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SIR Foundation
Advancing interventional radiology through research

SIR Foundation Summer Medical Student Internship Program

Institution Name: University of Virginia

Responsible mentoring physician: Luke R. Wilkins, MD

Length of proposed curriculum: **The internship should be 8 weeks and at least 40 hours per week.**

A. Please provide a brief description of how each of the following curriculum elements will be demonstrated/taught through your program.

The accepted trainee will join a research group with existing funding through the American Cancer Society and Department of Defense. The proposed research will expand on existing research projects. Prior to arrival at UVA, our research team will work with trainee to develop appropriate clinical/research question that expands our original research aims. The trainee will have the opportunity to work with Dr. Wilkins from Interventional Radiology as well as our collaborative research scientists (Drs. Wotton, Fu, and Brautigan) to develop the experimental design for the proposed research project. In addition, we will work closely with the University of Virginia, Center for Comparative medicine. Our lab has extensive experience in animal model research in a variety of species. The basic science lab work will be overseen by Drs. Wotton, Fu, and Brautigan. The reporting, collecting, and analyzing of collected data will be performed by our research team and directly overseen by Dr. Wilkins. Dr. Wilkins has experience in manuscript preparation, construction, and editing. Additionally, Dr. Wilkins' experience as Deputy Editor of Radiology: Imaging Cancer will assist in instruction on the editorial and publication process.

B. Please provide the details on the instructional setting and methodology (laboratory, classroom), description of any educational resources (PowerPoint presentations, textbooks, selected readings), and assessment techniques (question and answer sessions, tests) to be used in the process of instruction.

The physical space available to the trainee will depend on the project and research that is chosen. The full complement of the University of Virginia Health Sciences will be available to the trainee for use. Didactic instruction, informal teaching, and guided learning will be provided by the research team including Drs, Wilkins, Brautigan, Wotton, and Fu. Dr. Wilkins will lead the educational efforts and will be responsible for mentorship and assessment.

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ENVIRONMENT: University of Virginia Facilities

- Sheridan G. Snyder Translational Research Building Location of the Wilkins Lab at the Fontaine Research Park of the University of Virginia located approximately 1 mile from the Medical Center. All animal procedures, animal housing, and imaging will occur in this facility. It has 3000 ft2 for imaging work, including space for CT scanners and small animal housing. There are two conference rooms available for lab meetings and journal club. There are multiple workstations with cubicle space available for the trainee. Major Equipment which is located in the Snyder Building includes the following:
- Magnetic Resonance Imaging (MRI). 3T Magnetom Prisma (Siemens) with 15 channel TX RX knee coil and dedicated surface coils for MRS. In addition, there is ClinScan (Bruker/Siemens) 7 Tesla small animal MRI with broadband capabilities running software version VB15. The 7T ClinScan (Bruker/Siemens) state of the art small animal MR scanner was purchased with another NIH High-End Instrumentation grant (SS Berr PI, S10 RR019911. The ClinScan has a Siemens Avanto console, and Bruker gradients (600 mT.m-1 maximum strength, 6000 T.m-1.s-1 riserate). The system has 8 receiver channels for phased array imaging.
- Positron Emission Tomography and CT (PET/CT). Siemens Biograph mCT eco. 64-slice PET/CT with ultraHD PET and respiratory gating. Provides 81 (109) image planes across the 164 (221) mm axial field-of-view (2.0 mm slice spacing) and 3D Iterative reconstruction (OSEM) o Ultrasound. Philips CX50 for use in small animal imaging.
- Angiography. There is a dedicated animal OR within the vivarium complete with negative pressure ventilation and scrub sinks. Approved for use in survival experiments. OR has a dedicated Siemens Siremobil Compact C-arm with digital subtraction angiography (DSA) capabilities.
- Physiological Monitoring. Animals' heart rate and breathing will be monitored using SA Instruments (Stony Brook, NY) model 1025 for MRI and a model 1025L for PET and SPECT hardware/software systems for monitoring and gating system.
- Other equipment: We have standard molecular and cellular biology equipment such as Biosafety cabinets, incubators, water baths, PCR machines, electrophoresis equipment, refrigerators, freezers (-20°C and -80°C), liquid nitrogen storage tanks, and shakers. In addition, there are fluorescence microscopes, UV-VIS spectrophotometers, absorbance, fluorescence and radiation plate readers, a cryotome, and a phosphorimager. There are fume hoods, cold rooms, water purification system, autoclaves, balances, ovens, pH meters, and other small equipment.
- The Microscopy studio employs a fully motorized Zeiss upright AxioImager Z1 microscope equipped with the Apotome 2 module to produce confocal-like images. The microscope is paired with Axio Cam MRc5 and Axio Cam HRm digital cameras for image acquisition. The user interface controls all imaging devices and motorized hardware, and

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handles the images in a pyramid file format on a 64bit operating system. This system allows for acquisition of complex datasets including multi-channel and multi-dimensional image series.

- Animal: This project will use the vivarium in the Snyder Building. Animal health is monitored by a veterinarian and his staff and makes use of sentinel animals. UVa has an active Animal Welfare assurance on file with OLAW.
- Offices: The PI and co-investigators all have their primary offices adjacent to the Snyder Building or within the main ground of the UVA Health Systems complex. Additional office space is available for students, postdocs, fellows, and senior staff.
- Laboratory Space: There is ample lab space with hoods for organic chemistry work, and bench space for working on animals, preparing histological slides, etc.
- Pinn Hall in the Medical Center of the University of Virginia o Research Histology Core: The Core prepares paraffin embedded and frozen tissue sections for routine histology, special stains and immunohistological studies.
- Biomolecular Research Facility: This facility provides a range of services for analyzing DNA and proteins on a fee for service basis. Automated DNA Sequencing is run on a 3730 DNA Analyzer from the Applied Biosystems using BigDye Terminator v3.1 chemistry. High throughput sequencing activities are performed with an Illumina Genome Analyzer (Solexa) (Illumina Inc., San Diego, CA).
- West Complex in the Medical Center of the University of Virginia
- Brautigan Laboratory
    - UVA Center for Cell Signaling: This research center occupies 10,000 sq. ft. of contiguous space and shared facilities for six faculty groups, all on the same floor to share facilities and major equipment listed below, including 2 coldrooms, a darkroom with automated film processer, dedicated room for radioistope experiments, dishwashing and autoclave room, and a conference room. We have daily contact with researchers in other Center groups. This is a co-operative environment for about 50 biomedical researchers specializing in molecular and cell biology. The Center is located in a building connected by walkways to the adjacent Health Sciences Library and School of Medicine research buildings which house Departments of Microbiology, Biochemistry, Pharmacology, Physiology, Cell Biology and Biomedical Engineering with 15-20 faculty each. These principal investigators, their staff, postdoc fellows and students are available for consultation and assistance with protocols. There are seminars every day of the week, plus journal clubs and research conferences. The School of Medicine has fee-for-service core laboratories directed by Ph.D. scientists for Electron and Confocal Microscopy, Flow Cytometry, DNA sequencing, monoclonal antibody and transgenic mouse production, plus outstanding

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LC/MS/MS mass spectrometry with an Thermo LTQ Orbitrap Velos spectrometer for peptide sequencing and phosphosite mapping. For animal experimatation we have access to an AALAC-accredited vivarium directed by a veterinarian. Overall, this is vibrant academic environment with ~$200M/yr in sponsored programs and hundreds of biomedical scientists available to facilitate and support our research.

- Laboratory and Computer: The Brautigan group occupies a main laboratory, connected to a separate tissue culture room (with 2 sterile transfer hoods, incubators, refrigerators, waterbaths), for a total of 1000 sq. ft. Pipettes, mixers, power supplies, electrophoresis and transfer units, microcentrifuges, shakers and freezers for -20°C and -70°C are available for the proposed research. We have a G5 iMac, and in the adjoining laboratory there is a GL4 PowerMac computer for cellular imaging, plus Dell and Lenovo desktop computers with an Epson scanner. Computers are networked to Xerox color printers. All computers are directly linked to a campus-wide high speed network providing access to the Internet and library services that include subscriptions to most leading scientific journals.
- Major Equipment: Shared facilities and instruments in the Center for Cell Signaling, on the same floor include a LiCor 'Odyssey' infrared 2D scanner, Berthold "Flash 'n Glow" luminometer, Beckman LE80 ultracentrifuge, TLX Optima benchtop ultracentrifuge and Beckman scintillation counter, three Sorvall RC5B/C centrifuges and thermostated shaking incubators for plasmid and recombinant protein preparation. In addition, there are Pharmacia GradiFrac and GP250 FPLC chromatography systems in a shared coldroom, plus three Perkin-Elmer PCR 9700 thermocyclers, NanoDrop spectrophotometer, UltraLum transilluminator with CCD camera and printer, LabConCo SpeedVac and a lyopholizer. The Center has microscope/imaging systems for fixed and live cells: a Nikon 800E with a Hamamatsu 4742 CCD camera driven by Open Lab software. For live cell recording we share a Zeiss Axiovert 135 microscope with a Hamamatsu 4742 CCD camera and data acquisition and analysis system.

D. Please provide a brief outline of available research topics, one of which the student will select for completion as part of the program. The projects should be of a scope appropriate for completion within the limited time frame provided.

1. Evaluate changes associated with tumoral and parenchymal hypoxia when using liquid and particulate embolics. Will employ hypoxia targeting immunofluorescence scanning overlaid

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on tissue viability mapping to determine impact of tumoral hypoxia and study drug on tumor cell proliferation.

2. Evaluate whether human CRC cells cultured in vitro exhibit reduced proliferation in response to hypoxia alone and undergo apoptotic or necrotic cell death after addition of novel metabolic inhibitor under hypoxia. Will involve assay for induction of HIF-1α and MCTs in response to hypoxia in CRC cells. Trainee will test for the effects of genetic knockdown and overexpression of MCT4 on cell viability and responses to novel metabolic inhibitor under hypoxic conditions.
3. Optimize the delivery of novel metabolic inhibitor in embolic that will generate high local tissue concentrations of drug with adequate tumoral hypoxia and minimal surrounding liver changes. This will include testing for adequate drug loading and release. Work will involve partnership with Biomedical Engineering at UVA.
4. Test the efficacy of novel metabolic inhibitor delivery in a rabbit model of mCRC. This work will involve animal project design, protocol development, adaptation of animal model, and imaging surveillance optimization.