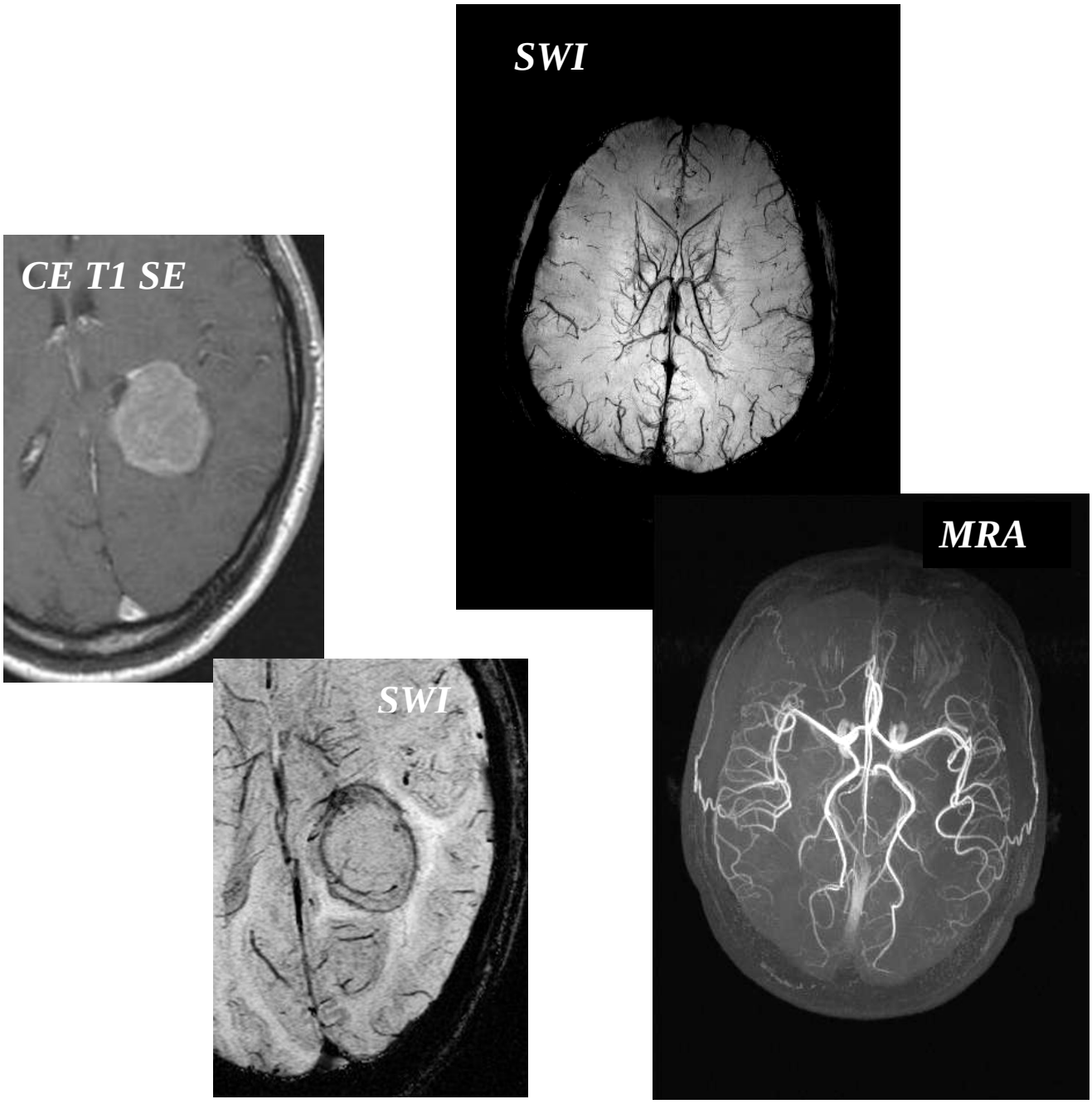

MTTC 05-024

A National Center of Excellence for Magnetic Resonance Imaging

Category I - Basic Research

Ewart Mark Haacke, Ph.D.
The Magnetic Resonance Imaging Institute for Biomedical Research

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PROGRAM PLAN

A. RESEARCH THEME AND PROJECT SCALE AND SCOPE

Section I: Introduction

We wish to create a center of excellence with a National impact focused on neuro-imaging and vascular research that will be centered in Detroit. This unique facility will enhance the role of the State of Michigan in the area of biomedical research as it applies to new imaging technologies. The center will use the resources of the MRI Institute, Wayne State University, Henry Ford Hospital, William Beaumont Hospital and Loma Linda University. Vascular imaging afflicts people of all ages, but more so the middle aged and elderly. Prevention of disease (such as atherosclerosis), monitoring disease (such as tumor angiogenesis) and conventional diagnosis (for general vascular problems, trauma and stroke) remain among the highest priority in patient care. MRI offers an exquisite means to non-invasively image the vascular system.

Goals: There are five major components of this proposal.

The first is the creation of a center of excellence in MRI that will serve as a hub for national research in vascular imaging. This will catapult Michigan into a position of national leadership in the area of MR imaging.

The second is the basic development of a strong research base in vascular imaging with major support from federal and industrial funding. Participating academic faculty and those positions supported by this proposal will be encouraged to develop their own fundable vascular projects. With these features in place, we will be able to go beyond the normal R01 approach for funding and apply for program project grants, centers of excellence grants, training grants and garner support from NIH, pharmaceutical companies and MR manufacturers for clinical trials. The potential is also there to attract the involvement of current high tech stand alone imaging centers in Michigan to participate in these studies.

The third is evaluating new methodologies over a large patient population hosted by the Center of Excellence through all of its collaborative members. We will work closely with industry in the testing of current and newly developing vascular technologies. The potential is to test ideas not over dozens of cases but over hundreds of patients in very short time periods on the order of a few months rather than a few years. The resulting validation of these new vascular imaging capabilities will have important implications to clinical progress here in Michigan.

The fourth is the spin-off of imaging related industries in Michigan through imaging patents and software developments. We have experience in patenting imaging concepts and in building relevant software for these new methods. Both have the potential to bring in future support for the proposed national center of excellence.

The fifth is the enhancement of our academic programs. The success of this program will allow us to attract the best researchers, develop better imaging programs academically, attract the best students and form an internal vascular imaging center. Wayne State University and the Detroit

Medical Center have expressed an interest in having such a center as they believe that MR Angiography is the imaging modality of the future for imaging the body's vasculature. Wayne State University is also working on the creation of an imaging curriculum for its engineering and science schools. This has been approved by a number of departments. The final stage in this process will be to create a special graduate imaging certificate in imaging.

***Economic Impact for the State of Michigan**:*

We will request funding for three new imaging physicists, an administrator, three post-doctoral fellows, three students and some faculty support. The program will involve five research institutions: Wayne State University, William Beaumont Hospital, Henry Ford Hospital, Loma Linda University and the MRI Institute for Biomedical Research. All institutions are educational and/or research oriented non-profit charitable organizations. The successful completion of this program will bring significant NIH research dollars into Michigan, will attract industrial support from the MR manufacturers and pharmaceutical companies, will attract dozens of new jobs and will enhance imaging related educational programs in Michigan.

Section II: A Personal Synopsis of the Team Science Summary from the 2003/4 BECON Symposia at NIH

During the last twenty years, we have advocated the concept of team research. Having trained more than 50 people in this field, I can say that there is indeed potential to create a working environment with people of like minded philosophy to make team science a reality. Our goal is to create a National Center of Excellence in Magnetic Resonance Imaging. In conjunction with Wayne State University, a very strong foundation in MRI has been laid. A state-of-the-art research facility costing over $10,000,000 is now in place including two whole body human research systems at 1.5T and 4.0T and two animal systems at 4.7T and 11.7T. There are more than 10 faculty/staff involved and 18 students in this center. There are excellent major federal funding opportunities available to further enhance support for this idea. These include: program project grants, training grants, P41 center grants, SIG equipment grants, construction grants for new research facilities, and new funding directions set by the NIH Roadmap announcements such as the team science approach mentioned above.

Today, institutions and the scientists tied to them are continually competing with each other. Dozens if not hundreds of faculty replicate each other's work rather than complement it. In our opinion, the ability to incorporate the skills and knowledge of a large group of cooperating scientists and direct them offers the potential to dramatically speed up the testing of new ideas, new drugs and the care of the patient. The refinement of new technology could be reduced to 1 to 2 years instead of 5 to 10 years as is currently the pace. The ability to collect patient numbers on the order of 500 to 1000 would take 1 to 3 months rather than 1 to 3 years in many clinical trials. Finally, the consolidation of working software would be facilitated rather than the proliferation of dozens of software programs that are in the control of businesses and often inaccessible for change to the researchers and users. The BECON summary from the NIH proposes a change in the philosophies of both the NIH and academia:

Team science should have a focus on enabling new technologies
with an interdisciplinary approach that cuts across disciplines and institutions.

Section III: General Research Rationale

To date, magnetic resonance imaging has been used predominantly to collect morphological information, although it is also used to monitor perfusion and blood flow. These areas of interest have gained broad clinical acceptance. Still, there remains no unified approach to vascular imaging. There are a number of key unanswered questions from a clinical or research perspective that include: imaging the microvasculature, imaging with high resolution to visualize the smaller vascular structures, mapping oxygen saturation, imaging microhemorrhage and imaging atherosclerosis. A complete picture of the vascular system requires all of the above.

Further, there are no national centers in Magnetic Resonance Imaging. We believe that we can address the issue of "team research" in a revolutionary new approach that should have the potential for major funding from the National Institutes of Health (NIH) in terms of collaborative research from National Institutes of Biomedical Imaging and Bioengineering (NIBIB), a P41 application from the National Center for Research Resources (NCRR) division, individual investigator driven NIH grants, and major funding from both the MR manufacturers and the pharmaceutical companies. We have presented these ideas in two invited sessions to the NIH; one to the NIBIB and one to the NHLBI. We have received constructive input from the staff there on how to proceed with this new concept. Specific recommendations were made to follow up on this smaller seed funding from the MTTC with a larger $5,000,000 proposal to the NIH once proof of concept had been achieved. Significant interest was expressed in this new paradigm.

We list below a number of ongoing research projects most of which are in the process of being funded. We do not ask for support for these projects directly. *Rather, we ask for support for the new staff who will collaborate with all the sites and establish the research foundation to enhance the grant funding of research in the State of Michigan.* We seek funding to support the infrastructure of this new endeavor, the hiring of several MR physicists and associated staff to carry out the technical developments.

Future Funding: We have been involved in the development and clinical testing of the following novel methods in vascular imaging: MR angiography (MRA), MR venography (MRV), susceptibility weighted imaging (SWI), oxygen saturation imaging (OSI) and perfusion weighted imaging (PWI). We are pioneers of the first 4 methods. We either have submitted are looking at submitting proposals in the following areas:

1) Susceptibility Weighted Imaging (SWI) - $2,700,000 submitted to NHLBI on 10/29/04

2) Imaging the Vasculature of the Brain Using MRI - $2,980,000 submitted to NHLBI on 10/01/04

3) Improved Characterization of Tumors in MRI using SWI - $2,200,000 submitted to NCI on 11/03/04

4) We have an industrial grant to study SWI which supports some equipment at Wayne State University and some students through the MRI Institute for Biomedical Research.

5) We are in the process of preparing a grant using vascular imaging for studying trauma that will consist of a core MRI component, a radiologic component, a neuro-psychiatric component and an animal component. We have permission to submit this grant for $5,000,000.

6) We are submitting a grant to create a new imaging curriculum at Wayne State University for $1,000,000 through the Howard Hughes Medical Institute.

7) To bring together this expertise at a more professional level, we will apply for five year grant funding to have an annual meeting on "Vascular Imaging of the Brain". Special visits from the Californian participants will be arranged with their travel being covered by the individual institutions.

8) Finally, during this start up phase, *we plan within the next three years to submit a P41 proposal through the NIBI, NHLBI and NINDS to gain long term support for this center of excellence. This proposal will request $5,000,000 in funding over a five year period to cover infrastructure, staff and research needs.*

9) Both the School of Medicine and the DMC are interest in creating a vascular institute that will have a strong link to a new expanded WSU imaging research center. We are currently preparing a white paper with a plan of action to create this new entity. (Fund raising will require $30,000,000 for space, equipment and faculty.)

Section IV: Goals and Research Directions

i) implementation of the five goals

The first goal was to create a center of excellence in MR vascular imaging. This has been discussed above and its structure and organization are presented in detail in sections C, D and E below under organizational issues.

The second is the basic development of a strong research base in vascular imaging. The hiring of the Center staff will make it possible to tie together the research elements of the participating faculty to create a new synergy that we believe will be more productive than single individual efforts. The idiom: "the sum of the whole is greater than the sum of the parts" certainly holds true here. This goal is also discussed in further detail in sections C, D and E below under organizational issues.

Each grant focus will be attacked by coordinating a group responsible for the acquisition of preliminary data and writing of the proposal. These people will work closely together under the aegis of the group coordinator or principal investigator of the specific proposal (one of the staff that we will hire). They will receive support from the MRI Institute in both scientific information and management. The MRI Institute will be the center for training and recruiting the new staff and post-docs. Each of these new staff will focus on the task of not only implementing the novel technologies required for the individual projects but also participating in the collection of the data, writing up the results and helping to write new grant proposals. They will become liaisons

with the MR manufacturers and the pharmaceutical companies. They will also serve as the local technical support for the various investigators and projects. Finally, the more experienced staff could serve as mentors for those in other institutions. We will have to consider the question: "How can these grants be designed to cut across institutions and yet meet NIH budgetary constraints?" One good piece of news is that in the future NIH will no longer penalize collaborative efforts by counting the indirects of a second institution as part of the directs of the submitting institution. Further, NIH now allows the concept of co-PIs, a major step in sharing resources across departments within a given university and across universities. As progress is made in these areas, we will have to assess the abilities of each institution and its equipment.

The third is evaluating new methodologies over a large patient population. Once the research for a given project, such as susceptibility weighted imaging or perfusion weighted imaging, for example, reaches the point of being tested clinically, the method will be taken to the affiliate sites and tested over 100s to 1000s of patients in short time periods. A major focus will be to analyze and write up articles for submission to major journals such as Radiology and Journal of Magnetic Resonance Imaging. This type of effort and result should lead to strong interactions with industry who look to highly productive groups to answer their questions. Given that the pharmaceutical industry claims they spend nearly $20,000,000 per month in testing a single new major drug, this offers an excellent approach for them to do a better job in less time for less money. (See the projects discussed in detail below.)

One of the weaknesses in imaging has been the poor follow up of basic developments. This has not necessarily been the fault of the inventors or original investigators, but rather a lack of resources to follow through with a large enough cohort of patients to draw decisive conclusions. Here are some examples where this transpired in areas that have long been recognized as important and yet remained unproven when it came to carefully designed trials.

- *MR Angiography (MRA)*
  - *Over ten years to get HCFA approval – why was there a lack of numbers!*
- *Diffusion Weighted/Tensor Imaging (DWI and DTI)*
  - *Accessible for research but still improving after almost 20 years of development*
- *Perfusion Weighted Imaging (PWI and DCE)*
  - *Not FDA approved, despite being introduced 20 years ago*
- *Susceptibility Weighted Imaging (SWI)*
  - *Just getting introduced to the clinical users*

The fourth is the spin-off of imaging related industries in Michigan. Some of the imaging patents and software developments may well lead to the formation of new companies. We have already begun investigating taking the imaging software to this stage. From the perspective of the staff involved, there will initially be one staff position dedicated to directing the development of this software. There are many students who wish to be involved in imaging at Wayne State University. The MR group there already has 18 students and 10 faculty. Five of these are involved in processing. There is on the order of a student a week asking to get involved in imaging, so there is no paucity of skilled people to participate in this part of the project. The Center of Excellence can serve as a testing ground to ensure rapid development and evaluation of the necessary software used in many of the research projects that will be part of the center.

There are a lack of research or clinical databases available today. We need to investigate what type of databases best address access to technical and clinical research information as well as how clinical data is best stored to follow all HIPPA rules. These databases could become extremely important in the future and should be made available for the appropriate statistical analyses to all participants.

We can potentially also create a web-based access to much of this research. We have the specialized software for image processing (referred to as SPIN for signal processing in NMR) and we have specialized web-based software for database access (referred to as EnterPDA). These offer the potential for excellent support of databases. We will want to incorporate both of these so that communication between all participants in the center becomes easy and seamless and yet protects confidentiality rules.

The fifth is the enhancement of our academic programs. We currently are in the process of submitting a training grant to the HHMI to further develop our imaging program and curriculum at Wayne State University. This is a $1,000,000 for three years that if funded will lead to a potential 5 year extension to a more conventional training grant from the NIBIB. We believe that we have an excellent chance to get this grant with 18 interested faculty and our growing experience in imaging.

The staff at the Center of Excellence may well choose to participate in the teaching of new courses at the university, particularly focused on flow and perfusion in tissue, an advanced course in magnetic resonance imaging and in a seminar series on imaging methodologies in general where all faculty will participate. They will be considered for adjunct appointments in the Biomedical Engineering Department so that they too can have access to graduate students. Clinical education will benefit from this as well by enhancing the residency program in Radiology. (There is a dire need to enhance our reputation in Michigan to attract new clinical and Radiology faculty. This research program will help build up a confidence and an attraction to bring new talented clinical research oriented faculty to Michigan.) The evolution of clinical groups within the State may also be enhanced given the access to this new vascular technology. Prof. Wilbur Smith is thinking of creating a new vascular imaging clinical resource group with the view that MR imaging is soon to supplant other conventional methodologies currently in use in most Radiology Departments. This group could link with our interests to further develop the imaging software for direct clinical rather than having it for only research use.

The research projects that follow represent three focuses. The first is on using susceptibility weighted imaging in the study of neuro-vascular disease as an important new tool. The second is the role of perfusion weighted imaging and how it will be absolutely necessary to integrate SWI and PWI into a single protocol. We talk about this more at the end of the discussion of these projects in the implementation section. The third is the introduction of a new direction in the study of atherosclerosis. Although related of course to the vascular studies, it is a different application of the technologies discussed in the first two focuses. In the implementation section, we will also discuss the role of our developing software in the projects discussed below.

ii) Specific neuro-vascular imaging projects to be tackled (related to goals two and three)

There are many potential clinical applications for susceptibility weighted imaging (SWI) in conjunction with MR angiography (MRA) and perfusion weighted imaging (PWI). Over the last few years, several hundred cases of SWI have been acquired at Harper Hospital and several thousand at Loma Linda University where the protocol is used on all neuro-patients. It has been found that SWI is valuable for the study of the following: trauma, multiple sclerosis, aging, tumor angiogenesis and characterization, stroke and subtle bleeds, occult vascular disease, micro-hemorrhaging in cerebral amyloid angiopathy, Sturge-Webber disease, iron content and mineralization in the basal ganglia. There is a veritable gold mine of clinical research possibilities *if this method is properly compared to MR angiography, perfusion weighted imaging and possibly even diffusion weighted imaging*. Our focus will be on the first three given that that is our area of expertise.

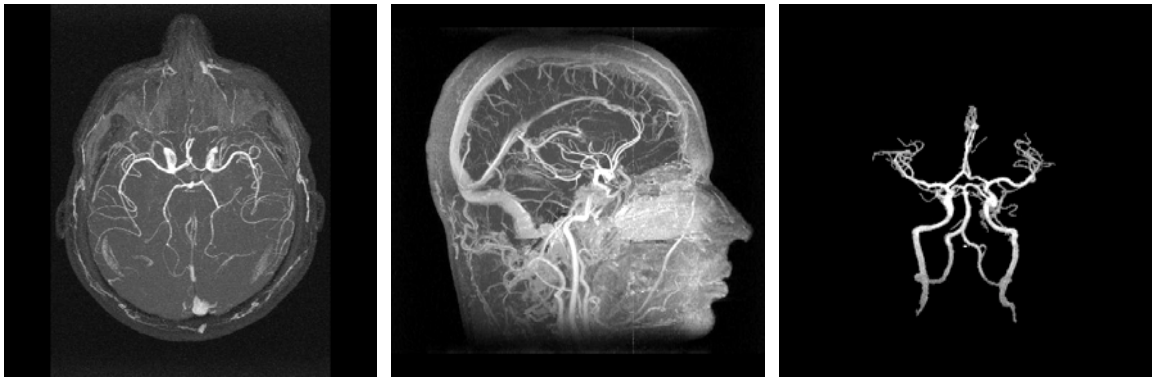
a) technical developments of SWI

A proposal on overcoming current technical problems was submitted on November 1, 2004 for review. It is a competing continuation grant for the first grant which ended in the spring of 2004. If funded it will bring in support for new researchers and student support at Wayne State University. This is a major focus of Dr. Haacke and his research group and will be handled for the most part by himself and Mr. Yingbiao Xu. However, we present this material here to give the reader an overview of what will be needed in the future technically and that we still have an opportunity here for further funding. The main objective of this work is to enhance the ability of SWI to become a standard clinical product by speeding up the data acquisition and accounting for the effects of local field inhomogeneities. Our pioneering work in understanding the blood oxygenation level phenomena[1-7] led to the concept of SWI[8-15]. Subsequently, a number of clinical applications developed including occult vascular disease, multiple sclerosis and arterio-venous malformations[16-28] followed shortly by breakthroughs in trauma and tumor imaging[29-31]. Although an exciting new technology, there are difficulties with the method. Currently, and especially at high fields, information at the edge of the brain is often distorted. We have developed a means to eliminate this effect. This powerful new tool will make SWI a robust clinical method. We will also look to track the venous signal, create simultaneous images of arteries and veins, and quantify effects from local bleeds or microhemorrhages. Finally, we will attempt to create a robust means to measure the local oxygen saturation in the brain, a most important step in determining tissue viability. We anticipate continued major support from industry and we already have a grant from Siemens Medical Systems to pursue this direction. This will take up to four hours per week for testing and development at the Wayne State University facility and when successful will be tested at the other sites as well.

b) high resolution vascular imaging of the brain

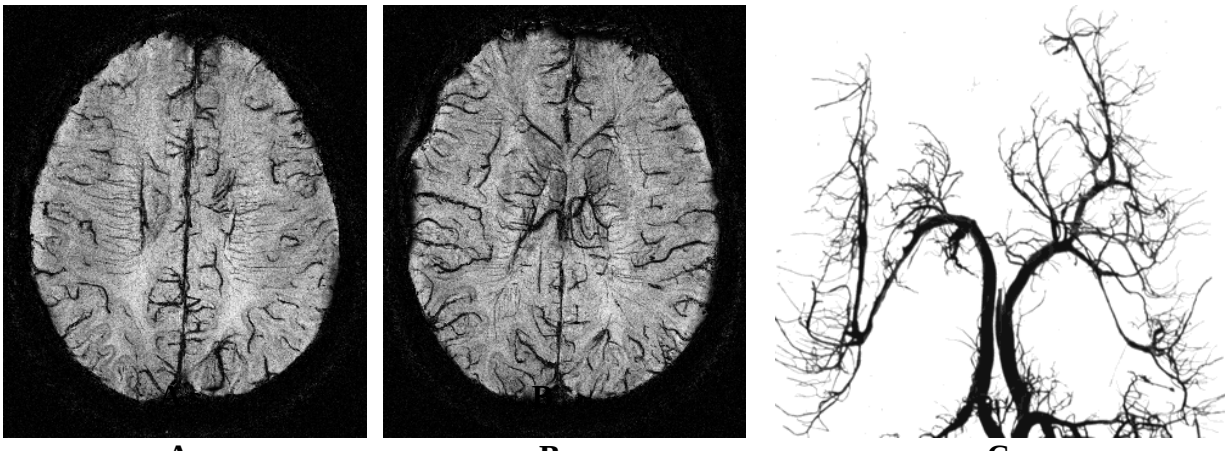
The ability to obtain high resolution vascular images with physiologic information is the key to understanding brain function and properly diagnosing disease. Specifically, the determination of tissue at risk requires conventional angiographic information as well as blood volume, flow and oxygen saturation. We propose to develop the technology to overlay 3D anatomic information with high resolution angiographic data for both arteries and veins for vessels as small as 250 microns. This has heretofore only been possible in cadaver brains.

We propose to collect state-of-the-art MRA data of the entire brain[2] that will serve as a national database for the best possible data[3-5] from an MR imaging approach, fully labeled with 3D viewing capabilities for a wide range of normal volunteers. In it, we promise to image vessels down to *250 microns* in size. We also will be able to develop a method to allow imaging of both arteries (using MRA) and veins (using SWI) but naturally separated. Our past work has also made it possible to segment the vessels from the background[4,5] to show both morphological and functional information (see Figure 1). This method will work best at the new clinical field strength of 3.0T[6]. Both high resolution MRA[7-12] and SWI offer a new frontier in imaging the brain's vasculature (see Figure 2). Finally, we will develop a health informatics component for the project that will provide information of interest to physicians and the general public on the cerebral vasculature. Possible topics include transient ischemic attack, stroke, hemorrhage, vascular malformations, and autoregulation of blood flow.



A **B** **C**

Figure 1: We have collected a set of 1 x 1 x 1mm^3 data over the entire brain for purposes of showing the feasibility of mapping vessels down to or smaller than 0.5mm using a contrast agent. **A.** Transverse MIP, **B.** Sagittal MIP and **C.** Vessel tracked data using a vessel tracking method developed in our laboratory to extract just the major arteries.



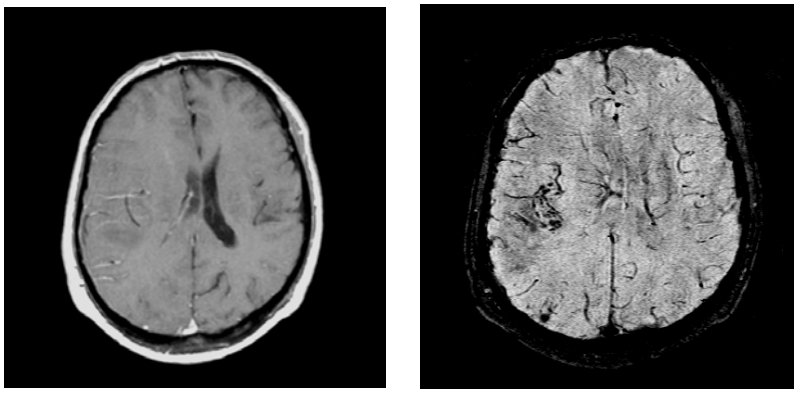
A **B** **C**

Figure 2: High resolution (0.25 mm^3) susceptibility weighted images of the brain. **A.** SWI minimum intensity projection over 2cm. **B.** SWI mIP over the next adjacent 2cm. **C.** Caudate and striate veins around the frontal horn. The ability to image such small vascular structures (200-300μ) at 1.5T and 3.0T rather than 7T or 8T has major clinical ramifications.

c) enhanced detection and characterization of tumors using MRI

Preliminary data for this proposal has already been collected and a grant was submitted October 1, 2004 to the NCI. We have recently prepared a paper studying 44 patients using SWI. It has been presented at the RSNA this last year and has been submitted to the Journal for Magnetic Resonance Imaging. Both our group[1,2] and the Vienna group[3] along with others without[4,5] and with functional enhancement using carbogen[6,7] have shown the value of susceptibility weighted imaging in detecting not only hemorrhage[8] but also changes in the tumor microvasculature[9,10]. We anticipate that the methodology we are developing will lead to improved detection of vascular diseases and tumour angiogenesis using MRA, SWI and perfusion weighted imaging (PWI). High resolution MRA will give us the feeding vessels, MRV will give us the draining veins, PWI the local perfusion and SWI the internal architecture of the tumor. Our results show that the SWI method can delineate tumors better than with the use of a contrast agent. More vasculature and more hemorrhage is seen using SWI than with any other method. Primary brain tumors are recognized and characterized by the presence of pathological vascularity. Therefore, the ability to image the vasculature in tumors is a key component in diagnosing their presence, characterizing their stage of development and assessing their activity levels. SWI offers the potential for early detection of tumor growth as it may be sensitive to the angiogenesis underway at this stage of the disease and that it may help differentiate malignant from less aggressive tumors. In this work we will evaluate the vascular content utilizing SWI on all patients with gliomas and compare their appearances with the vascularity shown in the surgically excised tumors.

There are numerous diseases that would benefit from a knowledge of perfusion and blood volume. These include stroke patients, vascular dementia patients and patients with other forms of vascular disease. The ability to obtain this information non-invasively and on a longitudinal basis is important for patient care. As the earlier results show, we are able to obtain MR angiographic results heretofore unattained with any other methods. Coupled with new high relaxivity contrast agents, we have important vascular detail available to the clinician to diagnose the disease and follow treatment.



A **B**

Figure 3: The ability to better visualize vascular abnormalities in tumor using SWI is demonstrated here where even with a contrast agent the conventional T1 image is unable to show the extent of the lesion.

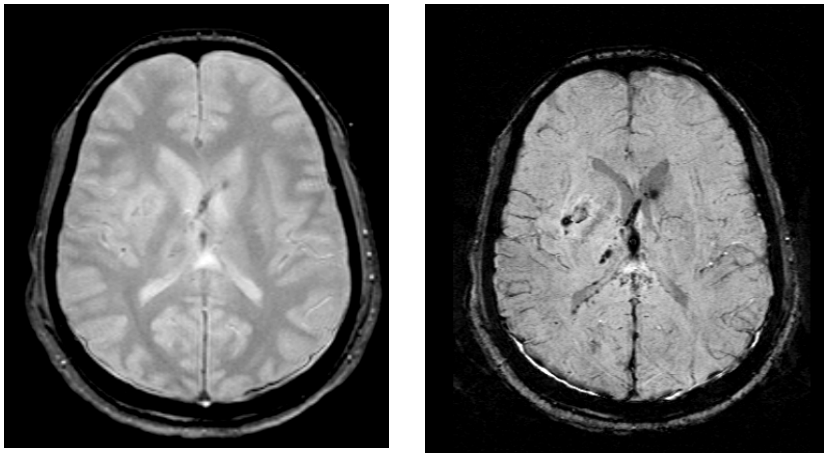
Summary of the first three projects: There is clearly a progression in these projects of using SWI by itself in the first to combining it with MRA in the second. The third project however is an example of the symbiosis needed by using SWI, MRA and perfusion weighted imaging or PWI. The latter adds to the understanding of the pathophysiology underlying the disease. Specifically, the incoming vascular structure is see with MRA while the outgoing structures and the change in oxygen saturation is seen with SWI. But we do not expect to see an abnormal change in oxygen saturation unless there is a concomitant change in the local flow or perfusion. This is where PWI comes in and why it is critical to begin an assessment of using MRA, SWI and PWI simultaneously in clinical studies. *The next two projects will again highlight the importance of focusing our efforts on creating a clinical neuro-protocol that incorporates all three methods.*

d) improved diagnosis of brain trauma using MRI

It is clear that recent developments in MRI can improve the radiologic diagnosis, grading and prognostication in traumatic brain injury (TBI) than is currently the case. Diagnosis in the context of TBI means relating clinical symptoms to real brain lesions (or surrogates). MR would provide surrogates of injury. Closed head injury results in stereotypic clinical symptoms which vary with the severity of the parenchymal injury and include: slowing of executive function, neuropsychiatric symptoms and somatic symptoms. Evidence suggests that the neurocognitive impairment shows the best correlation with the earliest signs of injury severity, such as length and depth of coma, post traumatic amnesia and confusional state. For years researchers have sought for the ability to detect diffuse axonal injury[1-8] and shearing and how these relate to observed effects. MR imaging has been used for some time to study brain trauma[9-14]. However, *until the advent of SWI*, closed head injury produced few abnormalities on imaging despite significant functional impairment[15-17]. With the development of more sensitive indicators of the nature, extent and location of brain injury, the hope is that treatment could be more precisely determined for patients with the ability to better relate symptom, cause and effect. *MRI is recognized as having the potential to be the new gold standard for visualizing hemorrhage in the human brain*. Recent papers have shown that SWI is exquisitely sensitive to micro-hemorrhages[15-17] and that diffusion imaging[18] is sensitive to cellular breakdown. Further, MR spectroscopy will be able to detect the status of important metabolites such as NAA, choline and creatine. The combination of these methods allows for an unprecedented ability to see the damage to the vascular system and the surrounding tissue.

We are currently working on a program project grant involving Wayne State University and Loma Linda University that incorporates improved diagnostic imaging as one part, longitudinal studies in comparison with cognitive behavior as the second part, and temporal animal studies examining the physiologic changes as measured *in vivo* with MRI and compared to the *in vitro* pathological examinations as the final part. The goal is to develop a solely MR image-based method of describing and grading brain injury[19-26] which is predictive of acute neurocognitive profiles, i.e., quality and severity of impairment. To achieve this objective, brain injury surrogates on MRI (SWI, perfusion, diffusion and MRS) will be related to neuropsychological deficits over TBI patients with varying severity of injury. We have contacted the program director at the NINDS for permission to submit a proposal with a budget of $1,000,000 per year (and received permission to do so). To prepare for this submission, we have had several meetings

and a workshop with Loma Linda University and WSU on this topic. We are collecting preliminary data for this research now and expect to submit a proposal by February 1, 2006.



A **B**

Figure 4 High resolution (1.0 mm^3) SWI comparison to conventional GE MRI in the brain.

A. 4 mm slice from a conventional 2D GE image with a TE = 20ms. **B.** 4 mm SWI mIP over two 2mm slices. Note the more obvious appearance of the hemorrhages in the SWI image. We believe that this increased sensitivity will make it viable to image small vascular changes in stroke or vascular dementia.

e) evaluating tissue viability in stroke patients using SWI

Current methods of acute ischemic stroke imaging are relatively crude. In the most common scenario, patients have a brain CT and if the CT is negative for hemorrhage and if the patient meets criteria for thrombolytic administration, they are considered for tissue plasminogen activator treatment[1-3]. The CT does not provide information on brain tissue viability. Although newer MRI techniques have been developed for acute stroke imaging, such as DWI and PWI, these tests still do not justify not collecting CT data[4,5]. In addition, these methods do not really provide information on whether brain tissue is still viable. DWI measures water molecule movement, which can be impeded due to factors other then stroke, and PWI evaluates blood flow, which does not always correspond with tissue viability[6,7]. Therefore, additional research is needed on developing new methods to determine whether brain tissue is still viable (and potentially salvageable) in the first few critical hours after ischemic stroke. We have collected over 80 stroke cases now with comparisons to CT. The results are excellent showing that SWI correlates with DWI but shows exactly the location of the stroke. We also find that SWI successfully predicts the regions of bleeding and agrees with the CT data but also shows areas of bleeding not seen with CT.

SWI should provide important insights in this area. In combination with DWI and PWI, it should be possible to draw much stronger conclusions about the brain's function.

Gradient echo imaging has proven to be a sensitive measure for both hemorrhage and blood products[8-12]. We believe that MR images collected using SWI[13-15] will be an order of magnitude more sensitive to blood products than CT. This will have important ramifications on the future care of patients with stroke who must undergo both a CT and MRI because CT is the current gold standard for visualizing bleeds. There have been many clinical trials evaluating neuro-protective agents that would benefit from the ability to collect data with just a single modality. We expect to garner industrial support via the pharmaceutical companies in this project as well as the MR manufacturers. The methods we are developing here will also be applied to the animal imaging methods by our colleagues at Henry Ford Hospital.

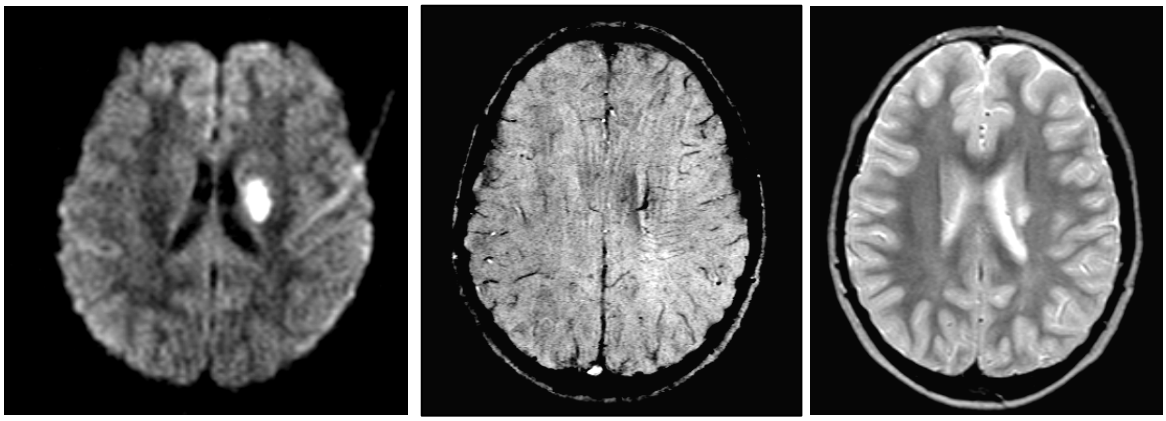


Figure 5 High resolution (1.0 mm^3) SWI comparison to conventional MRI in the brain. **A.** Conventional DWI image showing an infarct in the caudate nucleus. **B.** The SWI scan showing the potential tissue at risk on the left side related to circulation associated with the left caudate nucleus. The enhancement of the small vessels at this short TE is out of the norm and indicative of a change in local oxygen saturation or local blood volume. **C.** A conventional T2 weighted image showing edema in the same region. This increased sensitivity to deoxygenated blood and blood products is evident. With SWI, MRI has the potential one day to become the gold standard for the determination of location of stroke and whether or not any bleeding has occurred.

f) MRI Measures of Blood Brain Barrier Permeability

Permeability imaging as a means to study stroke and tumor vascularity: Breakdown of the blood-brain barrier occurs in many brain diseases, including stroke and brain tumors. We propose to develop MRI techniques to quantify blood-to-brain transfer or influx constants and BBB permeabilities for a range of MR contrast agents (MRCA's). From smallest to largest, these are: Gd-DTPA, gadomer-17, Gd-albumin complex (Gd-albumin), and ultrasmall particles of iron oxide (USPIO's). This is work by Jim Ewing and his group at Henry Ford Hospital. We wish to take adavantage of this experience and our experience in dynamic contrast enhanced imaging and merge it with the capabilities of susceptibility weighted imaging and MR angiography in general. This group is a strong complement to ours in its expertise.

Vascular Permeability in stroke: More than 80% of ischemic strokes are caused by cerebral artery thomboembolism[1]. Treatment with recombinant tissue plasminogen activator (rt-PA) is

effective in ischemic stroke, if administered within three hours post-ictus[2]. However, hemorrhage may occur upon recanalization in some patients, resulting in a poor outcome. An imaging modality that reflects on the safety of rt-PA treatment, i.e., predicts hemorrhage upon reperfusion, would have a significant effect on the approach to such therapy. This is important because there is a strong likelihood that increased blood brain barrier (BBB) permeability does predict hemorrhagic transformation (HT) in a reperfused infarct[3].

Intracranial hemorrhage is a critical factor affecting the efficacy and safety of thrombolytic therapy[1-3]. The NINDS rt-PA stroke trial has found that the risk of symptomatic hemorrhagic transformation (HT) during the first 36 h after the onset of stroke is significantly higher in patients receiving rt-PA than in placebo treated patients (0.6% versus 6.4%), and 61% of the patients with symptomatic HT died within 3 months[4]. HT of ischemic stroke has a natural incidence of 15% to 26% during the first 2 weeks[4,5] and up to 43% over the first month after cerebral infarction[4-6]. *Stroke patients with a higher cerebral blood vessel density appear to make better progress and survive longer than patients with lower vascular density.* We speculate that restoration of cerebral microcirculatory flow during the recovery process may involve changes in the collateral vessels and angiogenesis in the penumbra. The primary question to be addressed in this study is whether tissue vulnerable to HT can be identified before thrombolysis or after being treated with a thromobolytic agent. We will investigate HT before and after rt-PA treatment using Gd-DTPA contrast enhanced imaging, SWI and MTC in a rat model of embolic stroke.

Neovascular permeability in tumors: It is estimated that at least 17,500 new cases of primary brain and malignant neoplasms are diagnosed each year in the United States[7] As recommended by an NIH-sponsored workshop on the current state of tumor biology and potential clinical applications in Radiation Oncology, this proposal is designed to "develop non-invasive assays of anti-angiogenic radiation therapy effects that can be validated in preclinical models and extended to clinical studies[8]." Brain neovasculature is known to be more permeable than normal vasculature, and a cerebral tumor's vascular bed frequently does not form a barrier comparable to the blood brain barrier. As a consequence, the permeability of tumor vasculature can be vastly elevated from that of normal cerebral tissue, and may be strongly correlated with the aggressiveness of the tumor[9] . Thus, a technique which could quantify vascular permeability may well provide information about therapeutic efficacy in cerebral tumors. Currently dynamic contrast enhanced imaging is the major approach used to study perfusion using MRI.

The VEGF and angiopoietin families have a predominant role for vascular formation[10]. VEGF and its receptors are required to initiate the formation of immature vessels by vasculogenesis or angiogenesis during embryonic development. VEGF is also a potent vascular permeability factor that increases microvascular permeability to blood plasma proteins within minutes[10]. In addition to its effects on angiogenesis, Ang 1 protects the adult vasculature from vascular leakage. This application will investigate the effects of VEGF and Ang 1 on blood brain barrier (BBB) integrity, cerebral angiogenesis and axonal and dendritic plasticity after cerebral embolic ischemia in the rat and to explore the potential of VEGF and Ang 1 as new therapeutic interventions for the treatment of stroke. Clearly, the ability of a method like SWI to demonstrate a sensitivity to local changes in blood volume would be very important.

g) High resolution imaging of vessel wall using SWI

The study of atherosclerosis is an important area of vascular research. It affects all major vessels from the carotids, to coronaries to femorals. The ability to distinguish all types of plaque with non-invasive high resolution imaging would represent a major clinical breakthrough. MR techniques do exist using T2 images as well as T1 with contrast agents[1-13].

We wish to show that SWI can visualize the vessel wall for major vessels such as the carotid/femoral arteries. Once we have shown this, the next step is to demonstrate that SWI can distinguish between calcium, hemorrhage, fatty plaque, fibrous plaque and normal vessel wall. Finally, we would like to show that SWI correlates with the uptake of contrast agent into the vaso vasorum for damaged tissue. This was pioneering work initially done in my lab many years ago[14] that has now been taken by other groups using iron based agents to study macrophage involvement in damaged vessel wall[15]. We have already begun collecting preliminary data using SWI to visualize the vessel wall. This work will continue during the first year and a grant to study its utility in detecting atherosclerosis will be submitted in year two of this proposal.

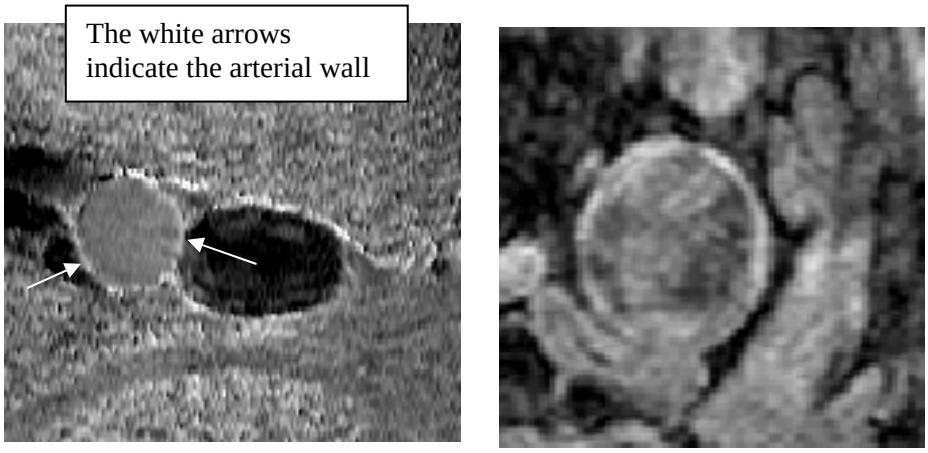


Figure 6: Susceptibility weighted imaging of vessel wall.

Left hand image: This image shows a high resolution phase image from a TE = 25ms scan acquired at 1.5T. Note the uniform signal in the artery and a decreased signal from the change of oxygen saturation in the vein. The vessel wall is shown as bright (meaning a diamagnetic shift occurs in the vessel wall). This is the first time a susceptibility weighted image has been used to visualize vessel wall. The fact that the contrast in the wall is different than the surrounding tissue is already indicative of the value of this method. The exciting aspect of this work is that SWI has the potential to differentiate between calcifications, fibrous and fatty plaque, hemorrhage and normal vessel wall with an in-plane resolution of better than 0.5 mm x 0.5mm. *Currently, it is possible to push the resolution down to 0.25mm x 0.25mm using a special carotid surface coil.* Further, the use of high field, 3T systems in the future will make for even better SNR images and increases the potential utility of this method. *Right hand image:*. This image is from a conventional T2 weighted scan acquired in an attempt to saturate the signal from the artery.

iii) Implementation of collaborative research and the role of the new staff

The experimental design aspect of the research discussed in sub-section (ii) above will be presented here. The collaborative sites have special skills in susceptibility weighted imaging, MR angiography and perfusion weighted imaging as they apply to trauma and stroke. This will be our initial focus in the first three years of the center from which we will develop new granting opportunities and new relationships with industry.

Scientist one and the focus on trauma: In collaboration with the faculty at Loma Linda University and Wayne State University, we will develop a neuro-imaging and spectroscopy protocol that includes SWI, PWI, MRA and DTI to study brain trauma. This will include not just establishing the relevant parameters for this protocol but also setting up all the necessary software analysis for it with SPIN. The collaborators on this project will include: Dr. Sehgal, Dr. Hu and Mr. Xu from Wayne State University as well as a number of other interested faculty within Neurology, Rehabilitation Therapy and Biomedical Engineering and their affiliated students. From Loma Linda Dr. Tong, Dr. Kido and Dr. Obenaus will participate.

There are four parts to establishing a working program project grant (PPG) in trauma. This center approach is not meant to replace the ongoing work in the areas of animal research, rehabilitation research or diagnostic radiology research. Rather, we are trying to fill important gaps in this work that relate to the ability to collect data over a larger patient population and to be able to analyze this data using SPIN. This requires a coordination of efforts and a focus that will drive the production of a coherent protocol for key pilot data to be used in applying for this PPG.

This person will coordinate efforts between all participating sites to try and get significant numbers for the pilot data for the trauma grant. This involves testing and designing the protocol, storing and accessing of data, processing of data and helping to write the grant for this project. The first steps will include: evaluating a new turbo-SWI approach for whole brain coverage in less than 5 minutes to fix the appropriate imaging parameters such as TR, TE, FA and resolution for trauma in particular. This can be done with a series of 5 volunteers and 5 case studies initially. The neuro-trauma protocol will include a DWI/DTI acquisition as well and both SWI and DTI will be compared on a population of the first 50 cases to see if SWI and DTI either complement each other (i.e., offer different information) or have any overlap. At this stage, a larger cohort can be studied and all parameters for all sequences fixed.

A second comparison will involve using multi-slice ASL and T2* PWI using a contrast agent an an echo-planar acquisition scheme. Again, the value and comparison of SWI and PWI will be performed. There may well be a strong correlation of PWI with SWI because a slower flow means a lower oxygen saturation and hence a stronger reduction in vascular signal. The same thing may also result from a local clot causing a local reduction in flow. Finally, a high resolution MRA scan will also be collected for further comparisons. The expected acquisition times for all the necessary sequences are as follows: turbo-SE (5 min), full 3D T1 weighted FLASH coverage of the brain (5 min), local high resolution MRA (5 min), turbo-SWI (5 min), ASL (5 min), DTI (10 min), inject contrast agent, EPI T2* PWI (5 minutes), SWI (5 min), a full 3D T1 weighted FLASH coverage of the brain (5 min) and a local high resolution MRA (5 min). Total scan time 55 minutes. Our goal is to keep the patient in the magnet only one hour. Some of

these sequences may be deemed unnecessary later such as the first or second MRA scan. Finally, an MRS scan will need to be run to evaluate the glutamate/glutamine process. This will add another 10 minutes to the scanning, but if one of the above sequences is deemed unnecessary the total scan time will still be around an hour.

When possible we will attempt to do a comparison between 1.5T and either 3T or 4T with these protocols. This will require a study of at least 5 volunteers at both field strengths and 5 actual patient studies to understand any differences. Although we don't expect the increased SNR to have a huge effect on the images there may be important subtle differences that result in revealing smaller occult lesions that could impact diagnosis of trauma. However, as far as spectroscopy is concerned (MRS), higher field offers a much improved spectra because of both improved SNR and also a more broadly spaced spectrum. For this reason, we may be able to detect GABA, glutamate and glutamine separately at 4T. We are in fact pursuing these studies at this time with Prof. Hu at Wayne State University. He will work with the post-doc and the site scientist on this aspect of the problem.

This person will also work closely with the clinicians in reviewing the data. Specifically, Dr. Sehgal, Dr. Tong and Dr. Kido will review the films and the post-doc will work with them during this process to enhance his/her knowledge of the anatomy, physiology and diagnostic process used to review the images by the Radiologists.

We expect several important papers to result from this trauma work that should set the trend in this area. The issue of data storage and access must be dealt with. We are currently experimenting with a publicly available local DICOM server that will let us accomplish access across institutions while maintaining HIPPA regulations.

Post-doc one – This person will work on the analysis and acquisition elements of the T2* PWI part of the project. The basic acquisition is straight forward but the interpretation of the data is not. We also will look into the approach of simultaneous T2* and T1 DCE. This allows for a self consistency check of the data. Jim Ewing has a lot of experience in extracting permeability from such data and we will compare the utility of this approach with the simpler interpretations of IAUC-60 and CIAUC obtained from T1 DCE data. This post-doc will be responsible for all processing aspects but will work with Mr. Yingbiao Xu an experienced programmer in SWI and with the to be hired software programmer in the use of SPIN. His/her goal will be to establish a viable quantifiable code in SPIN so that all analysis of the data can be done with SPIN. One of our goals in SPIN is to offer not only the algorithms for a given method but also an error map, something which is often not available with individual modules or even with commercial systems.

Scientist two and the focus on tumors and stroke: In collaboration with Henry Ford Hospital, William Beaumont Hospital and Wayne State University, we will develop a neuro-imaging protocol that includes SWI, PWI, MRA and DTI to study brain tumors. The collaborators on this project will include: Dr. Ewing and Dr. Jiang from Henry Ford Hopsital, Dr. Tong, Dr. Kido and Dr. Obenaus will participate from Loma Linda University and Dr. Sehgal and Dr. Hu from Wayne State University. These two projects go hand-in-hand here because of the interest in oxygen saturation and flow as well as for the general interests in vascularization.

The neuro-imaging protocol developed above will be equally valid in the study of tumor vasculature. Since the use of a contrast agent actually enhances the SWI images through a T1-T2* coupling mechanism, the ability to see smaller angiogenic-like structures will be improved. Again perfusion studies will be an important complement to SWI, DWI and MRA. The method we propose using high resolution 3D T1 weighted FLASH (or MP-RAGE) will lead to the better detection of small lesions and the ability to better map out the vasculature of the tumors for surgical planning. MRS has also been used to indicate reduced NAA levels and increased Creatine levels. MRS will be part of the standard tumor protocol.

One of our goals here is also to collect pilot data for a grant on tumor characterization with SWI, PWI, DWI and MRS. All four major institutes can become involved in this process. It will be the job of the second scientist to orchestrate this research. Although Dr. Sehgal along with the neurosurgeons at Wayne State University has collected data on 80 patients, to characterize them into individual classes is much more difficult as the numbers are then much smaller. For example, to focus just on gliomas and to obtain say 50 gliomas will require imaging another 80 cases. This can be done much faster with all groups working together. He will be the main collaborator in this project to help make this study available across institutes.

The stroke related work also requires similar procedures. For acute stroke a much faster protocol is required and is often limited to several quick T1, T2 and DWI scans. Now that SWI can be run in less than 5 minutes and parallel imaging allows for a reduction in time for an MRA scan by a factor of two, these two can also be added for less than 10 minutes extra. In the follow up of stroke patients, the conventional neuro-protocol discussed above can be used. We wish to collect pilot data for a stroke grant which will be submitted in year two of the grant. Dr. Dan Wycliffe of Loma Linda has experience with more than 50 stroke cases using SWI and DWI. He will be the main collaborator in this project to help make this study available across institutes.

Administrator – This person will be responsible for all elements of communication between institutes, coordinating the meetings, preparing documentation, ensuring proper fiscal policies are followed, ensuring the intellectual property rights are properly recognized, helping in the preparation of grant materials and all other necessary activities ensuring a smoothly functioning coordinated research effort. He/she will also help organize general meetings and reporting mechanisms. and all other necessary activities to support a smoothly functioning coordinated research effort.

Scientist three and the focus on MRA and atherosclerosis: In collaboration with William Beaumont Hospital and Wayne State University, we will develop a neuro-imaging protocol that includes SWI, MRA and SE black blood imaging to study the vessel wall and atherosclerosis. The collaborators on this project will include: Dr. Mark Haacke and Dr. John Bonnett from Wayne State University, and Dr. Anil Shetty from William Beaumont Hospital.

The ability to visualize vulnerable plaque might be considered the holy grail of imaging the vessel wall. Certainly as discussed earlier the ability to distinguish between different types of plaque and to visualize the formation of abnormal vessel wall are all important. High resolution, black blood double echo spin echo methods are being used today in an attempt to do this and with some success as well.

Here we plan to study a series of patients who will be scanned for potential carotid artery disease and who may be candidates for placing stents. Dr. John Bonnett will help with this project. At WSU alone they see several cases per week (several hundred per year). We plan to begin a study comparing SWI with the black blood SE method. We will also collect data both with and without contrast agent. We have previously shown that it may be possible to image the vaso-vasorum in that case and others have shown that macrophage effects can be seen as well. SWI is particularly sensitive to just these effects. In this protocol we will also run a conventional MRA scan and a high resolution T1 weighted scan for anatomical purposes.

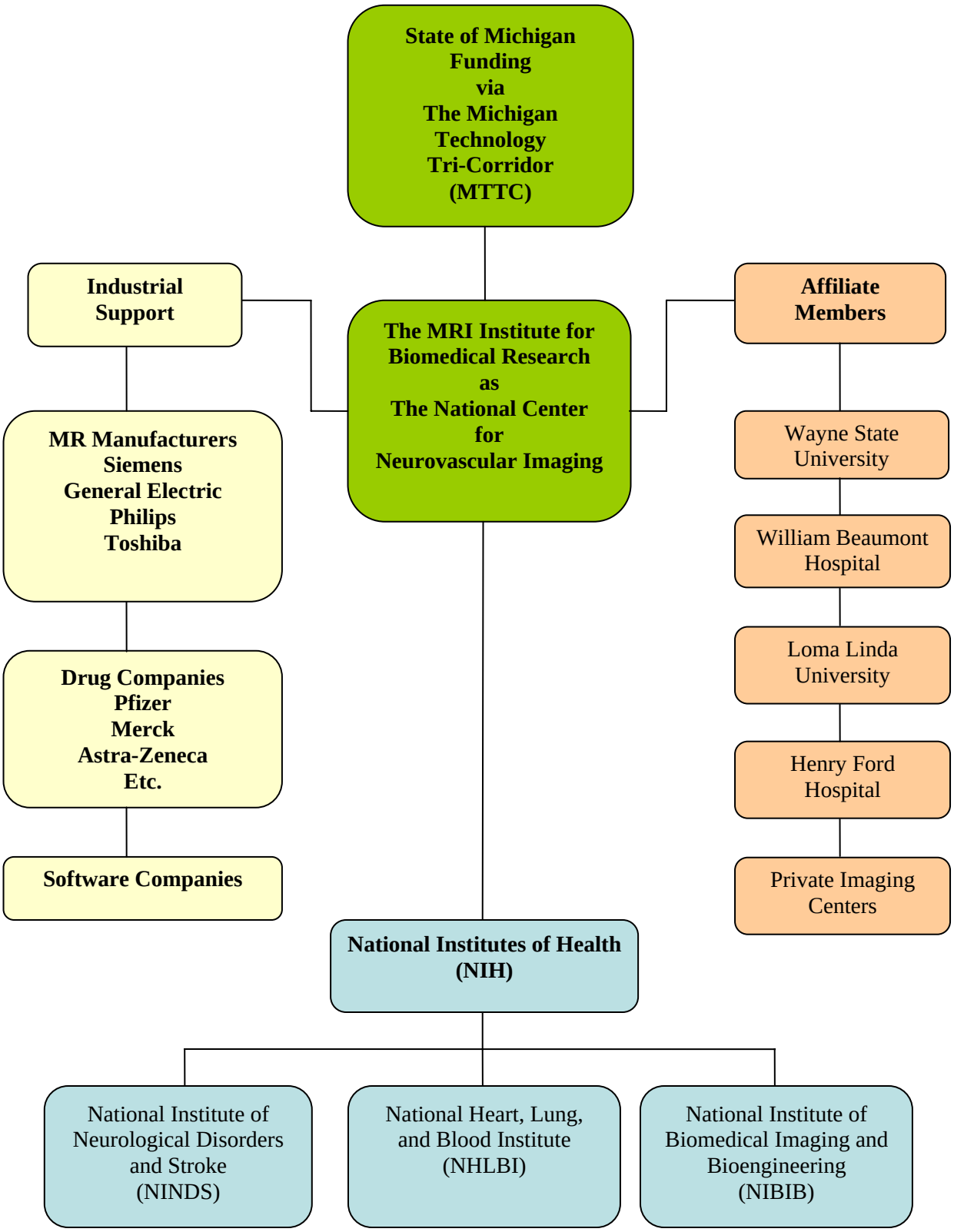
Post-doc two and MR angiography: MRA is a critical part of the neuro-protocol we have defined. Although there is a standard time-of-flight (TOF) sequence available on most systems, since we are using MRA post-contrast and since many systems now have either 8-channel coils and/or are also at high fields of 3T, the ability to increase resolution is more viable. Many systems now allow for up to 1024 point acquisitions but use highly asymmetric echoes. TOF is usually done without a contrast agent, but can in fact be quite useful if done post-contrast if sufficiently high resolution is acquired. This avoids the infamous problems of venous signal overlapping or confusing arterial signal. And with the advent of better vessel tracking routines with programs like SPIN become easier and easier to view in 3D. We are also working to incorporate partial Fourier analysis into SPIN which allows for a more accurate high resolution MRA image. The goal is to obtain 250u resolution in SWI and black blood SE images of the carotid artery wall as well as with a local contrast enhanced MRA of the region. This post-docs work will be valuable for all the neuro-protocols needing MRA. He/she will work with those programming SPIN to ensure proper validation of not only simulated data but also real MR images taken from phantoms. They will work closely with Ms. Jing Jiang in this process.

All three scientists: These people will also give presentations to the local institutions and to the BME students as a guest lecturer in MRI. They may participate in other imaging related courses. They may have access to students to enhance their productivity. In this way, they will be contributing to the growth of the imaging curriculum at Wayne State University.

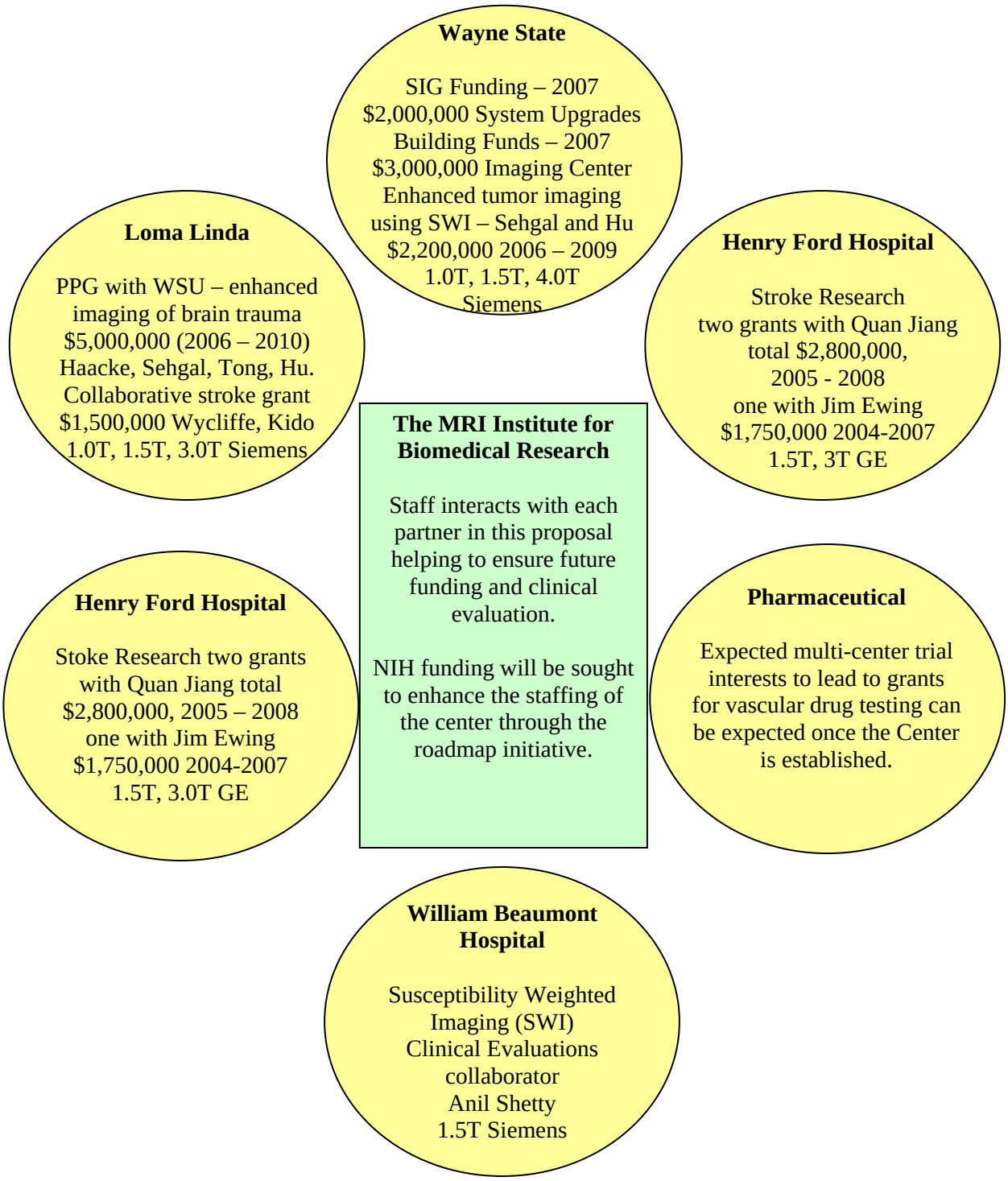
They are all expected to interact with their local environments and with the staff at the Institute. The focus on SPIN will take place at the Institute with help from Wayne State University staff and students. Throughout this process we will continue to develop or improve the technology at hand. Through experts like Mr. Xu, we can program the systems to create or modify sequences. We have a research agreement with Siemens that has allowed us to share methods across universities. (In fact, we have had a strong working relationship with Siemens since 1985. Over time they have contributed more than $2,000,000 to our research efforts in MRI.) The collection of preliminary data will be done at the various institutes – it is for this reason that they have offered free magnet time as needed. These funds are then considered a real contribution to the research program we are undertaking here.

Collaborative efforts: Wayne State University has made major commitments to imaging. They are allocating up to 20% of their available research time to this project (which comes to more than $500,000 annually). Likewise, Henry Ford Hospital has a major effort in MRI and they too have dedicated imaging time for us ($100,000 annually). Finally, the time and efforts by all the faculty and staff should serve as or be considered as a real financial contribution by the Institutes since they would otherwise be performing different duties at their home Institute.

"A CENTER OF EXCELLENCE FOR MAGNETIC RESONANCE IMAGING: AN OUTLINE OF PARTICIPANTS"



"A CENTER OF EXCELLENCE FOR MAGNETIC RESONANCE IMAGING: FUNDING"



This chart summarizes the main players, their studies, potential grants and support levels and, by proximity, how each of them will interact with the Center, with each other and with industry.