Novel contrast agents for multi-energy CT imaging

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Penn

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- Stock owner of PolyAurum

CT scanning

140 160



DP Cormode et al Contrast Media Mol. Im. 2014, 9(1):37-52





Energy dependence of X-ray attenuation



For a pixel at a given energy (E) the attenuation, $\mu(E)_{\text{total}},$ can be described as: $\mu(E)_{\text{total}} = \mu(E)_{\text{gold}} + \mu(E)_{\text{iodine}} + \mu(E)_{\text{photoelectric}} + \mu(E)_{\text{Compton}}$ where $\mu(E)_{\text{gold}} = \alpha(E)_{\text{gold}}.[\text{gold}]$



Slide courtesy of Roland Proksa, Philips Research Europe



Photon counting detector

Advantages of photon counting CT

- · Higher spatial resolution
- · Lower radiation dose
- · Lower noise
- Better spectral information
- · K-edge imaging of contrast agents
- > Need for agents based on different elements

> Potential for agents with different functionality

S. Si-Mohamed et al, NIMA, 2017, 873, 27-35

K-edge imaging



- · Specific imaging of iodine very difficult in photon-counting CT
- · Specific imaging needs elements with higher energy k-edges

S. Si-Mohamed et al, NIMA, 2017, 873, 27-35





Pros

- Produce excellent contrast
- · Good track record
- Cons · Very short half-lives
- Non-specific
- Increasing numbers of patients contraindicated
- K-edge too low

New contrast agents - nanoparticles



-May be compatible with patients with kidney disease
-Long circulation half-lives
-Efficient targeting
-Can be multifunctional, e.g. additional contrast, therapeutics

DP Cormode et al Contrast Media Mol. Im. 2014, 9(1):37-52

Au-HDL as a CT contrast agent



 $\ensuremath{\mathsf{HDL}}$. High Density Lipoprotein, an endogenous nanoparticle that interacts extensively with macrophages

Au-HDL has a gold nanoparticle at the core

Au-HDL is 9.7 nm in diameter

DP Cormode, T Skajaa et al, Nano Letters, **2008**, 3715-3723 DP Cormode et al, Radiology, **2010**, 774-782



Photon counting phantom scanning

DP Cormode et al, Radiology, 2010, 774-782

Photon counting CT in CV imaging





- Imaging three materials simultaneously in vivo?
- No whole mouse took 24 hours
- · Low count rate detectors

DP Cormode et al, Radiology, 2010, 774-782

Thrombus imaging

Bismuth nanoparticle, targeted to fibrin







LDLr expressing tumor

Ex vivo

D Pan et al, Angewandte Chemie, 2010, 9635-9639



Gold nanoparticles for photon counting CT

Gold labeled low density lipoprotein

 Accumulates in tumors that overexpress the LDL receptor IE Alijin et al, ACS Nano, 2013, 7(11):9761-70

Results from prototype clinical photon counting CT



- > Built by Philips (Haifa, Israel) Limited field of view (168 mm)
- > Located at the Douek Lab (Lyon)
 > Fast temporal resolution: 1s scan time
 > High spatial resolution: 0.25 mm
- ⊳ 4 slices, 2 mm z-coverage

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- Low radiation dose (~50% of conventional CT) ۶

Experimental parameters

- Scans were done at 120 kV and 100 mA
- > Thresholds: 30, 51, 78, 83, 98 keV
- > Contrast agent 1: iodinated small molecule > Contrast agent 2: PEG-coated gold nanoparticles: 12.5±2.4 nm core (TEM), 18.3±0.5 nm (DLS)



- > Synthesized 'conventional CT' images formed
- > Material decomposition into gold, iodine and water images



Distinguishing mixed contrast agents

DP Cormode et al, Sci Reports, 2017, 7, 4784

Imaging agent pharmacokinetics



Permitted by high temporal resolution of the scanner DP Cormode et al, Sci Reports, 2017, 7, 4784



Photon counting CT – a new tool for biodistribution







Photon counting CT – a new tool for biodistribution

TEM confirms that gold content is AuNP S Si-Mohamed et al, Nanoscale, 2017, 9 (46), 18246-18257

Multi-contrast peritoneal imaging



· Dual contrast imaging allows precise peritoneal imaging, valuable for planning surgery

S. Si-mohamed et al, Investigative Radiology, 2018, online.

Endoleak imaging

- Endoleaks are a common complication in endovascular aortic repair Require monitoring with CT throughout lifetime •
- •
- Conventional CT uses three scans (pre-contrast, arterial, venous) With SPCCT only one scan needed •
- •





Red=iodine J Dangelmaier et al, Eur. Radiol., 2018, 28(8):3318-3325

Three agent imaging



R Symons et al, Med. Phys., 2017, 44, 10, 5120-5127





Effect of AuNP size and surface functionality on monocyte loading



P Chhour et al, Bioconjugate Chem. 2017, 28, 1, 260-269

CT monocyte tracking in atherosclerosis

Done with a conventional microCT system



P Chhour et al, Biomaterials 2016, 87, 93-103

Benefits of photon counting CT for cell tracking

- · Eliminate laborious & error prone pre/post image analysis
- · Specific determination that contrast is due to labeled cells
- · More precise quantification of uptake

Use of AuNP to track cells in treatment of stroke with SPCCT



E Cuccione et al, in preparation

Novel SPCCT-specific contrast agent development

- · What is the effect of element on contrast generation?
- Element selection criteria
 - · Elements with k-edge in high x-ray flux region
 - Non-toxic, non-radioactive, affordable



Analysis: high attenuation rate, high CNR, and low noise level in SPCCT

J Kim et al, submitted

Phantom scanning

SPCCT scanner (University of Lyon): > A prototype SPCCT system > FOV: 168 mm in-plane, z-coverage: 2 mm > Gantry rotation time: 1 second (2400 projections per rotation)



Scanning conditions: > 5 axial scans (120kVp, 100mA) > 5 different energy thresholds (e.g. 30, 51, 78, 83, 98 keV for Au)





J Kim et al. submitted





Tantalum CT contrast agents • Coming out of GE research labs • Around 5 nm (renally excreted)



Tantalum SPCCT contrast agent



Criteria for translation of x-ray contrast agents



• NP less than ~6 nm can be excreted via the kidneys



Silver sulfide NP for renal excretion



Biodegradable metal nanoparticle CT agents

> These are translational nanoparticles since degradation allows for excretion

R Cheheltani et al, Biomaterials, **2016**, 102, 87-97 P Naha et al, J. Mater. Chem. **2014**, 2, 46, 8239-8248 AL Brown et al, Chem. Mater. **2014**, 26, 2266-2274 E Swy et al, Nanoscale, **2014**, 6(21):13104-12

Conclusions

- 1) Agent specific imaging is possible with high-count rate photon counting CT scanners
- 2) Can allow multi-agent imaging
- 3) Photon counting CT may prove beneficial for CT cell tracking
- 4) Alternative elements such as tantalum can produce greater contrast than gold in photon counting CT
- 5) Clearance of paramount importance for translation

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'Conventional' CT contrast



J Kim et al. submitted

In vivo dual contrast agent SPCCT imaging



In vivo imaging (rabbit), dual AuNP (PEG) and iodine injection DP Comode et al, Sci Reports, 2017, 7, 4784



Specific contrast agent detection

> Specific imaging of contrast & linear correlation with concentration

DP Cormode et al, Sci Reports, 2017, 7, 4784



Distinguishing mixed contrast agents

Rise in iodine contraindicated patients



- Diabetics commonly develop kidney disease
- · Iodinated contrast agents damage their kidneys further
- · Diabetics also at risk of CVD and need CT/fluoroscopy