RSNA R&E Foundation Education Scholar Grant
SAMPLE APPLICATION

NOTE: Personal information for the applicant and other investigators has been removed from this sample application.

Title:

Toward Clinical Translation of Interventional Molecular Imaging: An Educational Program for New Generations of Interventional Radiologists

Abstract:

Molecular imaging is an emerging technology for in vivo detection of biological events at molecular/cellular levels. It has demonstrated great promise in early diagnosis of diseases and precise guidance of advanced treatments, such as gene and cell therapies. Recent common interest in molecular imaging among diagnostic and interventional radiologists has led to a new concept, called “Interventional Molecular Imaging.” This concept, by combining interventional radiology (IR) with molecular imaging, aims to fully apply the advantages of both imaging fields. Specifically, interventional radiology can extend the capabilities of currently-available molecular imaging techniques in (i) reaching deep-seated targets; (ii) getting a close look at small targets; (iii) precisely guiding delivery of non-targeted imaging tracers/therapeutics; and (iv) super-selectively enhancing the effectiveness of targeted imaging and treatment.

To prompt successful translation of interventional molecular imaging from benches/animal labs to clinical practice, one of crucial steps is to get the new generations of interventional radiologists prepared for application of this new technology. To this end, we have designed an educational program that will provide IR trainees hands-on experience in interventional molecular imaging. Through practicing a relatively complex IR procedure, transjugular intrahepatic portosystemic shunt (TIPS), with subsequent molecular MRI-guided intraTIPS agent delivery on near-human-sized pigs, the trainees will not only gain understanding of the concept of interventional molecular imaging but also become familiar with the necessary techniques. We propose a 3-phase program, including (i) a 2-hour theory course on TIPS and interventional molecular imaging; (ii) a pre-clinical hands-on training on the TIPS procedure and subsequent MRI-guided intraTIPS agent delivery; and (iii) a hands-on experience in confirming successful agent delivery using various laboratory methods.

Our long-term goal is to attract the interest and attention of new IR generations to molecular imaging-integrated interventional technologies, and thereby facilitate the translation of interventional molecular imaging to clinical practice on humans.

Percent of Time Dedicated to this Project:
10% PI, 10% co-investigator

Priority Statement:

Molecular imaging, a frontier in modern medicine, is becoming a new member of medical imaging family. In the past years, RSNA has asserted tremendous effort in promoting the translation of molecular imaging to clinical practice. The progress of such translation has been slow, with the majority of the molecular imaging modalities remaining at the technical developmental phases. A primary reason for this is that many sophisticated molecular imaging techniques are developed by PhDs through multidisciplinary collaborations, including biomedical engineering, molecular biology, chemistry, and computer science. However, these PhDs do not have direct access to clinical patient care. On the other hand, most of practicing physicians are focused on busy routine clinical services. They do not really have opportunities to personally experience the advances in the basic scientific field of molecular imaging. In recent years, National Institute of Health (NIH) has emphasized “translational medicine,” which primarily aims to fill the gap, to establish the links between basic science and clinical practice. As an MD and PhD, I have been involved in both basic research and clinical practice in diagnostic imaging and interventional radiology (IR) for more than 20 years. I am confident that my MD/PhD background enables me to function as a “bridge” to bring the sophisticated molecular imaging techniques from benches/animal labs to clinical application on humans. In a recent issue of Radiology, I have initiated a new concept, named “Interventional Molecular Imaging.”1 This concept, by combining interventional radiology with molecular imaging, is aiming to fully apply the advantages of both imaging fields. In fact, interventional radiology can overcome many disadvantages of the current molecular imaging techniques. Interventional molecular imaging is becoming one of the frameworks to bring molecular imaging from benches/small animal labs to large animal suites, and to certain clinical applications in humans. It is time to

educate the new generations of interventional radiologists the new concept of interventional molecular imaging. To this end, we have proposed the present educational program via RSNA. In this program, by providing the IR trainees an opportunity to have initial hands-on practice of one of the most complicated IR procedures, transjugular intrahepatic portosystemic shunt (TIPS), we will introduce the trainees the concept of using molecular MRI to monitor intraTIPS delivery of diagnostic agents and, ultimately, therapeutic agents to inhibit one of the most common complications associated with this procedure, post-TIPS stenosis and occlusion. We strongly believe that the hands-on training on the complex TIPS procedure with molecular MRI-guided intraTIPS agent delivery should function as a vehicle to attract the interest and attention of new IR generations to molecular imaging-integrated interventional technologies, and thereby facilitate the translation of interventional molecular imaging to clinical practice on humans.

Budget:

(*Budget details have been **removed** from this sample*)

A. Personnel

- Xiaoming Yang, MD, PhD, Principal Investigator (10% in years 1 and 2)
- Feng Zhang, MD, PhD, Program Assistant (10% in years 1 and 2)

B. Supplies:

- Imaging Contrast Agents will be used for both DSA and MRI
- Glassware & Disposables (saline, culture, pipettes, etc) will be used to carry out in vivo experiments.
- Catheters & guidewires is needed to perform endovascular interventional procedures

C. Other Expenses:

- MR Scans: The subjects will be scanned on the Philips Achieva 3T Scanner
- X-ray imaging: The animals will undergo X-ray imaging-guided TIPS at UW South Lake Union Campus
- Domestic pigs will be purchased to prove the principle of the new concept
- Shipping and Processing fees
- Comparative Medicine Services: $1,200/pig
- Animal Housing:

Other Investigators:

Feng Zhang, MD, PhD
Research Scientist (1.2 Calendar Months in years 1-2), is a radiologist with comprehensive experiences on both medical imaging and interventional radiology. Dr. Zhang has worked on animal studies for several years. He is a primary scientist in our several projects on intraluminal MRI-guided delivery of tracers and therapeutics, such as genes and drugs. As an assistant of the educational program, Dr. Zhang will be responsible for coordinating the surgical and MR schedules, functioning DSA-surgical labs, operating MRI-guided intraTIPS agent delivery, carrying out pre- and post-procedure care of animals, processing data analysis of MRI-histologic correlation, and preparing a potential manuscript resulted from the educational program for Radiology.

Detailed Education Plan: (See Next Page)

A. Detailed Research Plan:

A.1. Introduction:

A.1.1. Rationale and Purpose:

Molecular imaging, an imaging technology capable of *in vivo* detecting biological events at the molecular/cellular level, has demonstrated great promise in early diagnosis of life-threatening diseases and precise guidance of advanced treatments, such as gene and cell therapies[2]. Recent common interest on molecular imaging among both diagnostic and interventional radiologists has led to establishing a new concept, called "Interventional Molecular Imaging"[1]. Interventional radiology (IR) can extend the capabilities of sophisticated molecular imaging techniques. Interventional molecular imaging is becoming one of the frameworks to bring molecular imaging from benches/animal labs to clinical applications in humans.

The purpose of the current program is to educate IR trainees (including IR fellows and residents as well as interventional scientists) the new concept of interventional molecular imaging, by providing them the opportunity to combine molecular MR imaging with the initial hands-on practice on one of the most complicated interventional procedures, transjugular intrahepatic portosystemic shunt (TIPS).

A.1.2. Objectives:

We hypothesize that the proposed educational program should provide IR trainees the knowledge and basic skills on interventional molecular imaging. Primarily, through the educational program, the trainees should be able to:

(1) Gain the initial hands-on experience on the basic techniques/steps of performing a TIPS procedure on near-human-sized pigs before they become skillful in clinical practice of such complicated interventional procedure on humans.

(2) Be familiar with the concept of interventional molecular imaging. By using the post-TIPS pig as a study model, the trainees will learn how to apply molecular MRI in monitoring intraTIPS delivery of an intracellular MR tracer to the TIPS walls, and, ultimately, a therapeutic agent to inhibit post-TIPS stenosis and occlusion.

(3) Develop academic interest in promoting clinical translation of advanced interventional molecular imaging techniques in treating disorders of various luminal organ systems, such as the gastrointestinal tract, urinary tract, female reproductive tract, and vasculatures.

A.1.3. Student population:

IR fellows and residents, as well as interventional scientists who are working on molecular imaging.

A.1.4. Previous experience:

Preliminary Works — An intraluminal MRI-guided interventional technology: We have developed a novel intraluminal MRI-guided interventional technology, with its key component — a FDA-approved intraluminal MR imaging-guidewire (MRIG)(Fig. 1).

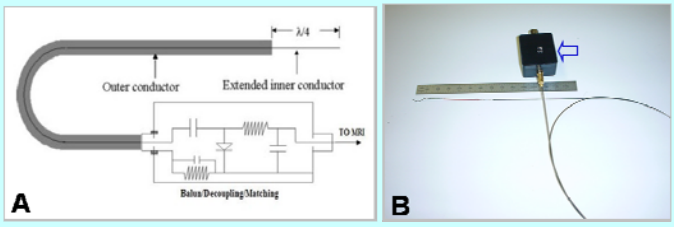

Fig. 1. (A) Electronic design of the MRIG, which is a co-axial cable with extension of its inner conductor. (B) A 0.032-inch MRIG, which can be connected to an MR scanner via the turning box (open arrow).

The MRIHG has unique "3-in-1" functions as (i) an intraluminal MR antenna for generating high-resolution MRI of luminal walls (such as the vessel wall)(Fig. 2)[3, 4]; (ii) a conventional guidewire for guiding intraluminal interventional procedures (such as endovascular balloon angioplasty and gene delivery)(Fig. 3)[3, 5-7]; and (iii) an intraluminal radiofrequency (RF) heating source for enhancing therapeutic effects (such as vascular gene therapy)(Fig. 4)[8-11].

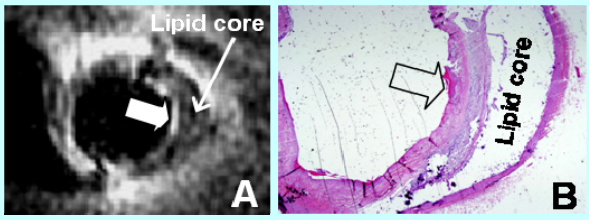

Fig. 2. (A) MRIG-mediated intravascular high-resolution MRI of an atherosclerotic vessel wall, clearly showing the fibrous cap (large arrow) and the lipid core. (B) Histology confirms a typical plaque with the fibrotic cap (arrow) and the lipid core. H&E stain.

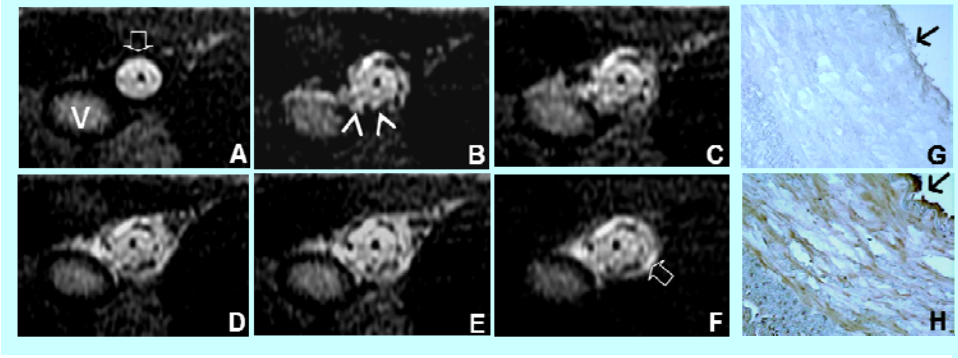

Fig. 3. Intravascular real-time MRI monitoring the transfection of gadolinium/green fluorescent protein (GFP) gene into the iliofemoral artery. ***A,*** Before gadolinium/GFP infusion, the plasty balloon is inflated with 3% T1-MR contrast agent. The open arrow indicates the artery. V=vein. ***B-F,*** During gadolinium/GFP infusion from minute 3 to minute 15 (at 3-minute intervals), the arterial wall is enhanced by the gadolinium coming from the gene infusion channels (arrowheads in ***B***) of the delivery balloon. At minute 15, the arterial wall is enhanced as a ring (arrow in ***F***). ***G&H,*** Immunohistochemistry of the control (***G***) and gadolinium/GFP-transfected (***H***) arteries. GFP is detected as brown-colored precipitates through all layers of intima (arrows) and media as well as adventitia.

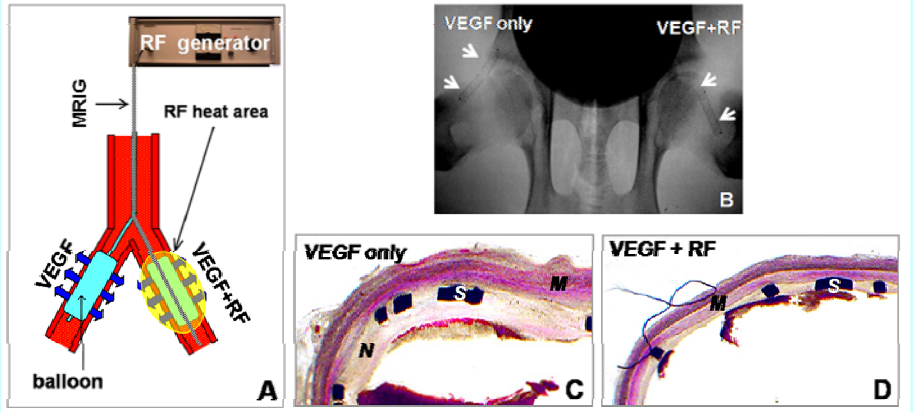

Fig. 4. Intravascular MRI-guided/radio- frequency (RF) heating-enhanced vascular endothelial growth factor (VEGF) gene therapy of in-stent stenosis. (A) Experimental design. The same amount of VEGF genes are locally delivered into bilateral stented iliofemoral arteries, while left gene-targeted artery is heated by RF via the MRIG. (B) X-ray imaging shows two stents (arrows) placed in bilateral iliofemoral arteries, while the right side treated with VEGF gene-only and the left side treated with VEGF gene plus RF-heating. (C&D) Axial histology shows less neointimal hyperplasia in VEGF/RF-treated left artery (D) than that in VEGF only-treated right artery (C). S=stent; M=media; N=neointima hyperplasia. H&E staining.

Based on these comprehensive experiences on the intraluminal MR technology, we will develop a novel interventional molecular imaging technology, named “IntraTIPS MRI-guided local delivery of therapeutics.”

At its initial step, the current educational program will focus only on intraTIPS MRI-guided local agent delivery technique. The scientific results achieved from this educational program could be considered as preliminary data to facilitate our further application of an extramural fund, which should enable us to expand this educational program to the next step, providing new IR trainees a chance to work on the development of a novel interventional technology – intraTIPS MRI-guided, radiofrequency (RF)-enhanced local gene/drug prevention of intraTIPS stenosis or occlusion.

A.2. Project Plans:

A.2.1. Activities:

A.2.1.1. Program sessions: The educational program will consist of three primary sessions, including (i) a 2- hour theory course on TIPS procedure and interventional molecular imaging; (ii) an initial hands-on exercise on the TIPS procedure with intraTIPS MRI-guided local agent delivery; and (iii) a training on basic skills of several laboratory methods for final MRI-histologic correlation and confirmation of successful intraTIPS agent delivery.

A.2.1.2. Activity Plan:

1. Theory course: All trainees will first participate in a 2 hour lecture on (i) the concept, basics, and current perspectives of TIPS; and (ii) the concept of interventional molecular imaging and its application in TIPS.

2. Preclinical hands-on training of TIPS procedure: All trainees will be enrolled in the initial hands-on practice for the basic steps of TIPS procedure and then use the TIPS model to practice the intraTIPS MRI-guided agent delivery approach. Figure 5 demonstrates the practice design.

(a) The hand-on practice will be performed on near-human-sized domestic pigs (60 Kg). The rationale for using pig is that the anatomic and physiologic characteristics of pigs are very similar to those of humans[12, 13].

(b) Pig management: We will use our standard protocols to manage the pigs pre-, during-, and post-procedure.

(c) TIPS procedure: We will perform TIPS using the established protocol. Briefly, under ultrasound imaging guidance, the right internal jugular vein will be accessed, and a TIPS access set will be advanced into a hepatic vein. After achieving the access to the right portal vein from the hepatic vein with the TIPS set needle, a pre-procedure portogram will be achieved and then a MR-compatible Viatorr stent will be deployed within the portosystemic shunt under fluoroscopy guidance (Fig. 6).

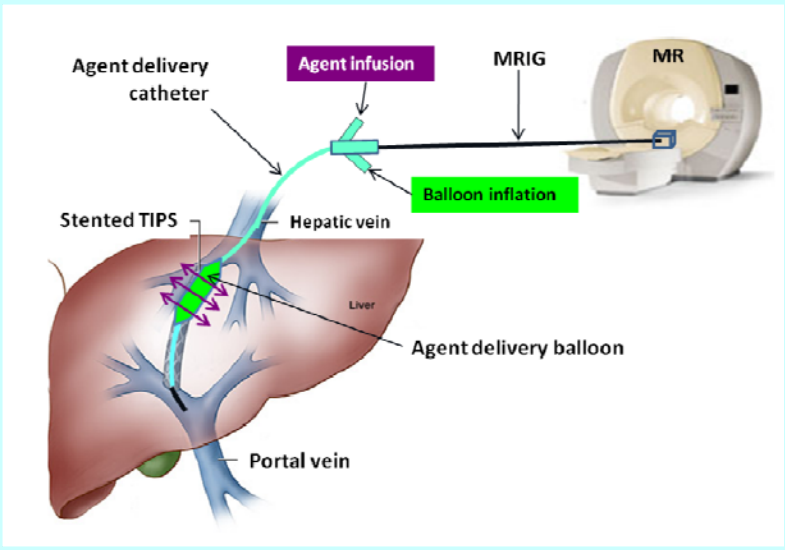

Fig. 5. Setting up of the novel intraTIPS MRI-guided local agent delivery into the TIPS wall. Over an intraluminal MR imaging-guidwire (MRIG), an agent delivery balloon is positioned into the TIPS, where the balloon is inflated and the interested agent subsequently infused. During the agent infusion, intraTIPS high-resolution MRI with the MRIG is performed to monitor the distribution of the locally delivered agent into the TIPS wall and peri-TIPS regions.

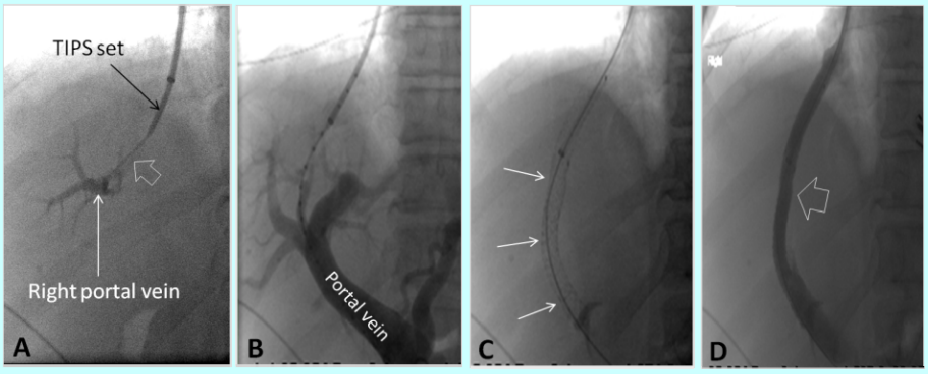

Fig. 6. X-ray imaging-guided placement of a TIPS. (A) The right portal vein is accessed by the needle (open arrow) of a TIPS set, and then a pre-procedure portogram is achieved (B). (C) A stent (arrows) is placed into the portosystemic shunt, followed by a post-TIPS portogram via the shunt (arrow on D).

The Viatorr stent will be deployed with no stent extension into the hepatic vein (HV)/inferior vena cava (IVC) junction, where post-TIPS stenosis or occlusion often occur due to intrashunt pseudoinitmal hyperplasia[13, 14]. Thus, we will achieve a pig model with TIPS, which should enable us to perform molecular MRI-guided intraTIPS local delivery of an agent. Subsequently, we will advance a specially-designed agent delivery balloon catheter into the intrashunt portion over a 0.032-inch MRIG (Fig. 7).

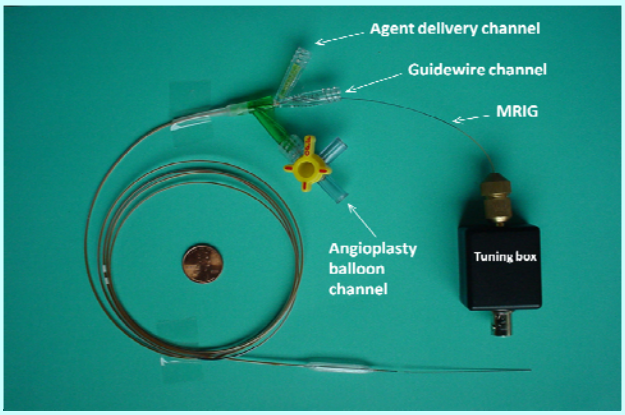

Fig. 7. The intraluminal agent delivery balloon catheter, which has three channels for agent delivery, guidewire placement, and angioplasty balloon inflation. The MRIG is placed within the guidewire channel of the balloon catheter.

(d) Molecular MRI-guided intraTIPS agent delivery: The pig will be transferred to a 3T MR scanner. Two surface coils will be placed around the liver and connected to the MR scanner via a dual phased-array adaptor. A three-dimensional (3D) MR portogram will be performed (turbo spin-echo (TSE), TR/TE=2800/1100 msec). Based on the MR portogram, we will acquire cross-sectional T1 high-resolution intraluminal MRI of the TIPS wall by operating the MRIG at a receive-only mode (fast spin-echo (FSE), TR/TE=100/2.8 msec). We will then locally deliver an MR agent into the TIPS wall, which will be monitored by using our previously-established *real-time MR fluoroscopy* (fast spoiled gradient-echo (FSPGR), TR/TE=500/2.1 msec) to monitor the distribution of the agent within the TIPS wall and its surrounding tissues (Fig. 3).

(e) The delivered MR contrast agent: We have selected a multifunctional agent, Motexafin gadolinium (MGd, Pharmacyclics, Inc.), as the primary MRI agent, which has been already evaluated through the clinical phase I to III studies[15, 16]. MGd is an intracellular agent with several unique functions as (i) a T1 MR contrast agent for MRI; (ii) a therapeutic agent that primarily accumulates in metabolically-active tissues, such as endothelial hyperplasia; and (iii) a bio-tissue marker emitting red-colored fluorescence for histology and laboratory correlation/confirmation[4, 17-19].

We will use our previously-established protocol to locally deliver 3-5 mL MGd (75 μg/mL), mixed with a Trypan blue dye (for histologic correlation, MGd/Blue=6/94), into the intraTIPS wall. The agent delivery balloon will be fully inflated with saline, and the MGd/blue will be constantly infused using a digital syringe pump at flow rate 10 mL/hour[11, 20].

3. MR Imaging analysis:

Qualitative analysis: We will compare the abilities to visualize MGd-enhanced TIPS walls/regions by comparing pre- and post-intraTIPS MGd delivery. Three investigators will independently read the cross-sectional MR images, and record the findings using the following grade system: (a) excellent = complete visualization of the entire TIPS wall/peri-TIPS tissues as a bright ring; (b) good = partial visualization of the TIPS wall/peri-TIPS tissues; and (c) poor = no visualization of any portion of the TIPS wall with no peri-TIPS penetration of MGd.

Quantitative analysis: On cross-sectional T1-MR images, we will quantify several factors, including:

(i) *SNRs and CNRs of TIPS walls:* We will measure (a) signal-to-noise ratio [SNR = the signal intensity of the TIPS wall relative to the standard deviation of the background noise]; and (b) contrast-to-noise ratio [CNR = (signal intensity of the TIPS wall – signal intensity of adjacent peri-TIPS tissue) relative to the standard deviation of the background noise]. Signal intensities will be measured by manually placing 6 region-of-interests (ROIs) along the TIPS wall, at the peri-TIPS tissue, and at the background tissue. We will then compare the average SNRs/CNRs between pre- and post-intraTIPS MGd delivery.

(ii) *Distance of MGd penetration/distribution in peri-TIPS tissue:* We will measure the width of MGd-distributed (or enhanced) area (starting from the inner border of TIPS wall) at the six ROI points of the TIPS wall. The measured MGd penetration distances with MRI will be correlated to the blue-dye penetration distances with following histologic conformation.

4. Histology confirmation: Immediately after achieving satisfactory MR imaging, we will euthanize the animals for subsequent MRI-histologic correlation and confirmation.

(a) Histology of TIPS segments: The entire TIPS segment with their adjacent tissues will be harvested and then sectioned at 8-μm slice thickness through using a laser-based microtome. We will select 12 slices at 12 levels with equal intervals through the entire sectioned slices, which should enable us to closely allocate the 12 histological slides to their corresponding MR images that will be achieved at 12 slices throughout the entire TIPS as well. Then, we will identify the distribution of agents within the targeted TIPS walls using various laboratory examinations, including:

(i) For qualitative analysis: We will use (i) confocal microscopy to detect red-fluorescent MGds; and (ii) hematoxylin and eosin (H&E) staining to further confirm the successful local delivery of blue-dye into TIPS walls and surrounding tissues.

(ii) For quantitative analysis: We will use digital microscopy to measure the distance of MGd/blue penetration and distribution.

(b) Histology of other organs/tissues: In addition, we will also collect the tissues from other organs (such as liver, pancreas, intestine, kidney, spleen, and lung) for controls using histologic examinations as described above.

5. Endpoint: To compare the results between pre- and post-TIPS MGd delivery, we will plot the average SNR/CNR of MRI vs. average MGd/blue penetration distance of MRI-histology. The results will be statistically compared using a Student t-test and ANOVA.

6. Justification of animal study groups: Each trainee will perform the hands-on TIPS procedure and the intraTIPS molecular MRI-guided agent delivery procedure on 2 pigs. We estimate 8 trainees from UW and beyond will participate in the training, and thus a total of 16 pigs will be used (8 trainees X 2 pigs = 16 pigs).

A.2.2. Time schedule:

The educational program will be conducted at the beginning of each academic year, usually July, when the new trainees enrolling the IR fellowship. All trainees will participate in (i) the 2-hour group theory course on TIPS and Interventional Molecular Imaging at day 1 of the program; and (ii) the group data reviewing conference at the end of the program.

To ensure each of trainees has a chance to perform the initial hands-on practice, we will schedule one trainee per TIPS procedure per day, and each trainee performing 2 TIPS procedures with molecular MRI-guided intraTIPS agent delivery in two separate days. We estimate to accept 8 IR trainees for 16 TIPS-MRI procedures, and we will arrange two TIPS-MRI procedures per week. Thus, the program period will be approximately 8 weeks (16 TIPS / 2 TIPS per week = 8 weeks) plus two days for the group theory course and data review course.

Detailed time schedule of each interventional molecular imaging-guided TIPS procedure is as follows:

9:am – 1:30pm: Hands-on practice on TIPS and molecular MRI-guided intraTIPS agene delivery.

2:00 – 5:00pm: Hands-on training on histologic slide preparation with different laboratory staining techniques.

A.2.3. Outcomes:

At the end of the training, each trainee should: (i) gain the first-hand experience on the complex interventional procedure, TIPS, which should facilitate his/her further clinical practice on human patients; (ii) understand the new concept of interventional molecular imaging; and (iii) be able to adapt this new concept into their future academic career and/or clinical practice.

In addition, the success of this program should enable us to gain experience on how to educate more interventional radiologists in promoting the clinical translations and applications of several advanced interventional molecular imaging technologies, including molecular imaging-guided/RF-enhanced nanoparticle-based therapy, internal radiation therapy, and gene therapy.

A.3. Evaluation:

1. Each trainee will complete a written report on the knowledge and skills acquired via the educational program.
2. Each trainee agrees to participate in a survey on the educational program.

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