AAPM 2017 JUL 30 – AUG 3 CONNECTING OUR PAST AND FUTURE TO DEFINE OUR PROFESSION 59TH ANNUAL MEETING & EXHIBITION | DENVER, CO

SAM Joint Therapy-Imaging Scientific Symposium: Nanoparticles from Imaging to Therapy

Nanoparticles from bench to MR-guided bedside

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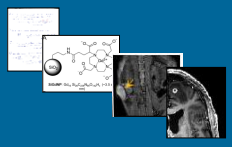

BRIGHAM AND WOMEN'S HOSPITAL | DANA-FARBER CANCER INSTITUTE | HARVARD MEDICAL SCHOOL

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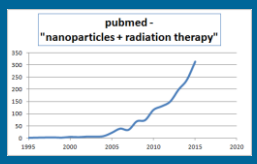
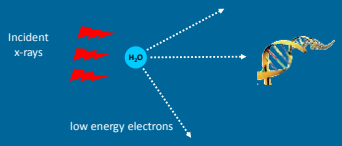
NP in radiation therapy



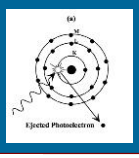
Killing cancer with physics



Photoelectric Effect

1921 Nobel Prize – Albert Einstein
"for his services to Theoretical Physics, and especially for his discovery of the law of the photoelectric effect"

1923 Nobel Prize – Robert Millikan
"for his work on the elementary charge of electricity and on the photoelectric effect"

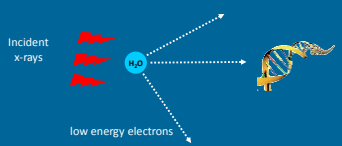


Atomic number

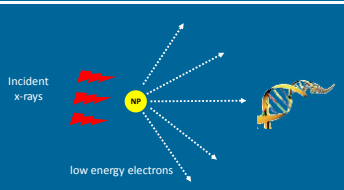
Probability of a photoelectric absorption ~ Z^3/E^3

Incident photon energy

Killing cancer with physics

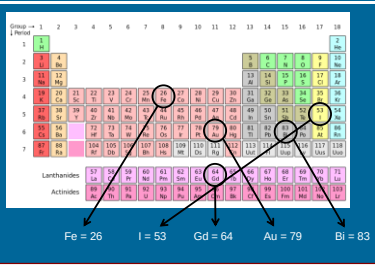


Killing cancer with physics



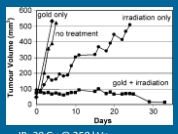
Probability of a photoelectric absorption ~ Z^3/E^3

Photoelectric Effect

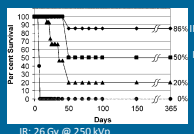


GNP with radiation therapy

In vivo studies demonstrated therapeutic potential for GNP



IR: 30 Gy @ 250 kVp
GNP: 1.35 mg/g IV



IR: 26 Gy @ 250 kVp
GNP: (t) 2.7 mg/g or (n)1.35 mg/g IV

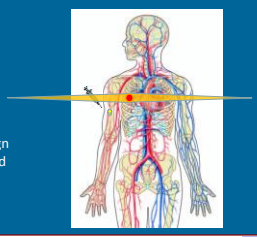
Hainfeld *et al.*, PMB 2004

Toxicity concerns

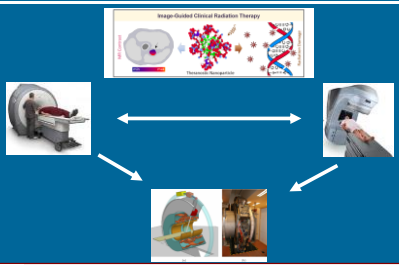
Double targeted therapy

1. Nanoparticles are targeted to the tumor
2. Radiation is targeted to the tumor

→ Imperfect targeting of NP is benign
→ Can reduce radiation dose needed



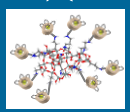
Nanoparticle for MR-guided RT



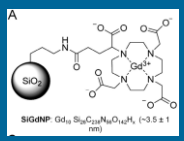
Nanoparticle for MR-guided RT

"AGuIX" (Activation and Guidance of Irradiation by X-rays)
NH TherAguix – Lyon, France

DOTA [Gd]



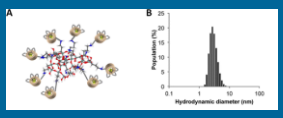
3-5 nm



Detappe *JCR* 2016

Nanoparticle for MR-guided RT

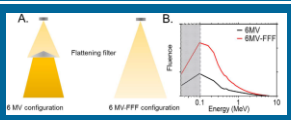
"AGuIX"
NH TherAGuix – Lyon, France

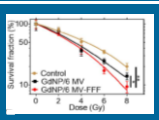


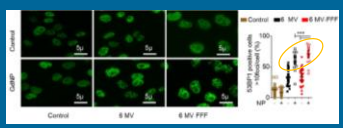
Main Characteristics of AGuIX Nanoparticles	
Chemical composition	$Gd_{10}Si_{40}C_{200}N_{50}O_{150}H_x$
Molar mass	8.5 ± 1 kDa
Size	3 ± 0.1 nm
Zeta potential	9.03 ± 5.5 mV

Kotb *Theranostics* 2016
Sancey *ACS Nano* 2015

Nanoparticle for MR-guided RT

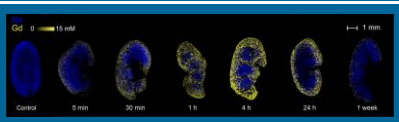




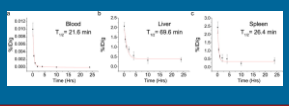


Detappe *Scientific Reports* 2016

Nanoparticle for MR-guided RT



Laser Induced Breakdown Spectroscopy (LIBS)



Sancey *ACS Nano* 2015

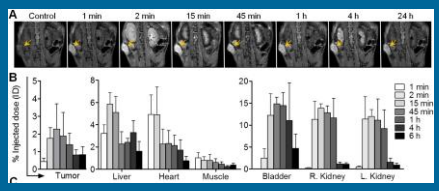
Nanoparticle for MR-guided RT

cynomolgus monkeys
(*macaca fascicularis*)

Detappe *JCR* 2016

Nanoparticles for imaging + therapy

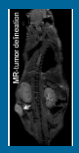
Capan-1 PDAC subcutaneous xenograft model



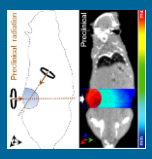
Detappe *JCR* 2016

Nanoparticle for MR-guided RT

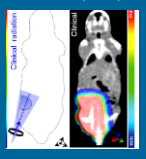
MRI "sim"



Pre-clinical RT (220 kVp)



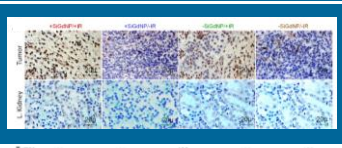
Clinical RT (6 MV)

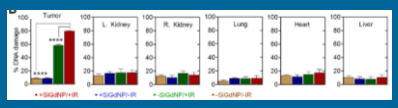


Detappe *Scientific Reports* 2016

Nanoparticle for MR-guided RT

DNA damage (γH2AX)

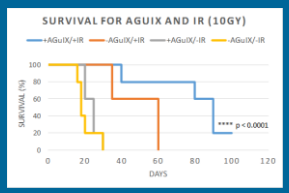




Detappe *Scientific Reports* 2016

Nanoparticle for MR-guided RT

AGuIX + clinical radiation therapy (6 MV)



Detappe *JCR* 2016

Phase 1 clinical trial

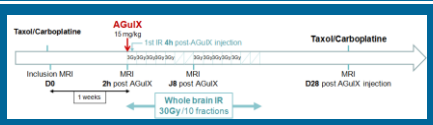
NANO-RAD NCT02820454

Radiosensitization of Multiple Brain Metastases using AGuIX Gadolinium Based Nanoparticles

Sponsor: University Hospital Grenoble Alpes

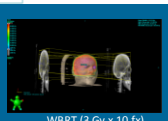
Dose escalation: 15, 30, 50, 75 , 100 mg/kg (n=3)

Phase 1 clinical trial



Study plan:

- "Inclusion" MRI (D0)
- Pre-treatment MRI w/ AGUIX (D8)
- 3 Gy/fx WBRT (D8 + 4 hrs)
- Mid-treatment MRI (D16)
- Post-treatment MRI (D36)



WBRT (3 Gy x 10 fx)

Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

Primary objective: Safety - Maximum Tolerated Dose (MTD)

Secondary objective 1: Pharmacokinetic characteristics of AGuIX

Secondary objective 2: MRI & AGuIX targeting

Secondary objective 3: Therapeutic Response

Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

Primary Objective: Safety

Results: no adverse effects for first three dose levels (9 patients)

Patients: Melanoma (4), NSCLC (4), Colon (1)

Dose escalation: 15✓, 30✓, 50✓, 75…, 100 mg/kg (n=3)

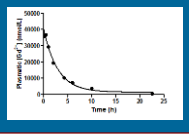
Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

Secondary Objective 1: Pharmacokinetics

Blood samples at T0, 15min, 30min, 1h, 2h, 4h, 6h, 10h (or 12h), 24h, D8

Urine samples over 24h (3 fractions of 4h and 1 fraction of 12h) and D8

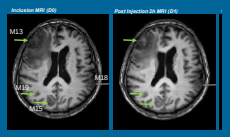


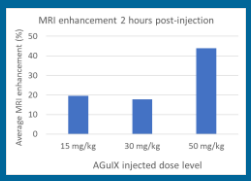
Biological 1/2 life ≈1-2 hrs
50% excreted by urine in first 24 hrs

Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

Secondary Objective 2: MR image contrast



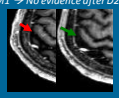


Courtesy Olivier Tillement (Lyon)

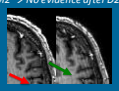
Phase 1 clinical trial

Secondary Objective 3: Therapeutic Response

M1 → No evidence after D28

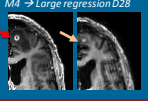


M2 → No evidence after D28

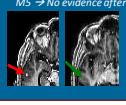


M3 → Medium regression D28

M4 → Large regression D28



M5 → No evidence after D28

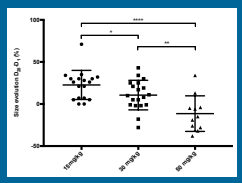


Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

Secondary Objective 3: Therapeutic Response

ΔSize



Tumor response as a function of AGuIX dose (melanoma patients only)

Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

NANO-RAD Trial Results

- Nine patients treated with AGuIX, MRI and WBRT
- No toxicities reported for the first three dose levels (fourth level ongoing)
- Biological half-life ~2 hrs. AGuIX found in tumors after 2 weeks
- MRI contrast observed
- Good clinical response (underpowered)
- Phase 2 trial in preparation

Courtesy Olivier Tillement (Lyon)

Phase 1 clinical trial

NANO-RAD Trial Results

✓ Safe

✓ MR image contrast

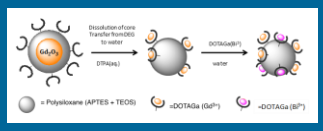
? Therapy benefit

Courtesy Olivier Tillement (Lyon)

Next level NP for MR-guided RT

"Bi-AGuIX"

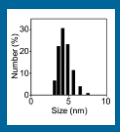
Replace some Gd (Z= 64) atoms with Bi (Z = 83) atoms
50/50 → 50% increase in photoelectric interactions



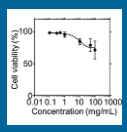
Detappe *Nano Letters* 2017

Next level NP for MR-guided RT

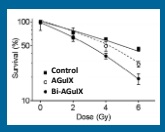
Bi-AGuIX has a Bi:Gd ratio = 1:2



Ultra-small (4-5 nm)



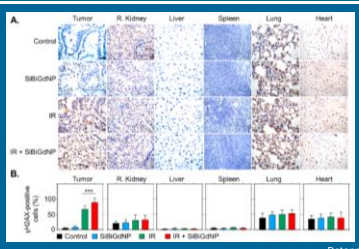
Non-toxic



More effective than AGuIX (Gd only)

Detappe *Nano Letters* 2017

Next level NP for MR-guided RT



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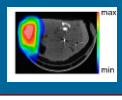
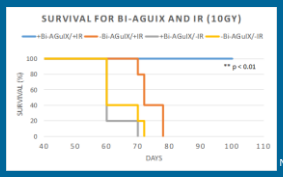
Next level NP for MR-guided RT

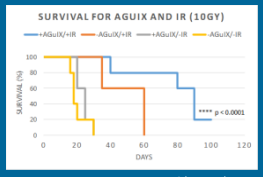




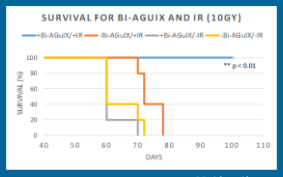
NSCLC (A549)

Detappe *Nano Letters* 2017

Next level NP for MR-guided RT



PDAC (capan-1)

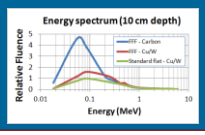


NSCLC (A549)

Detappe *JCR* 2016, Detappe *Nano Letters* 2017

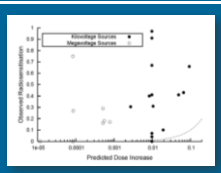
Clinical translational opportunities

Courtesy of James Robar (Halifax)



Berbeco *Med Phys* 2016

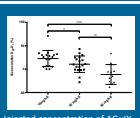
Mystery: Mechanism of action



Unknown mechanism of action?
or
Need better simulations ?

Summary

- Clinical translation of a Gadolinium-based nanoparticle
  - MR-guided radiation therapy
- Phase 2 trial being planned
- Upgraded nanoparticle under investigation

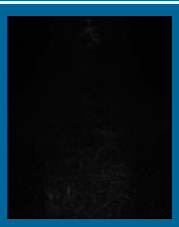


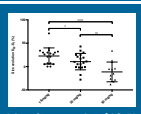
Injected concentration of AGuIX

Bi-AGuIX with clinical RT (6 MV)

Additional opportunities…
- Optimize NP targeting (active vs. passive)
- Optimize administration schedule
- Biochemical mechanisms
- Delivered photon energy spectrum

fin





Injected concentration of AGuIX

Bi-AGuIX with clinical RT (6 MV)

Postdoctoral fellowships currently available in nanomedicine and clinical beam's-eye-view imaging
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