

**Élisabeth Garanger, PhD**November 10<sup>th</sup> 1977 (age 32)

Laboratoire de Chimie des Polymères Organiques LCPO (UMR5629) - ENSCBP

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E-mail: [garanger@enscbp.fr](mailto:garanger@enscbp.fr)**EDUCATION**2001 – 2005: **PhD. in chemistry & biology** (Joseph Fourier University, Grenoble, FR)2000 – 2001: **MSc. degree in biological organic chemistry** (Blaise Pascal University, Clermont-Ferrand, FR)1997 – 2001: **Chemical engineering degree** (ENSCCF, Clermont-Ferrand, FR)  
Specialization in **fine and industrial organic chemistry**

1995 – 1997: Preparatory to French chemical engineering schools (ENSCR, Rennes, FR)

**PROFESSIONAL EXPERIENCE**

2009 – present:

**Laboratoire de chimie des polymères organiques**, Institut Polytechnique de Bordeaux (Bordeaux, FR)Research fellow in **Prof. S. Lecommandoux's** group

- **Development of theranostic agents from block copolymer-based nanomaterials.**

2006 – 2009:

(3 years)

**Center for Molecular Imaging Research**, Massachusetts General Hospital, Harvard Medical School (Boston, MA, USA)Research fellow in **Prof. L. Josephson's** group

- **Development of a new class of multifunctional reagents.**

A strategy to access multifunctional nanomaterials, imaging probes, and sensors with high levels of complexity was devised to overcome limitations associated with current synthetic methods. "Multifunctional single-attachment-point" (MSAP) reagents, featuring multiple functional groups and a single chemically reactive group, were designed from a peptide scaffold. A series of MSAPs were synthesized to permit multimodal detection (fluorochromes, metal chelates, immunoreactive haptens), to modify nanomaterial properties (hydrophilic polymers), or to confer a therapeutic pharmacological activity (drugs). When an MSAP is reacted with a substrate (*e.g.* a nanoparticle, a protein, a small molecule), a complex multifunctional probe is obtained in a single step. The MSAP-based strategy was applied (*i*) to obtain multifunctional gold nanoparticles,

(ii) to prepare a bioactive multifunctional protein for multimodal imaging of apoptosis, (iii) to study the localization *in vivo* of an integrin-targeting peptide, and (iv) to construct an hypervalent therapeutic antibody.

► **Synthesis and biological evaluation of a MR contrast agent of cell death.**

A thiazole orange (TO) fluorochrome was modified and attached to a paramagnetic Gd chelate to obtain GadoTO, a bimodal probe which maintained the nucleic-acid binding property and the impermeability to healthy cells of TO. Interaction of GadoTO with plasmid DNA was studied by relaxometry and fluorescence. GadoTO was employed to image cell death by fluorescence (FACS, microscopy) and MR (cellular  $T_1$  relaxation times).

2001 – 2005:

(3<sup>1/2</sup> years)

**Joseph Fourier University** (Grenoble, FR)

PhD. graduate student co-supervised by **Prof. P. Dumy** (LEDSS, CNRS UMR 5616) and **Prof. M.C. Favrot** (Institut Albert Bonniot, INSERM U578)

► **Design, synthesis and characterization of new targeting and vectorization systems in cancer**

Synthetic vectors targeting tumors and their associated neo-angiogenesis were synthesized and evaluated for drug delivery and molecular imaging applications. The vectors were devised to target the  $\alpha_v\beta_3$  integrin receptor and to simultaneously carry either a cytotoxic cargo or a contrast-enhancing agent. The core of the vector was composed of a regioselectively addressable cyclic decapeptide scaffold (RAFT) presenting two distinct domains allowing the spatial separation of the targeting and delivery functions. The template was decorated with multiple copies of a *cyclo*[-RGDfK-] peptide through chemoselective oxime ligation. Conjugation of the vector with diverse detection molecules (biotin, fluorescein, cyanin) allowed its biological evaluation *in vitro* and *in vivo*. *In vitro* experiments revealed the tetrameric version to be the most potent in receptor-specific binding and cell internalization. The lead structure RAFT(c[-RGDfK-])<sub>4</sub> proved to induce  $\alpha_v\beta_3$  integrin clustering and to be internalized through a receptor-mediated endocytosis. When administered systemically into immune deficient mice, (Cy5)RAFT(c[-RGDfK-])<sub>4</sub> detected solid tumors as well as disseminated metastases. The vector was further modified with cytotoxic molecules, including an antibacterial amphiphilic peptide, a chemotherapeutic drug or a toxin protein, which were linked through a disulfide bridge allowing their release into the targeted cells. Tumor-suppressing potencies were evaluated *in vivo*. The vector was also coupled to optical and nuclear imaging agents for the detection of deep tumors and metastases in mice.

2001:

(6 months)

**Sanofi-Synthelabo** (Sisteron, FR)

Scientist in **process chemistry** in a R&D laboratory

► Adaptation of a two-step reaction of the manufacturing process of Irbesartan (Aprovel<sup>®</sup>) to the laboratory scale. Study of new organometallic routes.

1999 – 2000:

(12 months) **Aventis Animal Nutrition** (Commentry, FR)  
 Scientist in **pharmaceutical science** and **chemical engineering**

- Development of a formulation of vitamins with suitable rumen stability.
- Quantification of solvent flows in manufacturing process.

1999:

(3 months) **Institute of Food Research** (Norwich, UK)  
 Associate scientist

- Characterization of the physicochemical properties of a complex polysaccharide protein (Caroubin) by NMR, FTIR, and SEM.

### SPECIFIC SKILLS

<i>Chemistry</i>	<i>Biology</i>
Biomolecules conjugation <ul style="list-style-type: none"> <li>- Chemoselective ligations</li> <li>- HPLC, SEC - analysis and purification</li> <li>- Mass spectrometry (ESI, MALDI)</li> </ul> Solid-phase peptide synthesis Fluorochromes for optical imaging Metal chelation for MR imaging	Cell biology <ul style="list-style-type: none"> <li>- Cell culture</li> <li>- Immunostaining</li> <li>- Flow cytometry</li> <li>- Fluorescence microscopy</li> </ul> Molecular biology <ul style="list-style-type: none"> <li>- Gel electrophoresis</li> </ul> <i>In vivo</i> experiments (mice)

### LANGUAGES

- ◆ **French: mother tongue**
- ◆ **English: fluent**
- ◆ **German: good notions**
- ◆ **Spanish: beginner**

**LIST OF PUBLICATIONS**

- 1/ E. Garanger, J.T. Blois, S.A. Hilderbrand, F. Shao, and L. Josephon; “Divergent Oriented Syntheses for the design of reagents for protein conjugation”; *J. Comb. Chem.*; **2009**; *In press*.
- 2/ D.E. Sosnovik, E. Garanger, E. Aikawa, M. Nahrendorf, J.L. Figuiere, G.Dai, F. Reynolds, A. Rosenzweig, R. Weissleder, and L. Josephon; “Molecular MRI of cardiomyocyte apoptosis with simultaneous delayed enhancement MRI distinguishes apoptotic and necrotic myocytes *in vivo*: Potential for midmyocardial salvage in acute ischemia”; *Circulation : Cardiovascular Imaging*; **2009**; *In press*.
- 3/ E. Garanger, S.A. Hilderbrand, J.T. Blois, D.E. Sosnovik, R. Weissleder, and L. Josephon; “A DNA-binding Gd chelate for the detection of cell death by MRI”; *Chem. Commun.*; **2009**; (29); 4444-4446.
- 4/ L. Sancey, E. Garanger, S. Foillard, G. Schoehn, A. Hurbin, C. Albiges-Rizo, D. Boturyn, C. Souchier, A. Grichine, P. Dumy, and J.L. Coll; “Clustering and internalization of integrin  $\alpha_v\beta_3$  with a tetrameric RGD synthetic peptide”; *Mol. Ther.*; **2009**; Vol. 17 (5); 837-843.
- 5/ E. Garanger, R. Weissleder, and L. Josephson; “A Multifunctional Single-Attachment-Point Reagent for Controlled Protein Biotinylation”; *Bioconjugate Chem.*; **2009**; Vol. 20 (1); 170-173.
- 6/ E. Garanger, E. Aikawa, F. Reynolds, R. Weissleder, and L. Josephson; “Simplified syntheses of complex multifunctional nanomaterials”; *Chem. Commun.*; **2008**; (39); 4792-4794.
- 7/ S. Foillard, Z.H. Jin, E. Garanger, D. Boturyn, M.C. Favrot, J.L. Coll, and P. Dumy; “Synthesis and biological characterization of a targeted pro-apoptotic peptide”; *ChemBioChem.*; **2008**; Vol. 9 (14); 2326-2332.
- 8/ E. Garanger, D. Boturyn, and P. Dumy; “Tumor targeting with RGD peptide ligands - Design of new molecular conjugates for imaging and therapy of cancers”; *Anticancer Agents Med. Chem.*; **2007**; Vol. 7 (5); 552-558.
- 9/ Z.H. Jin, V. Jossierand, J. Razkin, E. Garanger, D. Boturyn, M.C. Favrot, P. Dumy, and J.L. Coll; “Non-invasive optical imaging of ovarian metastases using Cy5-labeled RAFT-c(-RGDfK-)<sub>4</sub>”; *Mol. Imaging*; **2006**; Vol. 5 (3); 188-197.
- 10/ E. Garanger, D. Boturyn, J.L. Coll, M.C. Favrot, and P. Dumy; “Multivalent RGD synthetic peptides as potent  $\alpha_v\beta_3$  integrin ligands”; *Org. Biomol. Chem.*; **2006**; Vol. 4 (10); 1958-1965.
- 11/ E. Garanger, D. Boturyn, O. Renaudet, E. Defrancq, and P. Dumy; “Chemoselectively addressable template: a valuable tool for the engineering of molecular conjugates”; *J. Org. Chem.*; **2006**; Vol. 71 (6); 2402-2410.
- 12/ E. Garanger, D. Boturyn, Z.H. Jin, P. Dumy, M.C. Favrot, and J.L. Coll; “New multifunctional molecular conjugate vector for targeting, imaging and therapy of tumors”; *Mol. Ther.*; **2005**; Vol. 12 (6); 1168-1175.
- 13/ I. Texier, V. Jossierand, E. Garanger, J. Razkin, Z.H. Jin, P. Dumy, M.C. Favrot, D. Boturyn, and J.L. Coll; “Luminescent probes for optical *in vivo* imaging”;

*Proceedings of SPIE*: “Genetically Engineered and Optical Probes for Biomedical Applications III” D.J. Bornhop, S. Achilefu, R. Raghavachari, A.P. Savitsky Eds.; **2005**; Vol. 5704; 16-23.

**14/** D. Boturny, J.L. Coll, E. Garanger, M.C. Favrot, and P. Dumy; “Template assembled cyclopeptides as multimeric system for integrin targeting and endocytosis”; *J. Am. Chem. Soc.*; **2004**; Vol. 126 (18); 5730-5739.

**15/** Y. Wang, P.S. Belton, H. Bridon, E. Garanger, N. Wellner, M.L. Parker, A. Grant, P. Feillet, and T.R. Noel; “Physicochemical studies of Caroubin: a Gluten-like protein”; *J. Agr. Food Chem.*; **2001**; Vol. 49 (7); 3414-3419.

## **PATENTS**

**1/** L. Josephson, E. Garanger; “Methods and reagents for preparing multifunctional probes”; MGH case # 3847; *Pending patent application*.

**2/** L. Josephson, E. Garanger, S. Hilderbrand; “Vital fluorochrome-chelator probes for imaging”; MGH case # 20312; *Pending patent application*.

**LIST OF COMMUNICATIONS (ORAL *O* AND POSTERS *P*)****◆ Aquitaine Conferences / Polymers 2009**

*P* - « Block copolymer-based nanoparticles for therapy and imaging of different types of cancer »

Arcachon (FR), October 13-16<sup>th</sup> 2009.

**◆ EICB Young Scientists' Day**

*O* - « Multifunctional probes for multimodal molecular imaging »

Bordeaux (FR), May 28<sup>th</sup> 2009.

**◆ Meeting of the National Cancer Institute Alliance for Nanotechnology in Cancer**

*P* - « Simplifying the synthesis of complex multifunctional nanomaterials »

Chicago (IL, USA), September 8-10<sup>th</sup> 2008.

**◆ 236<sup>th</sup> ACS National Meeting & Exposition**

*O* - « Multifunctional Single-Attachment-Point reagents for probe design »

Philadelphia (PA, USA), August 18<sup>th</sup> 2008.

*This communication has been reported and discussed in C&EN news, August 25<sup>th</sup> 2008, Vol. 86 (34). <http://pubs.acs.org/cen/news/86/i34/8634notw2.html>*

**◆ Mechanisms of Carrier-Mediated Intracellular Delivery of Therapeutics**

*O* - « Mechanism of interaction and internalisation of a multivalent RGD peptide carrier targeting the tumor-associated  $\alpha_v\beta_3$  integrin »

Montpellier (FR), August 26<sup>th</sup> 2005.

**◆ 9<sup>ième</sup> Symposium de l'ICSN: « Cancer: targets, molecules and therapies »**

*P* - « Non-viral delivery of anti-angiogenic molecules for cancer imaging and treatment »

Gif-sur-Yvette (FR), June 10-11<sup>th</sup> 2004.

**◆ 8<sup>ième</sup> Colloque National d'Angiogenèse**

*O* - « Transfert ciblé non-viral de molécules anti-angiogéniques dans le cancer du poumon : efficacité thérapeutique et imagerie moléculaire »

Anancy (FR), May 7<sup>th</sup> 2004.

**◆ 10<sup>èmes</sup> Rencontres de Chimie Organique Biologique**

*O* - « Conception, synthèse et caractérisation de nouveaux systèmes de guidage et de vectorisation pour la cancérologie »

Aussois (FR), March 23<sup>rd</sup> 2004.

**◆ European Society of Gene Therapy**

*P* - « Synthesis and characterization of a new multivalent RGD-based vector for *in vivo* drug delivery to tumors and for medical imaging »

Edinburgh (UK), November 14-17<sup>th</sup> 2003.

♦ **Groupe Français des Peptides et des Protéines**

*P* - « Conception, synthèse et caractérisation de nouveaux systèmes de guidage et de vectorisation pour la cancérologie »  
Anglet (FR), October 19-23<sup>rd</sup> 2003.