PRISMAP
Medical Radionuclides
27 EU

Consortium Meeting 3

Public event 15/6/22

Chelators for rare earths

Enzo Terreno

Molecular and Preclinical Imaging Center

Department of Molecular Biotechnology and Health Sciences

University of Turin

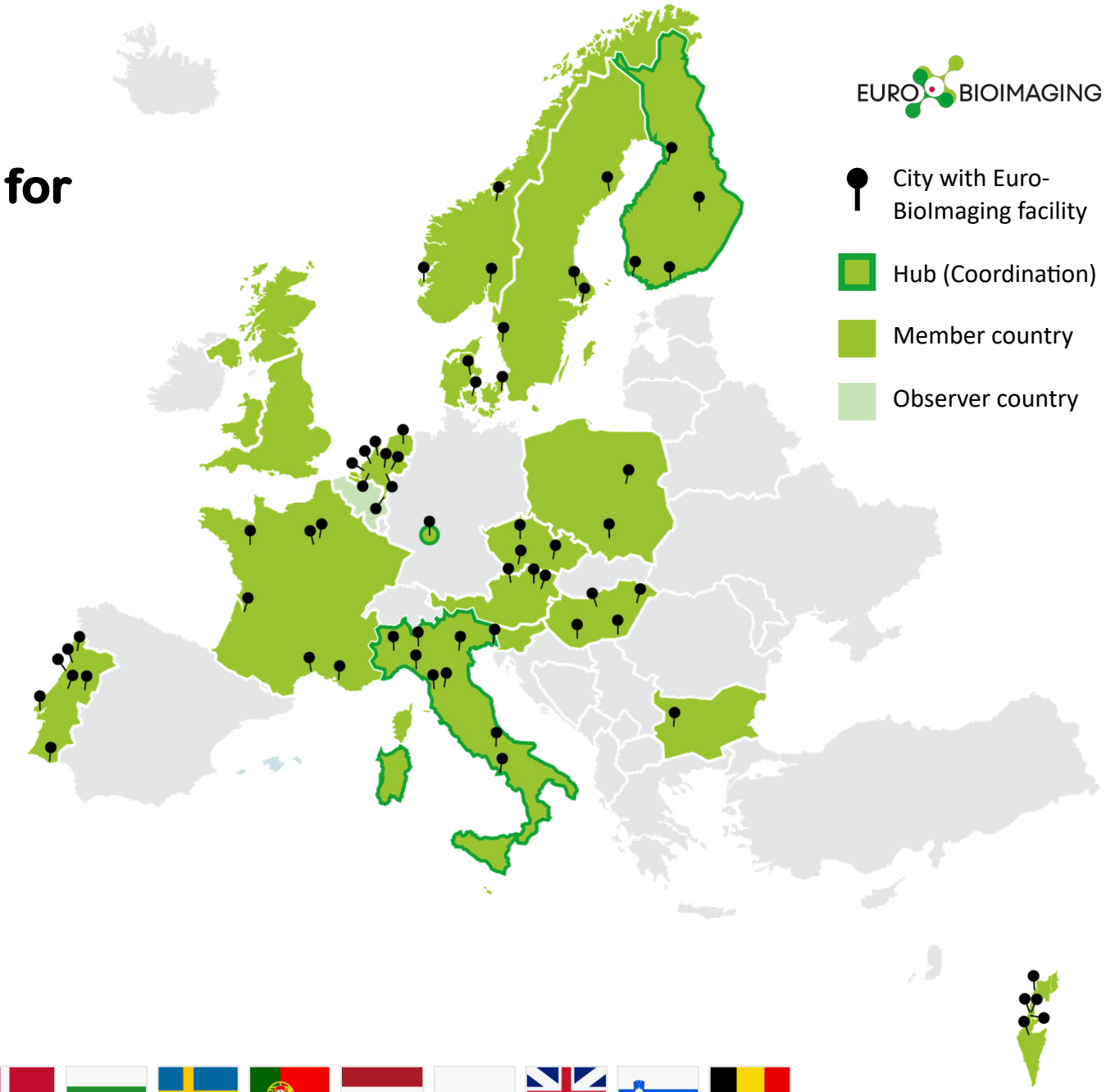
EURO BIOIMAGING
Image life, discover the future

The European research infrastructure for biological and biomedical imaging

50+
TECHNOLOGIES

149
FACILITIES

17
ERIC MEMBERS
(16 COUNTRIES & EMBL)



The Euro-BioImaging technology portfolio

Imaging across scales, from molecule to man

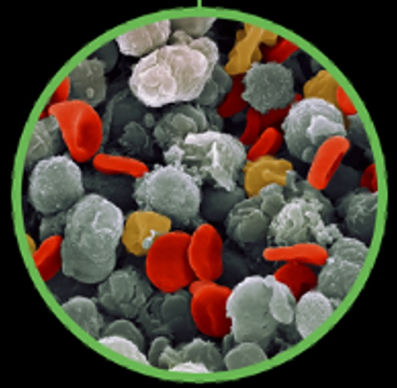
Atomic Force Microscopy

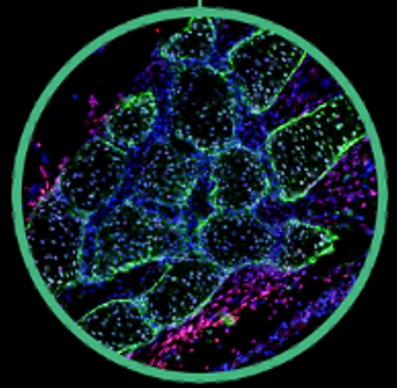
Preclinical Imaging

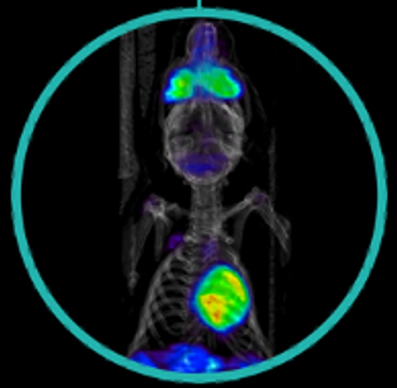
Light Microscopy

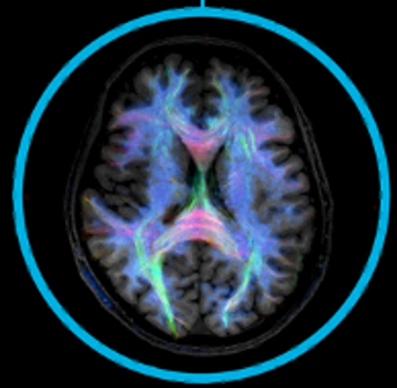
Electron Microscopy

Human Imaging









BIOIMAGING

MMMI: a multi-site Node

MMMI Node is distributed over four cities (Torino, Milano, Napoli, and Pisa), with 8 facilities involved structured in a JRU:

- **Turin:**

University of Torino (Coordinator)

- **Milan:**

San Raffaele Hospital

CNR Institute of Bioimages and Molecular Physiology

- **Pisa:**

University of Pisa

CNR Institute of Clinical Physiology

Gabriele Monasterio Foundation

- **Naples:**

CNR Institute of Biostructures and Bioimages

IRCCS SYNLAB SDN

MMMI Italian Node: facility@Torino

MMMI Multi-Modal Molecular Imaging Italian Node
EURO BIOIMAGING
www.mmmi.unito.it

UNIVERSITÀ DEGLI STUDI DI TORINO

University of Torino

Department of Molecular Biotechnology and Health Sciences

DBMSS Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

Center for Molecular Imaging Turin

prelinical 1 T MRI

preclinical 7 T micro-MRI

NIRF/BLI/X-ray imaging system

Center for Preclinical Imaging @BioIndustry Park (50 km north from Turin)

preclinical 3 T MRI

preclinical 7 T MRI

NIRF/BLI imaging system

1 US/PAI scanner

Center for Translational Imaging Turin

preclinical 7 T MRI

clinical 3 T MRI (coming soon)

preclinical PET/SPECT/CT scanner

Activities and Expertise @UniTO

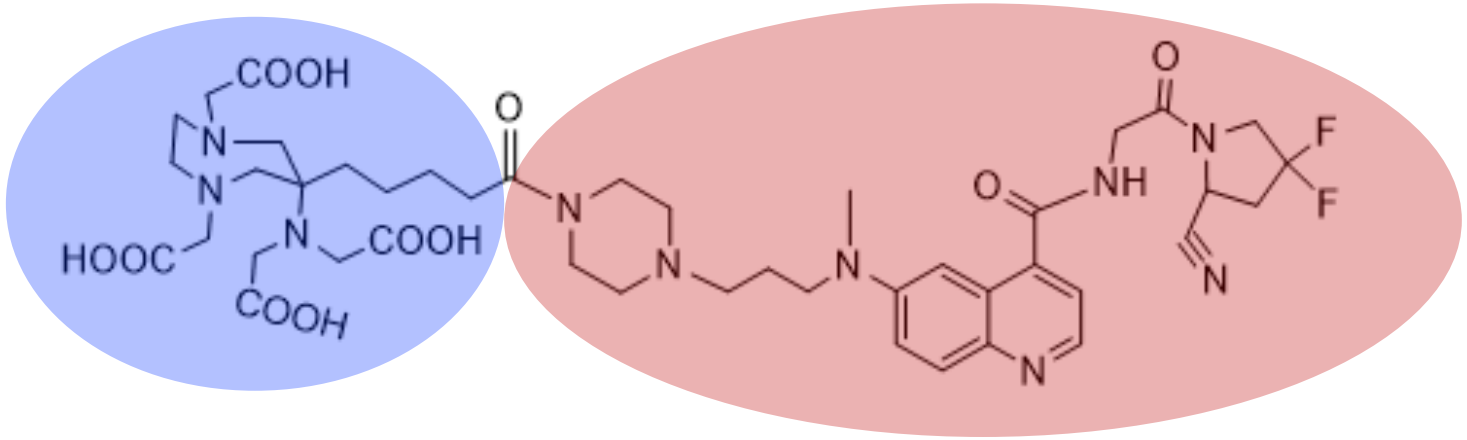
- Paramagnetic (based on Gd(III), Mn(II), and Fe(III) MRI contrast agents
- Design and preclinical validation of MRI-CEST Agents
- Development of ^{19}F-MRI probes and related imaging procedures
- Metabolic Imaging & hyperpolarized MRI probes
- Imaging tumor microenvironment
- MRI at low (and variable) magnetic field and Boron Neutron Capture Therapy Agents
- Development of (nano)probes for Image-Guided Therapy procedures
- Nano- and micro-systems for *in vitro* and *in vivo* diagnostics/theranostics

27 EU PRISMAP Medical Radionuclides

PRISMAP Call 1

Dual $^{152}Tb/^{149}Tb$ radiolabelling and preclinical validation of an AAZTA-FAPI ligand for diagnostic and theranostic applications

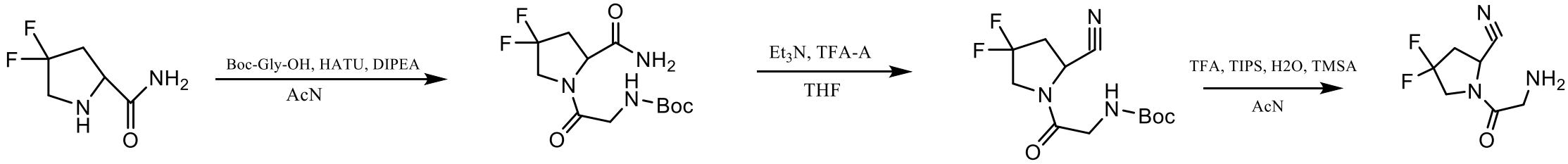
AAZTA-FAPI-46

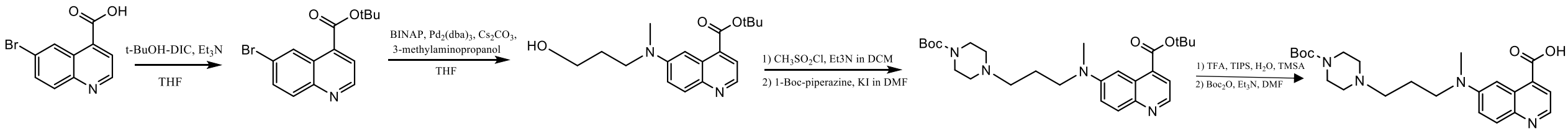


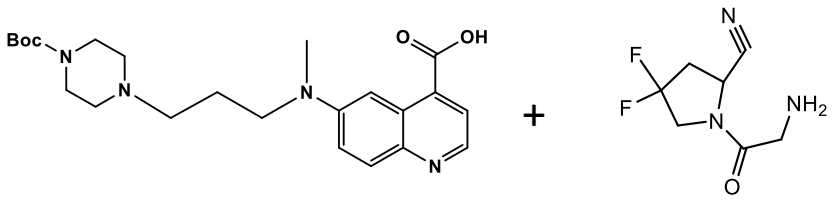
AAZTA chelator
(excellent for both d- and f-metals)

FAP inhibitor
(DOTA-chelator used on humans)

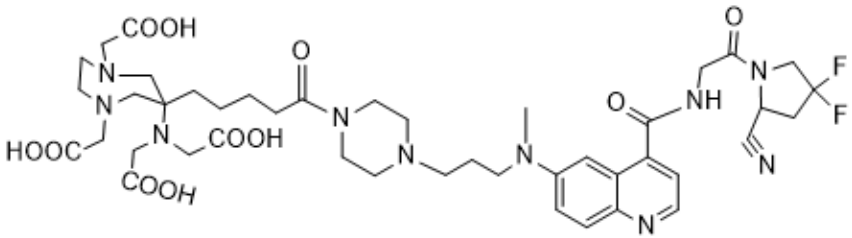
AAZTA-FAPI-46: synthetic procedure







1. amide coupling
2. Boc-deprotection
3. AAZTA coupling



(overall yield ~ 6%)

(purity > 98 %)

AAZTA: an excellent chelator for d- and f-metals

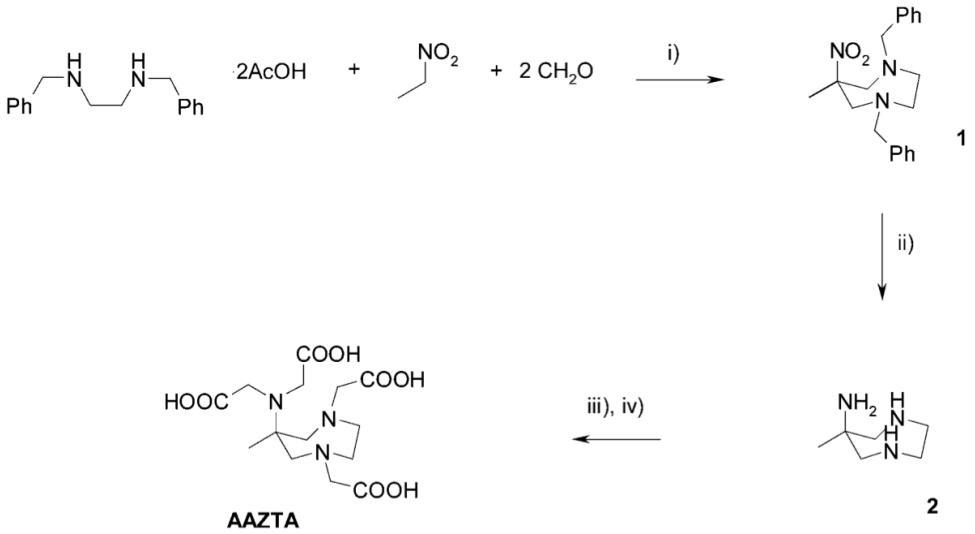
Inorg. Chem. **2004**, *43*, 7588–7590
Inorganic Chemistry
Communication

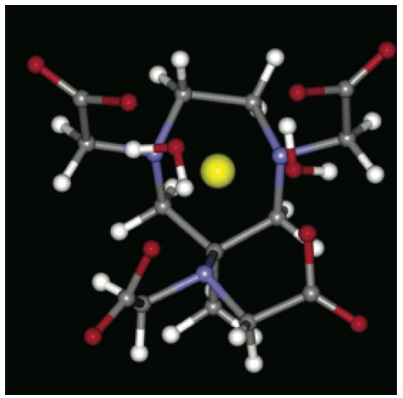
Proposed for the first time in 2004

[Gd-AAZTA]$^{-}$: A New Structural Entry for an Improved Generation of MRI Contrast Agents

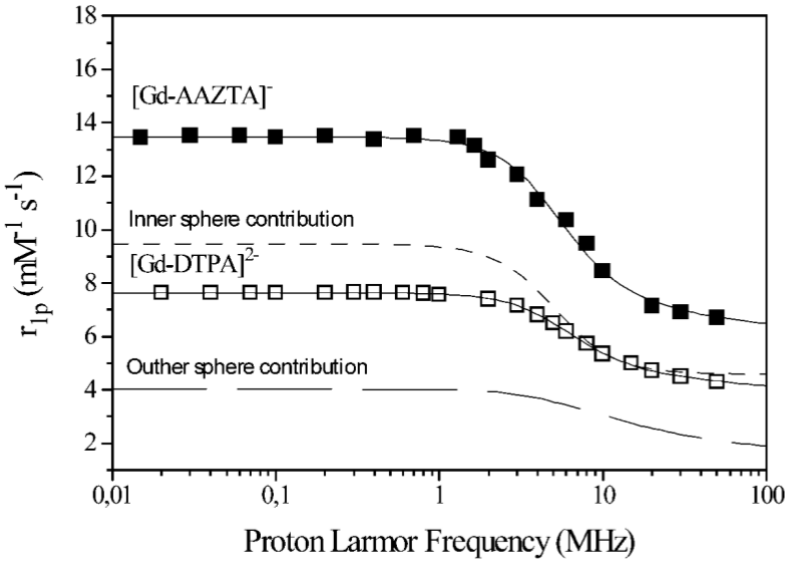
Silvio Aime,*,† Luisella Calabi,‡ Camilla Cavallotti,§ Eliana Gianolio,† Giovanni B. Giovenzana,§ Pietro Losi,‡ Alessandro Maiocchi,‡ Giovanni Palmisano,|| and Massimo Sisti||

Dipartimento di Chimica I.F.M., Università degli Studi di Torino, Via P. Giuria 7, I-10125 Torino, Italy, Bracco Imaging S.p.A., Via Folli 50, I-20135 Milano, Italy, Dipartimento di Scienze Chimiche Alimentari Farmaceutiche e Farmacologiche, Università del Piemonte Orientale "A. Avogadro", Via Bovio 6, I-28100 Novara, Italy, and Dipartimento di Scienze Chimiche e Ambientali, Università degli Studi dell'Insubria, Via Valleggio 11, I-22100 Como, Italy





[Gd-AAZTA]$^{-}$



2 fast-exchanging metal-coordinated water molecules

50 % of relaxivity enhancement compared

with clinically approved MRI agent

AAZTA: an excellent chelator for d- and f-metals

Nowadays, AAZTA returns 61 papers (Source: Scopus)

Equilibrium and Kinetic Properties of the Lanthanoids(III) and Various Divalent Metal Complexes of the Heptadentate Ligand AAZTA**

Zsolt Baranyai,[a, b] Fulvio Uggeri,[c] Giovanni B. Giovenzana,[d] Attila Bényei,[e] Ernő Brücher,[b] and Silvio Aime*[a]

CHEMISTRY A EUROPEAN JOURNAL

Chem. Eur. J. **2009**, *15*, 1696 – 1705

Table 2. Protonation and stability constants of metal complexes of the ligands H_4AAZTA and H_5DTPA (25 °C).

	H_4AAZTA 0.1 M KCl				H_5DTPA[a] 0.1 M KCl
	$\log K_{ML}$	$\log K^{H}_{MHL}$	$\log K^{H}_{MH_2L}$	$\log K^{H}_{MLH_{-1}}$	$\log K_{ML}$
Mg^{2+}	8.31 (0.01)	5.24 (0.06)	–	–	9.27
Ca^{2+}	12.76 (0.01)	3.34 (0.01)	–	–	10.75
Sr^{2+}	9.88 (0.01)	4.80 (0.05)	–	–	9.79
Mn^{2+}	15.44 (0.01)	2.83 (0.03)	–	–	15.2
Cu^{2+}[b]	20.51 (0.03)	4.00 (0.01)	2.72 (0.01)	10.81 (0.01)	21.5
Zn^{2+}	18.01 (0.02)	3.87 (0.01)	2.36 (0.02)	11.25 (0.03)	18.6
Pb^{2+}[c]	19.84 (0.04)	3.22 (0.04)	2.50 (0.05)	–	18.8
Cd^{2+}[c]	17.94 (0.01)	3.25 (0.01)	2.05 (0.02)	–	19.0
La^{3+}	17.53 (0.02)	1.97 (0.08)	–	–	19.48
Ce^{3+}	18.62 (0.01)	1.47 (0.03)	–	–	20.5
Nd^{3+}	19.41 (0.01)	1.73 (0.02)	–	–	21.6
Eu^{3+}	19.93 (0.01)	1.91 (0.01)	–	–	22.39
Gd^{3+}	20.24 (0.01)	1.89 (0.01)	–	–	22.46
Dy^{3+}	20.39 (0.01)	1.52 (0.03)	–	–	22.82
Er^{3+}	20.78 (0.02)	1.25 (0.06)	–	–	22.74
Yb^{3+}	21.59 (0.03)	–	–	–	22.62
Lu^{3+}	21.85 (0.04)	–	–	–	22.44

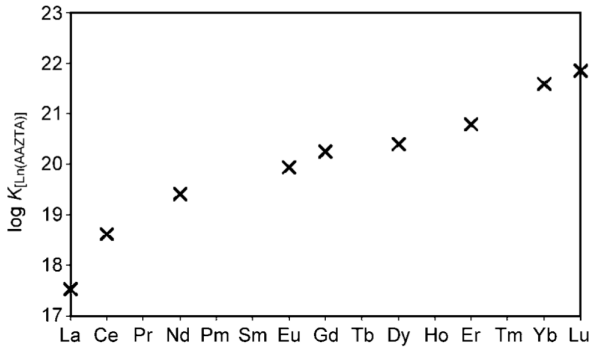


Table 4. Pseudo-first-order rate constants (k^{S}_{obs}) and half-life ($t_{1/2}$) for the dissociation of the complexes $[Gd(AAZTA)]^-$ and $[Gd(DTPA)]^{2-}$ at pH 7.4, $[Cu^{2+}] = 1\times10^{-6}$ M and $[Zn^{2+}] = 1\times10^{-5}$ M (25 °C, 1.0 M KCl).

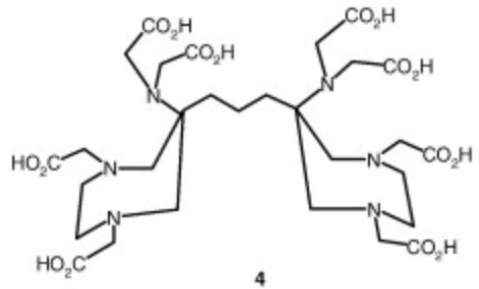
	$10^6\times k^{S}_{obs}$ [s^{-1}]	$t_{1/2}$ [h]
$[Gd(DTPA)]^{2-}$[a]	1.51	127
$[Gd(AAZTA)]^-$	0.045	4337

AAZTA: an excellent chelator for d- and f-metals

Improving the relaxivity by dimerizing Gd-AAZTA: Insights for enhancing the sensitivity of MRI contrast agents

Eliana Gianolio [a], Kondareddiar Ramalingam [b], Bo Song [b], Ferenc Kalman [a], Silvio Aime [a], Rolf Swenson [b]

Inorganic Chemistry Communications
Volume 13, Issue 5, May 2010, Pages 663-665



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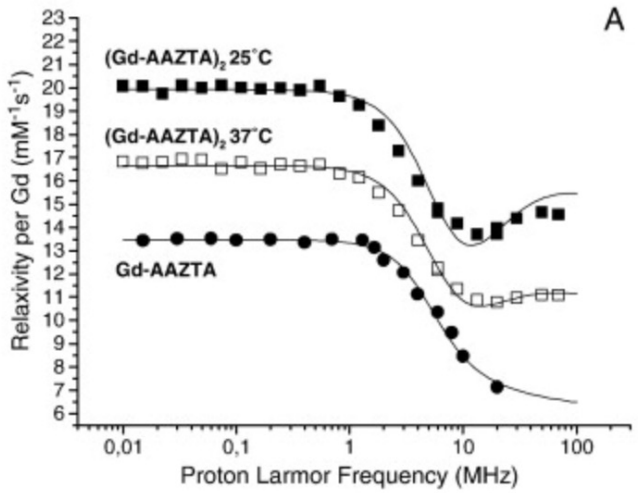
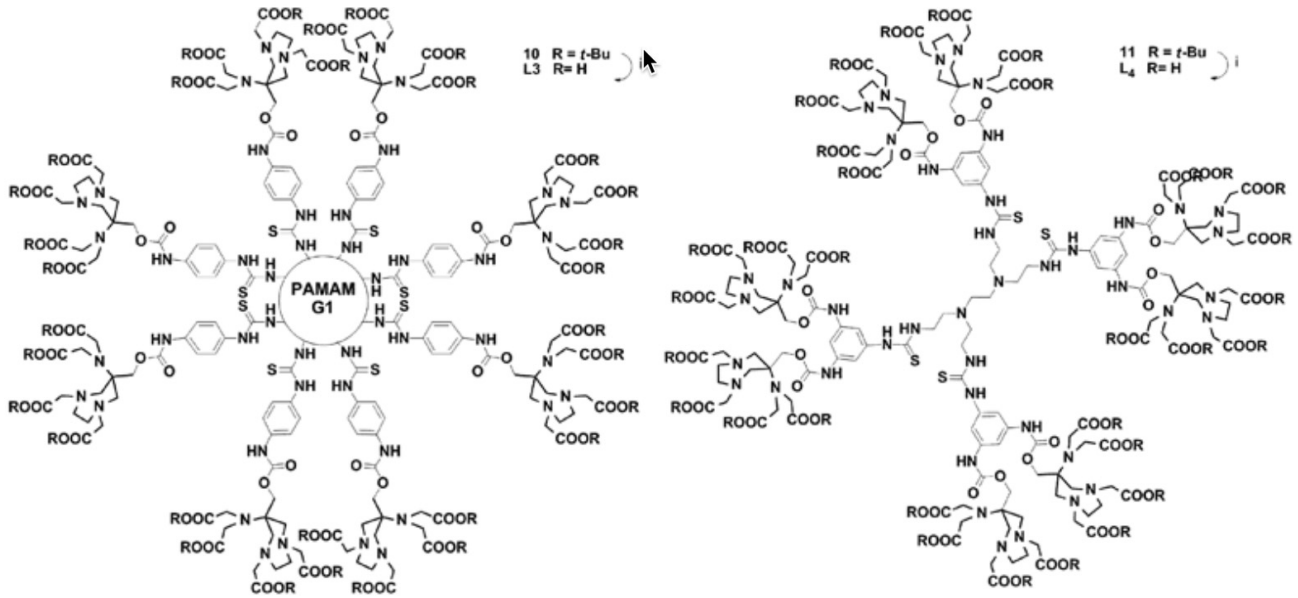


AAZTA-based bifunctional chelating agents for the synthesis of multimeric/dendrimeric MRI contrast agents†

Giuseppe Gugliotta,[a] Mauro Botta[a] and Lorenzo Tei*[a]

Organic & Biomolecular Chemistry 2010, **8**, 4569–4574



Relaxivity (per Gd) *ca.* 22-24 mM^{-1}s^{-1}

Molecular relaxivity *ca.* 180-190 mM^{-1}s^{-1}

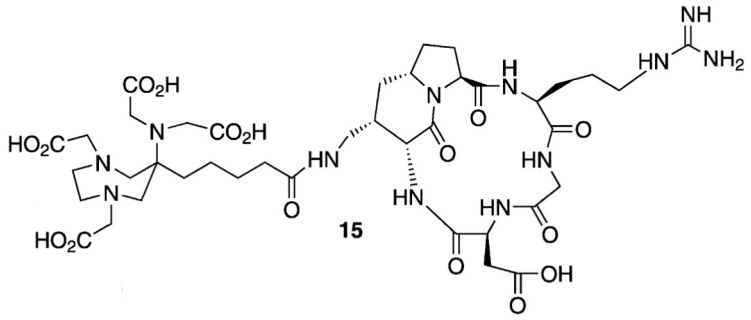
AAZTA: an excellent chelator for d- and f-metals

Synthesis of Gd and ^{68}Ga Complexes in Conjugation with a Conformationally Optimized RGD Sequence as Potential MRI and PET Tumor-Imaging Probes

Leonardo Manzoni,*[a] Laura Belvisi,*[b, c] Daniela Arosio,[a] Maria Paola Bartolomeo,[d] Aldo Bianchi,[c] Chiara Brioschi,[d] Federica Buonsanti,[d] Claudia Cabella,[d] Cesare Casagrande,[c] Monica Civera,[c] Marilenia De Matteo,[c] Lorenza Fugazza,[e] Luciano Lattuada,[d] Federico Maisano,[d] Luigi Miragoli,[d] Cristina Neira,[d] Michael Pilkington-Miksa,[c] and Carlo Scolastico[b, c]

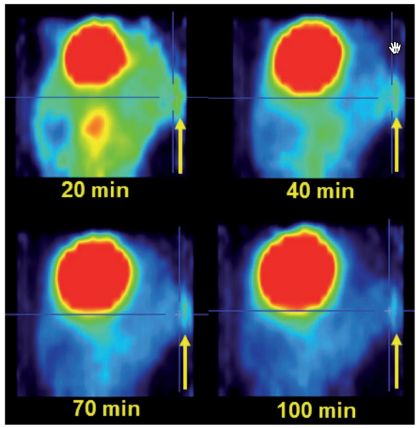
CHEMMEDCHEM

ChemMedChem **2012**, *7*, 1084 – 1093

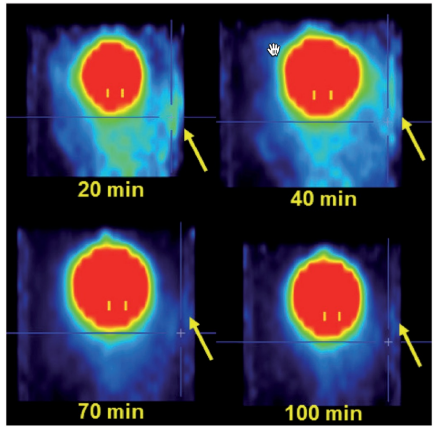


AAZTA-cRGDopt

Preclinical validation
U87MG xenograft on mice



Ga68-AAZTA-cRGDopt



Ga68-AAZTA

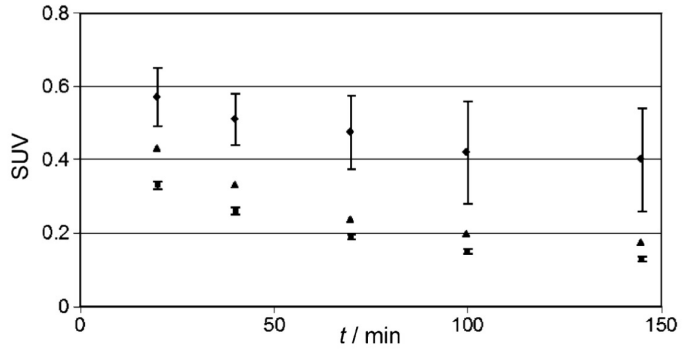


Figure 7. Time course uptake of **15**(^{68}Ga) alone (◆), in co-administration with *c*(RGDfV) (▲), and ^{68}Ga(AAZTA) (■) in U-87 MG xenograft mice.

AAZTA: an excellent chelator for d- and f-metals

Chem Commun (Camb). 2013 Jan 21;49(6):579-81. doi: 10.1039/c2cc37544c. Epub 2012 Dec 4.

Structure and stability of hexadentate complexes of ligands based on AAZTA for efficient PET labelling with gallium-68

Bradley P Waldron [1], David Parker, Carsten Burchardt, Dmitry S Yufit, Melanie Zimny, Frank Roesch

Org Biomol Chem. 2013 Feb 13;11(10):1683-90. doi: 10.1039/c2ob27200h.

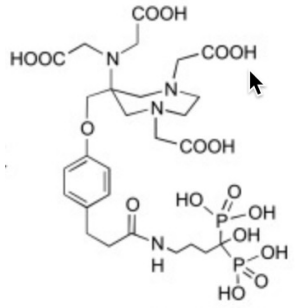
Orthogonal synthesis of a heterodimeric ligand for the development of the Gd(III)-Ga(III) ditopic complex as a potential pH-sensitive MRI/PET probe

Nikolay Vologdin [1], Gabriele A Rolla, Mauro Botta, Lorenzo Tei

Nucl Med Biol. 2016 Jun;43(6):360-71. doi: 10.1016/j.nucmedbio.2016.03.002. Epub 2016 Mar 10.

New (68)Ga-PhenA bisphosphonates as potential bone imaging agents

Zehui Wu [1], Zhihao Zha [1], Seok Rye Choi [1], Karl Plössl [1], Lin Zhu [1], Hank F Kung [2]

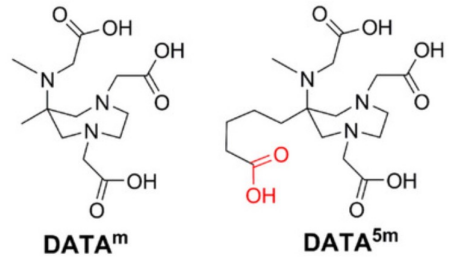


PhenA-HBP, **4**

Chemistry. 2017 Aug 1;23(43):10358-10371. doi: 10.1002/chem.201701508. Epub 2017 Jul 12.

Equilibrium, Kinetic and Structural Properties of Gallium(III) and Some Divalent Metal Complexes Formed with the New DATA ^{m} and DATA ^{5m} Ligands

Edit Farkas [1], Johannes Nagel [2], Bradley P Waldron [3], David Parker [3], Imre Tóth [1], Ernő Brücher [1], Frank Rösch [2], Zsolt Baranyai [1 4]



DATA^{m} DATA^{5m}

AAZTA: an excellent chelator for d- and f-metals

Angew Chem Int Ed Engl. 2017 Feb 13;56(8):2118-2122. doi: 10.1002/anie.201611207. Epub 2017 Jan 18.

AAZTA: An Ideal Chelating Agent for the Development of ^{44}Sc PET Imaging Agents

Gábor Nagy [1 2], Dezső Szikra [1 2], György Trencsényi [1 2], Anikó Fekete [2], Ildikó Garai [1], Arianna M Giani [3], Roberto Negri [3], Norberto Masciocchi [4], Alessandro Maiocchi [5], Fulvio Uggeri [5], Imre Tóth [6], Silvio Aime [7], Giovanni B Giovenzana [3 8], Zsolt Baranyai [5 6]

J Inorg Biochem. 2020 Mar;204:110954. doi: 10.1016/j.jinorgbio.2019.110954. Epub 2019 Dec 5.

Gallium-68 and scandium-44 labelled radiotracers based on curcumin structure linked to bifunctional chelators: Synthesis and characterization of potential PET radiotracers

Giulia Orteca [1], Jean-Philippe Sinnes [2], Sara Rubagotti [3], Michele Iori [3], Pier Cesare Capponi [3], Markus Piel [2], Frank Rösch [2], Erika Ferrari [4], Mattia Asti [3]

Eur J Nucl Med Mol Imaging. 2021 Jul;48(8):2351-2362. doi: 10.1007/s00259-020-05130-0. Epub 2021 Jan 9.

Synthesis, radiolabeling, and pre-clinical evaluation of [^{44}Sc]Sc-AAZTA conjugate PSMA inhibitor, a new tracer for high-efficiency imaging of prostate cancer

S Ghiani [1], I Hawala [2], D Szikra [3 4], G Trencsényi [3 4], Z Baranyai [5], G Nagy [3], A Vágner [3], R Stefania [2], S Pandey [6], A Maiocchi [7]

EJNMMI Radiopharm Chem. 2019 Aug 1;4(1):18. doi: 10.1186/s41181-019-0068-1.

AAZTA ^{5}/AAZTA ^{5}-TOC: synthesis and radiochemical evaluation with ^{68}Ga, ^{44}Sc and ^{177}Lu

Jean-Philippe Sinnes [1], Johannes Nagel [1], Frank Rösch [2]

EJNMMI Radiopharm Chem. 2020 Nov 26;5(1):28. doi: 10.1186/s41181-020-00107-8.

^{68}Ga, ^{44}Sc and ^{177}Lu-labeled AAZTA ^{5}-PSMA-617: synthesis, radiolabeling, stability and cell binding compared to DOTA-PSMA-617 analogues

Jean-Philippe Sinnes [1], Ulrike Bauder-Wüst [2], Martin Schäfer [2], Euy Sung Moon [1], Klaus Kopka [2 3 4], Frank Rösch [5]

Nucl Med Biol. May-Jun 2021;96-97:80-93. doi: 10.1016/j.nucmedbio.2021.03.007. Epub 2021 Mar 26.

AAZTA ^{5}-squaramide ester competing with DOTA-, DTPA- and CHX-A″-DTPA-analogues: Promising tool for ^{177}Lu-labeling of monoclonal antibodies under mild conditions

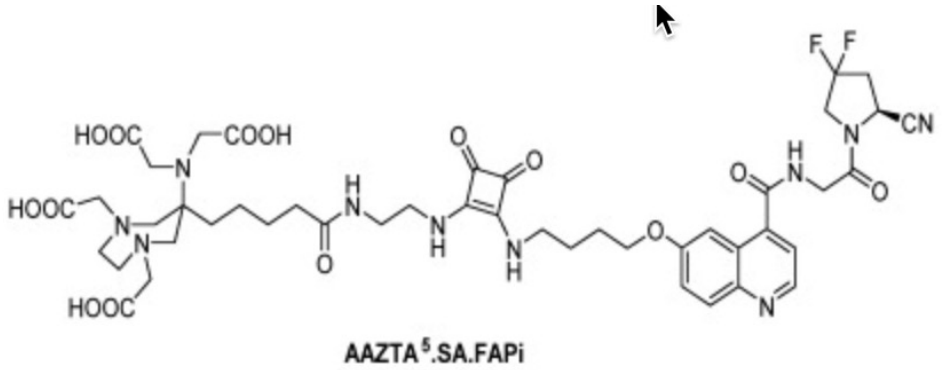
Benedikt Klasen [1], Euy Sung Moon [2], Frank Rösch [3]

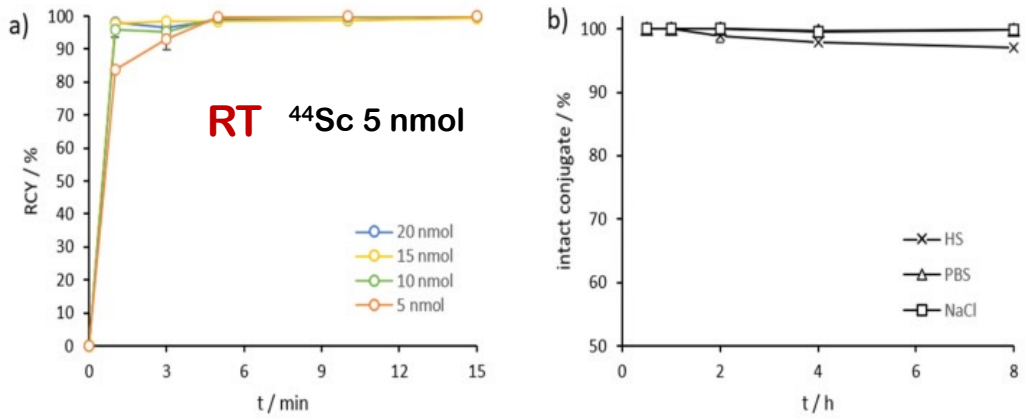
AAZTA: an excellent chelator for d- and f-metals

› Molecules. 2021 Jun 8;26(12):3482. doi: 10.3390/molecules26123482.

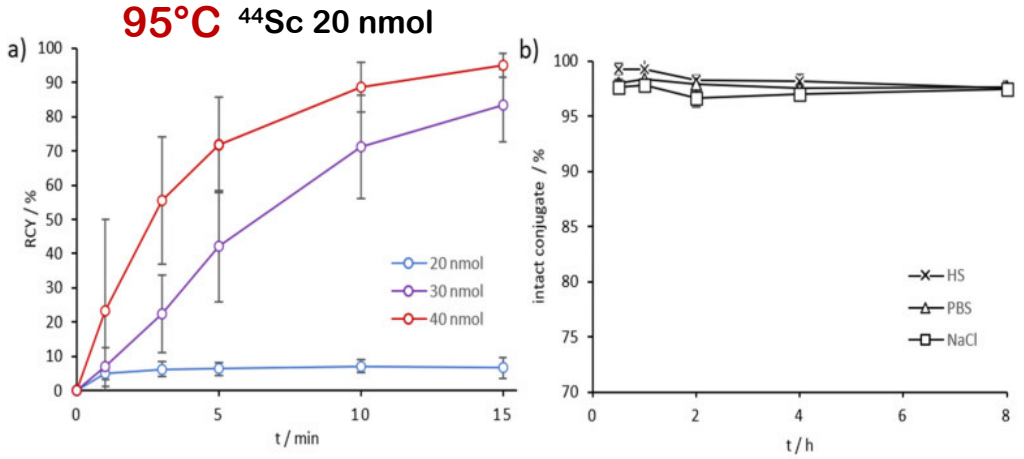
In Vitro Evaluation of the Squaramide-Conjugated Fibroblast Activation Protein Inhibitor-Based Agents AAZTA 5.SA.FAPi and DOTA.SA.FAPi

Euy Sung Moon [1], Yentl Van Rymenant [2], Sandeep Battan [1], Joni De Loose [2], An Bracke [2], Pieter Van der Veken [3], Ingrid De Meester [2], Frank Rösch [1]





Sc44-AAZTA5-SA-FAPi



Sc44-DOTA-SA-FAPi

PRISMAP Call 1

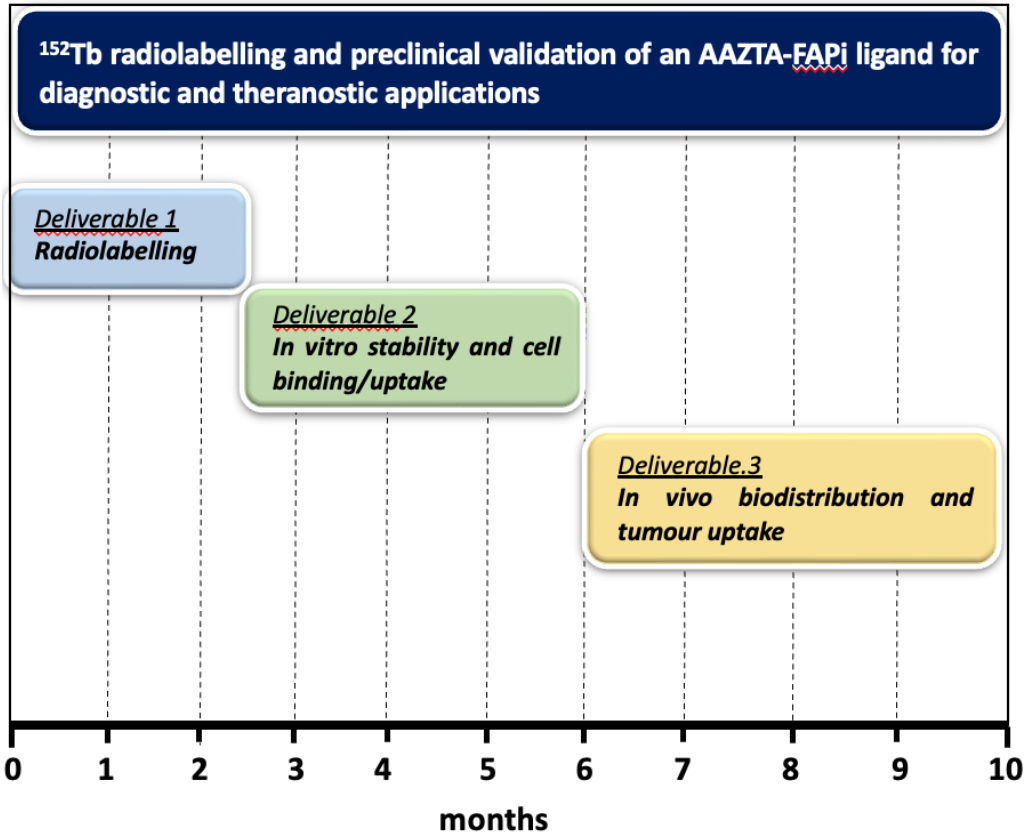
Dual ^{152}Tb/^{149}Tb radiolabelling and preclinical validation of an AAZTA-FAPI ligand for diagnostic and theranostic applications

The User Selection Panel decided to adapt the requested services following the hearings and matching the capacity of the consortium. The indication was to focus on ^{152}Tb imaging studies to gain practice in radiolabeling and submit a new project at a future call for studies with ^{149}Tb.

Radionuclide production
MEDICIS- CERN

Desired partners for biomedical applications

Nuklearmedizinische Klinik und Poliklinik Klinikum rechts der Isar der Technischen Universität München
Contact: PD Dr. Calogero D'Alessandria



Molecular & Preclinical Imaging Center
Department of Molecular Biotechnology and Health Sciences
University of Turin

Università di Torino
M B C
Molecular Biotechnology Center

Center for preclinical imaging

EURO BIOIMAGING
MMMI Multi-Modal Molecular Imaging Italian Node
www.mmmi.unito.it

MASTER'S DEGREE PROGRAMME IN

BIOTECHNOLOGICAL AND CHEMICAL SCIENCES IN DIAGNOSTICS

120 ECTS – 2 ACADEMIC YEARS –LANGUAGE: ENGLISH - BLENDED MODALITY

Why attending the course?

Diagnostics is one of the basement pillars of biomedicine that is experiencing a continuous and breakless evolution from basic research to clinical applications.

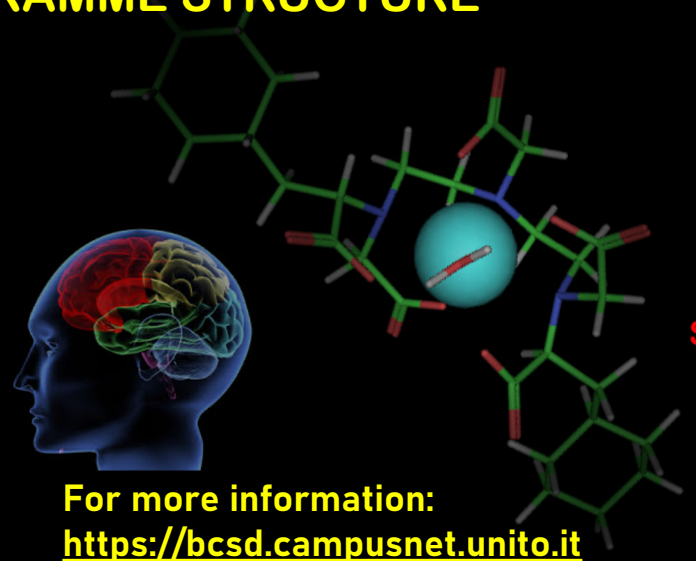
This MSc programme will give you a cutting-edge competence on the chemical and biotechnological aspects of this field, providing the state-of-the-art of concepts, tools, and technologies for in vitro diagnostics and in vivo medical imaging.

This educational path will open the way to a brilliant professional career in academic or industrial research, core faciity management, scientific administration.

PROGRAMME STRUCTURE

Main topics applied to diagnostic field

- Advanced concepts of chemistry and biotechnology
- Bioanaltycal methodologies
- Advanced cellular and molecular biology
- Setup of *in vitro* diagnostic kits
- Chemistry in medical imaging
- *In vivo* Medical Imaging
- Nanotechnology
- 'Omics'
- AI tools



For more information:
https://bcsd.campusnet.unito.it

Lessons and Practical Activities

Language skills

Specialized courses

Stages and Experimental thesis