Faculté des Sciences

Faculté de Médecine et de Pharmacie

Design of Vectorized Nanodiamonds as Contrast Agents for Prepolarized MRI at Earth Field: PrimoGAIA project

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I. Overview

PrimoGAIA is an innovative European project proposing and concreting a totally new approach strategy of medical exploration by bringing multidisciplinary consortium of academic researches and companies together to open a new path in the field of Magnetic Resonance Imaging (MRI). The development of contrast agents with EPR effect is required to be used to transfer spin polarization to ^{1}H spins from H_2O molecules (Overhauser effect). The overall technology will be much less expensive than the current clinical scanners which will allow distribution in developing countries.

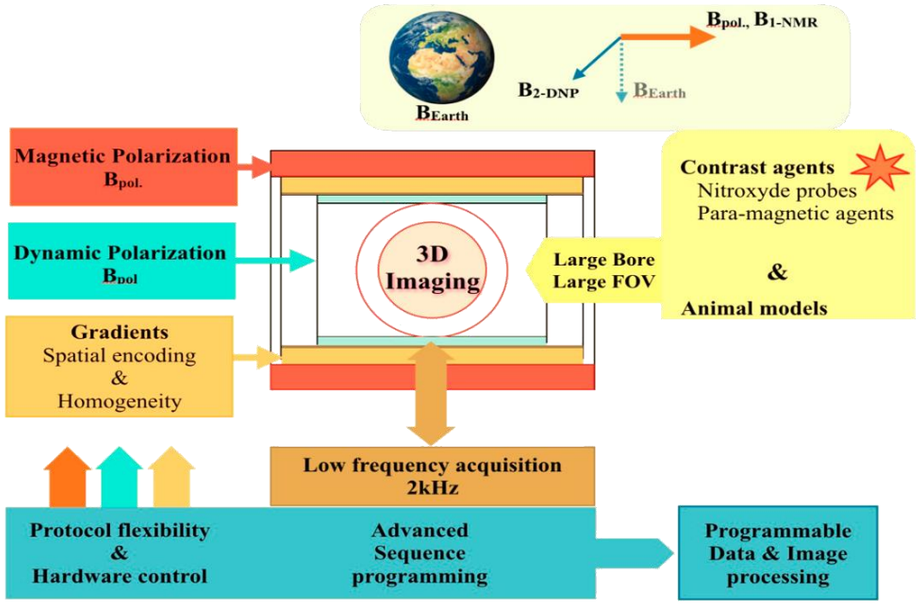

Fig. 1: Schematic overview of the PrimoGaia project
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Synthesis and characterizations of versatile contrast switches:

Activable prodrugs
(University of Torino, UTorino)

- Nanoprodrugs responsive to specify enzymatic activity
- Targeting (fonctionalization)

Nitroxydes
(University of Marseille CNRS)

- Development of shift nitroxides
- Saturation methods at earth field
- Enzymatic activity

Diamond-like carbon nanoparticles
(University of Mons, UMONS)

- Intrinsic properties
- Surface modification, conjugaison with PEG chains and biovectors

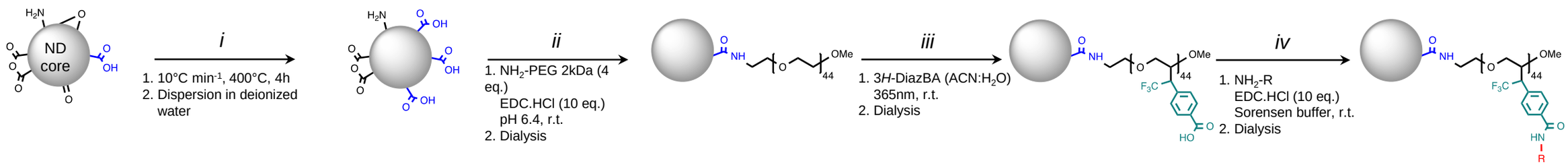
Our purpose:
To exploit intrinsic paramagnetic defects from nanodiamonds (NDs)

- **Suitable for EPR spectroscopy**
- **Large-scale synthesis in inddustries**
- **Biocompatible & non-biodegradable**
- **Inherent surface chemistry**

II. Purpose of the work

➔ To develop a stable and functionable nanodiamond-based platform for MRI at low magnetic field based on EPR

Particle initial state → Surface uniformisation → Thermal oxidation → Stabilization Biocompatibility → PEGylation → Insertion of a linker → Photochemistry → Grafting of a biovector → *Post*-functionalization



ND | ND-COOH | ND-PEG2kDa | ND-PEG2k-linker | ND-PEG2k-linker-R

Detonation NDs

- ND suspension from NanoAmando® $2\%_{wt./v}$

Properties

- Single EPR signal
- Biocompatible
- Versatile surface groups

1/ Thermal treatment of the powder

- TGA and XPS analysis[1,2]
- Ambient and static air annealing[3]

2/ Dispersion in water

- Ultrasonication
- Centrifugation

Polymeric coating

- Polyethylene glycol
- $M_w^{coating}$
- Stabilizing agent
- Biocompatible

(grafting in progress)

Incorporation of a UV-sensitive crosslinker to provide functional groups on the coating

Grafting of specific biovectors (folate, RGD peptide, … for targeting applications

Optimizations with dies/Gd^{3+} chelates

- NH_2-R

Imaging

[1] Laboratory of Polymeric and Composite Materials, SMPC lab, Prof. Jean-Marie Raquez, UMONS.
[2] Laboratory of Chimie des Interactions Plasma-Surface, ChIPS lab, Prof. Rony Snyders, Materia Nova, UMONS.
[3] Laboratory of Analyse Pharmaceutique, Prof. Bertand Blankert, UMONS.
[4] Pourcelle *et al., Bioconjugate Chem.* 2015, 26, 5, 822–829.

III. Preliminary results

Nanodiamond particle initial state

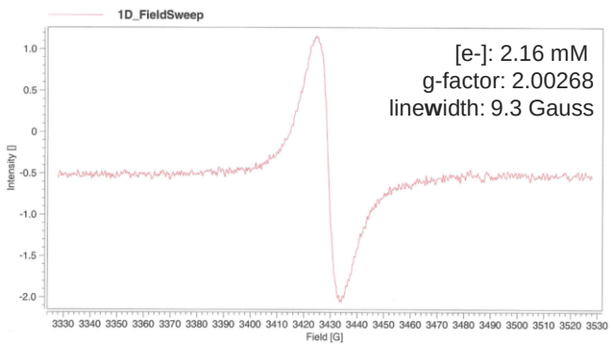


Fig. 1: EPR spectrum of aqueous suspension of detonation NDs (J.M. Franconi)

➔ Unique paramagnetic intrinsic properties
Detection and quantification *via* EPR

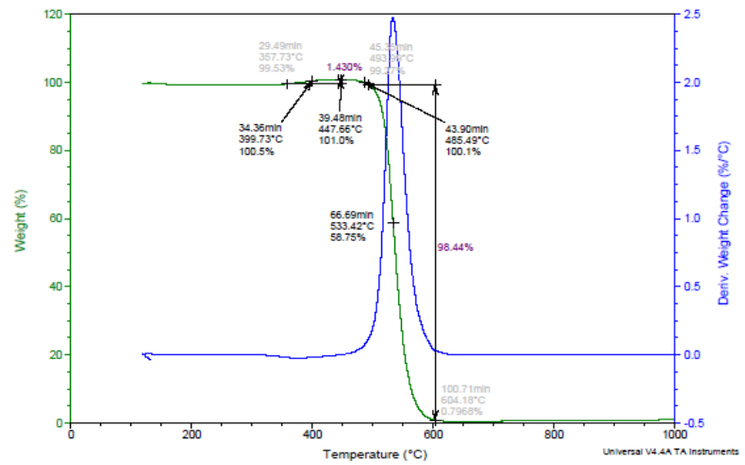


Fig. 2: TGA curve of ND powder under ambiant and static air[1]

➔ TGA and XPS studies: annealing conditions

i) Thermal oxidation & dispersion

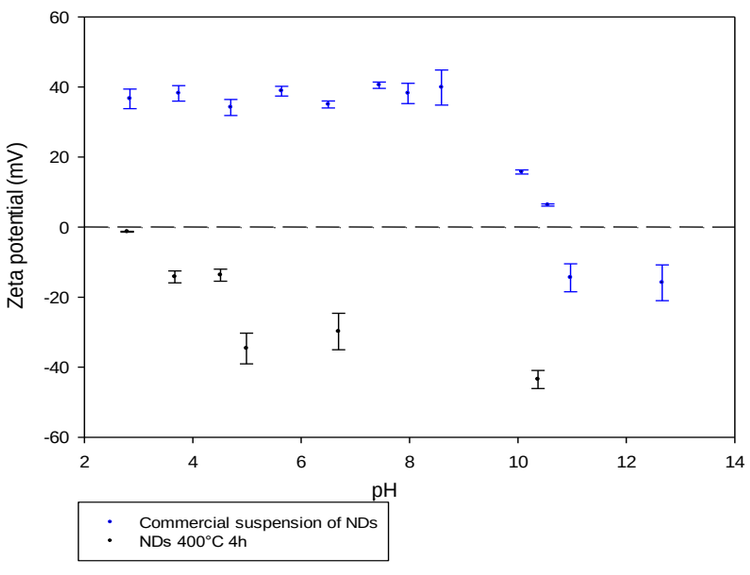


Fig. 3: Zeta potential vs. pH measurements of NDs and ND-COOH samples (0.04%$_{wt./v}$)

Samples	C1s	O1s	O/C ratio
NDs [untreated]	94.2	3.8	0.04
NDs [10°C min^{-1}, 400°C, 4h]	89.2	9.4	0.1

250%

Tab. 1: Atomic percentages (%) of carbon and oxygen elements and O/C ratio from XPS analysis

➔ acidic surface (COO^-)
COOH: 27 nmol mg^{-1} (titration)

ii) PEGylation (in progress)

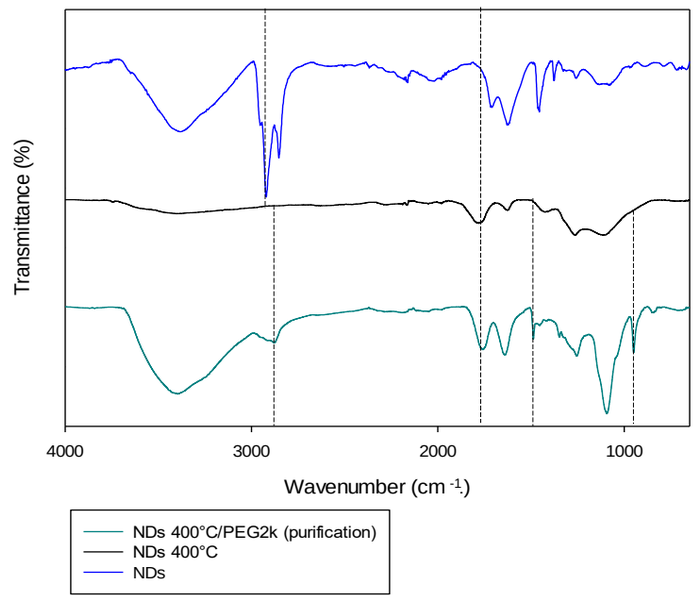


Fig. 4: FTIR spectra of ND, ND-COOH and ND-PEG$_{2k}$ powders

[1] Sylvie Montante, Laboratory of NMR and Molecular Imaging, 2012-2016, Prof. Robert N. Muller, Prof. Sophie Laurent, UMONS.

IV. Conclusions and perspectives

Conclusions:

- NDs:
  - Unique EPR signal due to intrinsec properties
- Surface chemistry:
  - Surface uniformisation by thermal oxidation and quantification of [COOH]
  - Covalent insertion of PEG chains onto surface
  - Preliminary experiments on grafting a linker using photochemistry have provided encouraging results for PEGylated nanomaterials (SiO_2-NPs, SPIONs) and NDs

Outlooks:

- Optimizations of steps *i* and *ii*
- EPR experiments (in progress)
- OMR phantoms / data imaging (at ultra low magnetic field) at the early stage of the strategy pathway
- Determination of the biological target to link a specific vector (NH_2-R)
- *In vivo / in vitro* essays
- Investigation of other EPR-active nanoscale platforms (*i.e.* polymersomes with TEMPO derivatives)

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