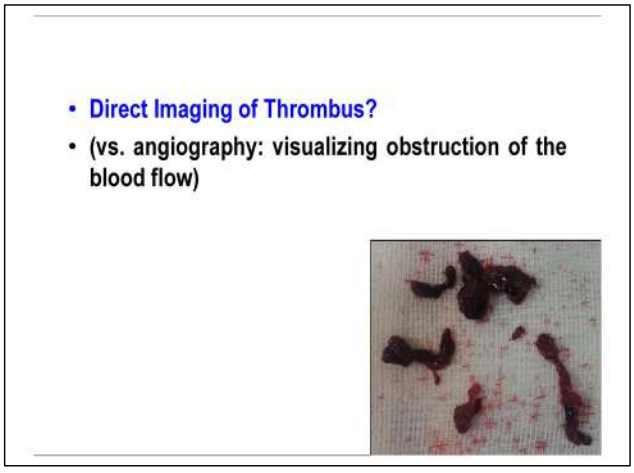
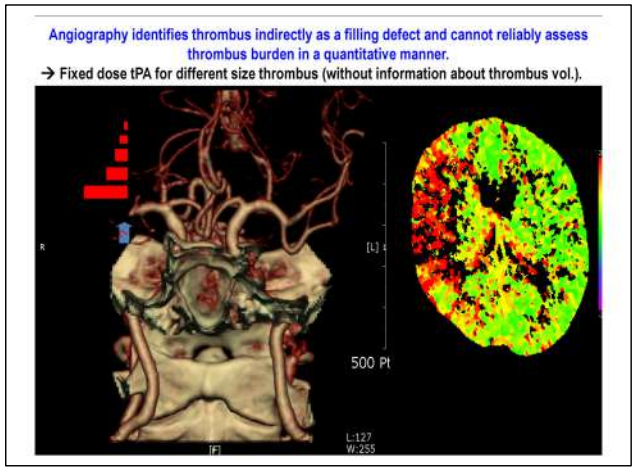
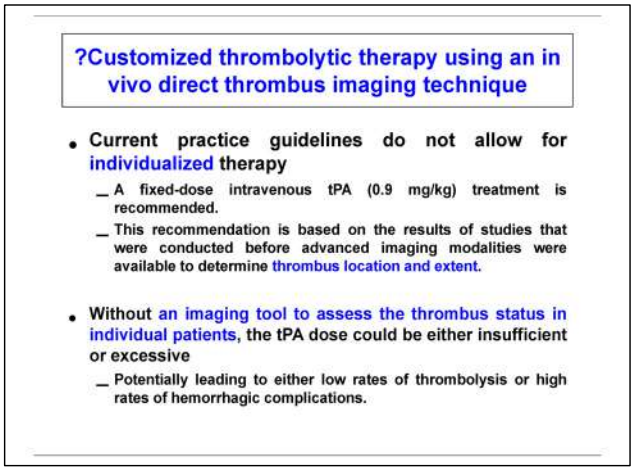
Direct thrombus imaging in stroke and thrombosis

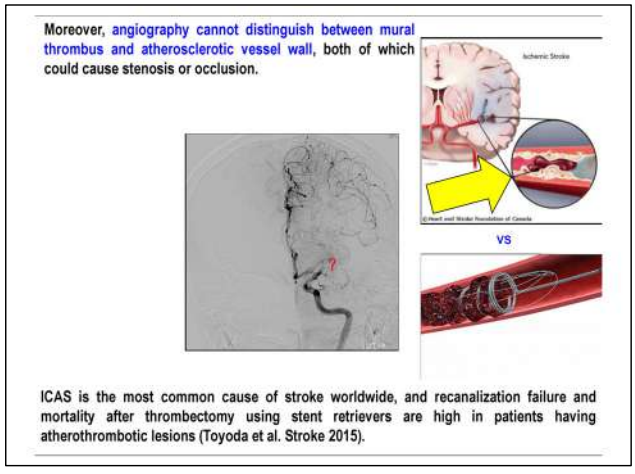
김 동 억
동국의대

Dong-Eog Kim, MD, PhD
Molecular Imaging & NEurovascular Research Lab. Dongguk University Ilsan Hospital, Korea









Direct thrombus imaging may guide 'future' thrombolytic therapy by enabling clinicians to

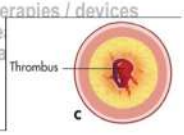
1. reduce tPA dose for smaller fragile thrombi
2. proceed directly to endovascular therapy for bigger compact thrombi that are likely to be highly resistant to conventional tPA doses
3. find good tPA respondents among patients with acute large vessel occlusion (LVO): for eg. LVO due to a tiny in situ thrombus or embolus superimposed on a cerebral artery with significant large artery intracranial atherosclerotic stenosis (ICAS)
4. better select specific endovascular therapies / devices and allow for technical refinements, leading to safer and more effective endovascular therapy

Direct thrombus imaging may guide 'future' thrombolytic therapy by enabling clinicians to

1. reduce tPA dose for smaller fragile thrombi
2. **proceed directly to endovascular therapy for bigger compact thrombi that are likely to be highly resistant to conventional tPA doses**
3. find good tPA respondents among patients with acute large vessel occlusion (LVO): for eg. LVO due to a tiny in situ thrombus or embolus superimposed on a cerebral artery with significant large artery intracranial atherosclerotic stenosis (ICAS)
4. better select specific endovascular therapies / devices and allow for technical refinements, leading to safer and more effective endovascular therapy

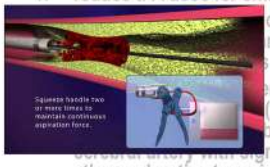
Direct thrombus imaging may guide 'future' thrombolytic therapy by enabling clinicians to

1. reduce tPA dose for smaller fragile thrombi
2. proceed directly to endovascular therapy for bigger compact thrombi that are likely to be highly resistant to conventional tPA doses
3. **find good tPA respondents among patients with acute large vessel occlusion (LVO): for eg. LVO due to a tiny in situ thrombus or embolus superimposed on a cerebral artery with significant large artery intracranial atherosclerotic stenosis (ICAS)**
4. better select specific endovascular therapies / devices and allow for technical refinements, le
and more effective endovascular thera



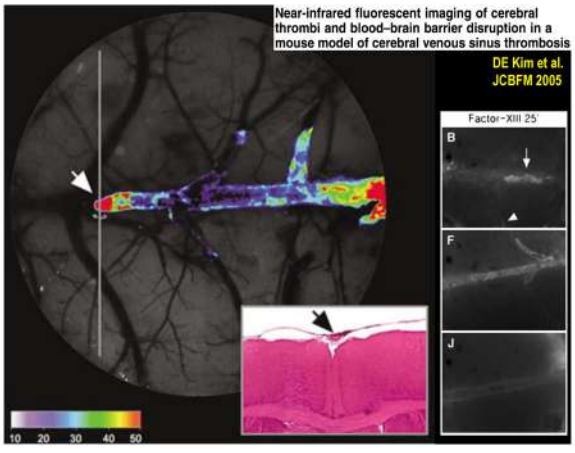
Direct thrombus imaging may guide 'future' thrombolytic therapy by enabling clinicians to

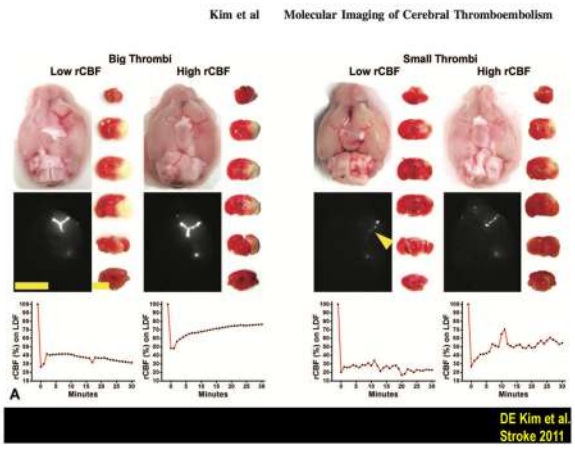
1. reduce tPA dose for smaller fragile thrombi



atherosclerotic stenosis (ICAS)

4. **better select specific endovascular therapies / devices and allow for technical refinements, leading to safer and more effective endovascular therapy**





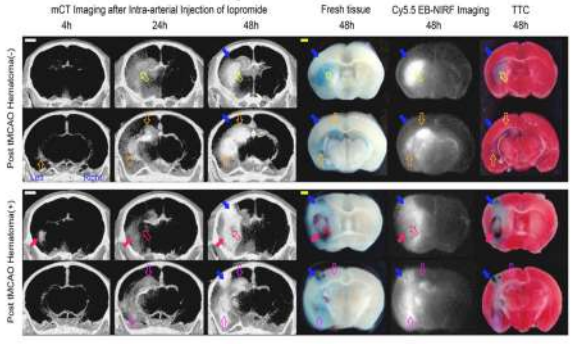
Poor depth penetration → Optical techniques do not allow a non-invasive imaging in vivo.

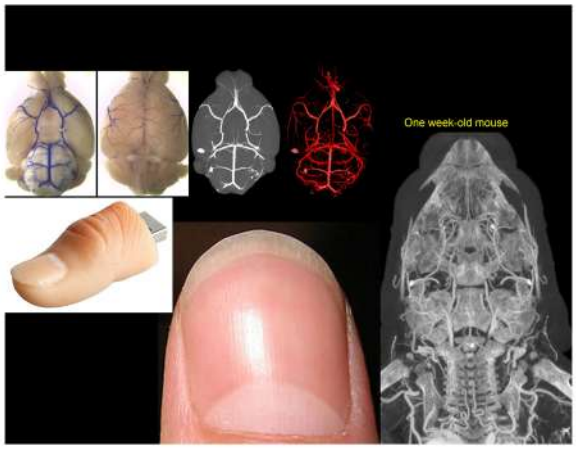
- **Q: Can we visualize thrombus serially in vivo?**
  - To advance to personalized thrombolytic therapy by demonstrating thrombus burden, distribution, and character in a prompt and quantitative manner

- **Modality of choice for direct thrombus imaging in stroke ?**
  - Computed tomography (CT) is the current standard for most clinical decision making in administering tissue plasminogen activator (tPA). However, non-contrast CT does not usually allow a precise assessment of extent and distribution of thromboemboli.

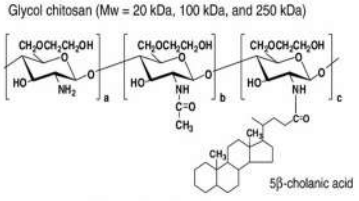
JY Park ~ DE Kim; Stroke 2014

A New Micro–Computed Tomography–Based High-Resolution Blood–Brain Barrier Imaging Technique to Study Ischemic Stroke





Glycol chitosan (Mw = 20 kDa, 100 kDa, and 250 kDa)



glycol chitosan-cholanic acid conjugates

In aqueous condition

Glycol chitosan (GC)

GC-AuNP

Angewandte International Edition Chemie

DOI: 10.1002/anie.201102892

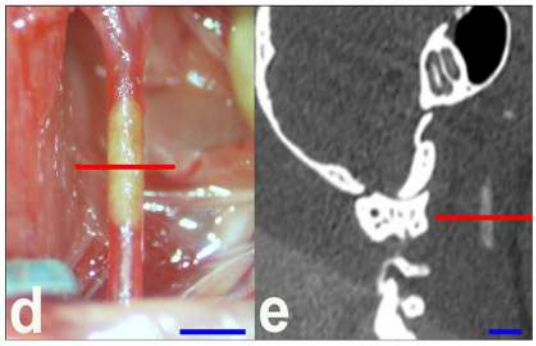
Imaging Agents

Tumor-Targeting Gold Particles for Dual Computed Tomography/ Optical Cancer Imaging**

In-Cheol Sun, Dae-Kyung Eun, Heebeom Koo, Chang-Yong Ko, Han-Sung Kim, Dong Kee Yi, Kuiwon Choi, Ick Chan Kwon, Kwangmeyung Kim, and Cheol-Hep Ahn**

DE Kim & JY Kim et al. Ann Neurol 2013

In vivo gold nanoparticle (AuNP)-microCT imaging detects thrombus promptly in mice exposed to $FeCl_3$ at the left carotid artery.



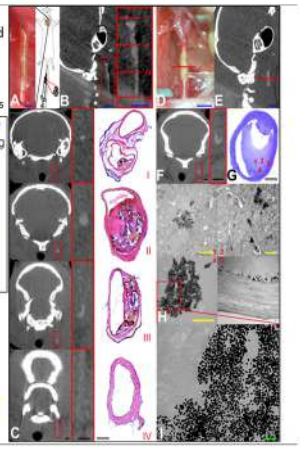
Hyperacute Direct Thrombus Imaging Using Computed Tomography and Gold Nanoparticles

Dong-Eog Kim, MD, PhD,[1] Jeong-Yeon Kim, MS,[1] In-Chool Sun, MS,[1] David Schellingerhout, MBChB,[2] Su-Kyoung Lee, BS,[1] Cheol-Hee Ahn, PhD,[3] Ick Chan Kwon, PhD,[3] and Keumgyoung Kim, PhD[3]

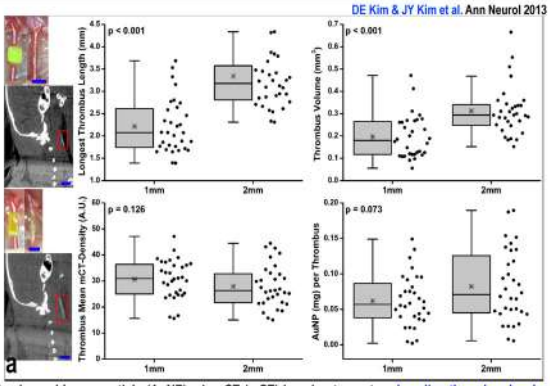
ANN NEUROL 2013;73:617–625

- A novel method to visualize thrombus directly in a mouse model of carotid thrombosis using microCT?
  - Is direct thrombus imaging possible ?
  - Fixed dose tPA vs. Customized thrombolytic Rx?
  - Visualize dynamic evolution of thrombus in response to tPA?

A close correlation between imaging & histology



DE Kim & JY Kim et al. Ann Neurol 2013

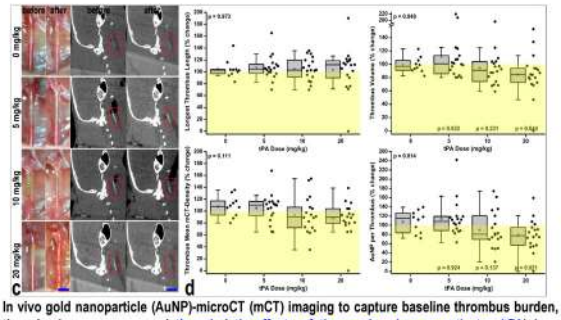


In vivo gold nanoparticle (AuNP)-microCT (mCT) imaging to capture baseline thrombus burden, thrombosis recurrence, and thrombolytic effects of tissue plasminogen activator (tPA) in a quantitative manner.

DE Kim & JY Kim et al. Ann Neurol 2013

In vivo gold nanoparticle (AuNP)-microCT (mCT) imaging to capture baseline thrombus burden, thrombosis recurrence, and thrombolytic effects of tissue plasminogen activator (tPA) in a quantitative manner.

DE Kim & JY Kim et al. Ann Neurol 2013



In vivo gold nanoparticle (AuNP)-microCT (mCT) imaging to capture baseline thrombus burden, thrombosis recurrence, and thrombolytic effects of tissue plasminogen activator (tPA) in a quantitative manner.

DE Kim & JY Kim et al. Ann Neurol 2013

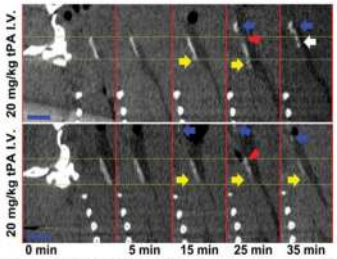


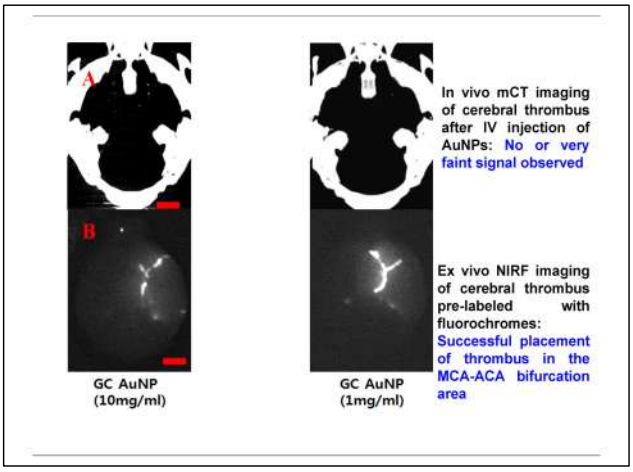
FIGURE 4: Representative serial microcomputed tomography images illustrating the dynamic nature of post–tissue plasminogen activator (tPA) thrombus evolution. In the

In addition to the potential implications in future clinical practice, the advanced imaging will likely have multiple uses in current basic / translational research.

AuNPs for mCT-imaging of carotid thrombus in mice: 100.0% success rate

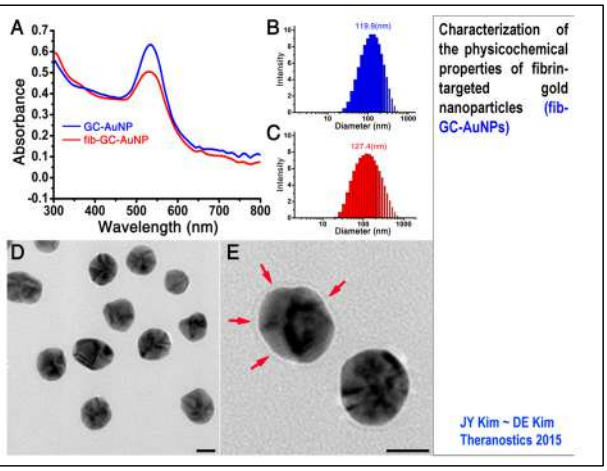
Objective: Advancing the understanding and management of thromboembolic stroke requires simple and robust new methods that would be useful for the in vivo assessment of thrombus burden/distribution and for characterizing its evolution in a prompt and quantitative manner.
Methods: Animals (n=127) with experimental models of thrombosis were imaged with microcomputed tomography 5 minutes (and/or ~3 weeks) after intravenous injection of glycol chitosan (GC) gold nanoparticles (AuNPs).
Results: Nanoparticles accumulated in the thrombus, allowing computed tomography visualization of both the presence and extent of primary and recurrent thrombi in mouse carotid arteries without a single failure of detection. Nanoparticle thrombus imaging was also effective in monitoring the therapeutic efficacy of thrombolysis (n=118 tissue plasminogen activator [tPA] therapies). Thrombus evolution (either spontaneous or post-tPA) could be mapped at high resolution in both space and time. Due to a long circulating half-life, GC-AuNPs remain available for entrapment into fibrin matrix for an extended period of time (up to 3 weeks), allowing repetition or ongoing monitoring of thrombogenesis and thrombolysis.
Interpretation: This is the first report on a hyperacute direct thrombus imaging technique using thrombus-seeking AuNPs and computed tomography. When translated into stroke practice, the thrombus imaging may allow us to advance to personalized thrombolytic therapy by demonstrating thrombus burden, distribution, and character in a prompt and quantitative manner. Further study into this area is indicated.

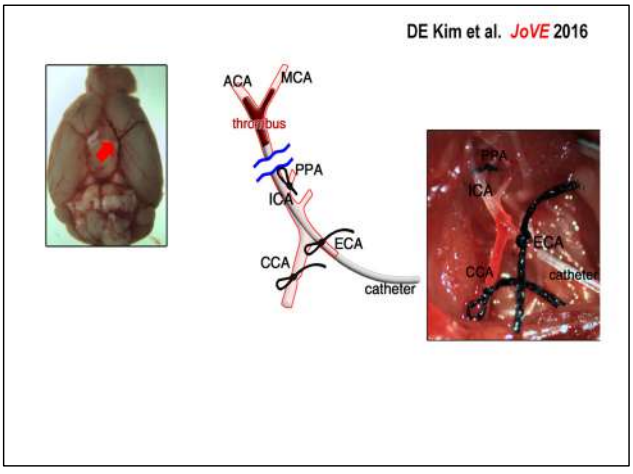
ANN NEUROL 2013;73:617–625

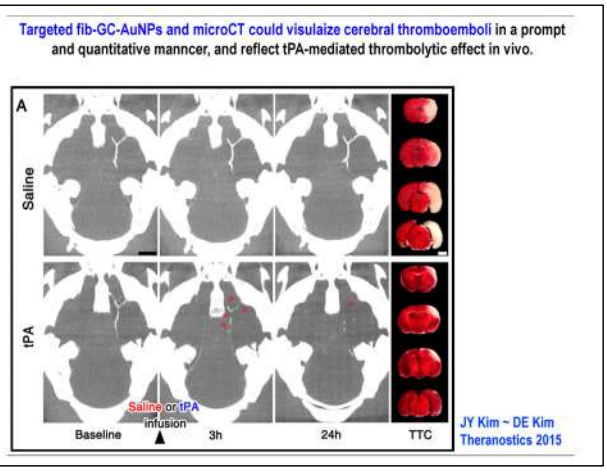


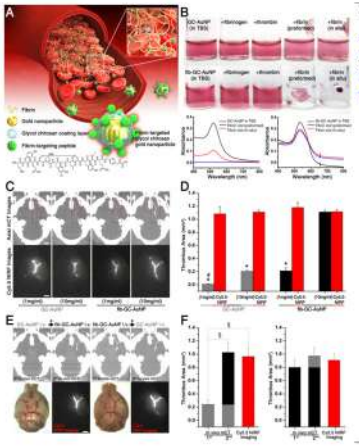
Question

- Can we visualize 'cerebral' thromboemboli and post-tPA thrombus evolution serially in vivo using a novel fibrin-targeted AuNPs ?



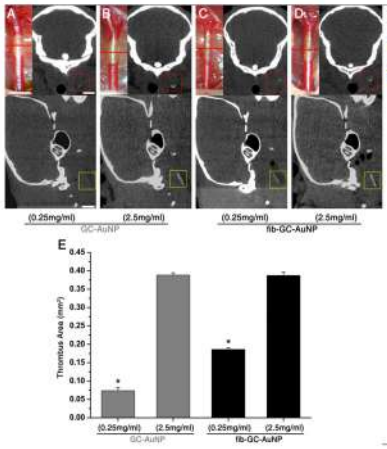






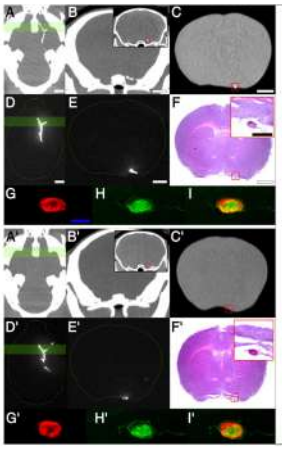
Targeted fib-GC-AuNPs are superior to non-targeted GC-AuNPs in fibrin-binding and mCT imaging of cerebral thromboemboli

JY Kim ~ DE Kim
Theranostics 2015



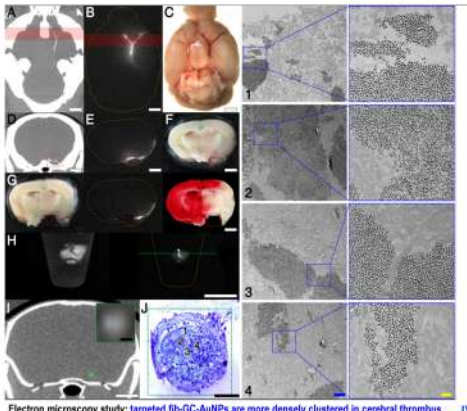
Targeted fib-GC-AuNPs are superior to non-targeted GC-AuNPs in mCT imaging of carotid thrombus

JY Kim ~ DE Kim
Theranostics 2015



Imaging-histology co-localization study: targeted fib-GC-AuNPs vs. non-targeted GC-AuNPs

JY Kim ~ DE Kim
Theranostics 2015

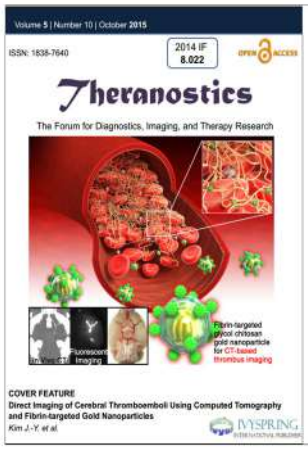


Electron microscopy study: targeted fib-GC-AuNPs are more densely clustered in cerebral thrombus than the non-targeted equivalent, correlating well with the more sensitive mCT visualization of thrombus by the targeted compound.

JY Kim ~ DE Kim
Theranostics 2015

A single-dose targeted fib-GC-AuNP injection and repeated mCT imaging to capture both the initial episode of acute cerebral thrombosis and subsequent recurrent episodes of carotid artery thromboses.

JY Kim ~ DE Kim
Theranostics 2015

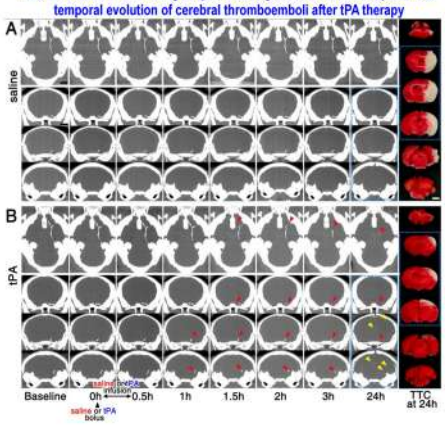


JY Kim ~ DE Kim
Theranostics 2015
Cover Article

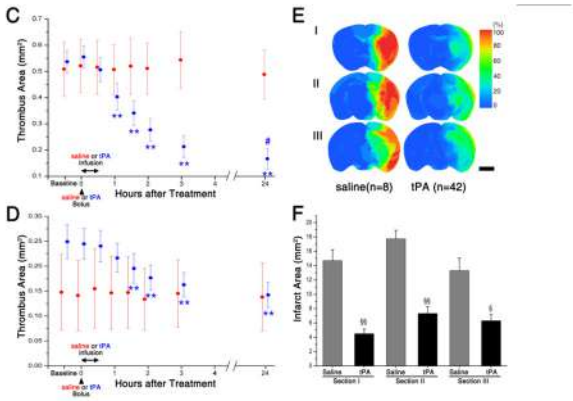
Q: Spatiotemporal Dynamsics of tPA Response of Cerebral Thromboemboli in Near-real Time?

Serially in the same mice in vivo

The first serial in vivo study to quantitatively assess a detailed spatial and temporal evolution of cerebral thromboemboli after tPA therapy

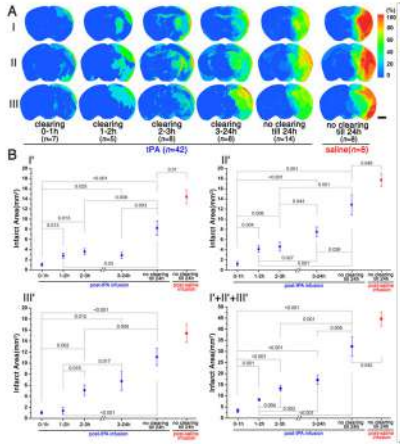


DE Kim et al. *Stroke* 2017



Targeted fib-GC-AuNP mCT imaging allows a prompt and quantitative assessment of the location, amount, and evolution of cerebral thromboemboli, after tPA therapy.

DE Kim et al. *Stroke* 2017

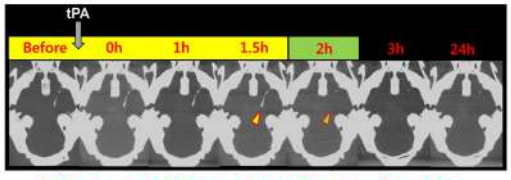


Early (vs. late) thrombolysis by tPA therapy gives rise to smaller final infarct sizes.

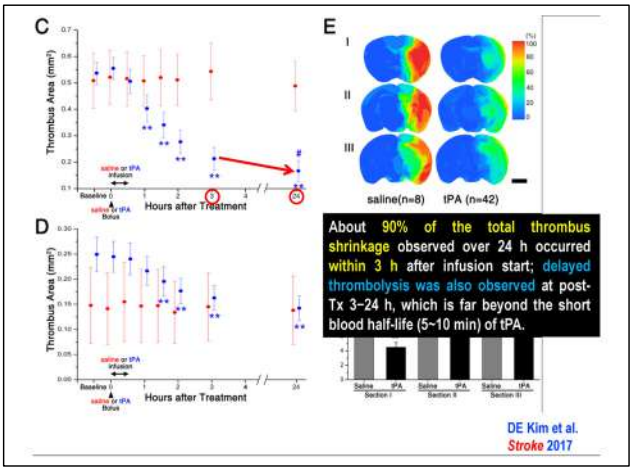
DE Kim et al. *Stroke* 2017

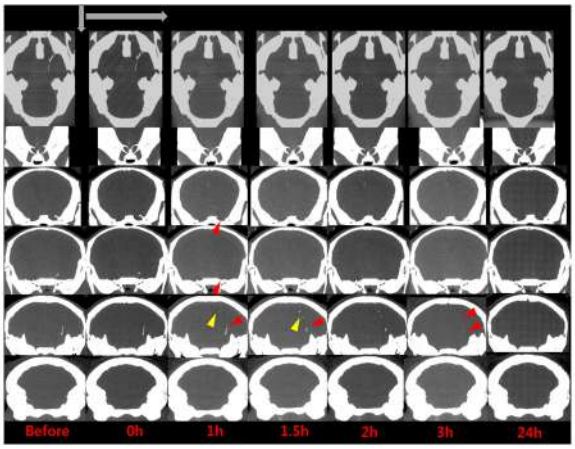
Lessons from Direct Thrombus Imaging Cases in Mice: Some Translational Points

Thrombi could dissolve rapidly at some point after resisting for a relatively long time....

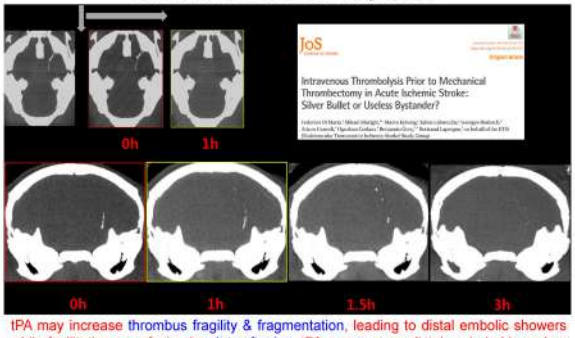


When and how should we decide whether to move on to mechanical thrombectomy? The sooner, the better?





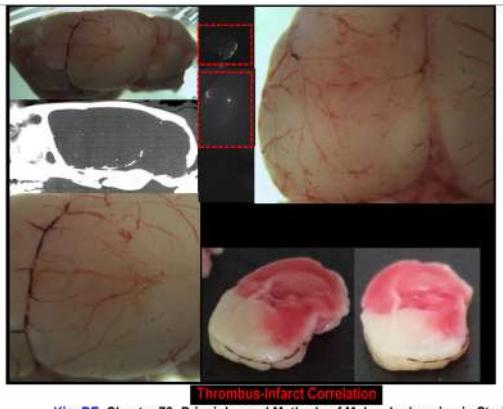
Thrombi could respond to tPA in different manners at different speeds.



tPA may increase thrombus fragility & fragmentation, leading to distal embolic showers while facilitating reperfusion by clot softening. tPA may re-open distal occluded branches 'after' mechanical thrombectomy.

Conclusion

- (CT-based) Direct thrombus imaging is likely to serve as a new, simple, and robust research tool in stroke
- When translated into stroke practice, it may allow us to advance to personalized thrombolytic therapy
  - by demonstrating thrombus burden, distribution, and molecular character in a prompt and quantitative manner.



Kim DE. Chapter 70: Principles and Methods of Molecular Imaging in Stroke, Primer on Cerebrovascular Diseases, Second Edition.


Acknowledgement
MINER Molecular Imaging & Neruovascular Research) Lab, Korea
– Kim JY, Kim JW, Lee SK, Jang HJ, Je KH, Kang JW, Oh JH
Korea Institue of Science & Technology, Korea
– Kim KM, Ryu JH, Sun IC, Kwon IC
Research Institute of Advanced Materials, Seoul National University, Korea
– Ahn CH
Center for Systems Biology, MGH, Harvard Medical School, USA
– Nahrendorf M, Krohn-Grimberghe M, Cremer S.
Experimental Neuroradiology, MD Anderson Cancer Center, University of Texas, USA
– Schellingerhout D
Global Research Laboratory for Thrombus-targeted Theranostics @
– Dongguk University Ilsan Hospital (Korean PI, Dong-Eog Kim) & Massachusetts GeneralHospital, Harvard Medical School (USA PI, Matthias Nahrendorf)