INSTITUTE OF ADVANCED BIOSCIENCES
Centre de Recherche – UGA / Inserm U 1209 / CNRS UMR 5309

MR-guided radiation therapy with gadolinium nanoparticles: from chalkboard to first clinical trials

Dr. L. Sancey

Prof. O. Tillement ILM UMR 5306 France

No conflict of interest

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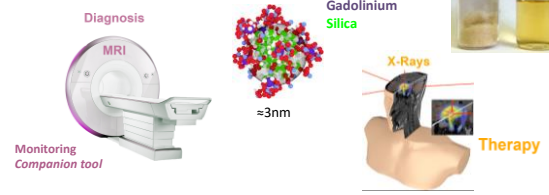
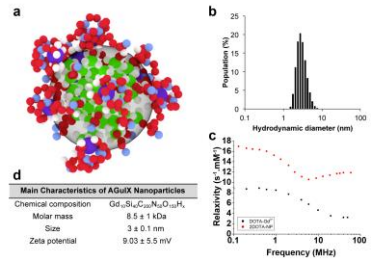
Patents: WO2011/135101 & WO2009/053644

MR-GUIDED RADIATION THERAPY

High-Z elements act as radiosensitizers/dose enhancers
Gadolinium (Z=64): T1-MRI contrast agent
AGuIX: activation and guiding of irradiation by X-ray



CHARACTERIZATION OF THE NANOPARTICLE



Relaxivity/MRI:
r_2/r_1= 1.14 (1.4T)
r_2/r_1= 2.2 (7T)

Complexation constant of DOTA on the NP for Gd
ln β ~ 24.78

Lux et al Angew Chem Int Ed Engl – 2011
Mignot et al Chem. Commun. 2013

CHARACTERIZATION OF THE NANOPARTICLE

Freeze-Drying: long-term stability
~50g lab-batches
700g GMP

MAGNETIC RESONANCE IMAGING

High spatial resolution (<mm)
High soft tissue contrast
High versatility

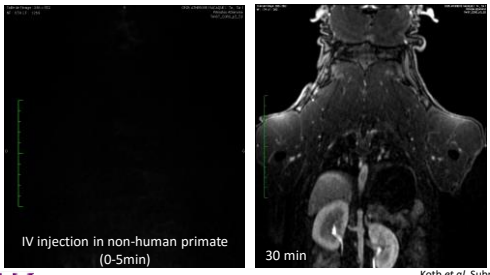
Low throughput
Low contrast agent sensitivity (≈mM)
~~**Difficult**~~ **quantification**

Tumor characterization
MRI simulation delineation
MRI guidance
Following the treatment efficacy

Precoce use of **companion tool**

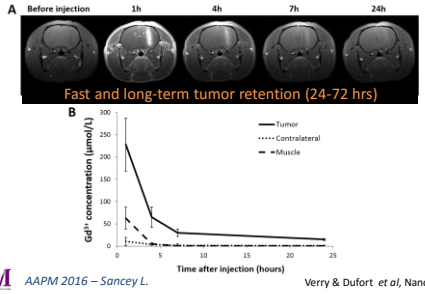
Enriched the patient population of « responders »
Adjusted treatment protocol

MR Imaging Properties



Kotb *et al*, Submitted.
Detappe *et al*, J Control Release 2016

MR IMAGING PROPERTIES

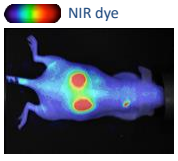


Verry & Dufort *et al*, Nanomedicine 2016

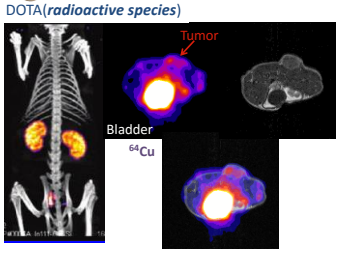
OTHER PRECLINICAL IMAGING MODALITIES

DOTA(***radioactive species***)

NIR dye



^{111}In



^{64}Cu

IN VITRO EFFICACY OF AGUIX

Photons

Investigator (team, town)	Radiation/energy	Cell line	NP/incubation time	Biological effect
R. Butterworth (personal communication) (Queen's University, Belfast, UK)	225 kV	Prostate—DU145	From 0.1 to 0.6 mM/71 h	1.17 < SF < 2.58
		Glioblastoma—T98G		SF = 1.23
		Prostate—PC3		1.15 < SF < 1.31
R. Berbeco[18] (Harvard, Boston, MA)	220 kVp 3-way	Cervical carcinoma—HeLa	0.6 mM/71 h	$SER_{10\%}$ = 1.18 DEF = 1.3
G. Rodriguez-Lafrasse[17] (University Lyon, Lyon, France)	250 kV	Head and neck squamous cell carcinoma—SCC61	0.6 mM/71 h	SE_2 = 0.66 or 0.72 SER = 1.205
			0.6 mM/71 h	SE_2 = 0.54 or 0.72 SER = 1.805
		SQ20B cancer stem cells	0.6 mM/71 h	SE_2 = 0.6 or 0.82 SER = 1.40
G. Rodriguez-Lafrasse (University Lyon, Lyon, France)[17]	250 kV	Head and neck carcinoma—SQ20B	0.6 mM/71 h	SE_2 = 0.61 or 0.75 SER = 1.22
			0.6 mM/71 h	SE_2 = 0.37 or 0.75 SER = 2.10
[illegible] (Institut Curie, Orsay, France)	[illegible]	Mouse lymphoma—EL4	0.30 mM	$SER_{10\%}$ = 2.08
R. Lacombe[19] (University of Paris-Sud, Orsay, France)	Ions He^{2+} beam (Uppsala, Sweden)	Chinese hamster ovary carcinoma—CHO	1.0 mM/60 h	SER = 1.14
R. Lacombe[19] (University of Paris-Sud, Orsay, France)	C^{6+} beam (200 MeV/nucl) (CIRIL, France)	Chinese hamster ovary carcinoma—CHO	1.0 mM/60 h	$SER_{10\%}$ = 1.58
G. Rodriguez-Lafrasse[17] (University Lyon, Lyon, France)	C^{6+} (51 keV/μm[-1]) (Ganil, France)	Head and neck carcinoma—SQ20B	0.6 mM/71 h	SER = 1.35
			0.6 mM/71 h	SER = 1.59

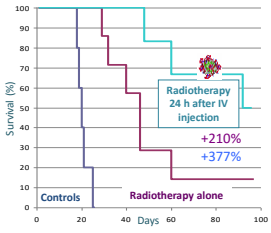
Heavy ions

Different cell lines, different energies, different teams but similar nanoparticle, similar effects: +30/40%

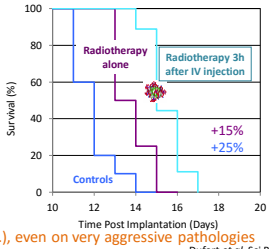
Sancey *et al*, Br J Radiol 2014

IN VIVO EFFICACY OF AGUIX

Rats-bearing 9L tumors



Mice-bearing B16F10 tumors



Very nice efficacy at low dose (I.V.), even on very aggressive pathologies

Dufort *et al*, Sci Rep 2016
Kotb *et al*, Theranostics 2016

REGULATORY PRECLINICAL TOXICITY STUDIES

- Performed on rats and nonhuman primates
- 2 IV injections (D1 and D8)
- HED tested: from 60 to 145 mg/kg
- **No difference of any ante-mortem or post-mortem parameter *vs.* control group** for both species and sex at any dose, except minimal and reversible renal vacuolation in rodents

Mortality, clinical signs, ophthalmology, body weight, food consumption, haematology, bioch. & urinary parameters, pathology, and toxicokinetics.

- Accumulation ratios: 0.92-1.08 / 0.85-1.04
- Blood half life: 0.83-3.04 / 2.09-3.57

=> HED: 121 mg/kg

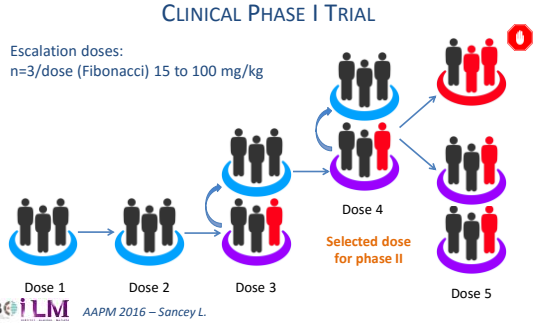
Clinical Trial Phase I

- **First-in-Man**
- **CHU Grenoble (France) – C. Verry, MD** (J. Balosso, MD-PhD / J-Y. Giraud, PhD)
- Multiple brain metastases including metastases from melanoma, lung or breast tumor (n>3 or large lesions)
- Life expectancy < 6 months
- Current treatment: 30 Gy in 10 sessions of 3 Gy, *in toto* IR
- Excluded: stereotactic IR, Cyberknife, Gammaknife

- Clinical trial phase I objectives
  - **Safety and pharmacokinetics**, with increasing doses
  - **MRI properties**: Distribution and tumor kinetics
  - **Survival** without IC progression, **overall survival**

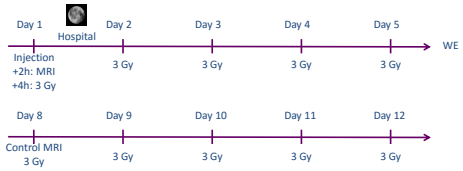
Clinical Phase I Trial

Escalation doses:
n=3/dose (Fibonacci) 15 to 100 mg/kg



Clinical Phase I Trial

Design of the study
- Dose escalation: 15 mg/kg → 30/50/75/100 mg/kg
- 3 patients / dose (15-20 patients)



Clinical Phase I Trial

Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
15mg/kg	30mg/kg	50mg/kg	75mg/kg	100mg/kg

In progress…

Conclusion

- AGuIX might be used for **MR-guidance** (T1 acquisitions)
- **Boosted radiation therapy**
- First clinical trial in progress for multiple brain metastases
- **Other possible clinical trials**:
  - Glioma, Pancreas, other (IV)
  - Uterus/prostate (IT)
  - Lungs (aerosolization)

TherAguix

…Founded in 2015…

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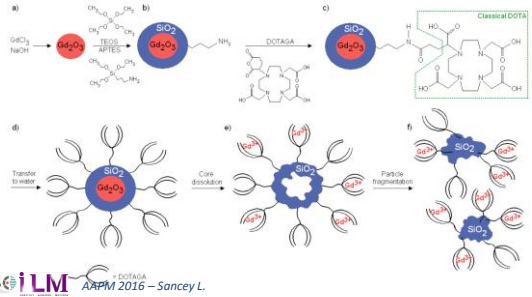
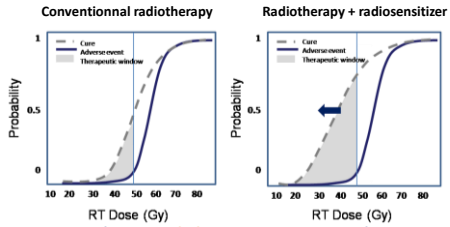
Association Biologie & Cancer

IAB ILM AAPM 2016 – Sancey L.

CHARACTERIZATION OF THE PLATFORM

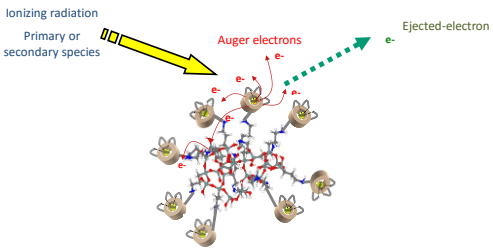


RADIOSENSITIZATION



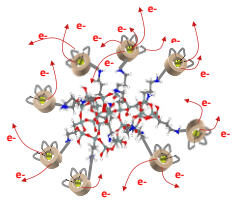
Expected results: significant benefit for the patient in terms of better local control, better tumor response and increased patient survival.

RADIOSENSITIZATION: POSSIBLE MECHANISM OF ACTION



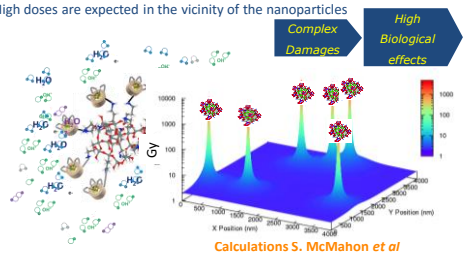
RADIOSENSITIZATION: POSSIBLE MECHANISM OF ACTION

Auger shower effect



RADIOSENSITIZATION: POSSIBLE MECHANISM OF ACTION

Nanodose effect: High doses are expected in the vicinity of the nanoparticles



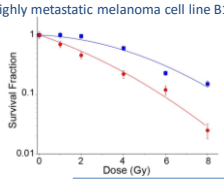
Calculations S. McMahon *et al*

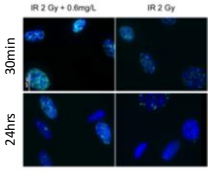
Sancey et al Br J Radiol 2014

Mura & Couvreur, Nanotheranostics for personalized medicine 2016

IN VITRO EFFICACY OF AGUIX

Highly metastatic melanoma cell line B16F10

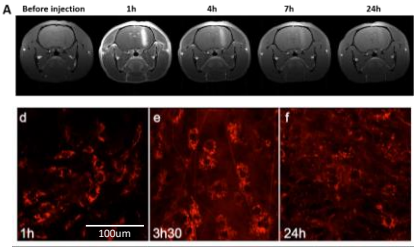




	α (Gy $^{-1}$)	D50% Gy	SF 2 Gy	% EF 2 Gy	SER 2 Gy	DEF
Control	0.04	4.5	0.96	-	-	-
0.6 mg/L AGuIX	0.26	1.8	0.56	52 %	2.08	1.3

Kotb *et al*, Theranostics 2016

IN VIVO EFFICACY OF AGUIX

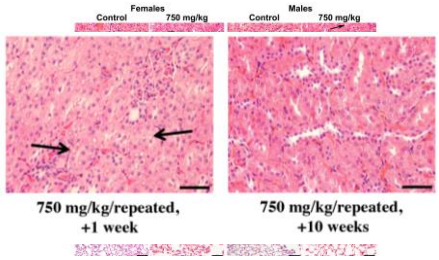


Tumor accumulation:

- Long-term (24-72hrs)
- EPR effect
- Cell internalization

Verry & Dufort *et al*, Nanomedicine2016
Kotb *et al*, Theranostics 2016

REGULATORY PRECLINICAL TOXICITY STUDIES



AGUIX FOR PATIENTS