Nanoparticles from bench to MR-guided bedside

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NP in radiation therapy

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NP in radiation therapy
Killing cancer with physics

![Diagram of x-rays and electrons](image)

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”

Probability of a photoelectric absorption ~ \( \frac{Z^3}{E^3} \)

Incident photon energy

Atomic number

Killing cancer with physics

![Diagram of x-rays and electrons](image)
Killing cancer with physics

Probability of a photoelectric absorption: \(Z^2/E^3\)

Photoelectric Effect

Gd = 64
Au = 79
Fe = 26
I = 53

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: 1.35 mg/g IV

IR only
No Tx

IR + 1.35 mg/g
IR + 2.7 mg/g
IR + 2.7 mg/g or IR + 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

“AGuIX” (Activation and Guidance of Irradiation by X-rays)

NH TherAguix – Lyon, France

Detappe CR 2016
Nanoparticle for MR-guided RT

“Aguix”
NH TherAguix – Lyon, France

Main Characteristics of Aguix Nanoparticles
- Chemical composition: Ge, Si, C, N, O, H
- Molar mass: 8.5 ± 1 kDa
- Size: 3 ± 0.1 nm
- Zeta potential: 9.0 ± 0.6 mV

Kotb Theranostics 2016
Sancey ACS Nano 2015

Nanoparticle for MR-guided RT

Koeppe Scientific Reports 2016
Sancey ACS Nano 2015

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 Scientists Reports 2016
Nanoparticle for MR-guided RT

DNA damage (γH2AX)

AGuIX + clinical radiation therapy (6 MV)

SURVIVAL FOR AGUILX AND IR (10Gy)

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

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

Study plan:
- "Inclusion" MRI (D0)
- Pre-treatment MRI w/ AGuIX (D8)
- 3 Gy/blk WBRT (D8 + 4 hrs)
- Mid-treatment MRI (D16)
- Post-treatment MRI (D36)

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)
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)

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**Secondary Objective 2: MR image contrast**

Inclusion MRI (D0)

Post Injection 2h MRI (D1)

Post First week treatment MRI (D8)

M7
M6
M13
M15
M19
M18

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**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

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*Courtesy Olivier Tillement (Lyon)*
Phase 1 clinical trial

Secondary Objective 3: Therapeutic Response

\[ \Delta \text{Size} \]

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

Courtesy Olivier Tillement (Lyon)

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

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

Ultra small (4-5 nm) Non-toxic
More effective than AGuIX (Gd only)

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
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

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

Fin

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