P04000 / P03999

! For in vitro or animal use only!

P04000 is a targeted contrast agent for angiogenesis molecular imaging. **P04000** targets αvβ3 integrin over-expressed on the neo-vessels. **P04000** is a nano-emulsion containing iron oxide particles, designed for T2*w MR sequences (susceptibility weighted imaging).

P03999 is the corresponding non-targeted contrast agent.

Main indications

Evaluation of angiogenesis status, evaluation of anti-tumoral treatment follow up based on αvβ3-expression

Molecular characteristics

- Hydrodynamic size: diameter is 180 nm
- Fe content: ~10^6 Fe atoms per particle
- Integrin targeting: 3 500 RGD per particles
- Recommended dose: 200 µmolFe/kg → 2.5 µL/g
  Example: for a 30g body weight mouse, injection volume is 75 µL
- Recommended imaging time: up to 1h post injection (unbound contrast agent cleared from the blood)
- Contrast mechanism: susceptibility effect
- Histology: Perl's staining
- In vitro quantification techniques: P04000 is a Fe-based contrast agent. Thus, it is necessary to take into account the endogenous iron content for quantification in biological media by ICP-AES or ICP-MS. Another way for USPIO quantification is relaxometry, which is poorly sensitive to endogenous iron content.

Storage

Need to be stored at 4°C in a closed vial and away from light.

Pharmacokinetics/Biodistribution

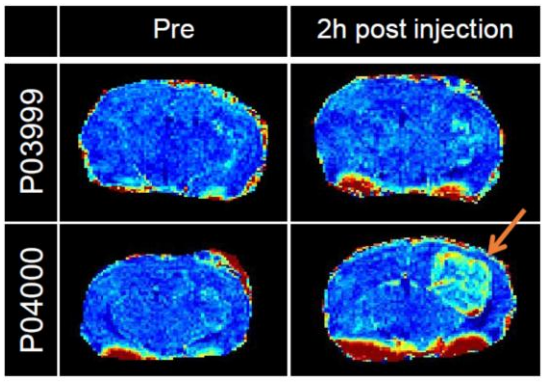
- In vitro affinity for αvβ3 integrin: **2 pM** of nanoparticles (evaluation of the contrast media affinity to the integrin αvβ3 by measuring the binding inhibition of radioiodinated echistatin)
- Blood pharmacokinetic : blood half-life
  - P04000: 6.6 ± 0.5 min
  - P03999: 11.5 ±1.3 min
  - Toxicity profile: no toxicity was detected after i.v. injection, no complement activation was observed with P04000 or P039999 as compared to PBS.

Characteristics of the vial

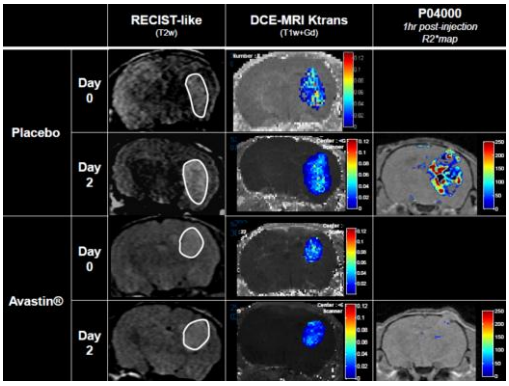
- Concentration: [Fe] = 4.47 mgFe/mL → [Fe] = 80 mmol/L (M_{Fe}=56 g/mol)
- Volume: 450 µL (5 mice dose approx.)
- Other animal species: please contact us

Legal conditions of use: see Chematech terms and conditions of sales
Contacts: info@chematech-mdt.com

Examples of applications



Anti-angiogenic treatment follow-up
R2* maps in a U87-bearing mouse model: specificity of P04000 as an αvβ3-specific imaging biomarker of angiogenesis. P03999, the non-targeted compound, is cleared from the tumor at the same imaging time [1]



Anti-angiogenic treatment follow-up and comparison to DCE-MRI
P04000 as an αvβ3-specific imaging biomarker for the early detection of anti-angiogenic treatment efficacy [2]

References

[1] and [2] Unpublished Guerbet data

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09/2013

Guerbet
Contrast for Life

CheMatech
macrocycle design technologies

P792 – Vistarem®

! For in vitro or animal use only!

Vistarem® (gadomelitol) is a monogadolinated MRI blood-pool agent of 5 nm diameter. Its pharmacokinetics and biodistribution profiles are consistent with that of a rapid-clearance blood-pool agent (RCBPA): **Vistarem®** is mainly excreted by glomerular filtration with limited diffusion across normal endothelium.

Main applications

DCE-MRI (K_{trans} modeling, tumoral characterization / treatment follow up), high resolution contrast-enhanced **MR angiography** (MRA), myocardial **perfusion,** arthrography, myocardial perfusion and viability

Molecular characteristics

- Hydrodynamic size: diameter is approximately 5 nm (compared to ~1 nm for Gd-DOTA)
- Gd content: 1 atom per particle
- Molecular weight: 6.5 kDa
- Recommended dose: 50 µmol/kg = 2.5 µL/g
  Example: for a 30g body weight mouse, injection volume is 75 µL
- Relaxivities *(37°C, 4% Human Albumin Serum)*

Bo (T)	1.5	2.35	3.0	4.7	7.0
r1 ($s^{-1}.mM^{-1}$)	27	15	12	7	5
r2 ($s^{-1}.mM^{-1}$)	68	67	68	66	63

Storage

Need to be stored at 4°C in a closed vial and away from light.

Pharmacokinetics/Biodistribution

Species	Rat	Rabbit	Pig
Doses(mmol/kg)	0.015	0.013	0.013
$T_{1/2}\,\alpha$ (min)	4±0	4.4±0.3	-
$T_{1/2}\,\beta$ (min)	32±0	41±4	30
Vd (mL/kg)	126±9	101±10	120
Cl (mL/min/kg)	5.6±0.2	2.8±0.2	51
C_5/C_0 * (%)	24±1	41.7±2.6	51

* plasmatic concentration at 5 min normalized by the theorical initial conc.

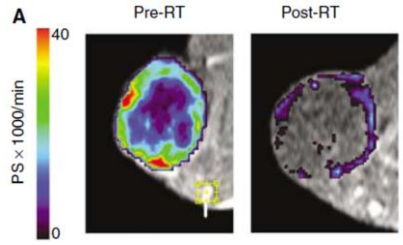
- $T_{1/2}$ in Human @ 13 µmolGd/kg = 2 h; VD = 220 mL/kg
- Total excretion within 7 days (80% urine, 15% feces)
- Distribution volume is smaller than that of a nonspecific agent (NSA) like Gd-DOTA (77 vs 250 mL/kg in rat)
- C_5/C_0 is higher than that of a NSA (58% vs 25% in rat)

Characteristics of the vial

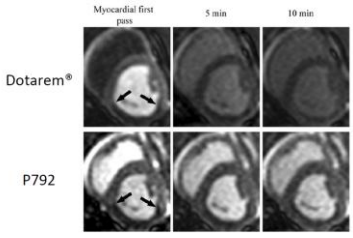
- Concentration: [Gd] = 20 mmol/L
- Volume: 450 µL (5 mice dose approx.)
- Other animal species: please contact us

Legal conditions of use: see Chematech terms and conditions of sales
Contacts: info@chematech-mdt.com

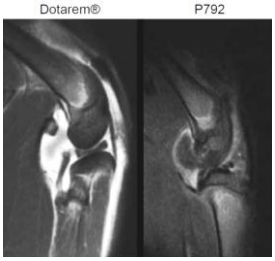
Examples of applications



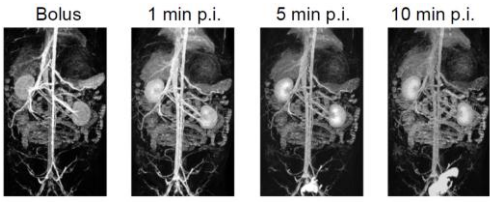
DCE-MRI
results of kinetic modeling of P792 contrast-enhanced MRI data [1]



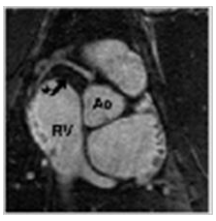
Myocardial perfusion and viability
Persistence of the delineation of the ischemic region with P792 as compared to Gd-DOTA in a pig model of cardiac ischemia [2]



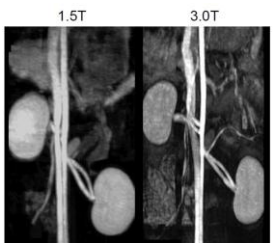
MR arthrography
Due to the low arthrographic effect, P792 accumulation allows to characterize synovial vascular permeability changes during synovitis [3]



MR angiography
Low dose P792 enhanced-MRA in Rabbit at 1.5 T [4]



MRA example
Coronary P792-enhanced MRA in Pig [5]



MR angiography
Low dose P792 enhanced-MRA in Rabbit at 1.5 T and 3.0T as compared to full dose of Gd-DOTA [6]

References

[1] Ceelen W et al. Br J Cancer 2007 [2] Dewey et al.Investigative Radiology 2004 [3] Watrin Pinzano A et al. Biomed Mater Eng 2008 [4] Ruehm et al. Magnetic Resonance in Medicine 2002 [5] Dirksen MS et al. Eur Radiol 2003 [6] Herborn CU et al. Invest Radiol. 2007

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P846

! For in vitro or animal use only!

P846 is an intermediate molecular weighted compound, constituted by a macrocyclic gadolinium chelate. **P846** is a LDA (Low Diffusable contrast Agent), meaning that P846 has a **blood pharmacokinetic very comparable to that of Gd-DOTA** or Gd-DTPA **but a limited extravasation within the capillary bed**.

Main applications

Contrast-Enhanced MR angiography, tissue perfusion (myocardium, tumor…), angiogenesis imaging (DCE, MRI, K_{trans} analysis, blood volume imaging, permeability measurement, treatment follow-up)

Molecular characteristics

- Gd content: one Gd atom per molecule
- Hydrodynamic size: diameter is 2-3 nm
- Molecular weight: 3.5 kDa
- Dose: due to high relaxivity of P846, the injected dose is lower than that of conventional contrast agent like Gd-DOTA

  Recommended dose: 50 µmol/kg = 2.5 µL/g

  Example: for a 30g body weight mouse, injection volume is 75 µL
- Relaxivities (37°C, Human Albumin Serum 4%)

B_0 (T)	1.5	2.35	3.0	4.7	7.1
r1 ($s^{-1}.mM^{-1}$)	32	28	24	15	11
r2 ($s^{-1}.mM^{-1}$)	41	39	34	31	29

- In vitro quantification techniques: P846 is a Gd-based contrast agent. Gd can be dosed by ICP-AES or ICP-MS. Another way to quantify Gd chelates is by T1 or T2 relaxometry, with assumption of r1 or r2.

Pharmacokinetics/Biodistribution

- P846 belongs to the LDA (low diffusable pharmacokinetics) class.
- Pharmacokinetics constants (unpublished Guerbet data):

Species	Mouse	Rat (n=4)	Rabbit (n=5)	Pig (n=5)
Doses (µmol/kg)	na	25	21	25
$T_{1/2}$ α (min)	na	7.5±0.3	2.6±0.6	na
$T_{1/2}$ β (min)	na	51±11	34.4±3.4	18
Vd (mL/kg)	na	315±31	167±5	134
Cl (mL/min/kg)	na	7.6±0.7	4.1±0.4	5.4
C_5/C_0 (%)	na	10.1±0.5	18.8±0.9	41

na : not avalaible

Characteristics of the vial

- Concentration: [Gd] = 20 mmol/L
- Volume: 450 µL (5 mice dose approx.)
- Other animal species: please contact us

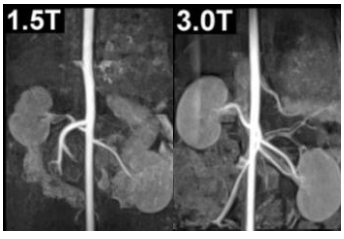
Storage

Need to be stored at 4°C in a closed vial and away from light.

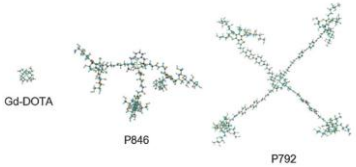
Legal conditions of use: see Chematech terms and conditions of sales

Contacts: info@chematech-mdt.com

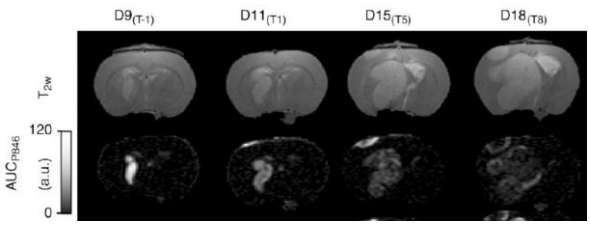
Examples of applications



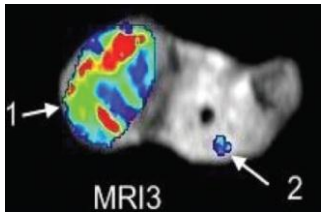
MR angiography
Coronal view of MR angiograms in Rabbit acquired after iv administration of 0.025 mmoL/kg of P846 at 1.5 T and 3.0 T [1]



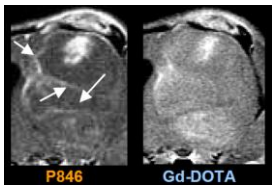
Molecular characteristics of P792 and P846 as compared to Gd-DOTA [4]



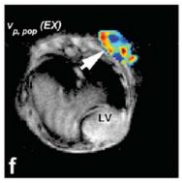
DCE-MRI
T2-weighted MR images and AUC P846 representative maps from animal follow-up after Sorafenib treatment [2]



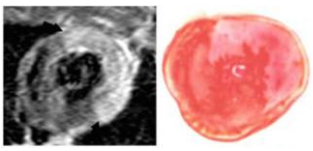
Dynamic Contrast-Enhanced MRI
analysis post-P846 injection [3]



DCE-MRI
Tumor heterogeneity imaging in a brain glioma rat model [5]



DCE-MRI
Parametric maps of plasma volume in a mice subcutaneous tumor model [6]



Myocardial perfusion and viability
Myocardial infarction imaging in a rat model [7]

References

[1] Peldschuss et al., Invest Radiol, 2008 [2] Lemasson et al., Radiology 2010 [3] Casneuf et al., Radiation Research 2011 [4] Heilmann et al., CMMI 2009 [5] Unpublished Guerbet data [6] Loveless, MRM 2011 [7] Jacquier et al, MAGMA 2008

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09/2013

P01240 (P904-Rho)

! For in vitro or animal use only!

P01240 is a bi-modal Ultra Small Particle of Iron Oxyde (USPIO) Guerbet Research Prototype designed for macrophage imaging. This compound is equivalent to **P904** but contains also Rhodamine B for a fluorescent detection. **P01240** can be used in preclinical studies in several applications such as cell labeling and trafficking and inflammation imaging.

Main applications

Cellular imaging: inflammation through macrophage imaging after i.v. injection (atherosclerotic plaque, Alzheimer disease, multiple sclerosis, osteo-arthritis…), metastatic lymph node imaging, liver tumor, in vitro cell labeling and cell trafficking

Molecular characteristics

- Hydrodynamic size: diameter is 25-30 nm
- Fe content: > 5000 Fe atoms per particle
- Fluorescent content: 7 rhodamines per particle
- Recommended dose: from 200 to 1000 µmol/kg
  Example: at 200 µmolFe/kg, for a 30g body weight mouse injection, volume is 75 µL
- Relaxivities (reference to P904 data at 37°C; 4% Human Albumin Serum, medium closed to plasma)

B_o (T)	1.5	3.0	4.7	7.0
r1 ($s^{-1}.mM^{-1}$)	14±1	7±1	4±0.5	1.6±0.2
r2 ($s^{-1}.mM^{-1}$)	90±5	90±5	92±5	94±5

- Qualitative techniques: Perl's staining
- In vitro quantification techniques: P01240 is a Fe-based contrast agent. Thus, it is necessary to take into account the endogenous iron content for quantification in biological media by ICP-AES or ICP-MS. Another way for USPIO quantification is relaxometry, which is poorly sensitive to endogenous iron.

Storage

Need to be stored at 4°C in a closed vial and away from light.

In vitro Macrophage uptake [1]

Incubation concentration (µgFe/mL)	Incubation time (hr)	THP-1 cell line (pgFe/cell)
200	24	1.8-2.3

Reference to P904 data

Pharmacokinetics/Biodistribution

Species	Doses (µmolFe/kg)	$T_{1/2}$ (min)	Vd (mL/kg)	Cl (mL/min/kg)
Mice	100	62	66	0.80
Rat	200	145±28	38±2	na
Rabbit	150	136±18	22±2	0.06±0.01
	350	164±12	22±0	0.05±0.00
	1000	220±6	22±0	0.04±0.00
Monkey	85	α= 1h β=16.5h	β=2500	0.62

Reference to P904 data

Characteristics of the vial

- Concentration: [Fe] = 4.47 mgFe/mL → [Fe] = 80 mmol/L (M_{Fe}=56 g/mol)
- Volume: 450 µL (5 mice dose approx.)
- Other animal species: please contact us

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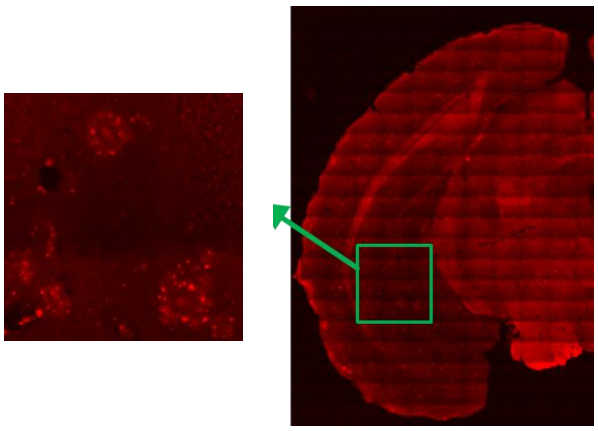
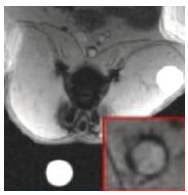
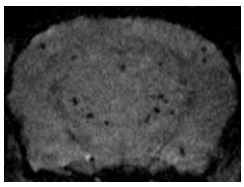
Examples of applications



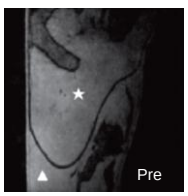
P01240-enhanced fluorescence microscopy
Alzheimer disease model [2]

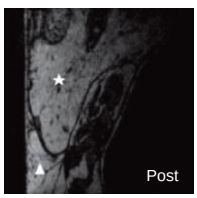


Inflammation imaging
Atherosclerotic Plaque model in Rabbit [3]



Neuro-Inflammation imaging
Alzheimer disease mice model [4]





Cellular imaging
P904-enhanced MR imaging allows specific cellular imaging of adipose tissue macrophages [5]

References

[1] Corot et al, ed. Molecular and Cellular MR Imaging: CRC Press, 2007 [2] Unpublished Guerbet data [3] Sigovan et al, Radiology 2009 [4] Raynaud et al, ISMRM 2010 [5] Luciani et al, Radiology 2012

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09/2013

P00449 – Gd-DOTA

! For in vitro or animal use only!

Gd-DOTA is an ionic macrocyclic gadolinium complex of the 1, 4, 7, 10 tetraazacyclododecane N, N', N'', N''' tetra-acetic acid designed for MRI imaging. Its parametric proprieties increase contrast enhancement in MRI. It is freely excreted by the kidneys and is very inert biologically.

Main applications

Detection of brain tumor, rachis pathology, whole body pathology (including angiography), osteo-articular imaging, brain perfusion, DCE – MRI

Molecular characteristics

- Macrocyclic and ionic Gd-based chelate
- Hydrodynamic size: ~1 nm
- Molecular weight: 560 Da
- Recommended dose: 100 µmol/kg = 2.5 µL/g
- Relaxivities (precision ±10%, 37°C, HSA 4%) [1]

Bo (T)	0.47	1.5	2.35	3.0	4.7	7.0
r1 ($s^{-1}.mM^{-1}$)	3.5	3.5	3.4	3.4	3.3	3.0
r2 ($s^{-1}.mM^{-1}$)	3.7	4.2	4.2	4.2	4.1	4.0

- Quantitative techniques: ICP-AES, ICP-MS, relaxometry…

Storage

Need to be stored at ambient temperature in a closed vial.

Characteristics of the vial

- Concentration: [Gd] = 40 mmol/L
- Volume: 450 µL (5 mice dose approx.)
- Other animal species: please contact us

Pharmacokinetics/Biodistribution

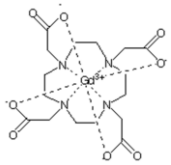
- Urinary excretion on 4 hours ~ 80%.
- Biliary excretion on 4 hours: less than 1%.
- Injected by i.v. route, the gadoteric acid principally flows in the extracellular liquids. It does not bind to serum albumin and does not cross the intact blood-brain barrier.

Species	Rat	Rabbit
Doses (mmolGd/kg)	0.1	0.1
$T_{1/2}\alpha$ (min)	2.8±0.2	4.1±2.3
$T_{1/2}\beta$ (min)	26±1	49.3±10.3
Vd (mL/kg)	260±18	170±19
Cl (mL/min/kg)	7.0±0.6	2.7±0.6
C_5/C_0 * (%)	13±0	19.4±1.4

for information: T1/2 in Human @ 0.1mmol/kg ~ 90 min.

Safety

- Very high stability of the ionic Gd-DOTA-complex [2]
- No teratogenic and no mutagenic effects have been observed in animals



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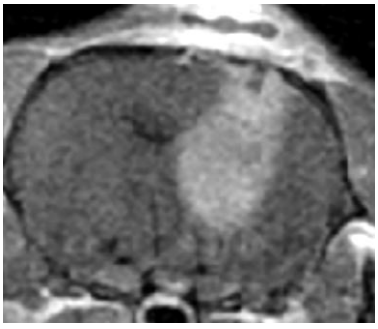
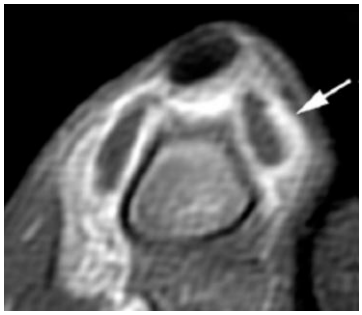
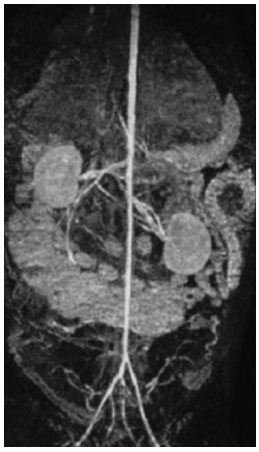
Examples of applications



Imaging of brain lesions
Gd-DOTA brain tumor enhancement in rat [3]



Osteo-articlar imaging
Rabbit model of Synovitis with Gd-DOTA enhancement (arrow) T1-w image [4]



MR angiography
Gd-DOTA-Enhanced MR Angiography in Rabbit [5]

References

[1] Unpublished Guerbet Data [2] Idee et al., Fundam Clin Pharmacol., 2006 [3] Van der Elst; ISMRM 2013 [4] Lefevre et al., Radiology 2011 [5] Ruehm et al, MRM 2000

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Guerbet
Contrast for Life

CheMatech
macrocycle design technologies

P904

! For in vitro or animal use only!

P904 is a Ultra Small Particle of Iron Oxide (USPIO) Guerbet Research Prototype designed for macrophage imaging. **P904** can be used in pre-clinical studies in several applications such as in **cell labeling and trafficking**, **inflammation imaging, angiography** and high sensitivity contrast-enhanced brain **functional MRI (fMRI)**.

Main applications

- Cellular Imaging: in vitro cell labeling, cell trafficking, lymph node and liver imaging, imaging of inflammation after iv injection (atherosclerotic plaque, Alzheimer disease, multiple sclerosis, osteo-arthritis…)
- Blood pool imaging: CE-fMRI, bolus and steady state T1w-MRA, quantification of cerebral blood volume or vessel size index (VSI)

Molecular characteristics

- Hydrodynamic size: diameter is 25-30 nm
- Fe content : > 5000 Fe atoms per particle
- Recommended dose: 200 µmol/kg = 2.5 µL/g

  Example: for a 30g body weight mouse injection, volume is 75 µL
- Relaxivities (data at 37°C; 4% Human Albumin Serum, medium closed to plasma)

B_0 (T)	1.5	3.0	4.7	7.0
r1 ($s^{-1}.mM^{-1}$)	14±1	7±1	4±0.5	1.6±0.2
r2 ($s^{-1}.mM^{-1}$)	90±5	90±5	92±5	94±5

- Qualitative techniques: Perl's staining
- In vitro quantification techniques: P904 is a Fe-based contrast agent. Thus, it is necessary to take into account the endogenous iron content for quantification in biological media by ICP-AES or ICP-MS. Another way for USPIO quantification is relaxometry, which is poorly sensitive to endogenous iron content.

In vitro Macrophage uptake [1]

Incubation concentration	Incubation time	THP-1 cell line
200 µgFe/mL	24 hr	1.8-2.3 pgFe/cell

Pharmacokinetics/Biodistribution

Species	Doses (µmolFe/kg)	$T_{1/2}$ (min)	Vd (mL/kg)	Cl (mL/min/kg)
Mice	100	62	66	0.80
Rat	200	145±28	38±2	na
Rabbit	150	136±18	22±2	0.06±0.01
	350	164±12	22±0	0.05±0.00
	1000	220±6	22±0	0.04±0.00
Monkey	85	α= 1h β=16.5h	β=2500	0.62

Characteristics of the vial

- Concentration: [Fe] = 4.47 mgFe/mL → [Fe] = 80 mmol/L (M_{Fe}=56 g/mol)
- Volume: 450 µL (5-mice dose approx.)
- Other animal species: please contact us

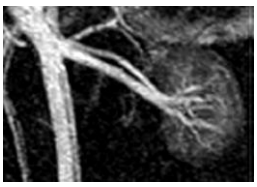
Storage

Need to be stored at 4°C in a closed vial and away from light.

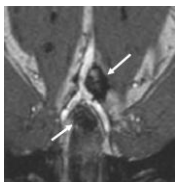
Legal conditions of use: see Chematech terms and conditions of sales

Contacts: info@chematech-mdt.com

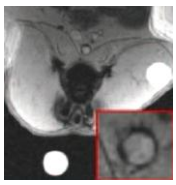
Examples of applications



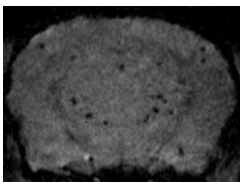
MR Angiography
High Resolution P904 enhanced-MRA in Rabbit during the bolus or at steady state [2]



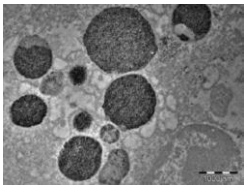
MR lymphography
P904-enhanced MR lymphography in Rabbit [3]



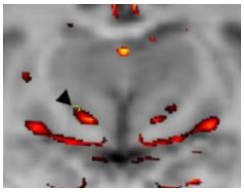
Inflammation imaging
Atherosclerotic Plaque model in Rabbit [4]



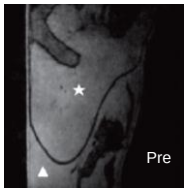
Neuro-Inflammation imaging
Alzheimer disease mice model [5]

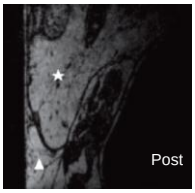


Cellular imaging
Accumulation of P904 in the phagosomes of a macrophage [6]



Blood volume imaging
Direct visualization of non-human primate subcortical nuclei with P904-enhanced MRI [7]





Cellular imaging
P904-enhanced MR imaging allows specific cellular imaging of adipose tissue macrophages [8]

References

[1] Corot et al, ed. Molecular and Cellular MR Imaging: CRC Press, 2007 [2] Kinner et al, Invest Radiol, 2011 [3] Kinner et al, Invest Radiol 2012 [4] Sigovan et al, Radiology 2009 [5] Raynaud et al, ISMRM 2010 [6] Lopez Castro et al, Nanoscale 2011 [7] Tani et al, NeuroImage, 2011 [8] Luciani et al, Radiology 2012

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