Promises and Challenges of Benchtop X-Ray Fluorescence CT (XFCT) for Quantitative *In Vivo* Imaging

August 3, 2016

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Acknowledgment

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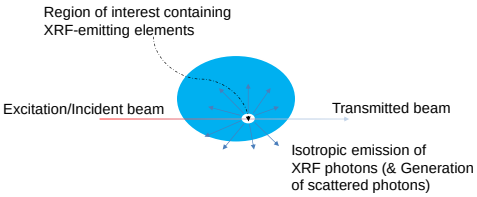
- Benchtop XFCT Research Consortium Members:
  UMass - A. Karellas, S. Vedantham, M. King
  Brookhaven National Lab – R. James, Y. Cui

Acknowledgment

- Paper/Grant Reviewers
- Funding support from *Georgia Tech, Georgia Research Alliance, DOD/BCRP/LCRP/PCRP, NIH/NCI/NIBIB, MDACC*

XFCT

- X-ray Fluorescence (XRF) Analysis + Imaging or CT



XFCT

- Typically utilizes a high flux monochromatic pencil beam to induce XRF photons – "synchrotron XFCT"
  - Boisseau 1986, Cesareo and Mascarenhas 1989, Hogan et al 1991, Yuasa et al 1997, Simionovici et al 2000, Schroer 2001, Takeda 2001, La Rivière 2004
- Stimulated emission tomography in its nature
- Material detection limit (sensitivity) of synchrotron XFCT typically on the order of parts per million (ppm)

Motivations for Benchtop XFCT

- Issues with synchrotron XFCT for biomedical applications
  - Accessibility, Dose, and Energy
- Emerging applications of metal-based nanoparticles such as gold nanoparticles (GNPs) for diagnostic/therapeutic purposes

Motivations for Benchtop XFCT

- Possibility to achieve multimodal mutiplexed quantitative (preclinical) imaging capability
  - Simultaneous microCT
  - Use of non-radioactive metal (nano-)probes for molecular imaging
  - Non-invasive determination of biodistribution of metal NPs

Characteristics of Benchtop XFCT

- Implemented with ordinary polychromatic x-ray source on a benchtop setting for wide availability
  - Quasi-monochromatization or proper filtering of polychromatic x-ray spectrum
- Utilizes compact energy-resolving solid state x-ray detector (without liquid nitrogen cooling)

Challenges of Benchtop XFCT

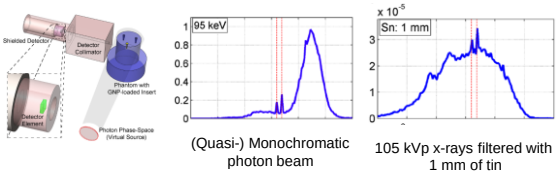
- Suffers adverse consequences from polychromatic nature of the excitation beam (especially for *in vivo* imaging applications)
  - requires prohibitively long scan/data acquisition time (when high sensitivity is required)
  - poor sensitivity (when performed with insufficient/short scan time)

Challenges of Benchtop XFCT

- Size of imaging objects limited by XRF photon energy
- Pessimistic outlook in the field (especially for human imaging applications - e.g., von Busch et al. 2005)

Benchtop XFCT

90° Scatter + gold XRF spectra



(Quasi-) Monochromatic photon beam

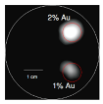
105 kVp x-rays filtered with 1 mm of tin

Manohar et al., *Med. Phys.*, Vol. 41(10), 2014

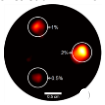
Benchtop XFCT

- Demonstrated first using GNPs and polychromatic pencil beam (110 kVp & 680 µm lead filter)
- Developed into the current cone beam XFCT (105 kVp & 0.9 mm tin filter)

~40 hours (pencil beam, 50 W)
Cheong et al. *PMB* 2010



~6 hours (cone-beam, 50 W)
Jones et al. *PMB* 2012



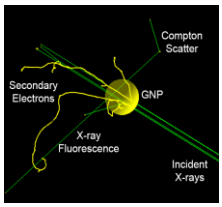
Benchtop XFCT

- Shown capability for multiplexed imaging (Au, Gd, & Ba) using a 3 kW clinical x-ray source under a pencil beam geometry (Kuang et al. 2012)
- Demonstrated (computationally) higher sensitivity of benchtop XFCT to detect gold/GNPs at low concentration vs. photon-counting k-edge CT (Bazalova et al. 2012, Feng et al. 2014)

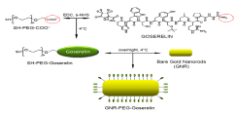
Benchtop XFCT

- For the last half-decade or so, numerous (~10) groups worldwide have contributed to benchtop XFCT research and development
- Ultimate goal of research is to develop benchtop XFCT into practical *in vivo* (molecular) imaging modality

Benchtop XFCT with GNPs

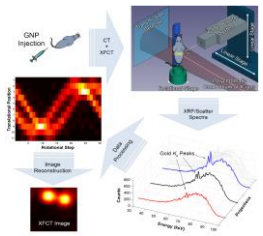


Photon irradiation of GNP
Manohar et al., *Scientific Reports,* 2016



Conjugation of GNP/GNR
Wolfe et al., *Nanomedicine,* 2015

Benchtop XFCT with GNPs



Manohar et al., *Scientific Reports*, 2016

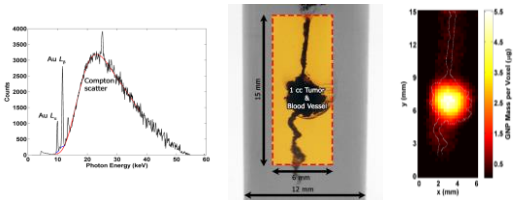
Benchtop XFCT with GNPs

- "K-shell Mode" based on detection of gold K-shell XRF photons (~67.0 and ~68.8 keV)
  - Higher energy allows imaging of larger objects
  - Can be used for tomographic reconstruction
- "L-shell Mode" based on detection of gold L-shell XRF photons (~9.71 and ~11.4 keV)
  - More suitable for direct 2D imaging with high resolution & high sensitivity

Benchtop XFCT with GNPs

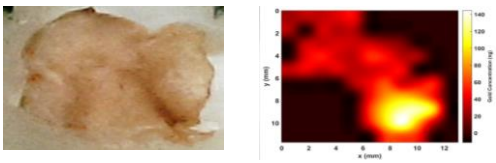
- Determination of GNP biodistribution or intratumoral distribution via *ex vivo* or *in vivo* imaging
- Quantitative molecular imaging using bioconjugated GNPs and other metal NPs

Benchtop XFCT with GNPs



L-shell Mode: Manohar et al., *Med. Phys., Vol 40(10), 2013*

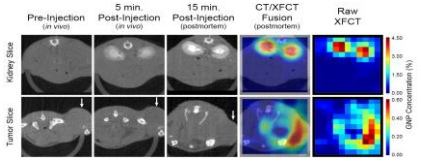
Benchtop XFCT with GNPs



L-shell Mode: HCT116 tumor sample loaded with Cetuximab-conjugated GNPs, Cho/Krishnan Group 2015 (AAPM 2016, SU-G-IeP3-7)

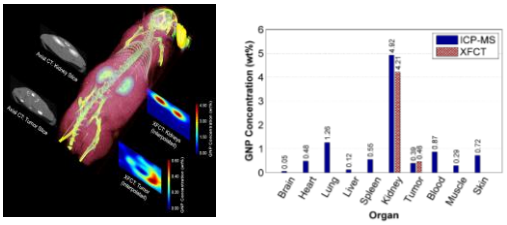
Benchtop XFCT with GNPs

- First successful demonstration of benchtop XFCT with GNPs as applied to small animal imaging (albeit performed *postmortem*)



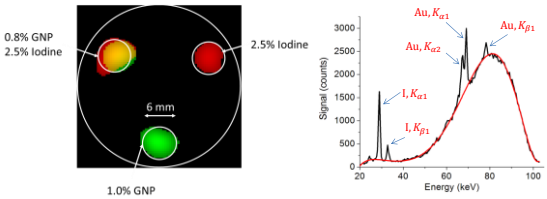
K-shell Mode: Manohar et al., *Scientific Reports, 2016*

Benchtop XFCT with GNPs



K-shell Mode: *Manohar et al., Scientific Reports, 2016*

Benchtop XFCT with GNPs



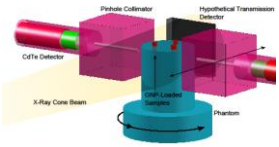
K-shell Mode: Multiplexed Imaging
Cho Group 2016 (performed by M Ahmad & S Yasar)

Benchtop XFCT – Current Status

- Cone-beam XFCT setup currently ready for *in vivo* imaging (with some limitations)
- Current detection limits for GNPs or gold
  - K-shell Mode: ~300 ppm
  - L-shell Mode: ~1 ppm (Manohar et al 2013, Ricketts et al 2013)

Benchtop XFCT – Current Status

- Simultaneous microCT capability (with some remaining challenge)
- Some degree of parallel data acquisition using multiple detectors
  - image from Jones et al., *PMB* 2012

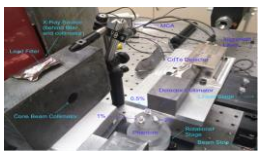


Benchtop XFCT – Current Status

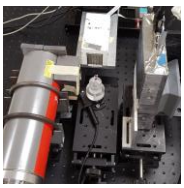
	Proof-of-Principle	*Ad Hoc*	Dedicated
X-ray Source	Hamamatsu L9631	Philips RT250	Comet XRS-160
Accelerating Potential (kVp)	105	125	125
Beam Current (mA)	0.40	25	24
Power (W)	42	3125	3000
Tin Filter Thickness (mm)	0.9	2	2
Acquisition Time per Projection (s)	60	15	10
GNP Detection Limit (wt%)	0.50	0.24	0.030
Phantom Imaging Time (hr)	6	1.5	1

Manohar et al., AAPM 2016 meeting, TH-AB-209-1

Benchtop XFCT – Current Status



Cone-beam XFCT setup
Cho Group @Georgia Tech, circa 2010



Work in progress since 2015
Cho Group @MDACC

Benchtop XFCT - Remaining Challenges

- 2D parallel data acquisition under cone-beam geometry
  - requires high energy resolution pixelated detector with proper collimation
  - necessary to achieve acceptable spatial resolution (~ 1 mm or less) & dose (on the order of 10 cGy per session) for preclinical animal studies

Benchtop XFCT - Remaining Challenges

- Further optimization/Quasi-monochromatization of polychromatic spectrum
- Simultaneous microCT using filtered/quasi-monochromatic incident beam (under K-shell mode – Manohar and Cho, IEEE/MIC, 2013)

Benchtop XFCT – Future Outlook

- Address key technical challenges over next 4 years
- Achieve detection limit (sensitivity) ~100 ppm or less in the case of GNPs/gold
- Available prototype with simultaneous microCT capability for routine *in vivo* imaging

Thank you for your attention !