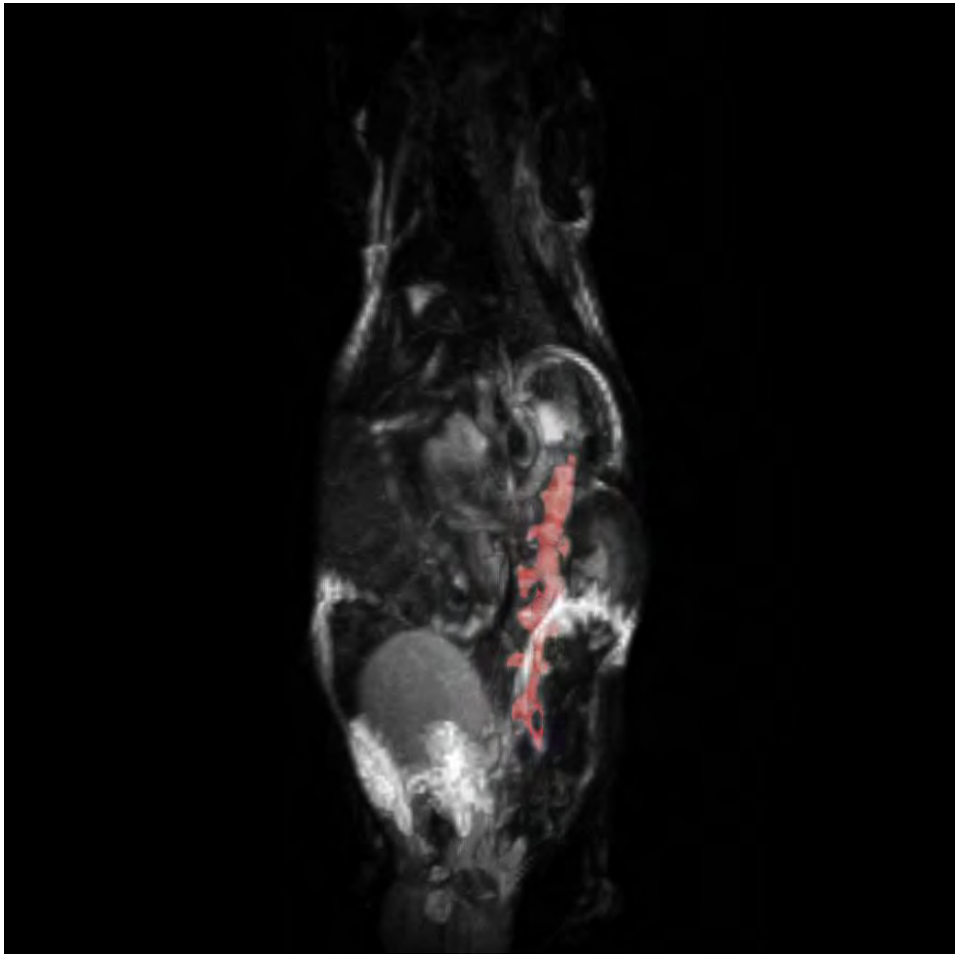




Ex vivo

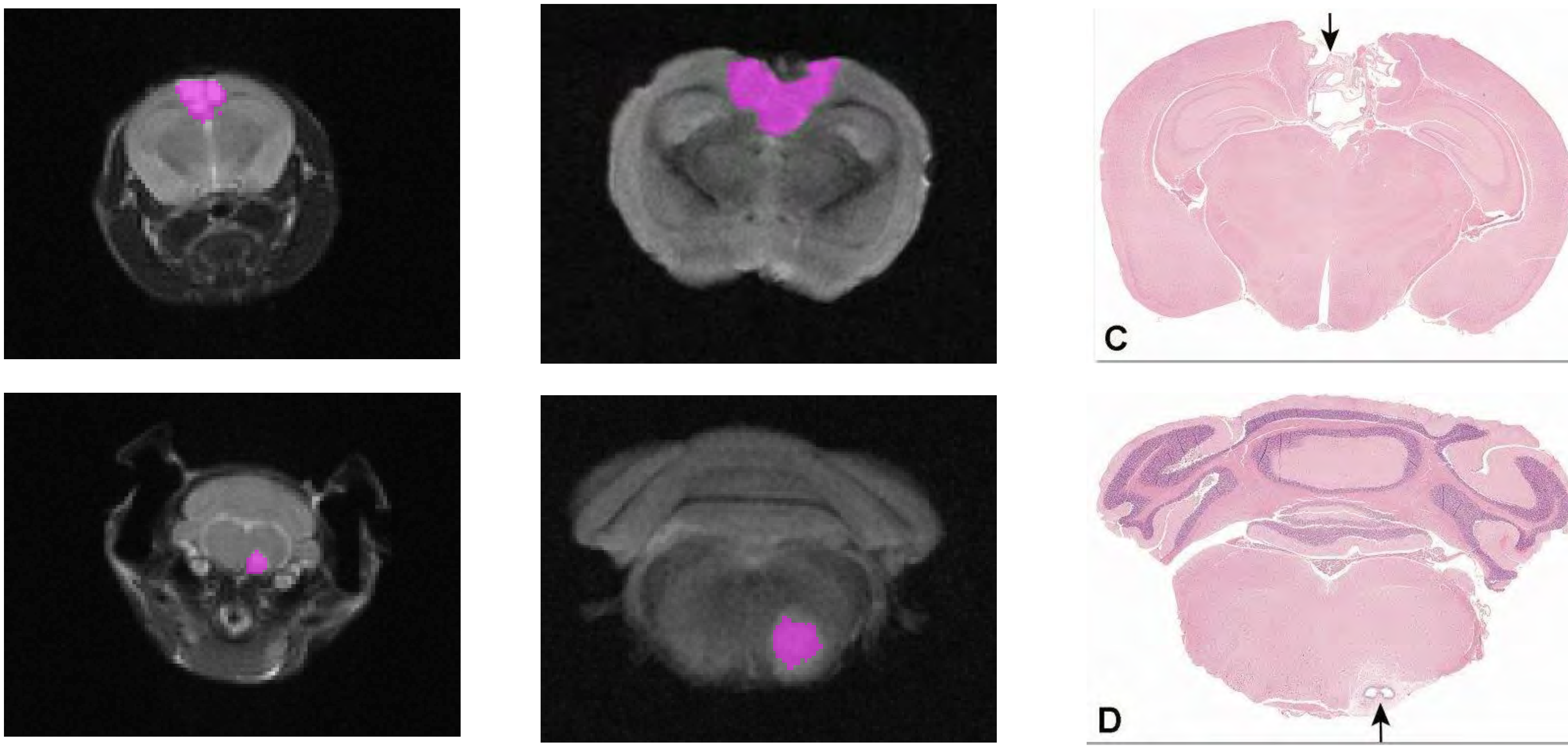
ROI	Color	Voxels	Volume mm^3
teratoma	red	1927	82.6201

3D rendering + segmentation of the Spinal Cord



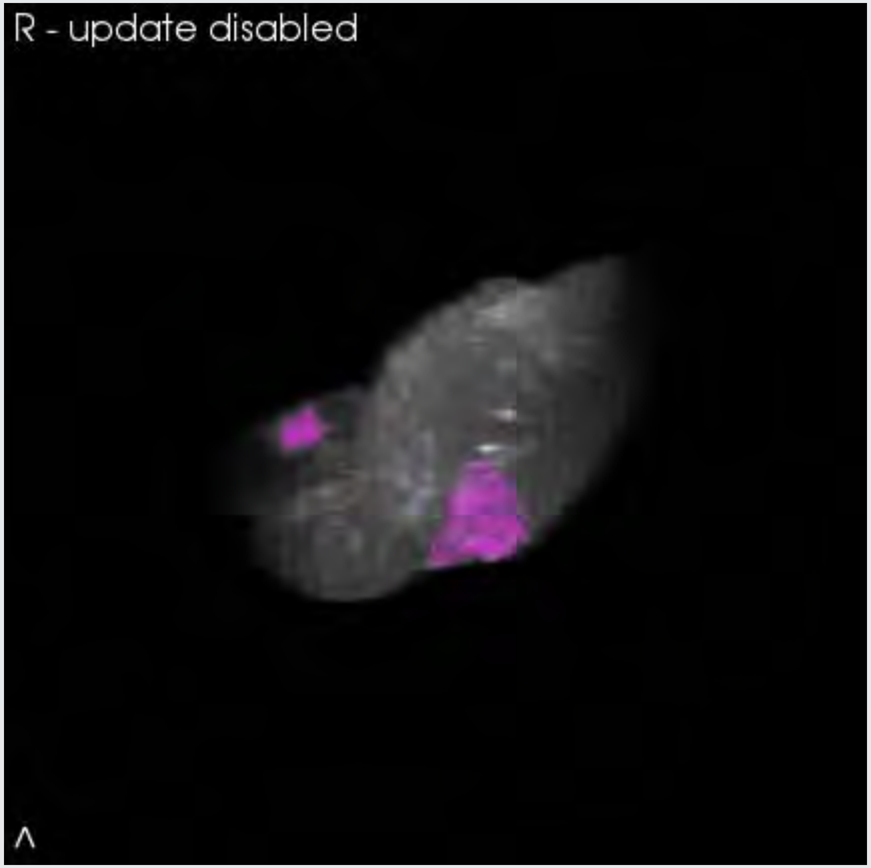
Brain Teratoma – *in vivo* & *ex vivo* MRI segmentation vs. Histology

In vivo | Ex vivo | Histology



ROI	Color	Voxels	Volume mm^3
tumor	magenta	20539	9.79376

3D rendering of the brain – pink areas are the teratoma



Results and Conclusions

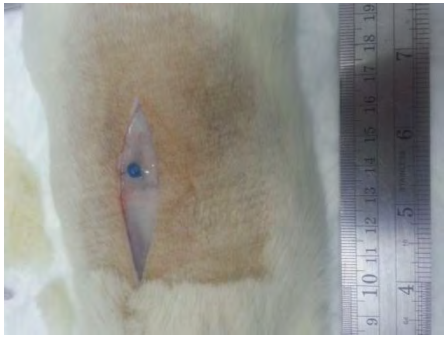
- Paresis developed in mice injected with the hESC
- *Both In vivo* and *Ex vivo* MRI located abnormal areas in the spinal column and brain
- Histopathology confirmed Malignant Teratoma
- The MRI technique can be used for time course observations for testing the carcinogenic potential of novel stem cells intended for clinical use.
- The MRI (*In Vivo* and *Ex Vivo*) were effective to accurately localize the teratomas in the brain and spinal cord.

Concept: MRI in Evaluation of Biodegradable Implanted Device

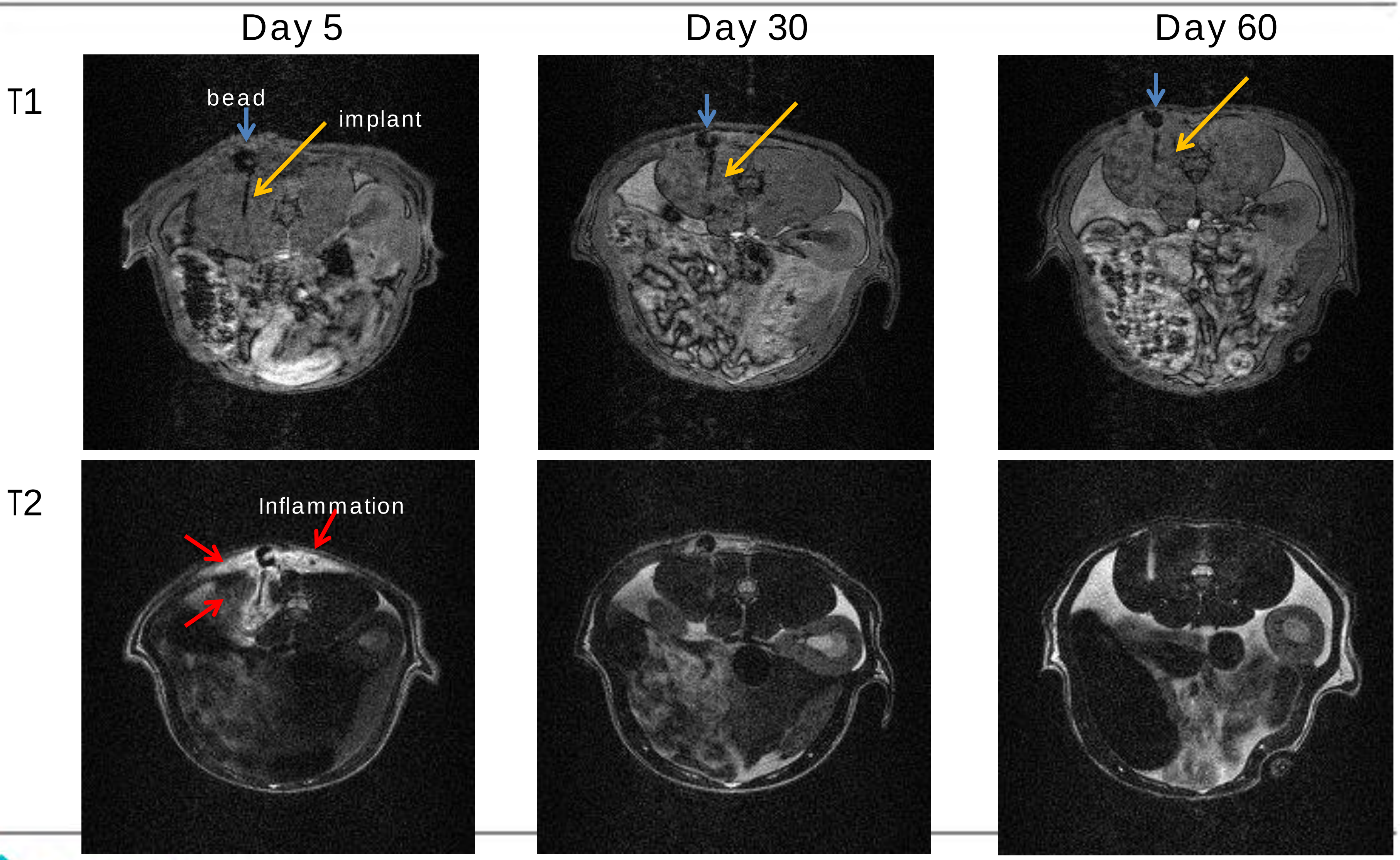
Biological Model and Objective

- Model: A double layer of a 5x5 mm^2 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 Follow-up of Implanted Device



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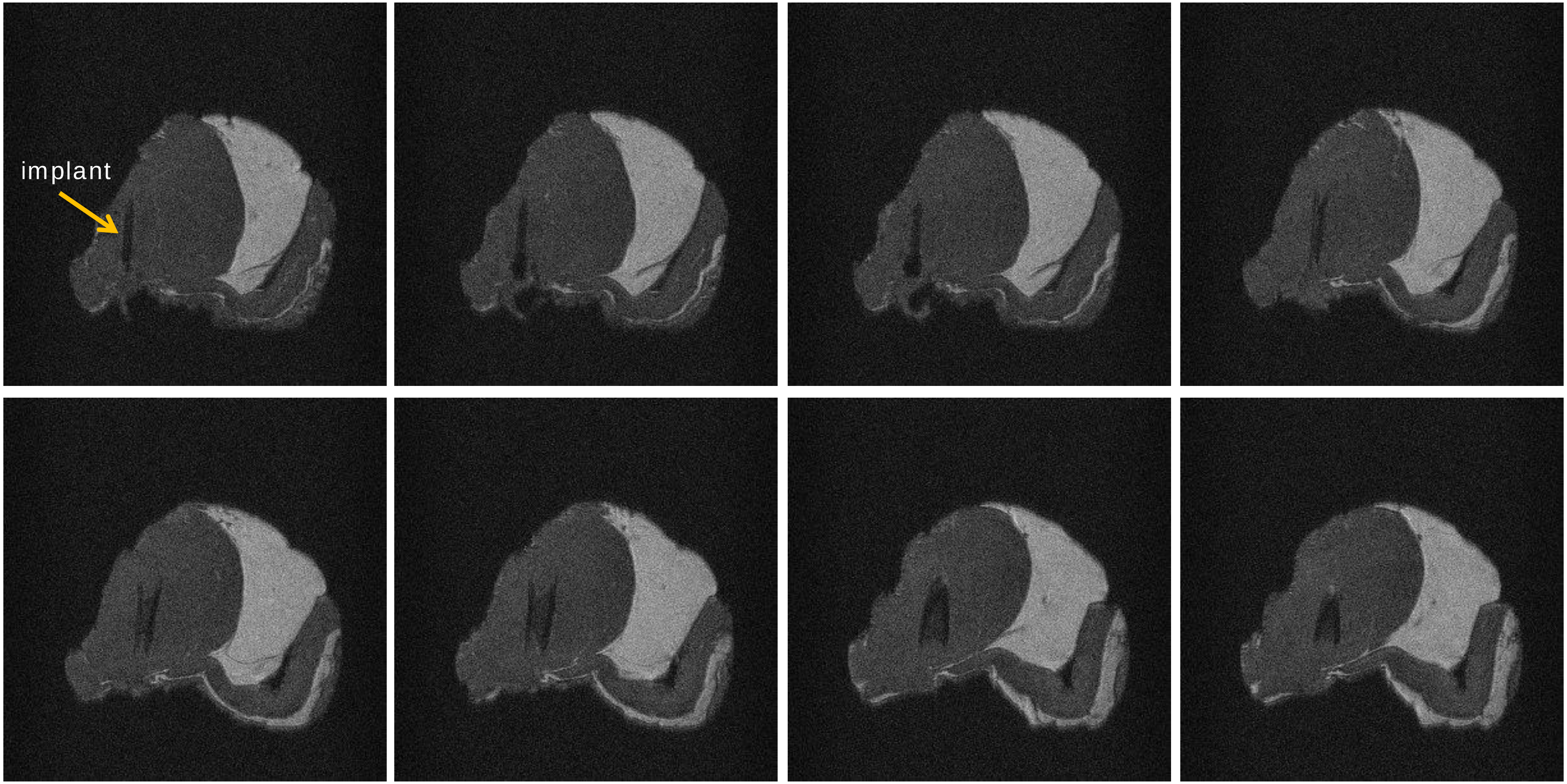
Ex vivo MRI of Implanted Device



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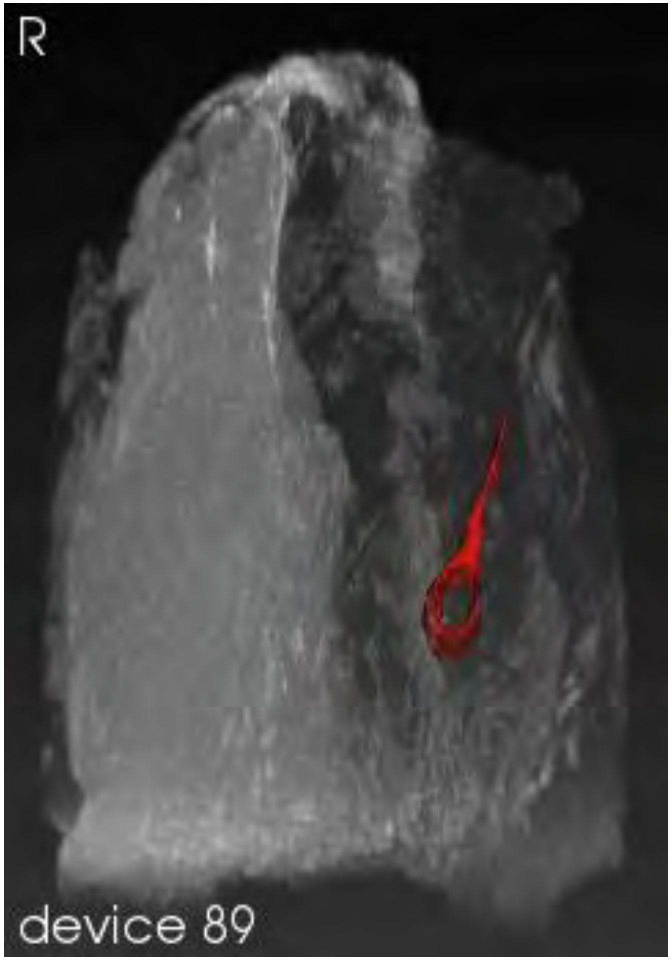
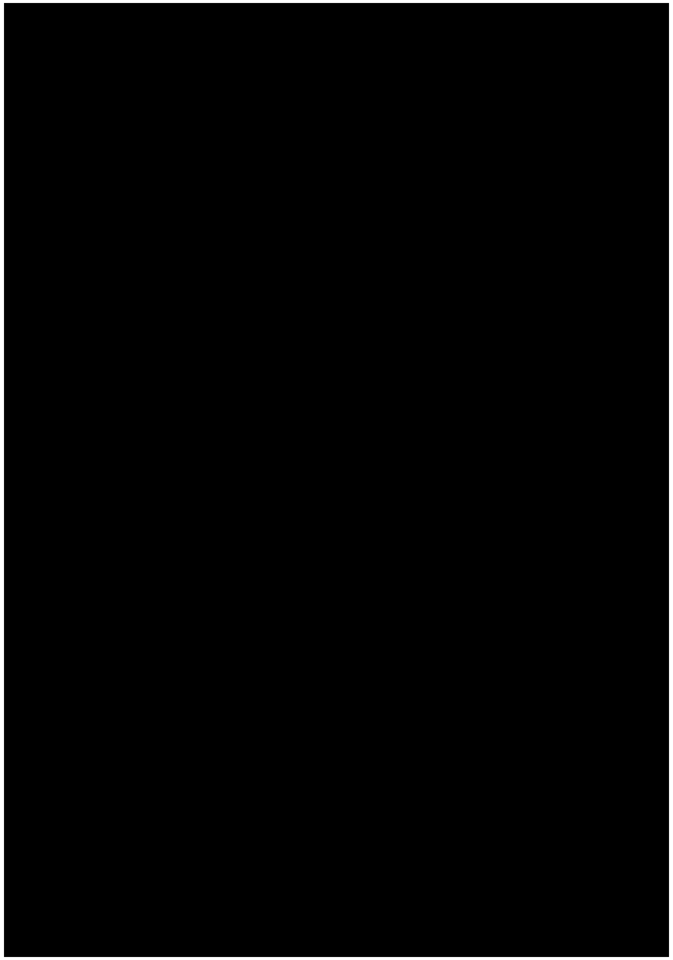
Ex vivo MRI of implanted device
3D rendering + segmentation

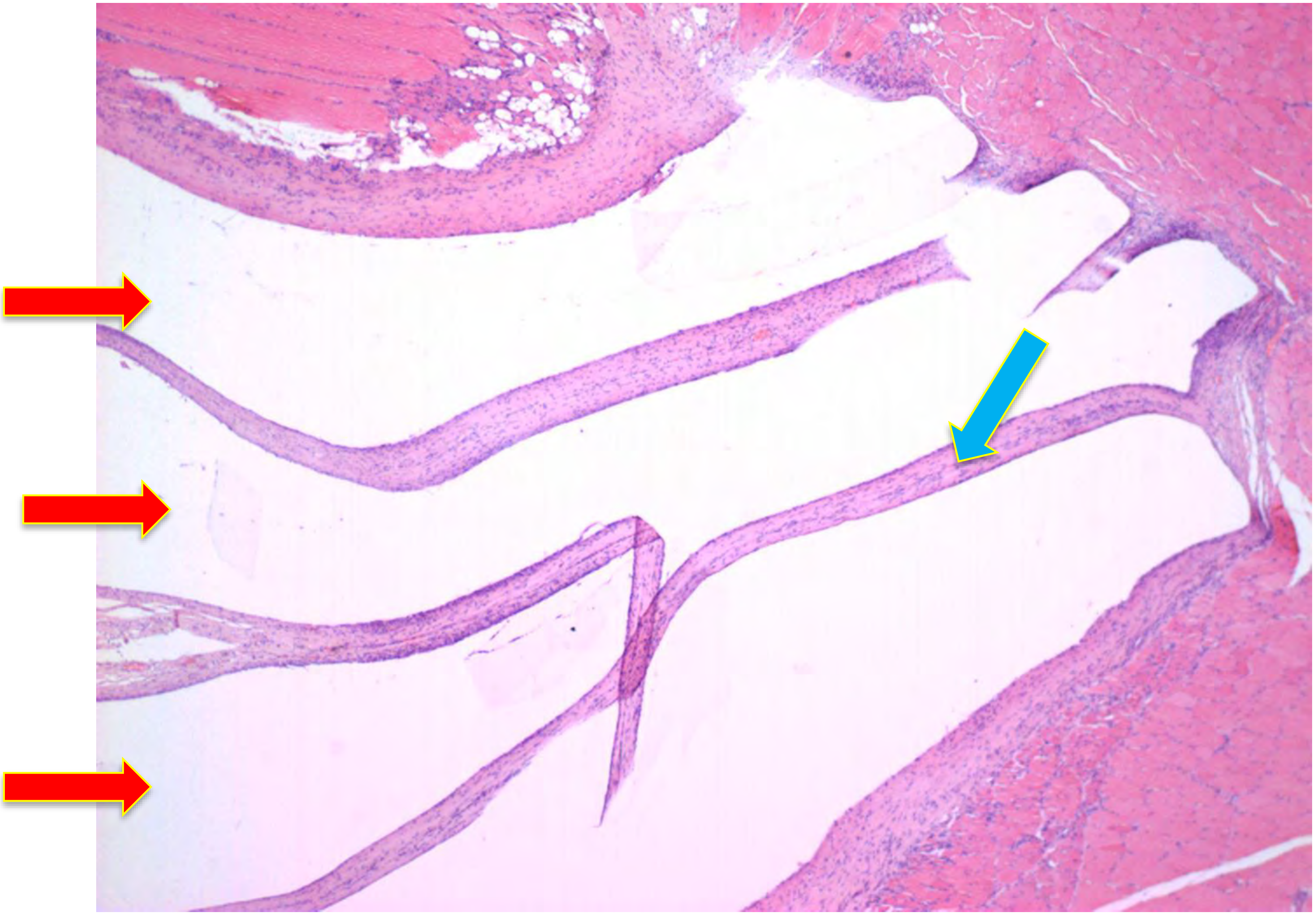




Volume of device : **32.2** mm^3

Histopathology view of the implantation site 60 days post implantation Note the cavities (red arrows) lined by mature connective tissue capsule (blue arrows).

No inflammatory reaction is present



Summary and Conclusion

- *In vivo* MRI could detect inflammation related to the implantation process and follow its progressive reduction. In addition, in vivo MRI was able to demonstrate the presence of the test device in the para-lumbar muscles up to 16 weeks post implantation.
- Accurate quantification of the device volume and shape was possible using *ex vivo* MRI.
- Combination of *in vivo and ex vivo* MRI with histopathology could be used to shed light into mechanisms of implantation and bio-degradation of such devices.

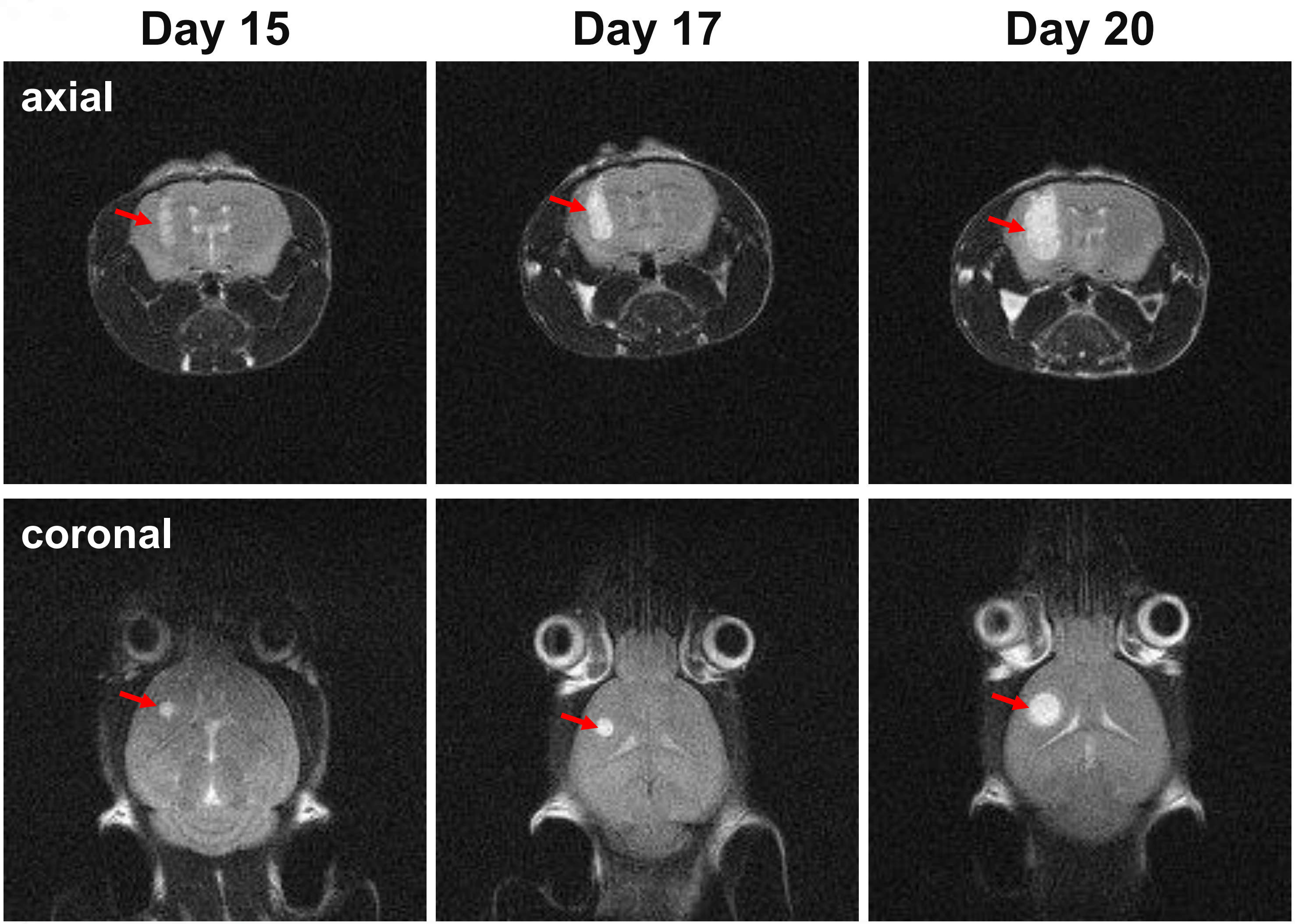
Concept: MRI in Preclinical Efficacy Testing of Anti-Cancer Drugs: Longitudinal Growth of a Brain Tumor

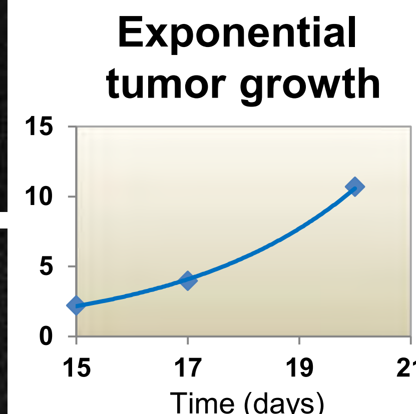
Biological Model and Objective

- Model: Murine Gl-261 glioma cells stereotactically injected into the right brain hemisphere of CB6F1 mice

- Objective: Longitudinal evaluation of tumor growth

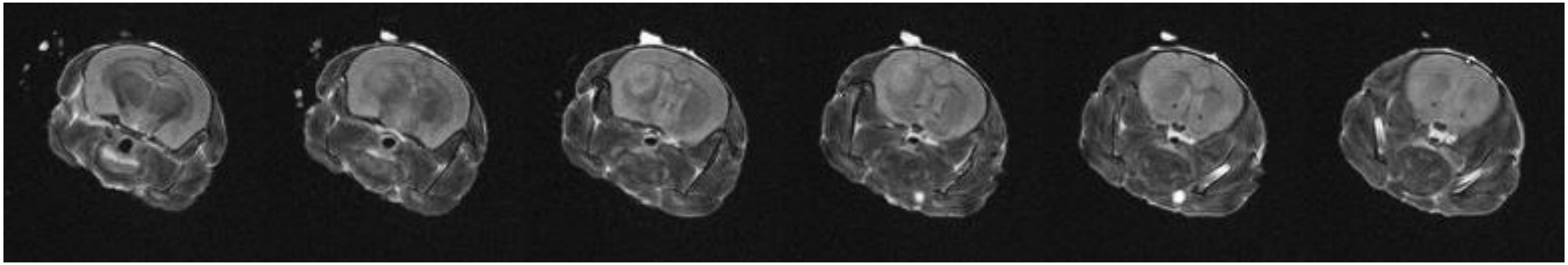
Longitudinal Evaluation of Tumor Growth
In Vivo MRI (T2)

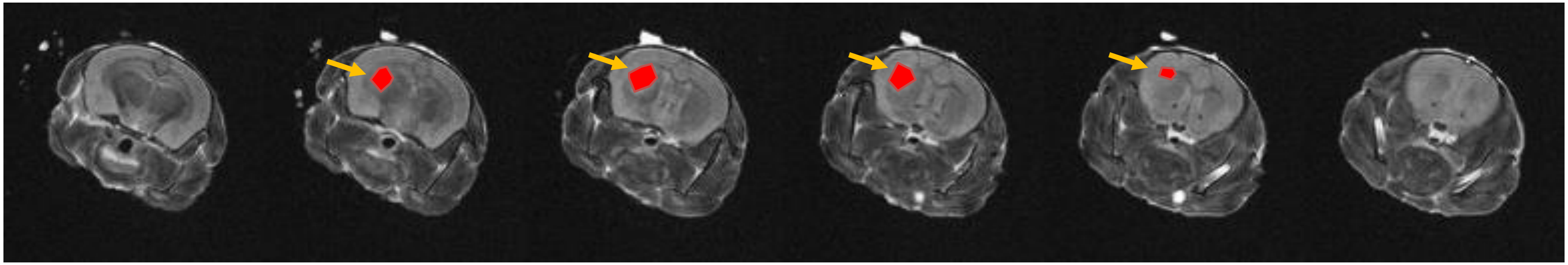




Tumor Segmentation – *Ex Vivo* MRI (T2)

Day 17 – axial

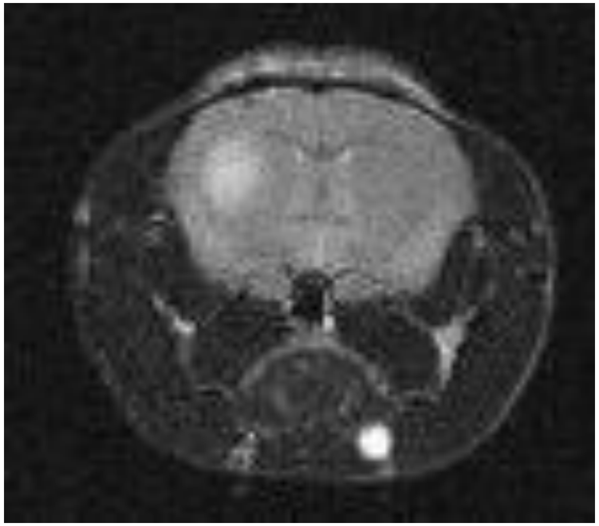


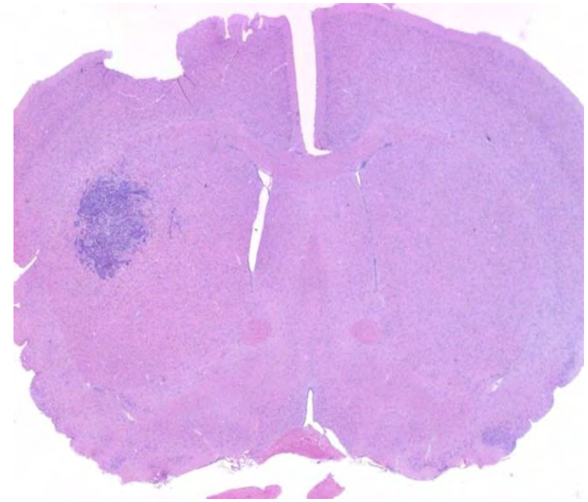


Tumor volume 6.6 mm^3

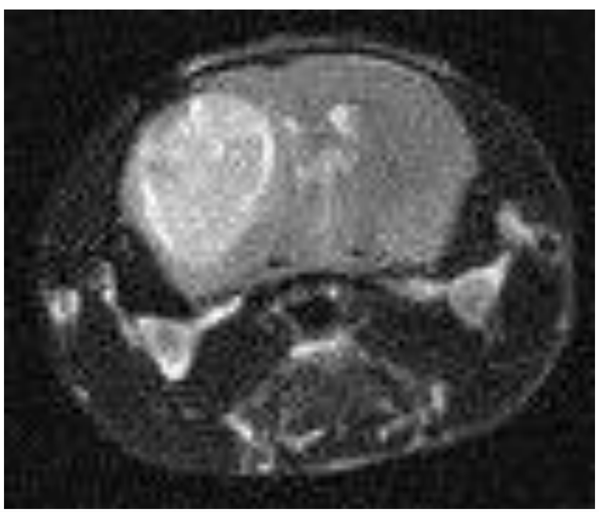
In Vivo MRI vs. Histology

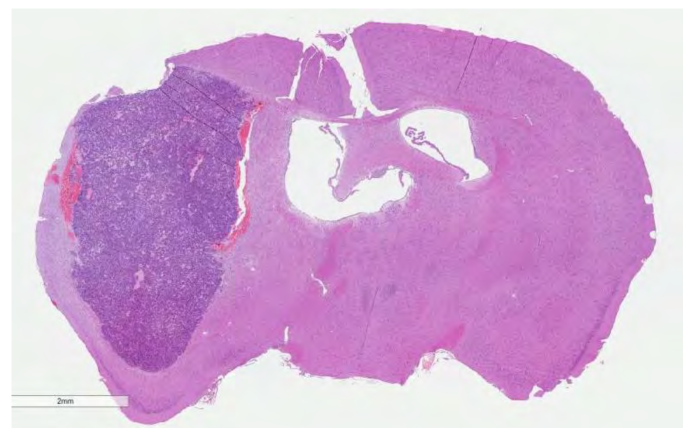
Day 15





Day 20





Summary and Conclusion

- *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

Study: Application of Compact MRI in Lung Metastasis model in mice

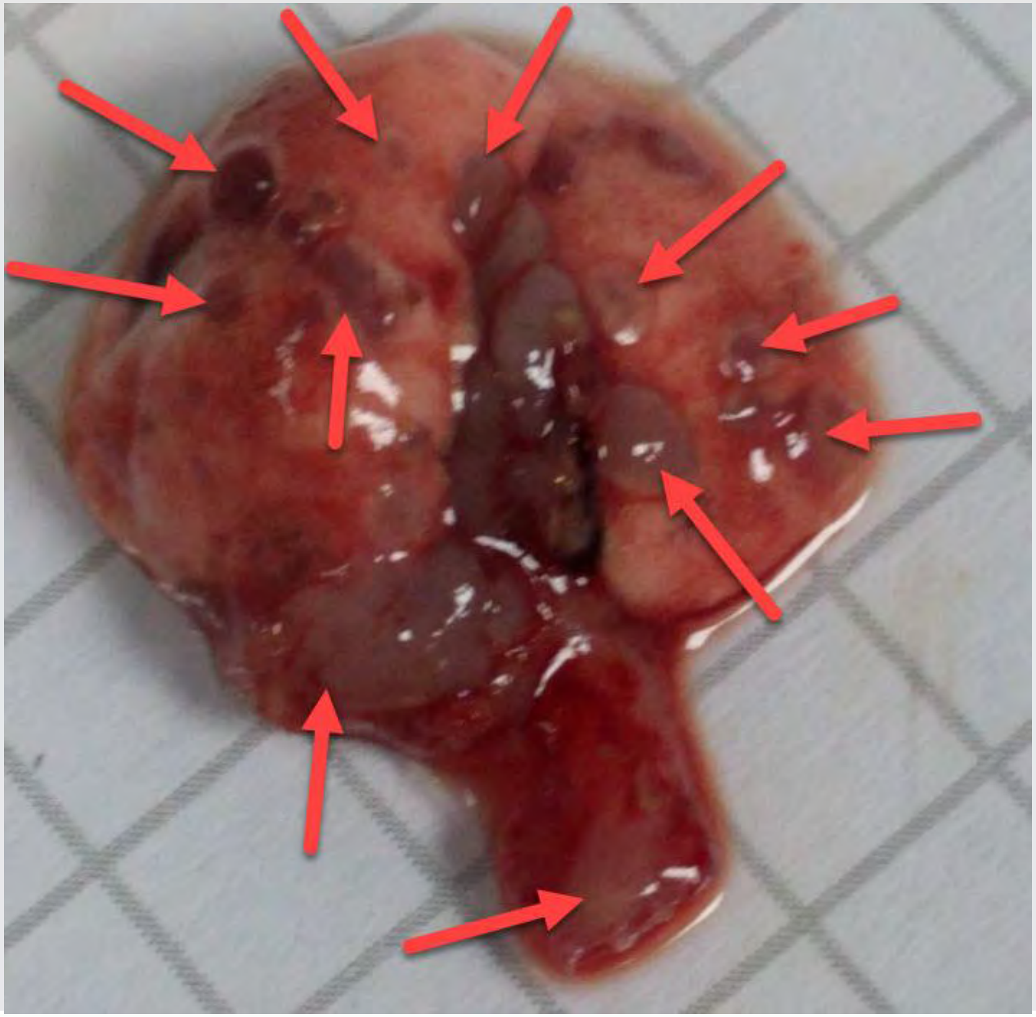
Objectives:

1. Assessment of the potential anti-tumor activity of a novel test item technology in a mouse breast lung metastatic model.
2. Validate the compact MRI as an additional more accurate and high-throughput method for the assessment of anti-cancer efficacy testing.

Experiment:

Intravenous injection of 2.5 X 104 4T1 ATCC cells to the tail of 8-10 weeks-old BALB/c mice. This Tumor is an animal model for Stage IV Human Breast Cancer. Animals were terminated 18 days post tumor induction and Ex-Vivo MRI scanning was accomplished on the lungs.

Macroscopic view of the lungs (before MRI scanning) Arrows indicate nodules of metastatic mammary cancer



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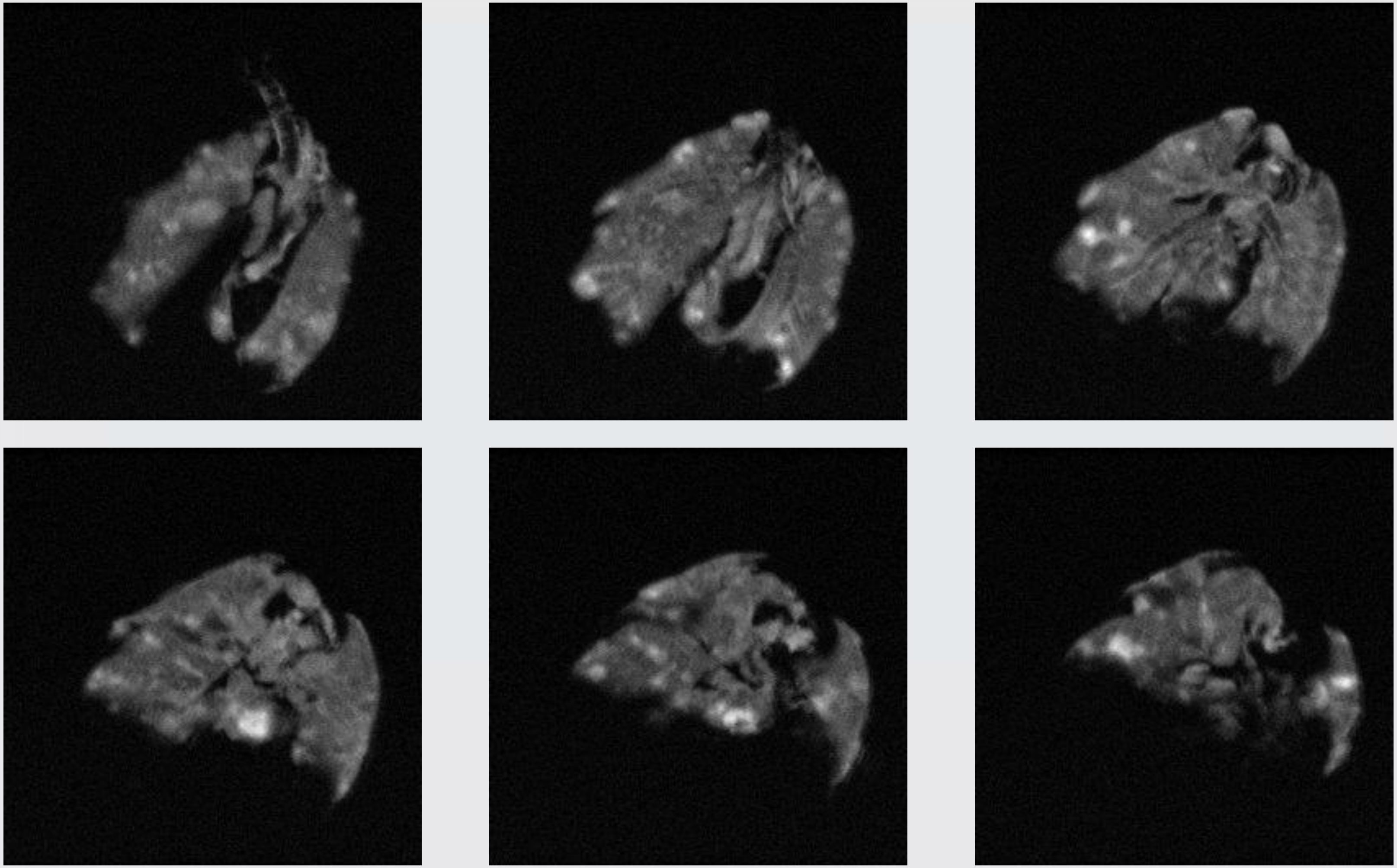
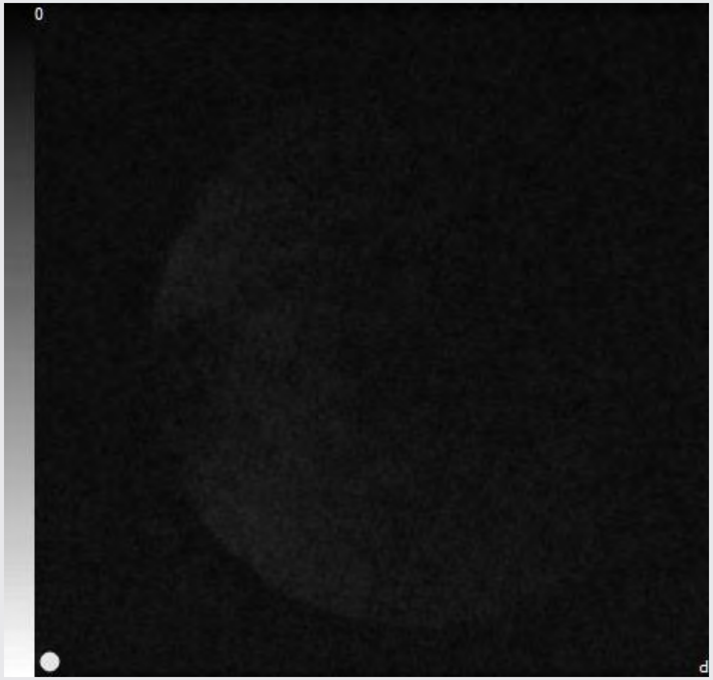
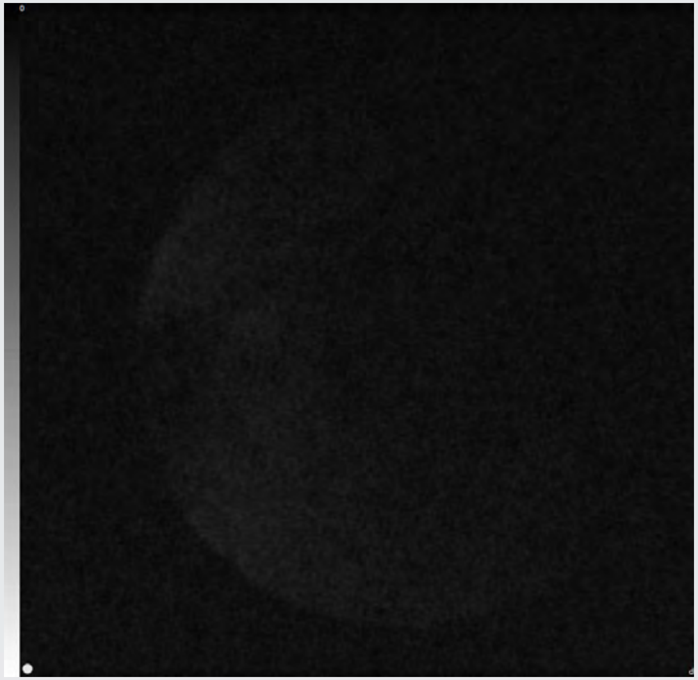
Sample LL3 – Ex-Vivo MRI scanning

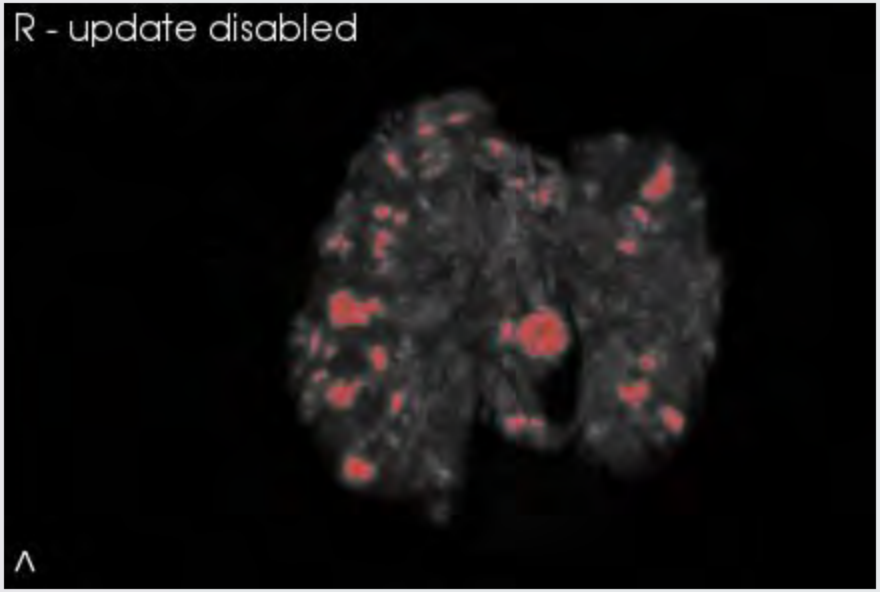


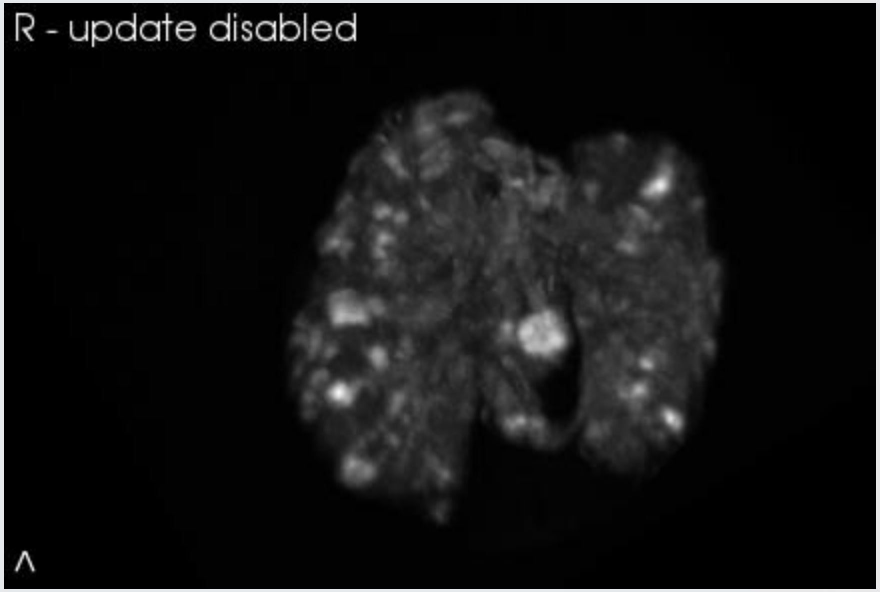
Sample LL3 - Segmentation





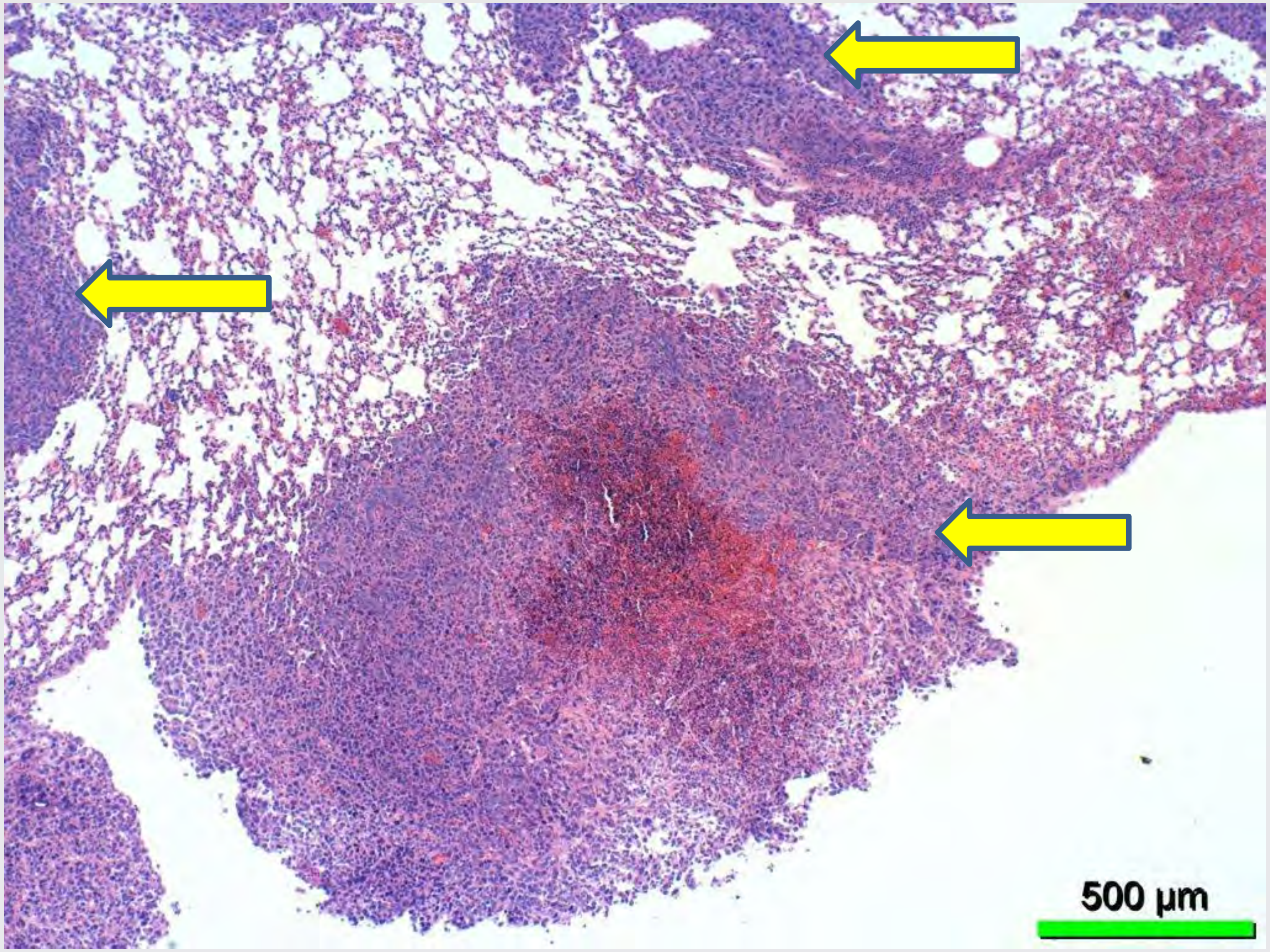
Sample LL3 – 3D rendering and quantification of lesions





ROI	Modality	Color	Voxels	Volume mm³
ROI #1	MR	red	8255	62.9806

Histological confirmation (i.e., validation) of multiple lung cancer nodules (arrows)



Summary and Conclusion

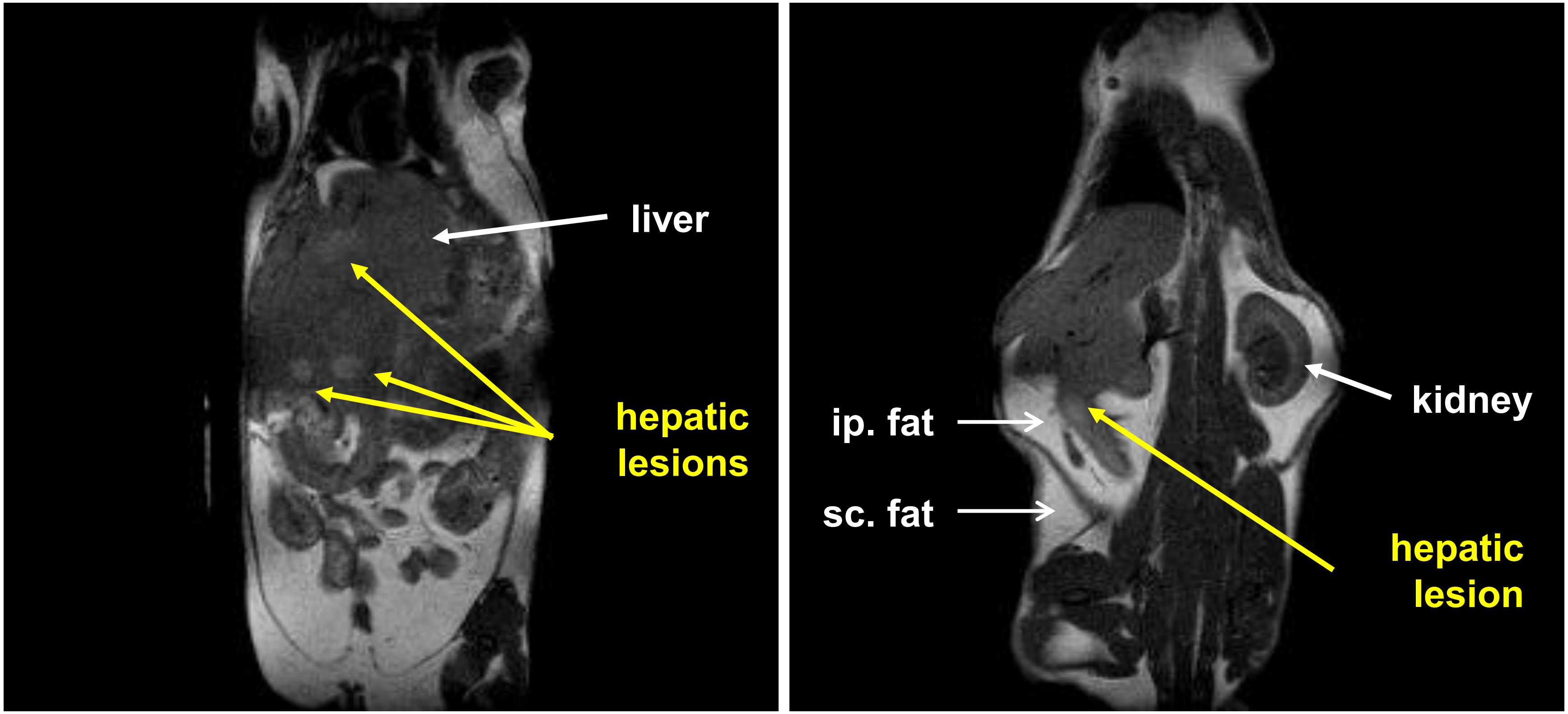
- *ex vivo* MRI evaluation provided a way to accurately determine the number and volume of the tumor within the lungs. This method is far more superior than the currently used macroscopic counting of the cancer nodule

- This model demonstrated the usefulness of the ex-vivo MRI for testing the efficacy of anti-cancer drugs

Concept: MRI in Preclinical Testing of Carcinogenic Potential: Focal hepatic lesions in mice

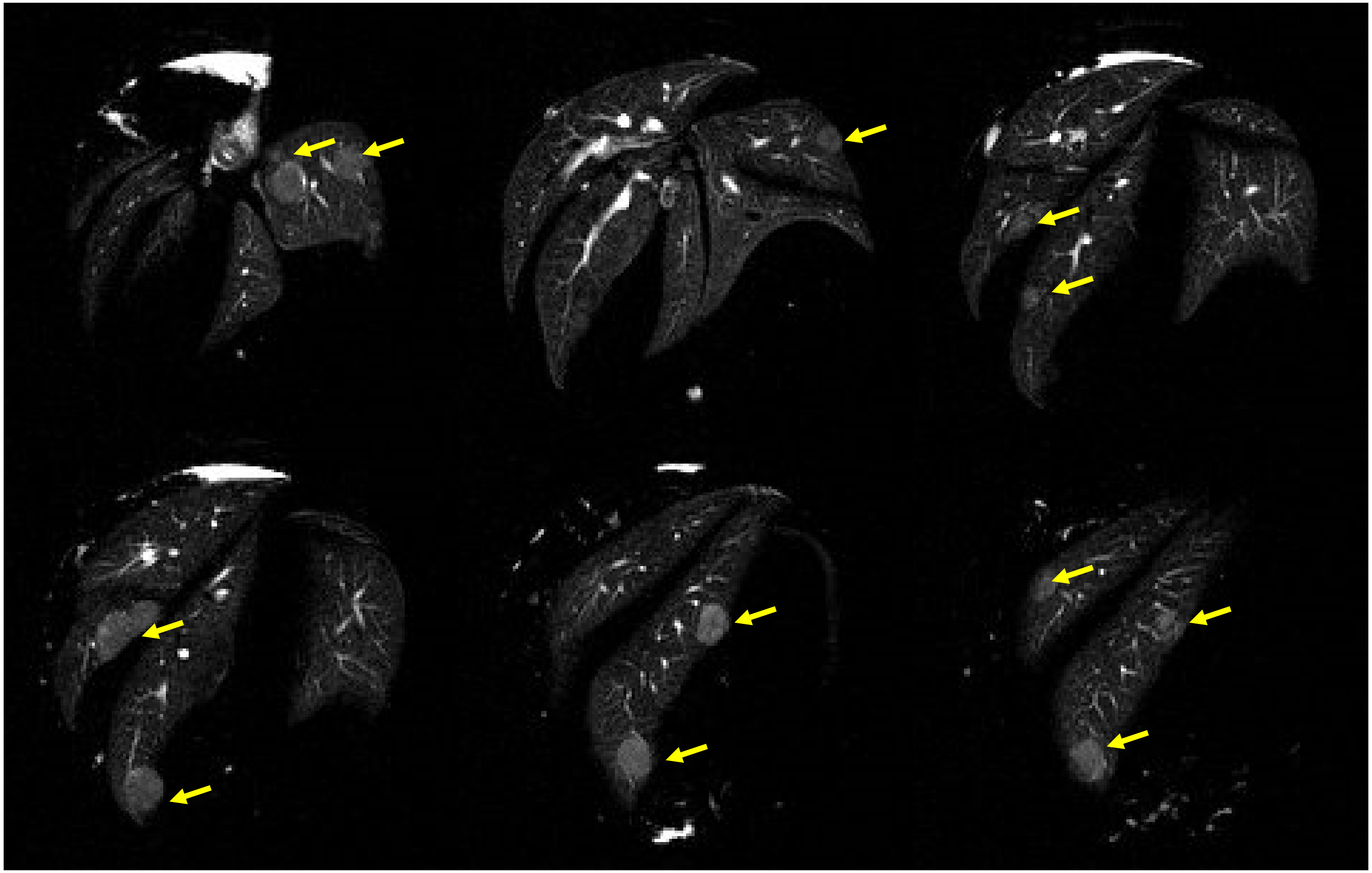
- Model: Mdr-/- mouse develops multiple focal hepatic lesions
- Objective: Detect and measure volume of multiple focal lesions

Detection of Multiple Focal Lesions in Mouse Liver - *In vivo* MRI



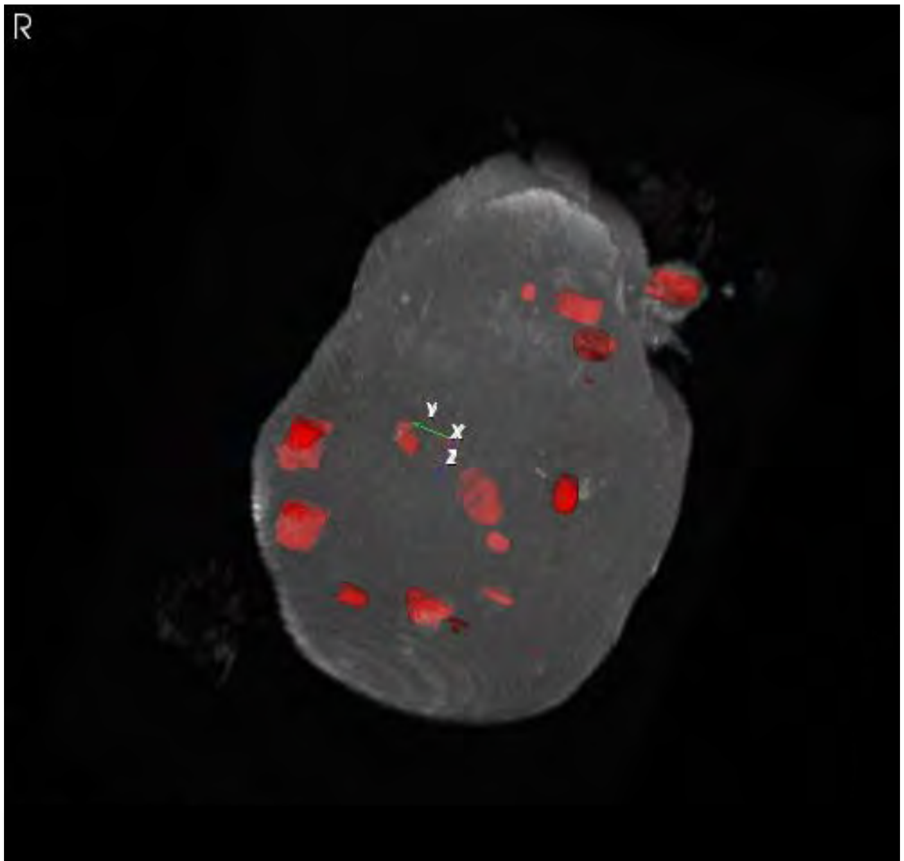
resolution 270 mm; slice thickness 1mm; acquisition time 3.5 min

Multiple focal lesions in mouse liver *ex vivo* MRI



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

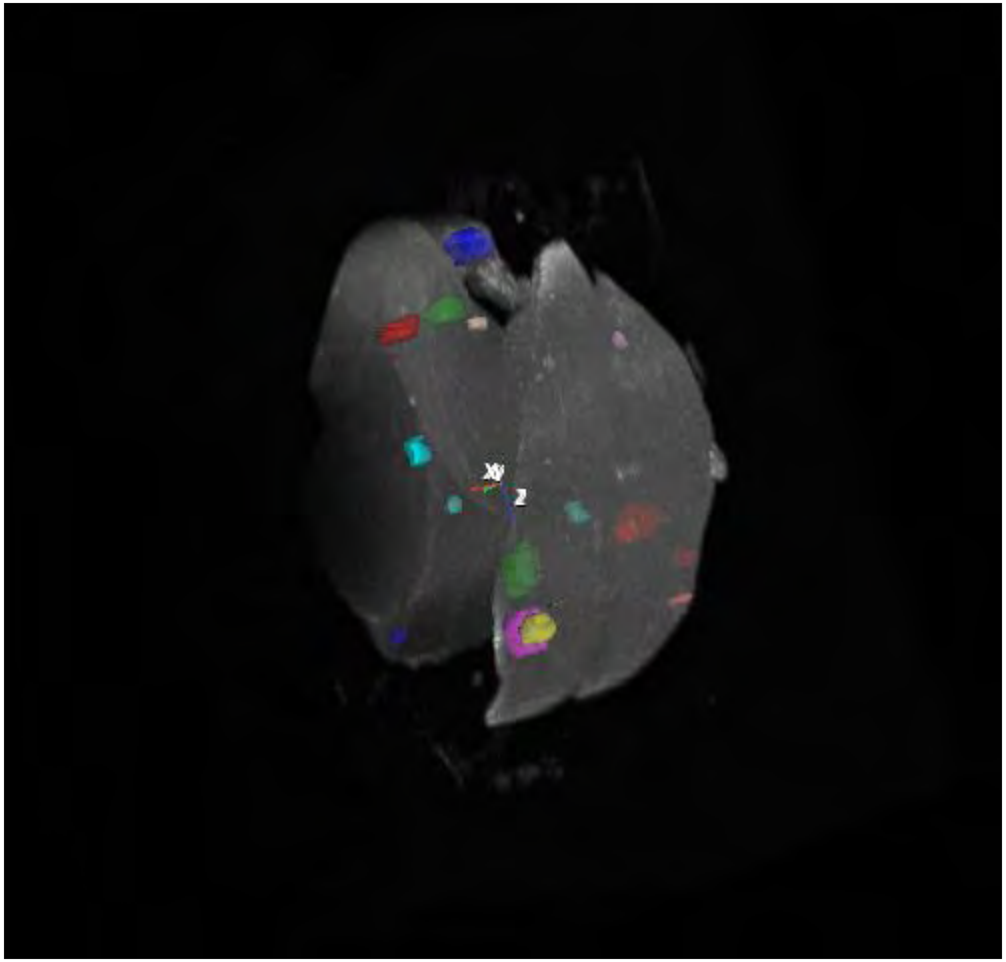
3D rendering + segmentation of Lesions Based on *ex vivo* MRI



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%)

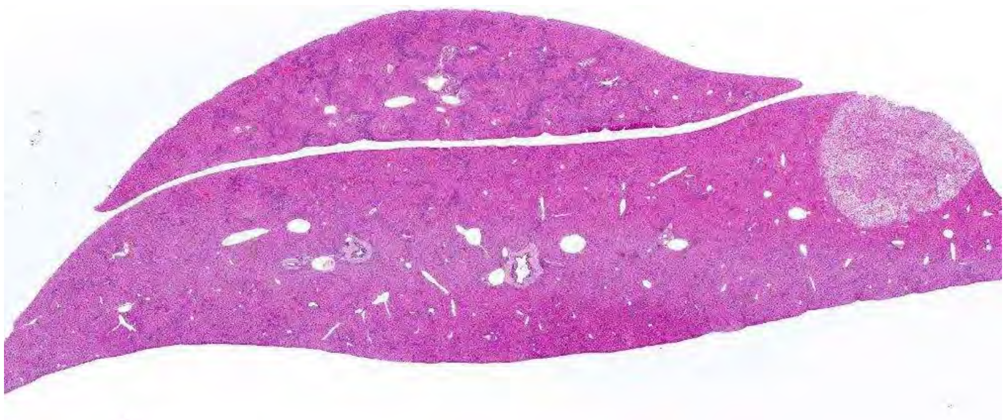
Individual Segmentation of Lesions Based on *ex vivo* MRI

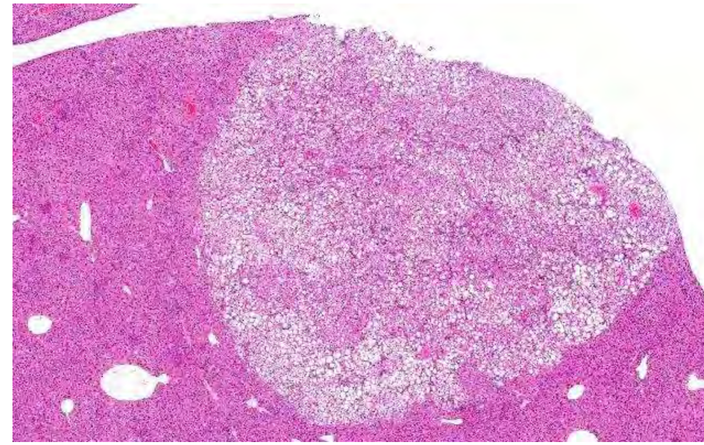


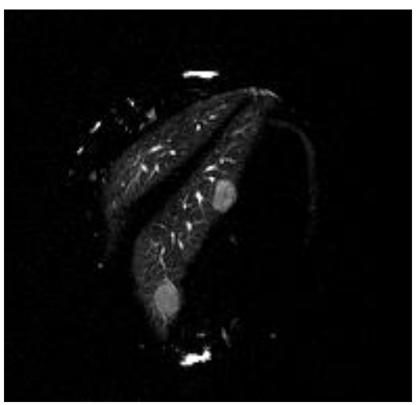
Segmentation of Lesions Based on *ex vivo* MRI

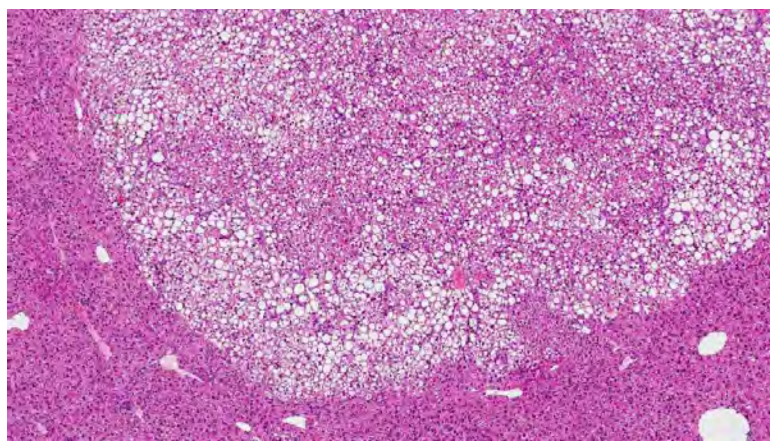
ROI	Colour	Voxels	Volume mm^3
1	Red	701	2.6741
2	Green	950	3.62396
3	Blue	1123	4.28391
4	Cyan	342	1.30463
5	Magenta	2047	7.80869
6	Yellow	831	3.17001
7	Dark red	2271	8.66318
8	Dark green	1961	7.48062
9	Dark blue	204	0.778198
10	Dark cyan	245	0.934601
11	Tomato	201	0.766754
12	Maroon	197	0.751495
13	Orchid	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





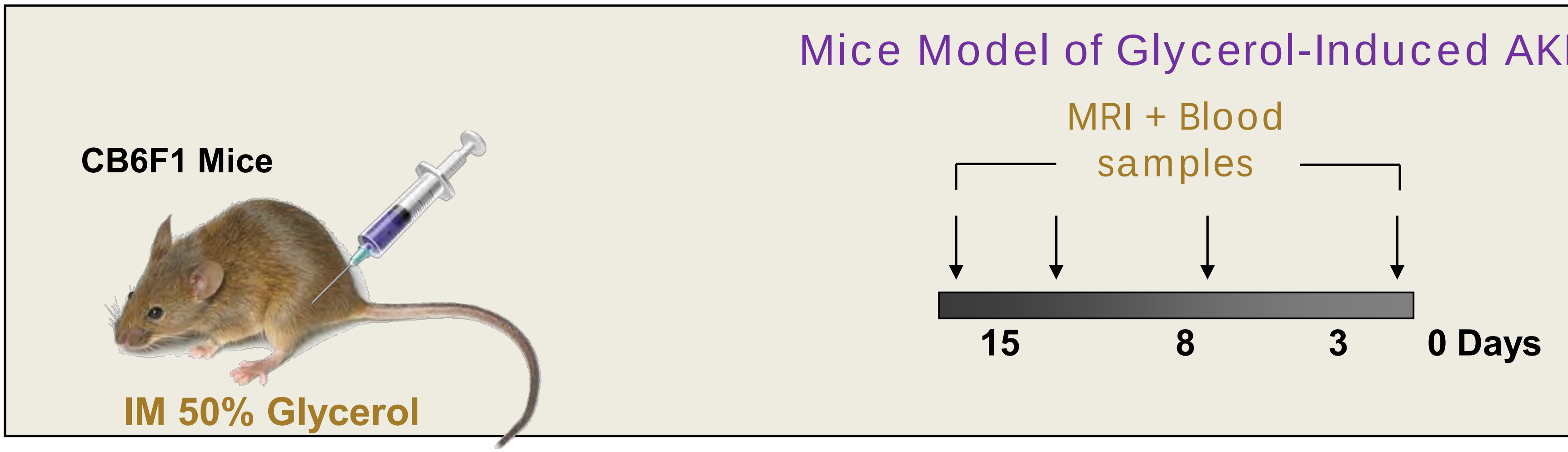




Summary and Conclusion

- *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

Concept: MRI in Preclinical Toxicity Testing of Drugs: Rhabdomyolsis -Induced Acute Kidney Injury (AKI) in Mouse



Control *vs.* Affected Kidney *in vivo* MRI

Day 3

cortex

medulla

Control

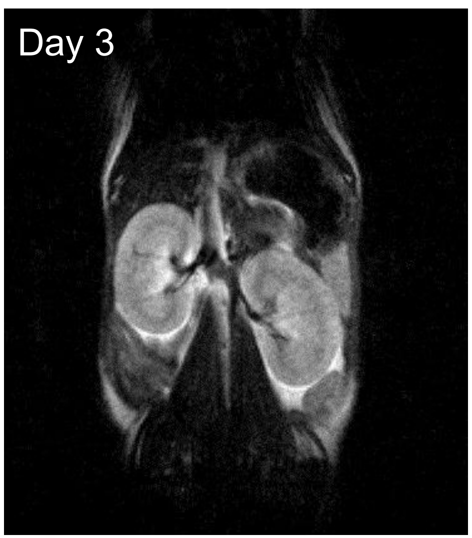
Affected

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

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

Following Disease Progression *in vivo* MRI

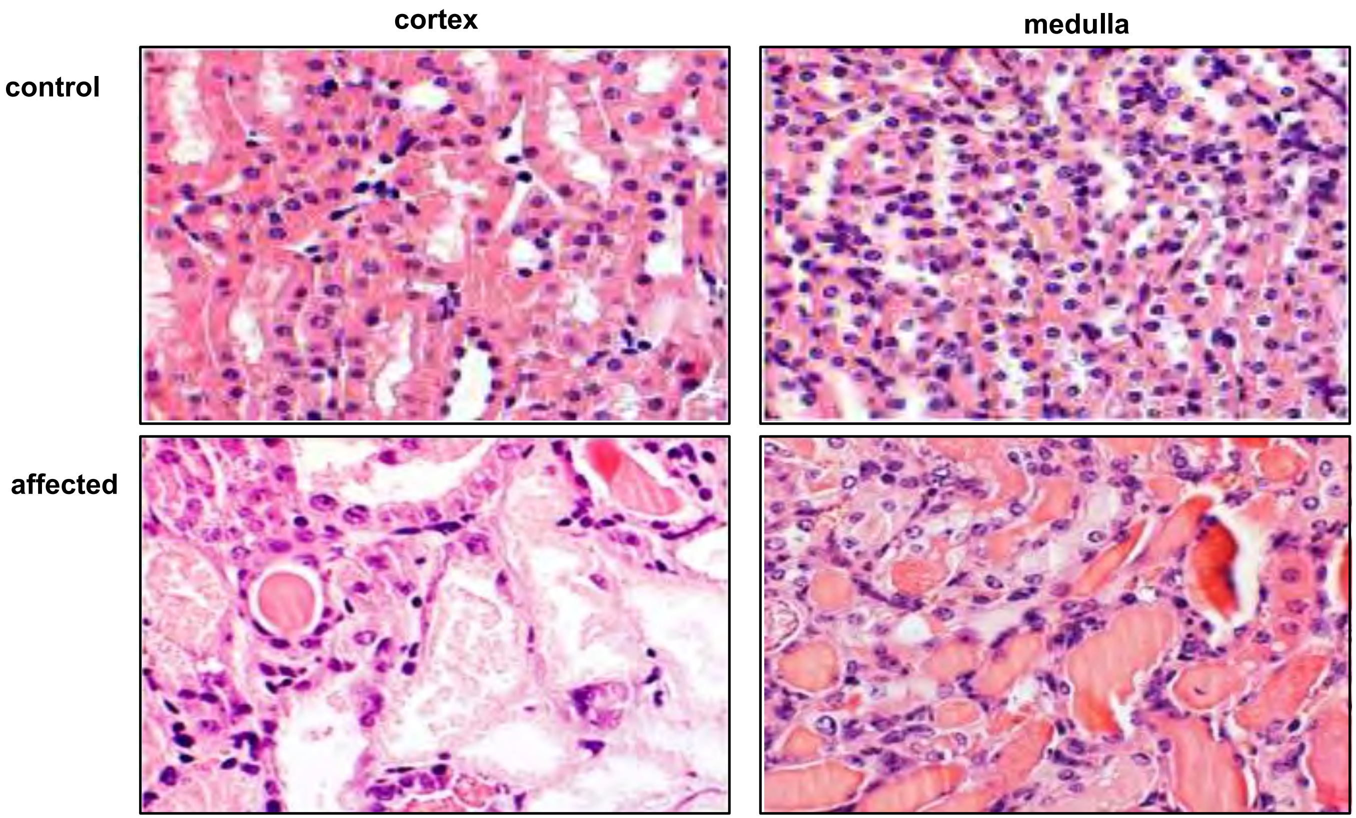
Contrast lost and kidney enlargement



Contrast and size recovered

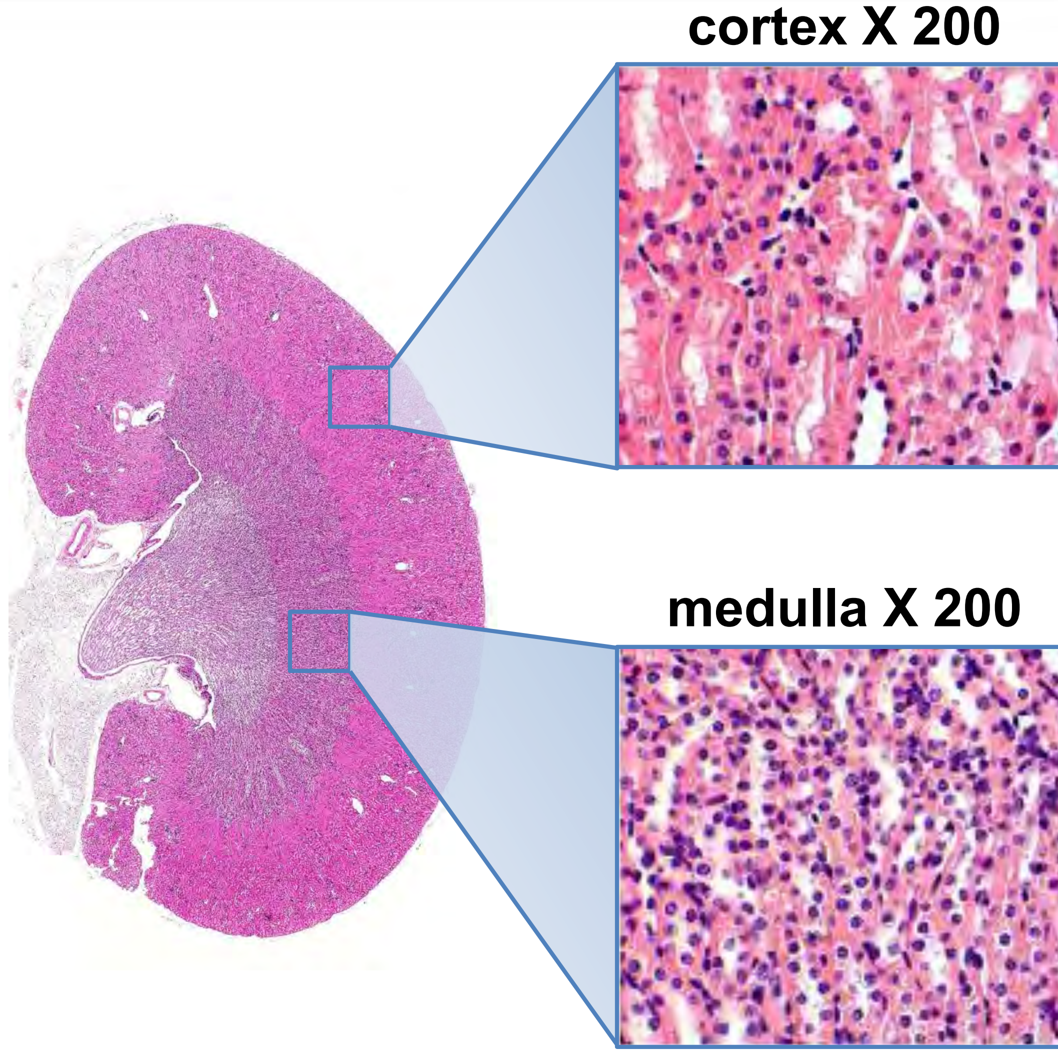
Rhabdomyolsis - Induced Acute Kidney Injury (AKI) in Mouse

Histopathology – Day 3



Ex-Vivo MRI and Histology - Control Kidney

Ex-vivo



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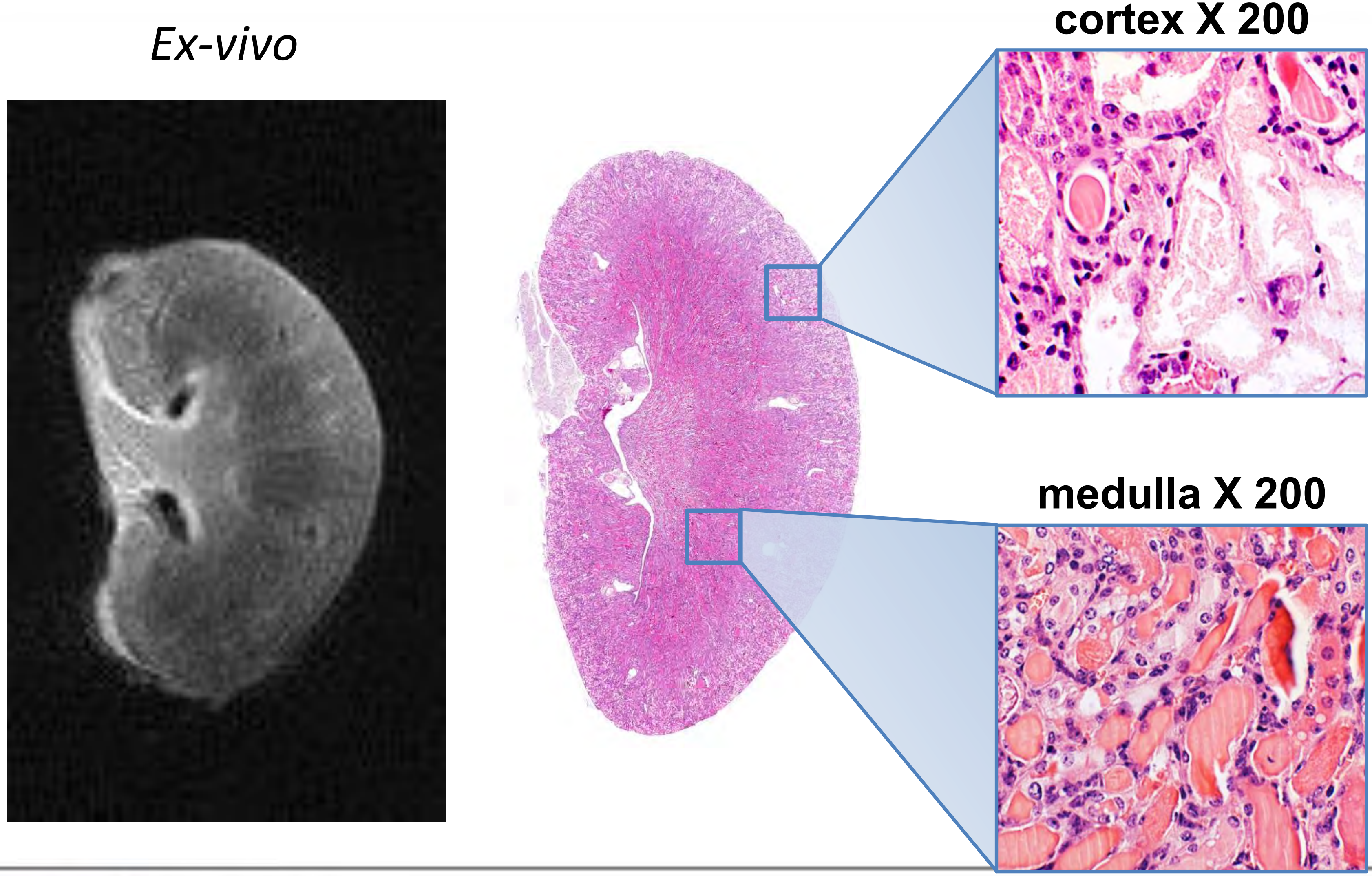
Ex Vivo MRI and Histology - Affected Kidney



Summary and Conclusion

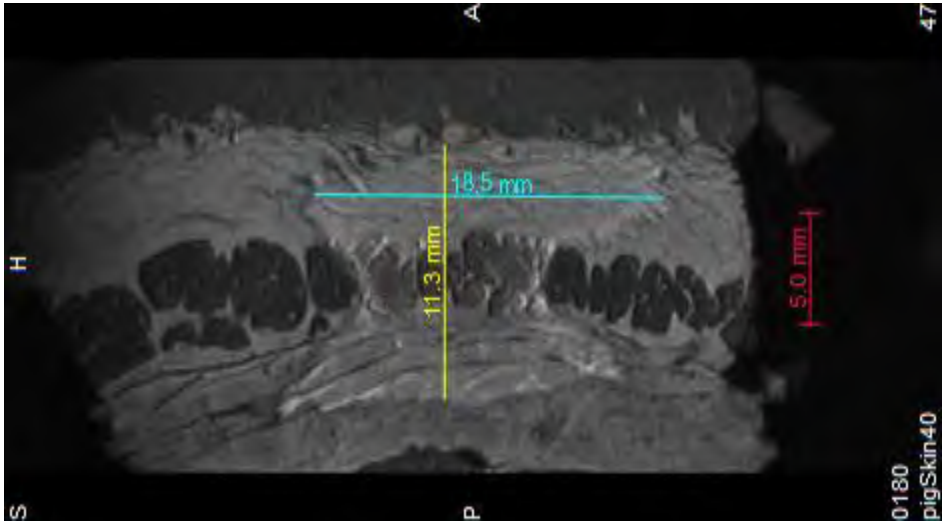
- *In vivo* and *ex vivo* MRI confirmed maximal cortical necrosis and medullary hyaline cast formation, as well as the organ recovery (regeneration).
- *In vivo* and *ex vivo* MRI were effective in identifying time-related toxic alterations in the renal cortex and medulla and their eventual recovery

Concept: MRI in Preclinical Tolerability (Irritancy) Testing of Drugs: Local Safety of Subcutaneous Formulations in the Pig

- 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

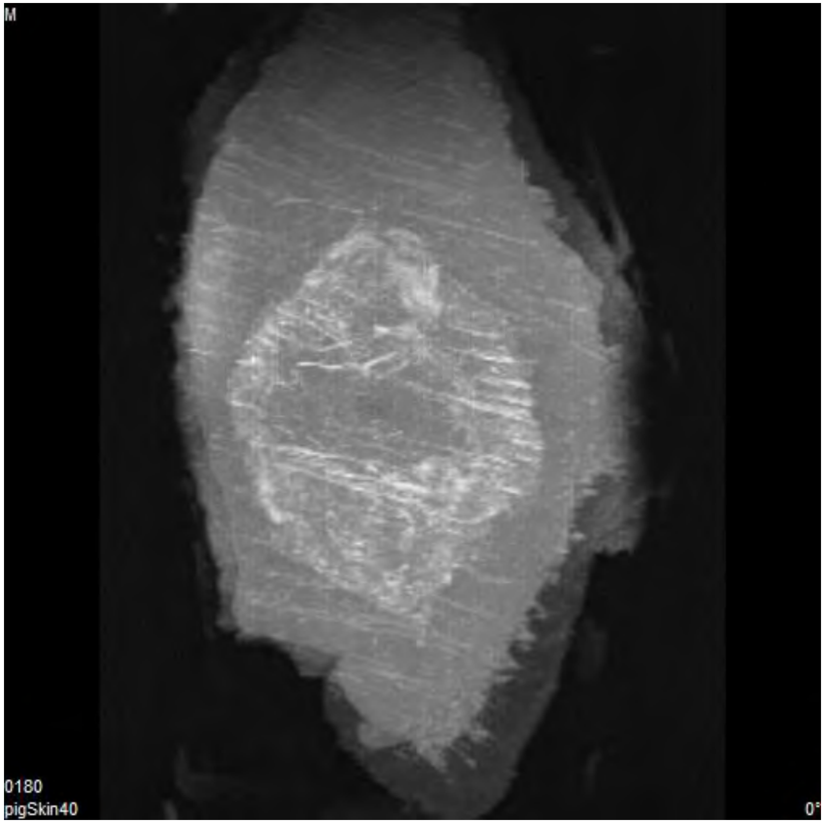
Subcutaneous Drug Injection into Pig Skin MRI *vs.* Histology

MRI (T1)



Histology

3-D Rendering and Segmentation (Quantification) of Affected Volume – *Ex vivo* MRI



Affected Volume **2200 mm^3**

Summary and Conclusion

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

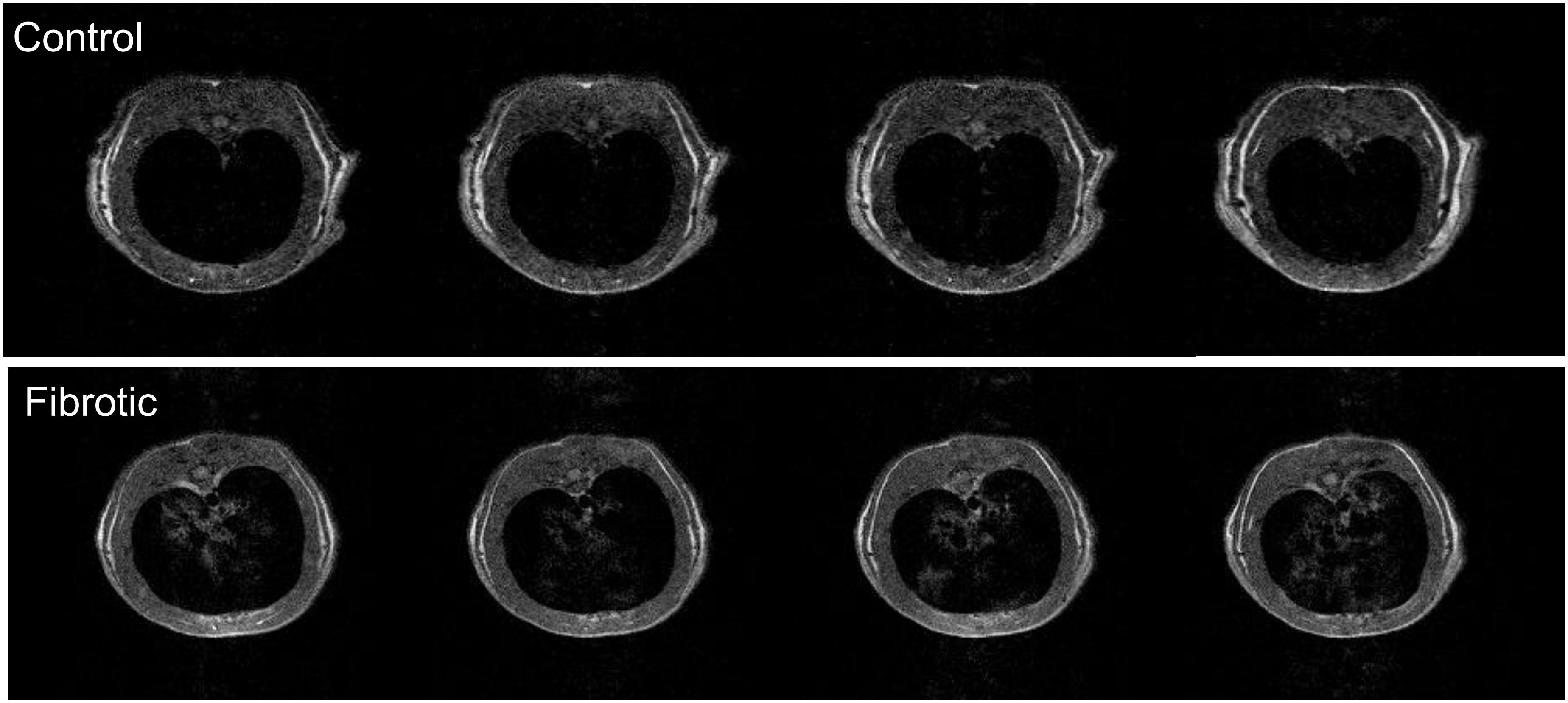
Concept: Preclinical Efficacy Testing of Anti-Fibrotic Drugs: Rat Lung fibrosis Model

- 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

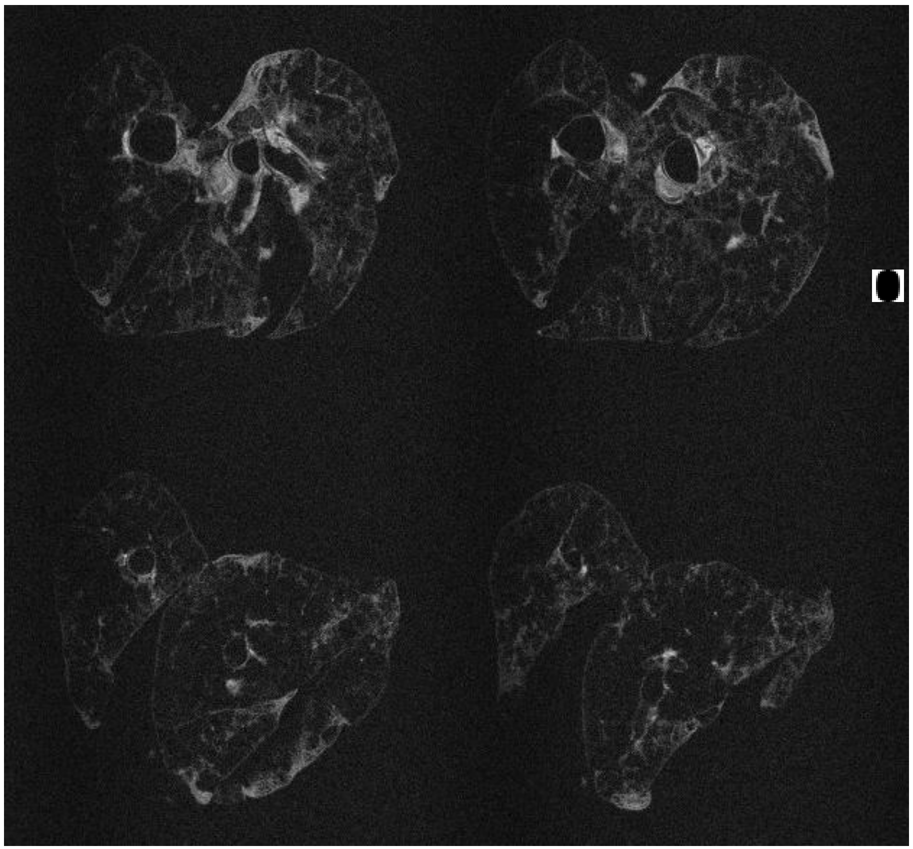


resolution 274 mm; slice thickness 1.2 mm; acquisition time 4.5 min

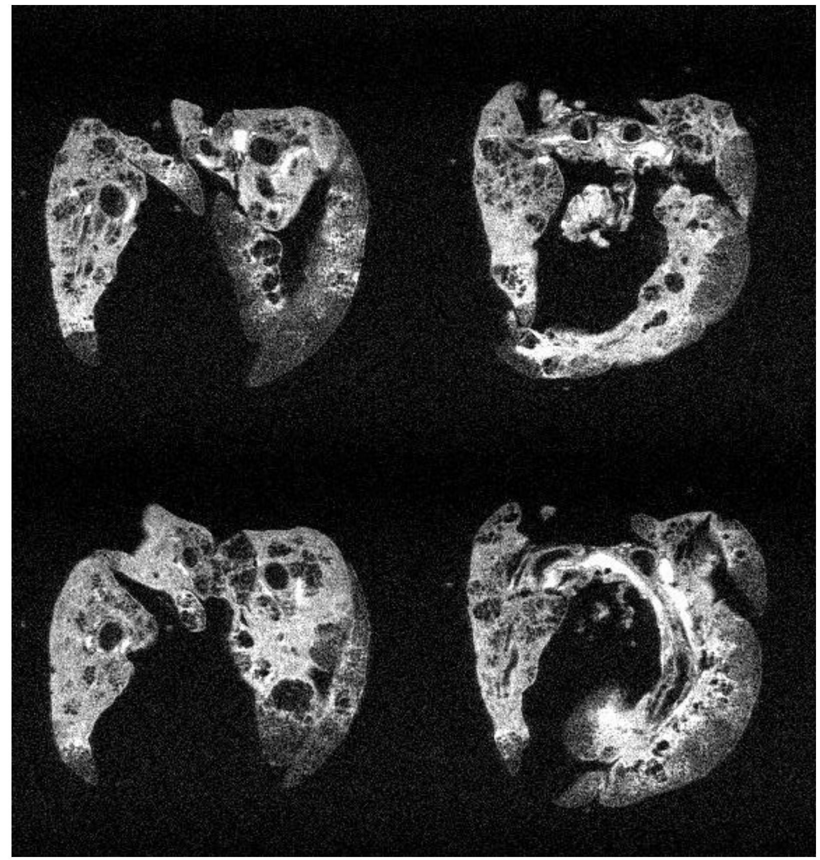
Control *vs.* Fibrosis – *Ex vivo* MRI

Day 11 Post Instillation

Control



Fibrosis



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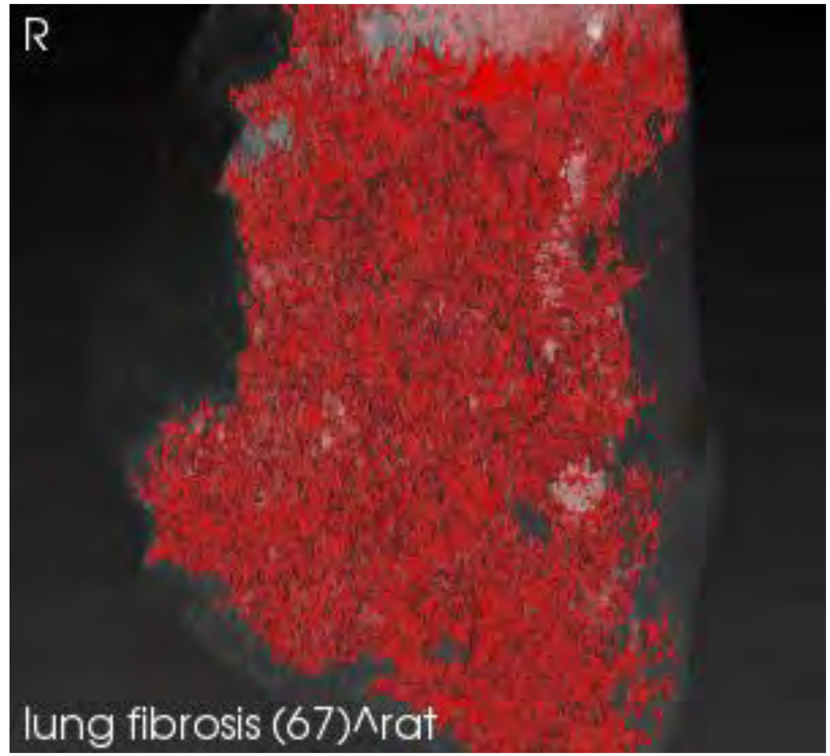
Fibrotic Rat Lung - Volume Quantification Based on *ex vivo* MRI

Day 11 Post Instillation

3D rendering

3D rendering + segmentation



Connective Tissue: **1267 mm^3**
Normal Tissue: 1396 mm^3

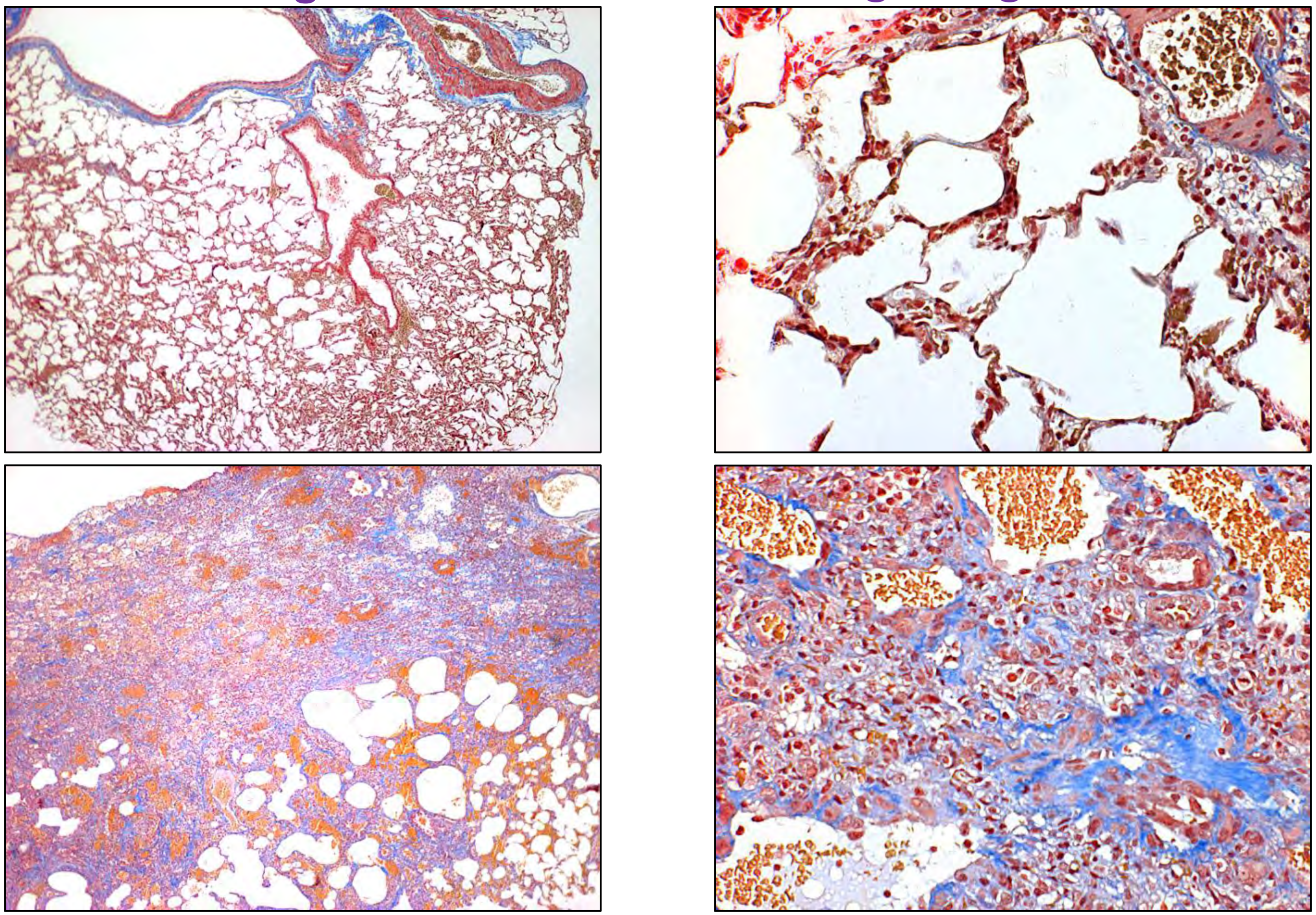
Histology - Masson's Trichrome

Low Magnification

High Magnification

Control

Fibrosis



Summary and Conclusion

- *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
- *vivo* MRI and *Ex vivo* MRI are capable to quantify the extent of disease, helping to compare the efficacy of different therapeutic modalities

In Conclusion: 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

MR HISTOLOGY: THE RATIONALE OR JUSTIFICATION FOR ADOPING IT

- Entire organ scanning for non-uniform tissues (e.g. uterus, brain). We can find lesions for which there is no other reliable alternative to identify of their existence
- Pre-screening of known target organs so that no detectable lesion is missed. This lessens the chance of getting equivocal results when it comes to low tumor burdens
- Most accurate results for tumor quantification endpoints
- Establishment of objective grading schemes based on characteristics that can be measured (percentage of organ affected, number of lesions present)
- Volume measurements made possible
- Longitudinal tracking of the progression of a lesion (i.e., testing on the same animal, and by this, saving number of animals in the experiment)

Regulatory Perspectives...

- Citing from Dr. Bob Maronpot's view concerning the future use of imaging data in conventional pre-clinical studies submission to the FDA (i.e., this view was stated when dealing with a draft manuscript, now in preparation for Toxicologic Pathology, section sponsored by the Regulatory Committee of the STP, dealing with future application of imaging technologies):

- "...We just have to take the stance that imaging as an adjunct to conventional histopathology makes the histopathology that much better and allows for better sampling. The imaging also provided three-dimensional quantitative data. I suspect providing imaging along with conventional histopathology could have positive regulatory consequences ... Once FDA starts getting that sort of information, it may evolve to become a desirable component of a submission. "

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Thank You

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