Design, synthesis and structure of peptides and proteins

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"Give us the three-dimensional structure of a given protein, for example, an interesting therapeutic target; put your finger in a given surface patch; and we will be able to design for you a very efficient, selective and protease resistant (peptide or non-peptide) ligand." This sentence is still more a dream than a reality, but it reflects one of the most important research lines developed in our laboratory. Improving our knowledge of the rules that govern molecular recognition is clearly, behind all our endeavours in this field. With this aim, we study protein-protein interactions in general and protein self-assembly in particular. Our lines of research not only contribute to enhancing our knowledge of molecular recognition mechanisms, but also provide numerous opportunities in terms of drug discovery. However, many additional unknowns remain to be addressed in order to advance in this field. Several of these are also the focus of our research activities: how can we design a peptide to ensure efficient cellular uptake?; it is possible to remotely control the disruption of amyloid fibrils?; can we use peptides to shuttle drugs across the blood-brain barrier? Finally, methodological improvements are constantly required for all scientific activities. This is the focus of our more recent work in NMR for conformational analysis, improving solid-phase peptide synthesis or developing computational evolutionary algorithms for drug discovery.

Protein-protein interactions

The challenge of dividing finite geometric objects into isometric segments has fascinated structural and synthetic chemists for decades. In a seminal paper published in 1983, Mislow and colleagues analysed the intriguing way of cutting an apple known as "*la coupe du roi*". Figure 1 illustrates how a pair of homochiral segments can be obtained from an achiral object (in this case, an apple) by first making two vertical half-cuts, one from the top to the equator and the other from the bottom to the equator, followed by two non-adjacent horizontal cuts. Although this concept has been applied to the retrosynthetic analysis of highly symmetric organic compounds, such as fullerene C(60) or cyclic diketones, as well as to helical organometallic compounds, to the best of our knowledge it has never been applied to proteins.

Rabbit uteroglobin (UG) can be dissected into two identical homochiral halves either by the conventional reduction of the two disulfide bridges or via "*la coupe du roi*". In the former case, which has been extensively studied in the literature and probably occurs in determined physiological conditions, two identical HS- (1,2,3,4)-SH dithiol 70mers are formed. In the latter, reported for the first time in our publication (Nicolás *et al*, 2005), two identical homochiral halves are also formed (*ie*, α(1,2)-S-S-α(3,4) disulfide 70mers). Independently of how UG is "dissected", the two identical UG halves form a globular noncovalent dimer, the folding of which is most likely driven by interhelical interactions. The importance and specificity of these interactions are highlighted by

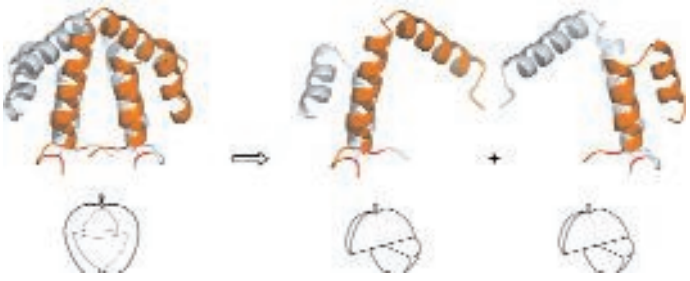

Figure 1. "Coupe du roi" *bisection of proteins. Spontaneous tetramerisation of two peptides that span the sequence of the rabbit uteroglobin monomer.*

the ability of a mixture of α(1,2)-SH and α(3,4)-SH to regioselectively form α(1,2)-S-S-α(3,4) and, therefore, to form the noncovalent 140mer by spontaneous oxidation in aqueous solution. The results obtained in this study suggest that the *"coupe du roi"*-nicked UG has interesting molecular recognition properties, suggesting its potential as a utile, readily synthesised framework for the design of biologically active molecules.

This study with UG is but only one example of the five systems that we are currently working on a two-fold interest: to improve our understanding of protein-protein recognition and to modulate the stability of protein-protein aggregates.

Like UG, HIV-protease (HIV-1 Pr) is also a dimer, but in this case non covalent. We have recently developed an efficient NMR method for the characterisation in solution and at atomic level of the interaction of enzyme inhibitors with a mode of action based on inhibiting dimerisation (Frutos *et al*, 2007). Also with HIV-1 Pr, we have developed an extremely robust ^{19}F-NMR-based method for screening protease inhibitors (Frutos *et al*, 2006).

The B-domain of *S. aureus* Protein A is our benchmark for the design of helical peptides based on D-amino acids with the capacity to retain the same side-chain topology as helices made using native L-amino acids. D-amino acids are also the focal point of our efforts to design efficient amyloid aggregation inhibitors. Last year, in collaboration with Chris Dobson and Carol Robinson in Cambridge (Carulla *et al*, 2005), we reported in *Nature* how the individual protein copies from an amyloid fibril recycle efficiently from the fibril to the solution and back to the fibril. These findings are very promising for the design of synthetic amyloid aggregation inhibitors. Our efforts in this direction are well advanced.

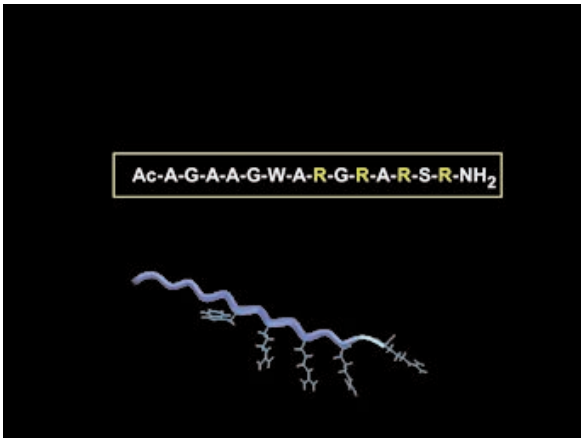

Figure 2. *Chemical structure of CAN4, a synthetic ligand that interacts with the P53 tetramerisation domain.*

Protein-surface recognition

Targeting protein surfaces that are involved in protein-protein contacts is among the most promising strategies for the development of new drugs. These contacts are key in almost all biological processes, and ligands that modulate such contacts would be highly valuable tools for the treatment of diseases. Nevertheless, protein surfaces have only recently been exploited as therapeutic targets, and many research groups are now searching for compounds that specifically recognise given areas of protein surfaces. These molecules could then be used for therapeutic applications, such as tools for chemical genetics studies, or to impart chaperone-like effects to stabilise the native conformation of a protein and/or rescue destabilised mutants. (See Figure 2.)

Surfaces involved in protein-protein interactions are typically large and flat, and, compared to cavities such as enzyme active sites, are highly solvated and rich in polar residues. Small molecules require surface pockets in order to bind to proteins with high affinity, and this hampers their capacity to disrupt protein-protein interactions. Although promising candidates have recently been obtained by screening libraries of small compounds, the principles for integrating surface recognition into the preliminary design of compounds have yet to be established.

NMR studies have been previously used by our group to demonstrate that a nonpeptidic tetraguanidinium compound recognised an anionic patch on the surface of the tetramerisation domain of p53 in aqueous solution with a K_D of 50 μM (Salvatella *et al*, 2004). We have now reported (Martinell *et al*, 2006) a designed peptide ligand (Figure 2) that interacts with the same anionic patch on the surface of the p53 tetramerisation domain in aqueous solution. Using combinatorial chemistry, we have examined the different moieties that participate in the mutual recognition of the designed peptide CAN4 and the p53 tetramerisation domain. The conclusions from this study could be useful for the design of ligands directed to other highly anionic protein-surface patches.

P53 is, again, only one of the systems that we are currently examining from the point of view of the design of binding ligands. Among these other proteins, we are devoting considerable effort to proline oligopeptidase (POP). POP is a non-validated therapeutic target for central nervous system (CNS) disorders, including schizophrenia and bipolar disorder. We have recently reported the use of a new ^{19}F-NMR-based screening method for POP inhibitors present in

aqueous plant extracts, which we have prepared starting from about 50 plants used in traditional Chinese medicine for the treatment of CNS-related disorders (Tarragó *et al*, 2006; Figure 3). An alkaloid, berberine, was identified as a new POP inhibitor and we are now working on the synthesis of berberine derivatives in order to improve the activity and selectivity of this compound. The screening of Chinese medicinal plants is one of the approaches that we are pursuing in our search for new POP inhibitors. Others include structure-based drug design and combinatorial chemistry. (See Figure 3.)

Cell-penetrating peptides

In recent years, cell-penetrating peptides (CPPs) have proven to be an efficient intracellular delivery system. The mechanism for CPP internalisation, which first involves interaction with the extracellular matrix, is followed in most cases by endocytosis and finally, depending on the type of endocytosis, an intracellular fate is reached (Pujals *et al*, 2006).

CPPs are considered potential vectors to carry drugs that have low bioavailability across cell membranes. Properties, such as amphipathicity, high guanidinium content, and hydrophobicity, have been reported to be essential for a peptide to be able to cross a cell membrane. A new family of CPPs of the general formula $(VRLPPP)_n$, in which two of these features, amphipathicity and arginine groups, have been imprinted on a polyproline sequence, was reported by our group some time ago (Angew Chem Int Ed, 2004). The key to the design of these compounds was to maintain a proline content of at least 50% to ensure that the molecules adopt a left-handed polyproline II (PP II) helical structure in solution with a periodicity of 3.0 residues per turn. The remaining 50% of residues were optimised for amphipathicity of the PP II helix. More precisely, hydrophobic Val and Leu residues were placed at 1, 3, 7, 9, ... positions, while polar Arg residues were placed at 2, 8, ... positions. Ultimately, a new family of non-cytotoxic peptides with good cellular uptake properties was obtained (Sweet Arrow Peptides). We are now studying whether the amphipathicity of the PP II helix of these compounds could be further increased by manipulation of the Pro-containing regions. Specifically, it was thought that replacement of a Pro residue located at the hydrophobic face of a PP II helix with another amino acid might increase the amphipathicity and/or enhance the cellular uptake properties of a given CPP. The synthesis of γ-(dimethylsila)proline, or silaproline (Sip), as a proline derivative with enhanced hydrophobicity, was recently reported by Cavelier *et al*. (J Am Chem Soc, 2004). We considered that this non-natural amino acid could be used for such a purpose. The most efficiently

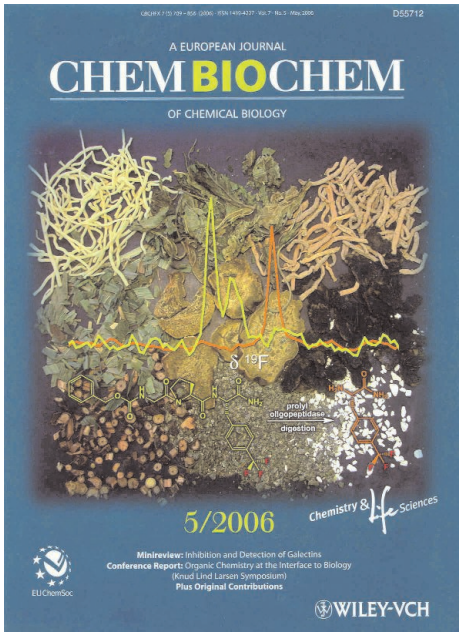

***Figure 3**. Cover of the ChemBioChem issue containing the article 'Identification of traditional Chinese medicinal plants with oligopeptidase activity using ^{19}F-NMR' (Frutos* et al*, 2006). The fluorine spectra of the fluorinated substrate (in yellow) and the fluorinated product (in orange) are shown over a background of some of the plants used in our study.*

internalised Pro-rich CPP [CF-$(VRLPPP)_3$, (1)] was chosen as a reference. Peptide 2 [CF-VRLPPSip$(VRLPPP)_2$ p_2] was designed by substituting Sip for Pro, which is located on the hydrophobic face of the amphipathic PP II helix. Using flow cytommetry, we have shown that, in Hela cells, replacement of a proline with silaproline causes a 20-fold increase in the cellular uptake of the proline-rich peptide. In addition, we have demonstrated that replacement of a Pro by Sip on the hydrophobic face of a Pro-rich amphipathic peptide does not perturb secondary structure or prevent peptide aggregation, and greatly enhances the cellular uptake of the peptide. In addition to highlighting the relevance of amphipathicity in CPP design, these results also emphasise the utility of Sip as a new source of amphipathicity (Pujals *et al*, 2006).

Peptide-nanoparticles: an opportunity for the remote control of protein self-assembly

Misfolded proteins self-assemble into insoluble fibrous deposits, thereby causing diseases called amyloidosis (Alzheimer's, Parkinson's, Huntington's, and type II diabetes among others). During self-assembly, there is an equilibrium between soluble monomer and increasingly larger insoluble aggregates, fibrils, which entangle and precipitate, forcing

the equilibrium toward aggregated forms. Formation of these fibrils requires energy (for example, in the form of stirring), but once formed, they are stable. Vigorous shaking and sonication, high hydrostatic pressure, and temperature cycling reverse the natural equilibrium and redissolve the precipitates. In collaboration with Marcelo Kogan and Victor Puntes, from the Universidad de Chile and Institut Català de Nanotecnologia respectively, we have addressed the combined use of gold nanoparticles and microwave irradiation for the remote manipulation of this aggregation process (Kogan *et al*, 2006).

The local heat delivered by metallic nanoparticles selectively attached to their target can be used as molecular surgery to safely remove toxic and clogging aggregates. We have applied this principle to protein aggregates, in particular to the beta-amyloid protein involved in Alzheimer's disease, a neurodegenerative disease where unnaturally folded proteins self-assemble and deposit forming amyloid fibrils and plaques. We have shown that it is possible to remotely redissolve these deposits and to interfere with their growth, using the local heat dissipated by gold nanoparticles selectively attached to the aggregates and irradiated with low gigahertz electromagnetic fields. We have used peptide sequences covalently attached to the surface of the nanoparticle as an anchor to ensure the attachment of the nanoparticle to the target protein aggregate. Simultaneous tagging and manipulation by functionalised gold nanoparticles of beta-amyloid protein at several stages of aggregation allow non-invasive exploration and dissolution of molecular aggregates.

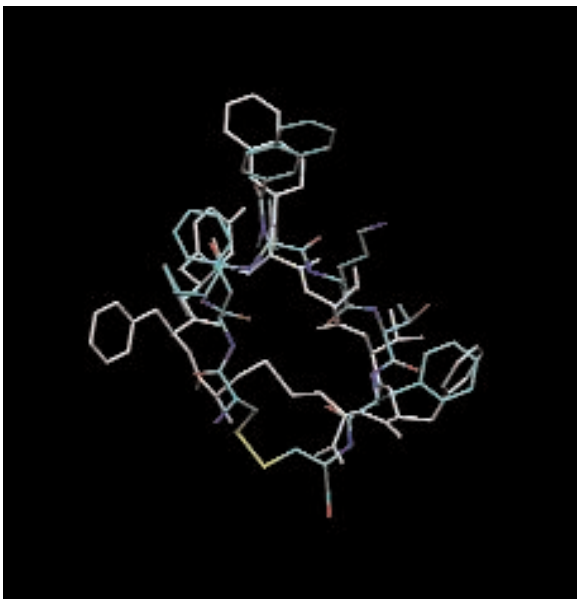

***Figure 4**. NMR 3D structures of the major and minor conformational isomers of a potent SSTR3-selective analogue of somatostatin.*

Conformational analysis

Conformational analysis of peptides and proteins is a key issue when addressing relationships between structure and biological activity. In collaboration with Fernando Albericio's group, our activity in this field focuses on NMR studies of cyclic peptides and depsipeptides, very often of marine origin, which show promising activities as anti-tumour agents (Cruz *et al*, 2005a,b)

In addition, in collaboration with Jean Rivier's laboratory at The Salk Institute in San Diego (California), we have also undertaken the conformational analysis of a group of new cyclic peptides which show activities of interest in the CNS.

Peptides play a major role in signalling processes in the CNS. The same molecule frequently interacts with many different receptors carrying out several biological functions. One of the most paradigmatic cases illustrating this behaviour is that of somatostatin (SRIF), H-Ala^{1}-Gly^{2}-c[Cys^{3}-Lys^{4}-Asn^{5}-Phe^{6}-Phe^{7}-Trp^{8}-Lys^{9}-Thr^{10}-Phe^{11}-Thr^{12}-Ser^{13}-Cys^{14}]-OH, a cyclic tetradecapeptide that acts as a neurotransmitter and neuromodulator in the CNS, as an inhibitor of the release of numerous hormones and as a regulator of cell proliferation and differentiation. SRIF establishes high-affinity interactions with a family of at least five receptor subtypes, SSTR1-5. Although all receptors share common signalling pathways, they have specific functional roles and some biological responses show subtype selectivity. For example, SSTR2 mediates mainly the inhibition of the release of glucagon and growth hormone. SSTR5 controls insulin secretion, and both SSTR2 and SSTR5 mediate the antiproliferative effects of somatostatin on cellular growth processes in tumours. However, the individual functions of the somatostatin receptors *in vivo* are still not fully understood.

Given its wide range of physiological functions, SRIF is a target for the development of receptor subtype-specific analogues. Hundreds of somatostatin analogues that bind with some selectivity to receptor subtypes are currently available and extensive structural studies have been done to ascertain the minimum structural requirements of the analogues for selective binding. To date, a distinct pharmacophore model has been proposed for analogues binding predominantly to SSTR1, SSTR2/SSTR5 and SSTR4 receptors. It appears that the consensus structural motif for these selective ligands requires a unique arrangement of several side chains, which are critical for selective binding. For SSTR3-selective analogues, no

structural information is available to elucidate their binding affinity and selectivity.

A study on cyclic peptides using high field NMR (800MHz) in water solution and molecular dynamics calculations describes, for the first time, the 3D structure of a potent SSTR3-selective analogue of somatostatin. From these data a structural motif has been proposed that could be responsible for SSTR3 selectivity (Gairí *et al*, 2005; see Figure 4.)

New methods in peptide and protein synthesis

Polymers made of amino acids (polyamino acids, peptide copolymers) are emerging as promising therapeutic compounds. These polymers have widespread applications in the field of drug delivery. Drugs are physically entrapped within the polymer matrix or chemically conjugated to the polypeptide for slow release in the biological milieu. A milestone example of therapeutic polyamino acid carriers is paclitaxel polyglumex, a biologically enhanced version of taxol conjugated to a polyglutamate polymer that has recently been *fast track* designated by the FDA for the treatment of advanced non-small cell lung cancer in women. In this context, polyproline polymers are also attracting much attention because of their therapeutic potential. Polyproline is soluble in water, and thus, has been used to solubilise poorly water-soluble proteins obtained by recombinant techniques. Most of these proteins, such as interferons and interleukins, are of high therapeutic interest. Polyproline polymers have also found use in affinity chromatography for the purification of platelet profilin. Recently, dendrimers composed of polyproline branches have been shown to be actively internalised by rat kidney cells and to entrap the antibiotic ciprofloxacin.

Polyamino acids are most conveniently synthesised by polymerisation of the corresponding amino acid *N*-carboxyanhydride. However, the case of proline is unique among coded amino acids as the α-amino group is bound to the side chain, thereby yielding a cyclic secondary amine (pirrolidine) and showing some conformational restrictions. These features probably underlie the poor synthetic yields obtained using currently available methods for α-amino acid N-carboxyanhydride (NCA) formation. Generally speaking, NCAs are achieved by treatment of the corresponding amino acid with phosgene, the so-called Fuchs method. In the case of proline, in contrast to other amino acids, the *N*-carbamoyl intermediate does not cyclise spontaneously, and the use of a non-nucleophilic base, typically a tertiary amine, is required for cyclisation to the NCA.

Procedures described in the literature require slow addition of solutions of phosgene at low temperature and the use of tertiary amines, such as triethylamine, which are difficult to remove and appear in variable amounts in the final crystallised proline NCA product. We are working on the preparation of Pro-NCA in high yields and purities using solid triphosgene and polymer-bound bases. We have recently reported a new procedure for the preparation of proline NCA in high yield and purity using polymer-supported tertiary amines. The polymer-supported amine can be recycled with a basic wash and filtration of the resin. The procedure facilitates the efficient preparation of polyproline polymers of potential therapeutic interest (Gulin *et al*, 2006; see Figures 5 and 6.)

Computer-aided molecular design

One of the goals of computational chemists is to automate the *de novo* design of bioactive molecules. Despite significant advances in computational approaches to ligand design and binding energy evaluation, novel procedures for ligand design are required.

Several research groups currently focus on the development of methodologies for the design of peptidic drugs. Structure-based drug design is an example of an effective technique, whereby the design process is tackled as an engineering problem, and high-throughput screening (HTS) of numerous compounds from combinatorial libraries is performed against a known target. We have recently proposed (Belda *et al*, 2005) a new *in silico* approach, dubbed ENPDA (Evolutionary structure-based *de Novo* Peptide Design Algorithm), which is a hybrid of the two aforementioned strategies. This approach allows the screening of large numbers of candidate peptides that are derived from a semi-rational process involving evolutionary computation.

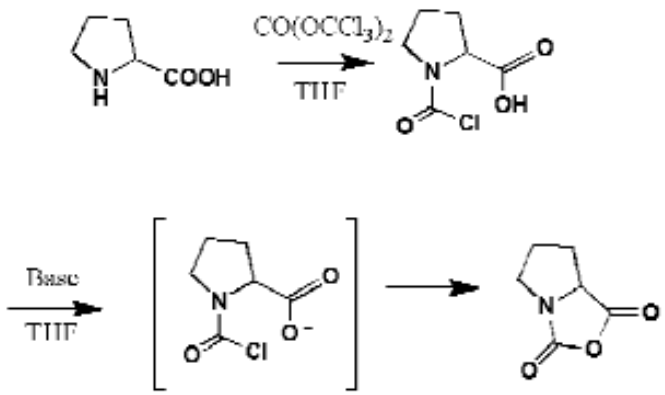

***Figure 5**. Synthesis of Proline NCA.*

We use evolutionary algorithms to generate potential peptide ligands of a given protein by minimising the docking energy between the candidate peptide ligand and a user-defined area of the target protein surface, or *surface patch*. To achieve this goal, an algorithm must address two main tasks. First, this high-dimensional chemical space must be examined using a competent search method. Second, the search space (*ie*, the set of all algorithmically treatable molecules) must be divided into regions of higher and lower quality to allow the prediction of desired properties.

The software we have developed has been successfully tested on the design of ligands for the proteins prolyl oligopeptidase, p53, and DNA gyrase.

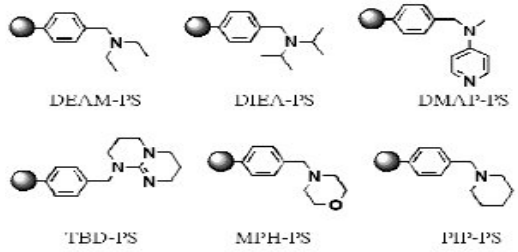

***Figure 6**. Polymer-bound tertiary amines used for the preparation of Proline NCA.*

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RESEARCH NETWORKS AND GRANTS

Aplicación de la RMN a la determinación y caracterización dinámica de estructuras de proteínas, a la identificación de ligandos y a la caracterización de los correspondientes complejos
GEN2003-20642-C09-04
Ministerio Ciencia y Tecnología: 2004-2007
Principal Investigator: Ernest Giralt

NANOFAR-Utilización de péptidos para la vectorización intracelular de nanopartículas
NAN2004-09159-C04-02
Ministerio Educación y Ciencia: 2005-2008
Principal Investigator: Ernest Giralt

Estudios estructurales y dinámicos de especies oligoméricas y fibrilares de Beta-Amiloide. Experimentos de intercambio protón/deuterio analizados por resonancia magnética nuclear (RMN) y espectrometría de masas (EM)
La Caixa: 2006-2008
Principal Investigator: Ernest Giralt

Diseño de ligandos peptídicos para el reconocimiento de superficies proteicas
BIO2005-00295
Ministerio Educación y Ciencia: 2005-2008
Principal Investigator: Ernest Giralt

Ajuts per potenciar i donar suport als grups de recerca - 013010, 2005SGR00663
Generalitat de Catalunya: 2005-2008
Principal Investigator: Ernest Giralt

Desarrollo de nuevos nanobiomateriales: Manipulación de la autoagregación y de la conformación de proteínas para reducir su toxicidad - Colaboración con la Universidad de Santiago (Chile)
Secretaría de Estado de Cooperación Internacional (AECI)
Ayudas para proyectos conjuntos de investigación, A/3388/05: 2006
Principal Investigator: Ernest Giralt

Síntesis de inhibidores peptídicos de la prolil oligopeptidasa (pop) ricos en prolina
PHB2005-0068-PC
Programa Hispano-Brasileño de Cooperación Interuniversitaria. Estancias de movilidad.
Ministerio de Educación y Ciencia: 2006-2007
Principal Investigator: Ernest Giralt

Diseño de "moléculas-espejo" de ligandos peptídicos: utilización de métodos de computación evolutiva
BIO2006-26119-E
Acciones Complementarias - Programa Explora Ingenio
Ministerio de Educación y Ciencia: 2006-2007
Principal Investigator: Ernest Giralt

Diseño, síntesis y estudio estructural de nuevos inhibidores de la dimerización de la proteasa del VIH
Exp 36606/06
FIPSE - Fundación para la investigación y la prevención del SIDA en España: 2006-2009
Principal Investigator: Ernest Giralt

COLLABORATIONS

Conformational analysis of somatostatin analogues
Jean Rivier (The Salk Institute, San Diego, USA)

Use of Silaproline in peptide research
Jean Martinez and Florine Cavelier (University of Montpellier, France)

Remote manipulation of protein aggregation
Marcelo Kogan (University of Chile, Santiago, Chile)

Mimicking discontinuous antigenic sites
David Andreu (University Pompeu Fabra, Barcelona, Spain)

Understanding resistance mechanisms against antimicrobial agents
Jordi Vila (Faculty of Medicine, University of Barcelona, Spain)

Cyclodepsipeptides as potential anticancer agents
Ricardo Pérez-Tomas (Bellvitge Hospital, University of Barcelona, Spain)

Structural studies in uteroglobin self-assembly
Ernesto Nicolás (Organic Chemistry Department, University of Barcelona, Spain)

Application of mass spectrometry to the study of protein-protein interactions
Eliandre Oliveira (Proteomics Platform, PCB, Spain)

Self penetrating proline-rich dendrimers and γ-peptides
Miriam Royo (Combinatorial Chemistry Platform, Parc Científic de Barcelona, Spain)

Synthesis and conformational analysis of cyclodepsipeptides from marine origin
Fernando Albericio (IRB Barcelona, Spain)

Mass-spectrometric analysis of post-transductionally modified proteins
Ferran Azorín (IRB Barcelona, Spain)

AWARDS

Susana Gordo (PhD Student)
Modifying p53 tetramerisation by designed calyx[4]arene compounds
Best oral presentation in the young investigator mini-symposium: Dr. Bert L Schram Award (29th European Peptide Symposium and the ESCOM Science Foundation), Gdansk-Poland, September 2006

Meritxell Teixidó
Novel approaches to study drug delivery to the brain
Best poster by a young scientist: Dr. Bert L Schram Award (29th European Peptide Symposium and the ESCOM Science Foundation), Gdansk-Poland, September 2006

Ernest Giralt's group, March 2006.