Department of Radiology, Neurology and Neurosurgery
Division Neuroimaging and Intervention

Ajay K. Wakhloo, M.D., Ph.D., FAHA
Matthew J. Gounis, Ph.D.
I. Martijn J. van der Bom, Ph.D.
Juyu Chueh, Ph.D.

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DISCLOSURES

- Stryker Neurovascular (Consultant, Research Grant)
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- Covidien/ev3 (Consultant, Research Grant)
- Boston Biomedical Association (Consultant)
- Philips (MAB, Research Grant, Equipment support)
- Postgraduate Course Harvard Medical School (Speaker)
- Baptist Hospital, Miami, Florida (Speaker)
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- 1-R21-NS061132-01A1
MAIN AREAS OF INNOVATION IN INTERVENTIONAL NEUROSURGERY

- Robotics
- Imaging
- Stroke
- Electro-physiology
- Gene therapy
- Immune therapy

Diagram shows the main areas of innovation in interventional neurosurgery.
RESEARCH FRONTIERS AND FUTURE IN INTERVENTIONAL NEUROSURGERY

OTHER AREAS ARE ..... 

• Pain Treatment
• Spine Intervention
• Training Standards in INS
• Politics of INS
• Changes in Healthcare and Impact on INS

...but our perspective and our ongoing Research and Future in INS...
Innovation- the driving force

Starts generally in a well know environment
Motivation (“role model”)
Different answers to same existing problems
Great changes begin with few supporters
Perseverance needed for execution
Ordinary people in extraordinary circumstances
(self proof, alienation, poverty, minority, etc.)
Sensitivity (for observant, perceptive, understanding, connection, open-mindedness, etc.)
Inspiration (inspīrō: breath in)— the “divine dust”? 
Inspiration leads to Innovation and is driven by unexpected observations and connections thereof.
That’s how I was doing angiograms...

Dr. Burt Lane, NYU in “The Exorcist”
Major risk factors
- Hypertension
- Atrial Fibrillation
- Carotid Artery Disease
- Intracerebral stenosis
- PFO
- CABG
- Aneurysms

7 M Stroke survivors: Level of disability
- None 29%
- Minor 35%
- Moderate 18%
- Major 18%
- DEATH

Ischemic Stroke
- Blockage
- Brain or neck artery

Hemorrhagic Stroke
- Break in artery wall
- Bleeding
- Brain artery

- 795,000 strokes annually
- 37,000 bleeds

Major risk factors:
- Ischemic (blockage) 80-85%
- Hemorrhagic (bleeding) 15-20%

75-90%
MULTIMODALITY STROKE WORKFLOW

0-4.5 hours

T1/T2, Perfusion, Diffusion MRI

Fluoroscopy, CE XperCT, XperCT, Perfusion X-ray

Stroke IV Therapy

Stroke Diagnostics

4-6 hours

Stroke IA Interventional Therapy

NEW ENGLAND CENTER FOR STROKE RESEARCH
Envisioned Stroke Workflow

Hemorrhagic Stroke

2D Fluoro + Rotational Angiography

Ischemic Stroke

Xper CT

XperGuide For Ventricular Drainages

CBV

2D Perfusion

3D Roadmap on VasoCT

VasoCT

XperCT

CBV

2D Perfusion
Ischemic Stroke – “Singular Unit”

Imaging Integration: Flat-Detector (FD) Technology Enables *in situ*:

CT-like Imaging

High Resolution Stent Visualization

Functional Imaging

Struffert, Strother et al. AJNR, 2012
Voxel-Based Mapping of C-arm CT Cerebral Blood Volume to Infarct Probability in a Canine Model of Ischemic Stroke

Kajo van der Marel, Ju-Yu Chueh, Ajay K Wakhloo, Matthew J Gounis
Quantitative analysis of high-resolution, contrast-enhanced, cone-beam CT for the detection of intracranial in-stent hyperplasia

Thomas F Flood,1 Imramship M J van der Bom,1 Lara Strittmatter,2 Ajit S Puri,1 Gregory H Hendricks,2 Ajay K Wakhloo,1 Matthew J Gounis1
High-Resolution Optical and Angiographic CT Imaging of Flow-Diverter Stents for Assessment of Vessel Wall Apposition

Kajo van der Marel, Matthew J. Gounis, Robert M. King, Ajay K. Wakhloo, Ajit S. Puri

New England Center for Stroke Research, Department of Radiology, University of Massachusetts Medical School, Worcester, MA, USA
Hemorrhagic Stroke

Flat-Detector Technology Enables *in situ*:

3D Angiography

Color-Coded DSA

Pereira et al. AJNR, 2012
KEY QUESTIONS

1. what are our current tools in the angiography suite?

2. what do we want to do with the angiography suite?

3. what are our limitations and how should the future Neurovascular Unit look like?
EPIGENETICS

EPIGENETIC MECHANISMS
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

HEALTH ENDPOINTS
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

MORPHOLOGICAL AGE-DEPENDENT DEVELOPMENT OF THE HUMAN CAROTID BIFURCATION

ETIOLOGY

- genetic defect
  - new mutation
- hypertension
  - shear stress
- inflammation
  - subendothelial
- repair mechanisms
- intimal lesion
- endothelial cells
  - smooth muscle cells
- secretion
- proliferation
- local flow disturbance
- bFGF
- VEGF
  - ?
- 
- O₂ depletion
- extracellular matrix
- collagen degradation
- proteolytic activity
- collagen synthesis
- protein synthesis
- remodeling of vessel wall
- aneurysm development

-exogenous factors
  - smoking
  - alcohol
  - medicine
-plasma factors
  - platelets
  - coagulation cascade
  - gelatinase
  - elastase
  - α₁-antitrypsin

-familial inheritance

-genetic defect
WHERE ARE WE TODAY WITH ATHEROSCLEROSIS?


- Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. *Nat Genet*. 2011;43:940-7


- Carotid plaque and candidate genes related to inflammation and endothelial function in hispanics from Northern Manhattan. *Stroke*. 2011;42:889-896
Hypertension
Atherosclerosis
Infection
Trauma

Acquired Diseases 95%

Collagen disorders
ADPKD

Congenital Diseases 5%

Structural abnormalities, degradation of internal elastic lamina

Expression of MCP-1

Inflammation

Expression MMP-2;9

Aneurysm formation

Immune system

Repair and stabilization

Progressive degeneration and rupture

Complement activation, lipid accumulation, neovascularization
Impact of Monocyte Chemoattractant Protein-1 Deficiency on Cerebral Aneurysm Formation

Tomohiro Aoki, MD; Hiroharu Kataoka, MD, PhD; Ryota Ishibashi, MD; Kazuhiko Nozaki, MD, PhD; Kensuke Egashira, MD, PhD; Nobuo Hashimoto, MD, PhD

Background and Purpose—Recent studies have suggested that chronic inflammation actively participates in cerebral aneurysm (CA) formation. Macrophages accumulate in CA walls and express proinflammatory genes promoting CA progression, but the molecular mechanisms of monocyte/macrophage recruitment into CA walls remain to be elucidated.

Methods—Monocyte chemoattractant protein-1 (MCP-1) expression in experimentally induced CAs was assessed by immunohistochemistry and Western blotting. The role of MCP-1 in CA formation was examined by MCP-1−/− mice and a plasmid DNA encoding a dominant negative mutant of MCP-1 (7ND). MCP-1 expression in human CAs was examined by immunohistochemistry.

Results—MCP-1 expression was upregulated in aneurysmal walls at the early stage of CA formation. MCP-1−/− mice exhibited a significant decrease of CA formation and macrophage accumulation with decreased expression of matrix metalloproteinase-2, -9, and inducible nitric oxide synthase. Immunohistochemistry for the DNA binding form of nuclear factor-kappa B showed nuclear factor-kappa B activation in MCP-1-expressing cells. Blockade of MCP-1 activity by 7ND resulted in the inhibition of CA progression in rats. In human CAs, MCP-1 was also expressed in CA walls.

Conclusions—These data suggest that MCP-1 plays a crucial role in CA formation as a major chemoattractant for monocyte/macrophage. MCP-1 expression in CA walls is induced through nuclear factor-kappa B activation. MCP-1 may be a novel therapeutic target of medical treatment preventing CA progression. (Stroke. 2009;40:942-951.)
Aspirin as a Promising Agent for Decreasing Incidence of Cerebral Aneurysm Rupture

David M. Hasan, MD; Kelly B. Mahaney, MD; Robert D. Brown, Jr, MD, MPH; Irene Meissner, MD; David G. Piepgras, MD; John Huston, MD; Ana W. Capuano, MPS, MS; James C. Torner, PhD; for the International Study of Unruptured Intracranial Aneurysms Investigators

**Background and Purpose**—Chronic inflammation is postulated as an important phenomenon in intracranial aneurysm wall pathophysiology. This study was conducted to determine if aspirin use impacts the occurrence of intracranial aneurysm rupture.

**Methods**—Subjects enrolled in the International Study of Unruptured Intracranial Aneurysms (ISUIA) were selected from the prospective untreated cohort (n=1691) in a nested case–control study. Cases were subjects who subsequently had a proven aneurysmal subarachnoid hemorrhage during a 5-year follow-up period. Four control subjects were matched to each case by site and size of aneurysm (58 cases, 213 control subjects). Frequency of aspirin use was determined at baseline interview. Aspirin frequency groups were analyzed for risk of aneurysmal hemorrhage. Bivariant and multivariable analyses were performed using conditional logistic regression.

**Results**—A trend of a protective effect for risk of unruptured intracranial aneurysm rupture was observed. Patients who used aspirin 3× weekly to daily had an OR for hemorrhage of 0.40 (95% CI, 0.18–0.87; reference group, no use of aspirin), patients in the “< once a month” group had an OR of 0.80 (95% CI, 0.31–2.05), and patients in the “≥ once a month to 2×/week” group had an OR of 0.87 (95% CI, 0.27–2.81; P=0.025). In multivariable risk factor analyses, patients who used aspirin 3 times weekly to daily had a significantly lower odds of hemorrhage (adjusted OR, 0.27; 95% CI, 0.11–0.67; P=0.03) compared with those who never take aspirin.

**Conclusions**—Frequent aspirin use may confer a protective effect for risk of intracranial aneurysm rupture. Future investigation in animal models and clinical studies is needed. (Stroke. 2011;42:3156-3162.)
Simvastatin Suppresses the Progression of Experimentally Induced Cerebral Aneurysms in Rats

Tomohiro Aoki, MD; Hiroharu Kataoka, MD, PhD; Ryota Ishibashi, MD; Kazuhiko Nozaki, MD, PhD; Nobuo Hashimoto, MD, PhD

Background and Purpose—The pathophysiology of cerebral aneurysms (CAs) is linked to chronic inflammation and degradation of extracellular matrix in vascular walls. Because statins have protective effects on various vascular diseases independent of their lipid-lowering effects, we investigated the effect of simvastatin on CA progression.

Methods—CAs were induced in Sprague-Dawley rats with or without oral administration of simvastatin. The size and media thickness of CAs was evaluated 3 months after aneurysm induction. Expression of macrophage chemoattractant protein-1, vascular cell adhesion molecule-1, endothelial nitric oxide synthase, interleukin-1β, inducible nitric oxide synthase, matrix metalloproteinase-2, and matrix metalloproteinase-9 in aneurysmal walls was examined by reverse transcriptase–polymerase chain reaction and immunohistochemistry. To examine whether simvastatin has a suppressive effect on preexisting CAs, simvastatin administration started at 1 month after aneurysm induction.

Results—Rats treated with simvastatin exhibited a significant increase in media thickness and a significant reduction in aneurysmal size compared with control rats. Treatment with simvastatin resulted in reduced expression of macrophage chemoattractant protein-1 and vascular cell adhesion molecule-1, increased expression of endothelial nitric oxide synthase, and reduced the number of macrophage infiltration. In quantitative polymerase chain reaction and immunohistochemistry, simvastatin significantly inhibited upregulated expression of interleukin-1β, inducible nitric oxide synthase, matrix metalloproteinase-2, and matrix metalloproteinase-9 associated with CA progression. Gelatin zymography revealed decreased activity of matrix metalloproteinase-2 and matrix metalloproteinase-9 in aneurysmal walls by simvastatin treatment. Simvastatin also effectively inhibited aneurysm enlargement and thinning of the media of preexisting CAs.

Conclusions—Treatment with simvastatin suppresses the development of CAs by inhibiting inflammatory reactions in aneurysmal walls. Simvastatin also has a preventive effect on the progression of preexisting CAs. Simvastatin is a promising candidate of a novel medical treatment for the prevention of CA progression. (Stroke. 2008;39:1276-1285.)
PROPOSED NON-INVASIVE TARGETED TREATMENT

• Transfection of 7ND (dominant negative DNA of MCP-1) into skeletal muscle for anti-MCP-1 gene therapy. May prevent aneurysm growth and rupture.

• Anti-inflammatory drug, e.g., Aspirin (Corticosteroids?)
  – Inhibiting of MMP-2 and MMP-9
  – Inhibition of TNF-α
  – Reduction of NF κB
  – Antiplatelet effect?

• Statins
  – Reduced expression of MCP-1 and VCAM-1
  – Increased expression of eNOS
  – Reduced infiltration of Macrophages
Summary

- Understanding Epigenetics may be critical in CV disease including brain aneurysms.
- Carotid atherosclerotic disease and brain aneurysms may be linked.
- NFκB plays a role in cellular response to stress, to cytokines, lipid deposition and immune response.
- miRNA important regulatory molecule involved in dysregulation of NFκB.
- Drugs targeted at inhibition of MCP-1, VCAM-1, iNOS, MMP-2 and MMP-2.
- Flow diverter may serve as an excellent endovascular bypass to repair CV diseased segments.
II. NEURODEGENERATIVE DISORDERS

Parkinson's
Tay Sachs
ALS
Huntington’s
Developments in genetics and virology have resulted in new therapeutic agents (viral vectors, antibodies, and immunotoxins) for neurodegenerative disorders (Huntington’s, Tay-Sachs, Parkinson’s).

Because of their macromolecular size, these drugs cannot be given systemically.

Convection enhanced delivery (CED): Drugs are forced directly into the anatomy of interest through a needle/cannula (localized and small volume).

Objective: accurate placement of microcannula using multimodal image-guidance by machine calibration

Delivery of Therapeutics for Neurodegenerative Disease

Multi-Modal Image-Guidance of Localized Drug Delivery in Huntington’s Disease
Materials & Methods

- Pre-clinical trail to test safety and efficacy of adeno-associated viral vector (AAV) delivery of shRNAmir for knockdown mutant Huntington in brain of sheep.
- Prior to CED surgery, MR imaging (T2w-TSE, T1w-TSE, and MPRAGE) was performed for surgery planning.
- Non-invasive frame to hold and manipulate cannula was mounted onto the skull.
Materials & Methods

- Pre-clinical trial to test safety and efficacy of rAAV-mediated gene therapy for treatment of Tay-Sachs disease in non-human primates.
- Prior to CED surgery, MR imaging (T2w-TSE, T1w-TSE, and MPRAGE) was performed for surgery planning.
- Non-invasive frame to hold and manipulate cannula was mounted onto the skull.
Materials & Methods

- Incisions and burr holes were created for bilateral thalamic injections and unilateral ventricle injection.
- CBCT data was acquired and registered with MRI data.
- Cannula placement was planned on registered CBCT and MRI data.
Real-Time Imaging Feedback During Cannula Placement

van der Bom et al. JNIS, 2013
Delivery of Therapeutics for Neurodegenerative Disease

High-Resolution Cone Beam CT (CBCT) Enables Visual Confirmation

Huntington’s Disease

✓ Microcannula tip (300 µm) position was confirmed with CBCT registered with MRI
PERCUTANEOUS TRANSCATHETER AORTIC VALVE REPLACEMENT

Multi-Modal Image-Guidance

EchoNavigator
Intelligently integrated live X-ray and Echo

Courtesy of Philips Healthcare
BRAIN TUMORS

- Astrocytomas account for 80% of all malignant brain tumors
- 18,500 new cases of malignant primary CNS tumors in USA in 2005
- 43,800 new cases of both malignant and non-malignant primary CNS tumors in 2005
- Primary brain tumors account for 2% only of all cancers however
- 5-year survival rate 30% for anaplastic astrocytoma and
- 5-year survival rate 3.3% for gliobastoma
- 12,820 deaths associated with CNS tumors in 2006
MINIMALLY-INVASIVE TUMOR THERAPY

**Intravascular:**

Automatic Feeder Detection using Contrast-Enhanced CBCT for Ultraselective Chemoembolization

Miyayama et al, JVIR, 2012

**Percutaneous:**

Dual-Phase CBCT Immediate pre- and post TACE Predicts Tumor Response

Loffroy et al, Radiology, 2013

CBCT-based Thermometry

Abi-Jaoudeh et al, RSNA, 2012
Apollo Penumbra Aspiration catheter and Ultrasound 
Minimally invasive clot suction under Angioscope and 
Cone Beam CT guidance

With courtesy of Dr. Sam Hoh and Dr. Zauner, Santa Barbara, CA
Patient radiation doses is a major issue in Interventional Neuroradiology.

Appearance of radiation-induced skin injury approximately 18 to 21 months following multiple coronary angiography and angioplasty procedures – evidence of progressive tissue necrosis (Source: www.fda.gov/cdrh/rsnaii)
Equipment

• Biplane Philips Allura Xper FD20/20
  (Allura Clarity, just received FDA approval)

• DoseReductionSystem
  – Increased tube filtration
  – Automatic mask alignment
  – New reconstruction algorithm
  – Noise reduction

Söderman et al. Radiology 2013 (June 4, 2013 published on line before print)
WITHOUT DOSE REDUCTION

WITH DOSE REDUCTION
STEREOTAXY

WITHOUT DOSE REDUCTION  WITH DOSE REDUCTION

STEREOTAXY
DoseReductionSystem allows up to a 75% radiation dose reduction with equal or improved image quality when compared to standard DSA.
That’s probably how you will be doing.....

From “Startrack”