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Preface

The Organizing Committee welcomes you to the "XVI Congress of the SEQT: From a Classical to a New Age in Medicinal Chemistry" that takes place at the Centro de Investigación Príncipe Felipe in Valencia.

The XVI Congress of the SEQT focuses on: (i) the design of novel therapeutic agents, (ii) (bio)chemical strategies to answer biological questions, (iii) the incorporation of new technologies to the drug discovery process and (iv) new approaches to study complex therapeutic targets. The Scientific Committee has paid special attention to these objectives and has selected speakers, both from academia and industry, who can offer a multidisciplinary perspective on these subjects.

The celebration of this XVI Congress also pursues the creation of an atmosphere conducing to a close interaction between researchers from different backgrounds and professional activities. In that sense, we expect this opportunity will facilitate new contacts and collaborations among the participants.

Finally, we have tried to promote the active participation of young scientists through the selection of oral presentations describing their current research. In that sense, we hope that this XVI Congress provides them with an up-to-date view of the new developments on drug discovery in an interdisciplinary context between the Chemistry and the Biology.

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We wish you a very productive Congress and a very pleasant stay in Valencia.

The Organizing Committee

Committees

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Scientific Program

SUNDAY, SEPTEMBER 18TH, 2011

15:30 Registration

17:30 Opening
SEQT Awards. **Antoni Torrens**, Esteve
Inaugural Lecture: **Timothy C. Gallagher**, Bristol University
"Natural products as lead to nicotinic agonists. Exploring the chemistry of cytisine"

20:00 Cocktail

MONDAY, SEPTEMBER 19TH, 2011

MORNING SESSION **(Chairs: M.L. López-Rodríguez/M.J. Vicent)**

09:00 IS1: **Rosario González-Muñiz**, IQM-CSIC
"Looking for innovative bioactive compounds: underexplored approaches, creative synthesis"

09:30 IS2: **Andrés Trabanco**, Janssen
"Discovery of a potent and orally bioavailable positive allosteric modulator of mGluR2 for the treatment of CNS disorders"

10:00 Ramón Madroñero SEQT Award
IS3: **Valle Palomo**, IQM-CSIC
"Design, synthesis, enzymatic and cellular evaluation of novel neurogenic ATP-non competitive GSK-3 inhibitors"

10:30 Coffee Break

11:00 IS4: **Stephan A. Sieber**, TU Munich
"Natural products and their biological targets"

11:30 IS5: **Jesús Martínez**, Instituto de Nanociencia de Aragón
"Gold nanoparticles for gene therapy and photo-thermal ablation"

12:00 Oral Communications (OC1-OC4)
OC1: **Jordi Quintana**, Parc Científic de Barcelona
"The Chembiobank and EU-OPENSCREEN initiatives in Chemical Biology: Current status and case studies"

OC2: **Joaquín Campos**, Universidad de Granada
"Increased phosphorylation of the translation initiation factor eIF2α is associated with G_2/M cell-cycle arrest and apoptosis in breast cancer cells"
OC3: **Inmaculada Conejos**, Centro de Investigación Príncipe Felipe
"Polymer-drug conjugates for the treatment of Familial Amyloidotic Polyneuropathy (FAP)"
OC4: **Miriam Corredor,** IQAC-CSIC
"Chemical modulation of cellular signalling routes relevant to the control of apoptosis"

13:00 Lunch

AFTERNOON SESSION **(Chair: Enrique Pérez-Payá)**

15:00 Poster Session and Coffee

16:00 IS6: **Antonio Ferrer-Montiel**, Universidad Miguel Hernández
"TRPducins: a novel paradigm to modulate ion channel activity"

16:30 Oral Communications (OC5-OC7)
OC5: **Gianni de Fabritiis**, Universitat Pompeu Fabra
"Reconstructing an enzyme-inhibitor binding process by molecular dynamics simulations"
OC6: **Óscar Delgado**, Janssen
"Design, synthesis and biological evaluation of novel fluorinated ethanolamines"
OC7: **Rafael Gozalbes**, Centro de Investigación Príncipe Felipe
"Development and validation of QSAR-based ADME models for drug-like compounds"

TUESDAY, SEPTEMBER 20TH, 2011

MORNING SESSION **(Chairs: Javier Rojo/Silvia Ortega)**

09:00 IS7: **Félix Calderón**, GSK
"Open innovation in malaria: breaking the ice with Tres Cantos Antimalarial Set (TCAMS)"

09:30 IS8: **Paul Finn**, InhibOx Ltd
"The future of computer-aided drug design"

10:00 IS9: **Juan Granja**, Universidad de Santiago de Compostela
"Peptide nanotubes, a supramolecular approach for membrane targeting drugs"

10:30 Coffee Break

11:00 IS10: **Juan Miguel Jiménez**, Vertex Pharmaceuticals
"Discovery of orally active GSK-3 inhibitors for the treatment of neurodegenerative diseases"

11:30 Oral Communications (OC8-OC9)
OC8: **Mónica Sancho**, Centro de Investigación Príncipe Felipe
"Minocycline inhibits cell death and decreases mutant Huntingtin aggregation by targeting Apaf-1"
OC9: **María Jesús Pérez-Pérez**, IQM-CSIC
"Multivalent compounds based on 1,3,5-triazines targetting gp120: Anti-HIV evaluation and binding analysis with Surface Plasmon Resonance"

12:00 SEQT Meeting

13:00 Lunch

AFTERNOON SESSION **(Chair: Rodrigo J. Carbajo)**

15:00 Poster Session and Coffee

16:00 Oral Communications (OC10-OC14)
OC10: **Silvia Ortega-Gutiérrez**, Universidad Complutense de Madrid
"Development of a chemical toolset for the study of the endogenous cannabinoid system"
OC11: **Rafael Peláez**, Universidad de Salamanca
"Conformationally restricted macrocyclic analogues of combrestatins"
OC12: **Renato Márcio Ribeiro-Viana**, IIQ-CSIC
"Glyconanoparticles: Virus-like particle construction and anti-viral activity"
OC13: **Hugo Gutiérrez-de-Terán**, FPGMX
"Structure-based ligand design on adenosine receptors"
OC14: **Pilar Serra**, Universidad San Pablo CEU
"Molecular modeling studies for the design of new selective MMP2 inhibitors"

21:00 Gala Dinner

WEDNESDAY, SEPTEMBER 21ST, 2011

MORNING SESSION (Chair: María José Camarasa)

10:00 Round Table
"The new paradigm in the academy-industry collaborations"

11:00 Coffee Break

11:30 IS11: **Martin Drysdale**, The Beatson Institute for Cancer Research
"Fragment-based approaches to cancer drug discovery"

12:00 IS12: **Marc Marti-Renom**, Centro de Investigación Príncipe Felipe
"Comparative docking for predicting molecular targets of known drugs. A "kernel" for the tropical disease initiative"

12:30 Concluding Remarks

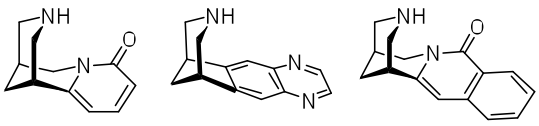
13:00 Lunch

Invited Speaker´s Abstracts

Timothy C. Gallagher

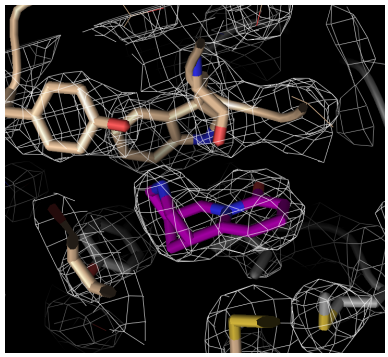
Natural products as lead to nicotinic agonists. Exploring the chemistry of cytisine

Cytisine **1**, a lupin alkaloid isolated from laburnum, occupies a pivotal role in nicotinic pharmacology as a partial agonist at the α4β2 subtype of neuronal nicotinic acetylcholine receptor.[1] More recently and because of this partial agonist profile, cytisine provided the discovery lead for varenicline **2**, Pfizer's smoking cessation agent which was launched in 2006.[2]



Cytisine **1** Varenicline **2** **3**

Our interest in this area lies in understanding the molecular basis of this partial agonist profile, and we have pursued a synthetic programme that has targeted specific structural variations aimed at answering this question. Substitution at certain parts of the cytisine scaffold is readily achieved, but synthesis also offers opportunities for variation within other regions of the heterocyclic scaffold and, critically, access to more fundamentally, core-modified cytisine congeners. Target selection has been guided by protein structure studies based on cytisine-acetylcholine binding protein (AChBP) complex (see figure[3]) which defined conserved ("aromatic box") and variable regions within the receptor. We have explored synthetic chemistry that provides quite new ligand variants, such as the cytisine-varenicline hybrid **3**, and the chemistry (major focus) and associated pharmacology will be presented, together with related methodology and mechanistic results.[4,5]



Acknowledgements: We thank EPSRC and the Rotary Foundation for financial support.

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Rosario González-Muñiz

Looking for innovative bioactive compounds: underexplored approaches, creative synthesis

At present there is an innovation gap in pharmaceutical drug discovery, with a decrease in the new molecular entities (NMEs) approved while funds poured into R&D consistently increased year by year. In this scenario, research groups from academia and public research centers can contribute, through their creativity and high flexibility, to the generation of ground-breaking knowledge that enable its translation into innovative products. The discovery and validation of new biological targets, the search for alternative mechanisms within already known targets, and the development of computational and synthetic methods leading to original molecular entities are among the affordable tasks.

To illustrate some of these possibilities, one of our approaches is focused in the search of inhibitors of the protein-protein interactions (PPI) involved in the molecular recognition between the Vascular Endothelial Growth Factor (VEGF) and its receptors, as an unconventional strategy to antiangiogenic agents. Starting from $VEGF_{17\text{-}25}$ and $Vammin_{1\text{-}13}$ fragments, a series of peptide analogues were designed to preserve the α–helix structure of this segment as in the corresponding native proteins, while keeping intact most of the amino acid residues identified as important for VEGFR recognition. The results obtained with these peptide derivatives could open a new line of research directed toward non-peptide small molecules, as an alternative to the existing antiangiogenic strategies.

In recent years, another main contribution from our group has been related to the generation of diverse heterocyclic chiral scaffolds from amino acid derivatives. Since molecular diversity is important for "hit" finding within chemical genetics and drug discovery programs, the development of diversity oriented synthetic approaches, aimed at synthesizing collections of compounds with high level of structural diversity (different molecular scaffolds, stereochemistries, and functional groups), is still a challenge to synthetic chemists. Within this context, we have been working in exploring the versatility of simple highly functionalized amino acid β-ketoesters for the generation of small libraries of innovative compounds. When tested for the modulation of TRP ion channels, some components of one of these libraries displayed potent and selective TRPV1 antagonist activity.

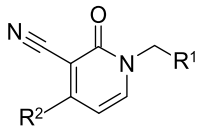
Acknowledgements: Supported by MICINN grants, Consolider-Ingenio 2010 (CSD2008-00005) and SAF2009-09323.

Andrés Trabanco

Discovery of a potent and orally bioavailable positive allosteric modulator of mGluR2 for the treatment of CNS disorders

Over recent years, there has been increasing interest in trying to identify mGluR2 PAMs which bind at a different site than glutamate, the orthosteric endogenous agonist.[1,2] This approach may offer several advantages, such as increasing mGluR2 signaling with greater selectivity compared to agonists, maintaining activity without inducing over-activation or desensitization based on continued transient and dynamic release of glutamate. Another potential benefit of this approach is the likelihood of identifying highly brain penetrant compounds, which has been a significant challenge for approaches based on orthosteric glutamate analogues.

Recent reports from our laboratories described series of imidazopyridones,[3] isoquinolones[4] and 1,5-disubstituted pyridones,[5] as mGluR2 PAMs. In this report the discovery of 1,4-disubstituted-3-cyanopyridones **1** as a new series of mGluR2 PAMs is presented. Initial SAR exploration is given along with more extensive characterization of some of the best compounds identified within the series.



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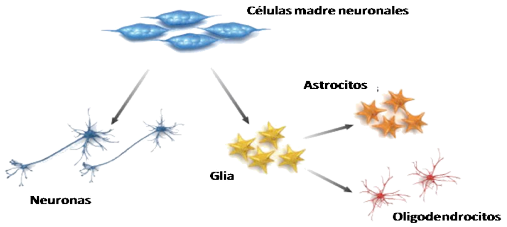
Design, synthesis, enzymatic and cellular evaluation of novel neurogenic ATP-non competitive GSK-3 inhibitors

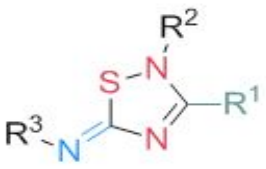
Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, or Amyotrophic Lateral Sclerosis (ALS), are characterized by a loss of neurons in particular regions of the nervous system. It is believed that this nerve cell loss underlies the subsequent decline in cognitive or motor function that patients experience in the nervous system. The discovery of the neurogenesis raises the possibility that the nervous system has an intrinsic capacity to repair itself. Even more important, evidence is now mounting that stimulating neurogenesis by various means can bring about functional recovery in animal models of neurodegenerative diseases.[1]

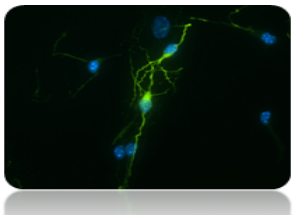
GSK-3 is a known target on the treatment of neurodegenerative processes. [2] The ATP-non competitive GSK-3 inhibitors have shown their potential and selectivity for this enzyme, since they are specific among different kinases.

Here we describe the design, synthesis and evaluation of novel ATP-non competitive GSK-3 inhibitors. We have synthesized 30 compounds, and some of them have also been studied in neurogenic and neuroprotection experiments. It can be seen from the results that these compounds have the ability to differentiate neural stem cells to adult neurons, and moreover, to protect primary cultures of astrocytes, microglia and neurons from the inflammation produced by LPS. Moreover, additional pharmacokinetic properties have been measured as well as their safety and tolerability. Finally, an experiment in a mouse model of spinal cord injury shows the neuroprotective effects of this family of compounds *in vivo*.

These properties make them very interesting compounds with a novel pharmacological property, and convert them into new prototypes as neurogenic drugs for the treatment of neurodegenerative diseases.







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Stephan A. Sieber

Natural products and their biological targets

After decades of successful treatment of bacterial infections with antibiotics, formerly treatable bacteria have developed drug resistance and consequently pose a major threat to public health. Since many antibiotics in clinical development and application still target only a limited set of cellular functions such as cell wall, DNA and protein synthesis, it is a desirable goal to expand the number and breadth of therapeutic targets combined with a deeper knowledge about their mechanism. To address this goal, we applied a chemical proteomic strategy termed activity-based protein profiling (ABPP)[1,2] that is designed to globally profile enzyme activities in complex proteomes. To identify novel targets for the treatment of multidrug resistant *S. aureus* (MRSA) strains, we utilized small natural product derived biomimetic β-lactone[3,4], β-lactam[5], showdomycin[6] and cinnamic aldehyde[7] molecules which were modified with a small tag for the visualization and identification of dedicated targets in complex proteomes by SDS-gel-electrophoresis and mass spectrometry (Figure 1). Structural variations in side chains of selected molecules led to an increased affinity for certain enzymes that played crucial roles in resistance and virulence.[8,9] The general utility of this approach was demonstrated by the chemical inhibition of a central *S. aureus* virulence regulator that resulted in a drastically decreased expression of major virulence factors which are key players in e.g. sepsis, tissue necrosis, inflammation and toxic shock.[10] Since this virulence regulator is highly conserved in many pathogens, our strategy could represent a global approach for the treatment of infectious diseases by disarming the bacterial virulence repertoire. Disarmed pathogens could then be easily eliminated by the human immune response. A drug based on this concept displays many advantages over conventional antibiotics, such as preserving the useful, cooperating microorganisms e.g. in the digestive tract, and exerting less selective pressure on pathogens, which may result in decreased resistance development.

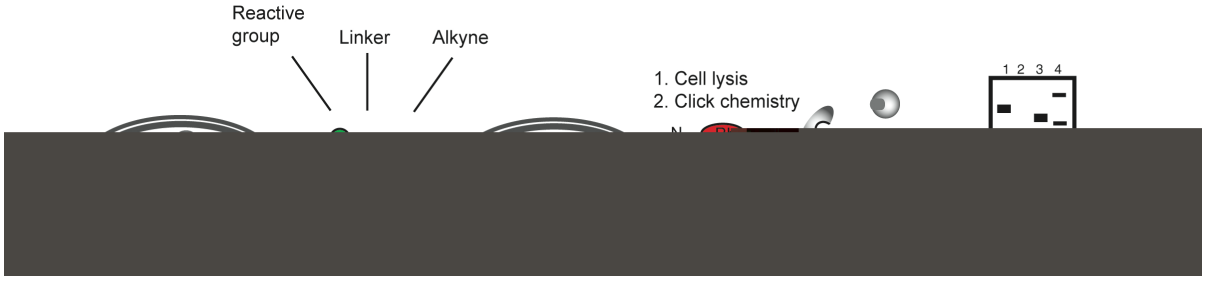

Figure 1: Identification of cellular targets of small molecules.

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Jesús Martínez

Gold nanoparticles for gene therapy and photo-thermal ablation

The use of inorganic nanoparticles as drug release systems and as molecular markers is nowadays gaining power[1]. One of the most used nanoparticles for biomedical applications is the gold nanoparticles (AuNPs)[2]. Our research group has been working in two different strategies for the use of AuNPs in therapy:

-) **Gene Therapy**: Small interfering RNAs (siRNA)[3] show significant potential in new molecular approaches to down-regulate specific gene expression in cancerous or viral-infected cells. However, there are still significant obstacles to be overcome such us its extremely short half-lives and its degradation by RNases. To overcome some of these challenges, we have developed multifunctional gold nanoparticles loaded with fluorescent dyes, cell penetrating peptides and siRNA complementary to the proto-oncogene myc. This biofunctionalization has allowed the interaction between NPs and biological systems, ranging from in vitro cultured human cells to in vivo animal models (primitive Hydra and complex vertebrate mouse). This new nanoplatform constitutes a very efficient siRNA carrying system.

-) **Photo-thermal Ablation**: Physical properties of gold nanoparticles are mediated by their size, shape and structure (solid or hollow).[4] A very interesting property, in the point of view of biotechnological applications, of asymmetric gold NPs is their LSPR band. This band is located in the near infrared radiation (NIR),[5] in the called "biological window". In principle, gold NPs irradiated with an intense light source (laser) in the same wavelength of the NPs absorption, will mainly transform this absorbed energy in heat. Here we describe a simple and straightforward synthesis route to produce gold triangular nanoprisms that we have called NanoNachos (NNs) due to the characteristic shape they present. The LSPR of NNs can be tuned along the NIR range. In contrast to most of the previously reported methods to produce Au nanoprisms in high yield, toxic polymers are not required in our method. The feasibility of NNs as transducers for photothermal therapy is proven at the single cell level. Besides the simplicity of the synthesis method, makes NNs very interesting probes for applications in nanomedicine.

Acknowledgements: This work has been funded by ERC-NANOPUZZLE, ERANET-NANOTRUCK projects and ARAID

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Antonio Ferrer-Montiel

TRPducins: a novel paradigm to modulate ion channel activity

The transient receptor potential vanilloid 1 (TRPV1) channel is a thermosensory receptor implicated in diverse physiological and pathological processes. The TRP domain, a highly conserved region in the C-terminus adjacent to the internal channel gate, is critical for subunit tetramerization and channel gating. We found that peptides patterned after this protein domain block TRPV1 activity by binding to the intracellular side of the receptor and, presumably, interfering with protein-protein interactions at the level of the TRP domain that are essential for the conformational change that leads to gate opening. Palmitoylation of active peptides reveals that they are moderate and selective TRPV1 antagonists both *in vitro* and *in vivo*, blocking receptor activity in intact rat primary sensory neurons and their peripheral axons. The most potent lipidated peptide, TRP-p5, blocked all modes of TRPV1 gating with micromolar efficacy ($IC_{50} \leq 10$ μM), without significantly affecting other thermoTRP channels. In contrast, its retrosequence or the corresponding sequences of other thermoTRP channels did not alter TRPV1 channel activity ($IC_{50} > 100$ μM). TRP-p5 display anit-hyperalgesic and anti-prurito activity in a model of chronic hepatic failure. Therefore, these palmitoylated peptides, that we coined TRPducins, are non-competitive, voltage-independent, sequence-specific TRPV1 blockers with in vivo activity. Our findings indicate that TRPducin-like peptides may embody a novel molecular strategy that can be exploited to generate a selective pharmacological arsenal for the TRP superfamily of ion channels, as well as other channel families.

Acknowledgements: Funded by MICINN, CONSOLIDER-INGENIO, GVA-PROMETEO, and Diverdrugs.

-Valente, P, Fernández-Carvajal A, Camprubí-Robles M, Gomis A, Fernandez-Ballester G, Viana F, Gonzalez Ros JM, Belmonte C, Planells-Cases, R, **Ferrer-Montiel A**. Membrane-tethered peptides patterned after the TRP domain (TRPducins) selectively inhibit TRPV1 channel activity. **FASEB J.** 25, 1628-1640. 2011.

Félix Calderón

Open innovation in malaria: breaking the ice with Tres Cantos Antimalarial Set (TCAMS)

Malaria is a major global disease caused by parasites of the genus *Plasmodium* which are transmitted to people when infected female anopheles mosquitoes feed on human blood. In 2009, more than 200 million of cases of malaria were reported [1] causing nearly one million deaths mostly amongst pregnant women and young children. In regions where malaria is endemic, the humanitarian and economic burdens are considerable and in 2007 the Bill and Melinda Gates foundation, supported by other global health agencies, initiated an agenda that the ultimate aim of which is the eradication of malaria.

Where should the search for leads for new antimalarial drugs start? in 2010, we at GlaxoSmithKline (GSK) published the Tres Cantos Antimalarial Set (TCAMS). 13,533 compounds which are the result of screening nearly 2 million compounds from the GSK corporate collection (http://www.ebi.ac.uk/chemblntd).[2]

Being able to select a high quality series for lead optimization from over 13,000 potential starting points presents to the medicinal chemist community with both an unprecedented opportunity but also a challenge. A clear strategy is required to rapidly identify those molecules which have both the best chance of being converted into differentiated antimalarial drugs and which are also likely to have the lowest risk of attrition in development. So,

How to break the ice with the TCAMS?

The talk will disclose our open-innovation strategy in drug discovery programs in diseases of the developing world focusing on updating our recent progress in exploiting the TCAMS.[3]

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3. (a) An Invitation to Open Innovation in Malaria Drug Discovery: 47 Quality Starting Points From the (TCAMS). *Submitted*. (b) The First Report of Exploration of Leads from the Tres Cantos Anti-Malarial Set (TCAMS): Cyclopropyl Carboxamides with Good Oral Bioavailability in CD-1 Mice and with Efficacy in a *Plasmodium falciparum* Murine Model. *Submitted*.

Paul Finn

The future of computer-aided drug design

With its origins in statistical QSAR methods developed in the 1960s, computer-aided drug design (CADD) has developed into one of the standard tools used in drug discovery in both industrial and academic settings. During these last decades, the scope of computational methods has grown enormously, to include a vast range of approaches including machine learning, pharmacophore elucidation, ligand-based and target-based virtual screening methods, to name but a few. In parallel, there has been an explosion in our knowledge of protein structure from experimental methods (mostly X-ray crystallography) to which computer-aided drug design methods can be applied. There are now many examples of the clear contribution that CADD has made in advancing a diverse range of drug discovery projects.

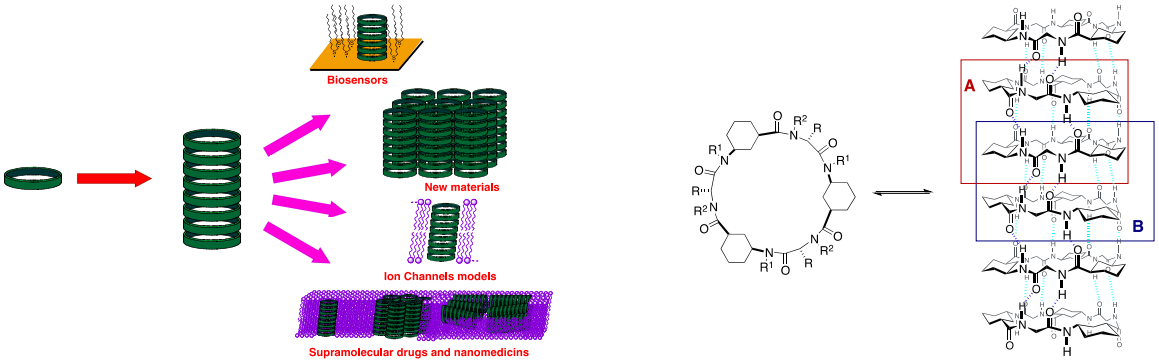
Despite this progress much remains to be done and there are currently many exciting developments in this field. In this presentation we will start with a brief summary of the current status of CADD. This will be followed by reviewing how the latest advances in software, hardware and the internet are combining to open up new possibilities that will, for example, enable medicinal chemists to explore vast chemistry spaces much more efficiently and effectively, using search techniques that capture the shape and properties of compounds rather than their chemical constitution. In the final section, some of the key challenges for the future will be discussed.

Juan Granja

Peptide nanotubes, a supramolecular approach for membrane targeting drugs

Peptide nanotubes are a new class of biomaterials-based supramolecular assemblies formed by stacking of cyclic peptide in a flat conformation.[1] The cyclic peptides are specially designed to adopt the flat conformation with all the backbone amide groups (carbonyl and N-H) lying perpendicular to the plain of the ring. In this conformation all the side-chains are outwards projected modifying the surface characteristics of the tubular ensemble. Among other applications, specially designed peptides subunits effectively interact with the lipid bilayers forming channels and other structures, destroying their ionic balance.[2]

In the last few years we have been working with cyclic peptides that contain cyclic gamma-amino acids that self-assemble into nanotubes under appropriated conditions.[3] These cyclic peptides allow the modification of the outer surface and also their inner cavity. In this communication we will describe our studies toward the design of membrane interacting nanotubes.



Acknowledgements: This work was supported by the Spanish Ministry of Education and Science and the ERDF [(CTQ2010-015725, and Consolider Ingenio 2010 (CSD2007-00006)], by the Xunta de Galicia (PGIDIT08CSA047209PR and GRC2006/132), and European project Magnifyco (NMP4-SL-2009-228622).

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Juan Miguel Jiménez

Discovery of orally active GSK-3 inhibitors for the treatment of neurodegenerative diseases

Deregulation of GSK-3 is associated with a number of major human pathologies including type II diabetes and neurodegenerative diseases. Therefore this kinase is considered to be an attractive target for intervention. However, the central role-played by GSK-3 in regulating basic developmental processes has raised concerns about long-term inhibition that could lead to excessive cell proliferation and the activation of oncogenic substrates like β-catenin.

This presentation will outline the discovery, using structure based drug design, of potent and selective GSK-3 inhibitors that only modulate a subset of the enzyme's effects with favorable consequences for safety. These compounds preferentially inhibit GSK-3 tyrosine autophosphorylation (pTYR) over GSK-3 Ser/Thr kinase activity against substrates such as β-catenin. The inhibition of GSK-3 p-Tyr results in partial inhibition of enzymatic activity (~90%) resulting in selective downstream effects.

Using E16 hippocampal neurons cultured in vitro, we demonstrate that inhibition of GSK-3 at levels that selectively affect TYR residue autophosphorylation, results in increased branching of both axons and dendrites. These findings suggest that such inhibitors may provide benefit in neuroregeneration following injury.

Having demonstrated that partial inhibition of GSK-3 at p-TYR concentrations correlates with mechanisms that are beneficial to neurorepair, we examine the effects of our inhibitors in an MCAO model of stroke. The compounds were dosed orally 24 hours post-stroke injury and was continued for 14 days thereafter. Significant reversal of behavioral deficits is achieved at doses where selective inhibition of pTYR over β-catenin is observed. The in vivo effects correlate with induction of neurotrophic factor BDNF, increased neural stem cell proliferation in the SVZ (BrdU), and enhanced angiogenesis (vWF) in the penumbra ipsilateral to the infarct.

Martin Drysdale

Fragment-based approaches to cancer drug discovery

The use of weak binding "fragments" of molecules is now recognised as an efficient and robust method of hit identification in the drug discovery process. The use and integration of fragment hits into successful lead optimisation is the critical determinant of whether this technology will become accepted as a significant tool in drug discovery. A number of compounds which have evolved using fragment based hit identification are now in phase I-III clinical trials suggesting that this is a technology which will find a permanent place in the armoury of the Drug Discovery Scientist.

At the newly established Drug Discovery Programme at the Beatson Institute for Cancer Research we are exploiting the basic biology strengths within the Beatson Institute and wider Cancer Research UK network, to investigate some of the most exciting and challenging cancer targets. Central to our strategy is Fragment-Based Drug Discovery methods and we will use NMR and Surface Plasmon Resonance as primary tools for fragment-based hit identification. I will discuss some results around our initial forays into some of these areas.

Marc Marti-Renom

Comparative docking for predicting molecular targets of known drugs. A "kernel" for the tropical disease initiative

Conventional patent-based drug development incentives work badly for the developing world, where commercial markets are usually small to non-existent. For this reason, the past decade has seen extensive experimentation with alternative R&D institutions ranging from private-public partnerships to development prizes. Despite extensive discussion, however, one of the most promising avenues - open source drug discovery - has remained elusive. We argue that the stumbling block has been the absence of a critical mass of preexisting work that volunteers can improve through a series of granular contributions. Historically, open source software collaborations have almost never succeeded without such "kernels".

We used a computational pipeline for: (i) comparative structure modeling of target proteins, (ii) predicting the localization of ligand binding sites on their surfaces, and (iii) assessing the similarity of the predicted ligands to known drugs. Our kernel currently contains 143 and 297 protein targets from ten pathogen genomes that are predicted to bind a known drug or a molecule similar to a known drug, respectively. The kernel provides a source of potential drug targets and drug candidates around which an online open source community can nucleate. Using NMR spectroscopy, we have experimentally tested our predictions for two of these targets, confirming one and invalidating the other.

The Tropical Disease Initiative kernel, which is being offered under the Creative Commons attribution share-alike license for free and unrestricted use, can be accessed on the World Wide Web at http://www.tropicaldisease.org. We hope that the kernel will facilitate collaborative efforts towards the discovery of new drugs against parasites that cause tropical diseases.

Oral Communications

Jordi Quintana

The Chembiobank and EU-OPENSCREEN initiatives in Chemical Biology: Current status and case studies

The Chembiobank initiative in Spain (CBB, http://www.pcb.ub.cat/chembiobank/) has built a chemico-biological library and annotated database, which will be described. The library contains nearly 15.000 compounds both from commercial and from academic origins. The annotated database has been developed to ensure proper registration and searching of chemical structures, analytical chemistry data, logistics / compound management information, and virtual screening and experimental screening data associated with the Chembiobank library compounds.

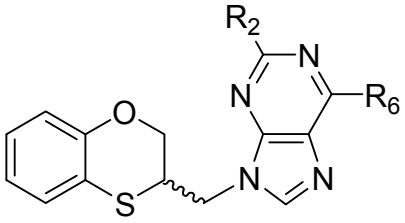
Three case studies describing the Chembiobank workflow, structure and applications will be shown: a) how to profile compounds of academic origin towards targets of therapeutic interest; b) how to find new possible therapeutic applications for commercially available compounds (reprofiling); and c) how may the Chembiobank workflow help the medicinal chemistry community.

This Chembiobank initiative is coordinated with other Chemical Biology initiatives being developed in several European countries, in the ESFRI-funded European Research Infrastructure on Open Screening Platfoms, the EU-OPENSCREEN initiative (www.eu-openscreen.eu). This project is currently in its Preparatory Phase and its status and future implications and benefits for the medicinal chemistry community in Europe will be described.

Joaquín Campos

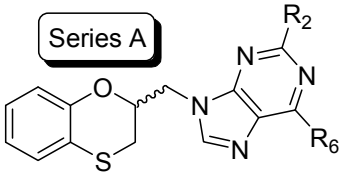
Increased phosphorylation of the translation initiation factor eIF2α is associated with G_2/M cell-cycle arrest and apoptosis in breast cancer cells

The use of cancer treatment is still very limited because of the difficulty of the development and discover of novel agents that selectively kill tumour cells or inhibit their proliferation without general toxicity. We propose the preparation and study of the anticancer activity of isomers of **1**, **2**, and **3**.[1]

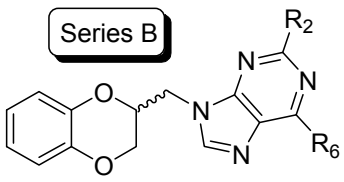


1 R_2 = H, R_6 = Cl
2 R_2 = H; R_6 = Br
3 R_2 = R_6 = Cl

Series A and B are bioisosteric series in which sulfur is replaced by oxygen. In general, (*RS*)-9-(2,3-dihydro-1,4-benzoxathiin-2-ylmethyl)-9*H*-purines **4-7** (series A) show a better activity than their isosteres (*RS*)-9-(2,3-dihydro-1,4-benzodioxin-2- ylmethyl)-9*H*-purines **8-11** (series B).



4 R_1 = H; R_2 = Cl
5 R_1 = H; R_2 = Br
6 R_1 = R_2 = Cl
7 R_1 = H; R_2 = NH_2



8 R_1 = H; R_2 = Cl
9 R_1 = H; R_2 = Br
10 R_1 = R_2 = Cl
11 R_1 = H; R_2 = NH_2

Moreover compounds **4-6** with the purine moiety linked to the position 2 of the six- membered ring are more potent than compounds **1**, **2** and **3**, in which such a link is established at position 3. The most active compound (**6**), with two chlorine atoms at positions 2 and 6 of the purine ring, shows an IC50 = 2.75 ± 0.02 μM against the MCF-7 human breast cancer cell line.[2] In general, compounds with electron- withdrawing substituents on the purine ring (**4-6** and **8-10**) present better activity than compounds substituted with an amino group (**7** and **11**).
The induction of the G2/M cell-cycle arrest and apoptosis by the three most active compounds is associated with increased phosphorylation of eIF2α in human breast cancer cells.[3]

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Inmaculada Conejos

Polymer-drug conjugates for the treatment of Familial Amyloidotic Polyneuropathy (FAP)

Polymer Therapeutics are well-known as effective drug delivery systems with demonstrated clinical benefits since the 90's.1 In particular polymer conjugates are considered new chemical entities capable to improve bioactive compound properties and decreasing their inherent limitations. Currently, a second generation of conjugates focused on improved structures, combination therapy or new molecular targets are needed to move this platform technology further.2 Following these concepts, novel specific nanoconjugates for the treatment of neuropathological disorders are proposed in this study.

Familial Amyloidotic Polyneuropathy (FAP) is a neurodegenerative disorder characterised by systemic extracellular deposition of a mutated protein called transthyretin (TTR) as amyloid fibrils in several organs, mainly in the peripheral nervous system. This disease is characterised by an ascending sensorimotor polyneuropathy and progressive dysautonomia, becoming usually fatal 10 to 15 years after its onset. TTR has been proposed to trigger neurodegeneration through engagement of the Receptor for Advanced Glycation End products (RAGE). Prof. Saraiva et al. have discovered a specific peptidic sequence (named RAGE peptide) able to suppress TTR aggregate-induced cytotoxicity in cell culture3 by means of TTRagg-peptide interaction, which impedes protein recognition by the receptor. This interaction is conserved across mouse and human species. Based on this finding, avoidance of TTR-aggregates cytotoxicity is a promising target for therapeutic propose in FAP treatment.

Due to the well-known limitation of specific peptide delivery *in vivo*, mainly due to a low stability and possible immunogenecity. Here we report, the PEGylation of RAGE peptide through two different types of linkage: peptidic and disulphide bond. Conjugates were biophysically characterised, also looking at conformation in solution, and its activity as TTR cytotoxicity inhibitors was studied. The results obtained allowed us to confirm that after the correct linker and conjugate conformational design, PEGylation of RAGE peptide can retain drug activity *in vitro*. A decrease in toxicity, immunogenicity and an enhancenment of peptide stability in blood is expected after PEGylation. This would offer the possibility to develop, for the first time, efficient macromolecular FAP inhibitors for clinical applications.

Acknowledgements: The authors would like to thank the Spanish Ministry of Science and Innovation (MICINN) (CTQ2007-60601, CTQ2010-18195, FPU grant (ref. AP2007-01665)), CIPF (Valencia, Spain) and Fundação para Ciencia e Tecnologia (FCT), Portugal.

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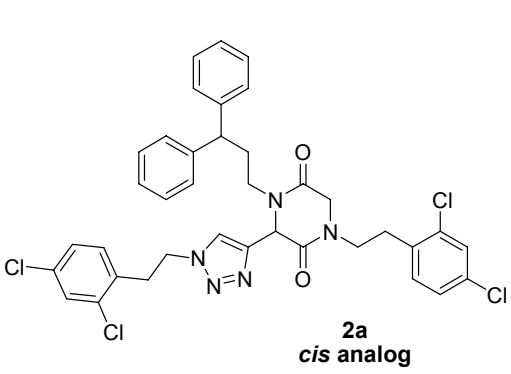
Miriam Corredor

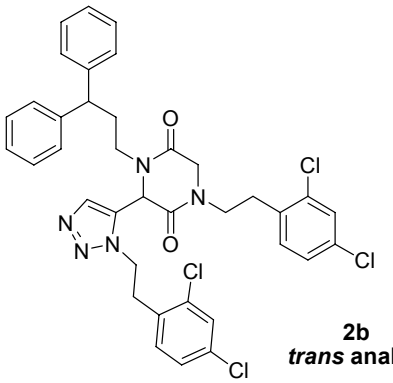
Chemical modulation of cellular signalling routes relevant to the control of apoptosis

Apoptosis is a biological process relevant to human disease stated that is regulated through protein-protein complex formation. The apoptosome is a multiprotein complex that is of interest for the development of apoptotic modulators.[1] We have previously reported a peptidomimetic compound bearing a 3-substituted-piperazine-2,5-dione moiety as potent apoptotic modulator.[2]

Structural studies of this compound have shown the presence of *cis/trans* isomers of the exocyclic tertiary amide bond in slow exchange, which should be of high relevance for off-target interaction in front of the biological target.[3] This information encouraged us to mimic those isomers through an isosteric replacement of the amide bond by a 1,2,3-triazole moiety (1,4- and 1,5-disubstituted triazole to mimic the *cis* and *trans* isomers, respectively).



2a
***cis* analog**



2b
***trans* analog**

The syntheses of these restricted analogs were carried out using the Ugi multicomponent reaction[4] followed by an intramolecular cyclization. The full NMR analysis (including ^{1}H-^{15}N correlations at natural abundance) of these compounds has led us to the unambiguous characterization of the corresponding substitution patterns. Finally, the results on the inhibitory activity of these compounds have provided highly useful information for improving the inhibition of apoptosome.

We acknowledge the financial support from MICINN (Grans SAF 2008-00048 and BIO2007-60066), the fellowship to M.C. from CSIC JAE program and Esteve S.A. for the SEQT award.

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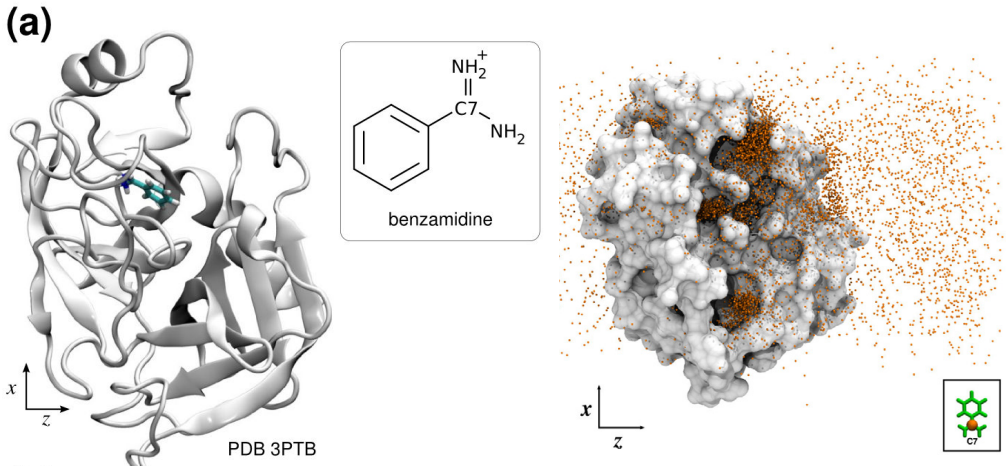
Gianni de Fabritiis

Reconstructing an enzyme-inhibitor binding process by molecular dynamics simulations

The understanding of protein-ligand binding is of critical importance for biomedical research, yet the process itself has been very difficult to study due to its intrinsically dynamic character. In this talk, we will go through the quantitatively reconstruct the complete binding process of the enzyme-inhibitor complex trypsin-benzamidine by performing 495 molecular dynamics simulations of free ligand binding of 100 ns each, 187 of which produced binding events with an rmsd less than 2 Å compared to the crystal structure[1].The binding events obtained are able to capture the kinetic pathway of the inhibitor diffusing from solvent to bound passing for few metastable intermediate states. Unexpectedly, rather than directly entering the binding pocket, the inhibitor appears to roll on the surface of the protein to the final binding pocket. The trajectories are analysed via a Markov state model-based analysis which additionally yields the kinetic parameters and binding affinity of the interaction. These results show an impressive predictive power for unconventional high- throughput molecular simulations. At the same time, the general methodology is easily applicable to other molecular systems becoming of interest to biomedical and pharmaceutical research.



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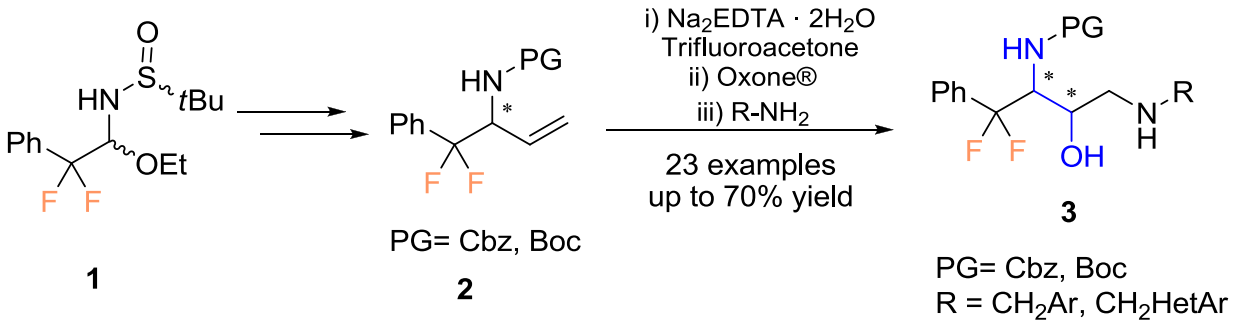
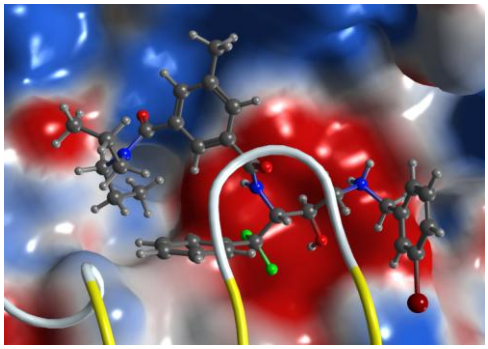
Óscar Delgado

Design, synthesis and biological evaluation of novel fluorinated ethanolamines

The preparation of novel fluorinated allylamines (2) and their use as key fragments for the stereoselective synthesis of hydroxyethyl secondary amine (HEA) type peptidomimetics[1] is described. Our strategy employs chiral fluorinated sulfinyl imines as synthetic intermediates, by reaction of hemiaminal precursors (1) with two equivalents of vinylmagnesium bromide. The subsequent oxidation of the allylic amines to the corresponding epoxides and their ring-opening with a range of nitrogen nucleophiles provided a library substituted hydroxyethylamines (3) holding a phenyldifluoro moiety.



The biological evaluation of these derivatives revealed compounds with remarkable BACE1 inhibitory activity. Docking studies showed the influence of the fluorine atoms in the binding mode of the synthesized ligands. Furthermore, compounds with antimicrobial activity against Mycobacterium and Nocardia species were found among our synthetic intermediates.



Acknowledgements: The authors thank the Ministerio de Educación y Ciencia (CTQ2007-61462/BQU, FPU Programme) and Generalitat Valenciana (GVPRE/2008/382 and S. Grisolía Programme) for financial support.

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Rafael Gozalbes

Development and validation of QSAR-based ADME models for drug-like compounds

ADME properties play a very important role in drug screening. Generally, they are evaluated at the early stages of drug discovery, especially in the case of screening campaigns based on biophysical techniques with low sensitivity (e.g., NMR). In this context, we have developed QSAR models for predicting water solubility and permeability of drug-like compounds.

For the solubility model, a set of relevant parameters for establishing a drug-like chemical space was defined. The comparison of chemical structures from the FDAMDD[1] and PHYSPROP[2] databases allowed the selection of properties that were more efficient in discriminating drug-like compounds from other chemicals. These filters were applied to the PHYSPROP database and 1,174 chemicals with known solubility data were retained. Several QSAR models were developed from this set of compounds, and the best one was further validated with a set of 102 drugs with reported experimental solubility data[3].

Another QSAR model was developed for predicting intestinal drug permeability. The set of relevant properties for establishing a drug-like chemical space was applied to a database of compounds with Caco-2 permeability values obtained from previous studies. Several QSAR regression models were then developed from this set of drug-like structures. The best model was selected based on the accuracy of correct classifications obtained for training and validation subsets previously defined, including 17 structures from the FDA Biopharmaceutics Classification System (BCS). Further validation of the model was performed by applying it to 21 drugs for which we determined experimental Caco-2 values[4]. In both cases (solubility and permeability) a good agreement between predictions and experimental values confirmed the reliability of the equations. Also, since the models were developed with very simple easy-to-calculate descriptors, they are of general applicability to large collections of *in silico* chemicals.

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Mónica Sancho

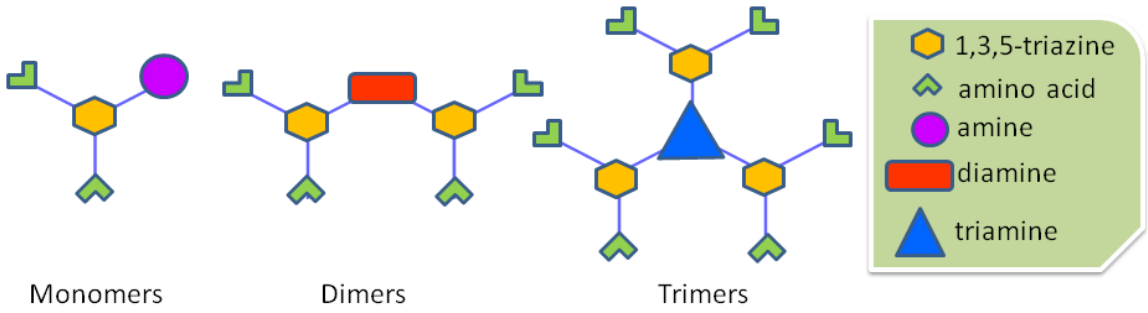
Minocycline inhibits cell death and decreases mutant Huntingtin aggregation by targeting Apaf-1

Minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is a second-generation tetracycline that can cross the blood-brain barrier and has anti-inflammatory and neuroprotective effects. The potential of minocycline as a drug for treating Huntington's disease (HD) has been studied however, the molecular mechanism underlying the neuroprotective properties of minocycline remains elusive. In this study, we tested the hypothesis that a principal cellular target of minocycline is Apaf-1, a key protein in the formation of the apoptosome, a multiprotein complex involved in caspase activation. Minocycline binds to Apaf-1, as shown by nuclear magnetic resonance spectroscopy, and inhibits apoptosome activity *in vitro* and in *ex vivo* models. As a consequence minocycline-treated cells as well as Apaf-1 knock-out cells are resistant to the development of mutant huntingtin-dependent protein aggregation.

María Jesús Pérez-Pérez

Multivalent compounds based on 1,3,5-triazines targetting gp120: Anti-HIV evaluation and binding analysis with Surface Plasmon Resonance

Interaction with the HIV viral envelope glycoprotein 120 (gp120) is an attractive approach in the search for novel anti-HIV agents, including their potential use as microbicides. Inspired by the interesting inhibitory properties that lectins show against HIV-replication through their interaction with gp120,[1] we here describe the design, synthesis and anti-HIV evaluation of three series of 1,3,5-triazine derivatives (monomers, dimers and trimers) functionalized with aromatic amino acids meant to mimic interactions that lectins establish with gp120. Interestingly monomers were inactive against HIV replication, dimers showed a limited anti–HIV effect while the trimers showed a more significant antiviral activity with EC50 values in the lower μM range.[2] These findings most likely reflect the requirement of multivalency of the 1,3,5-triazine derivatives to display anti-HIV activity, mimicking lectins. Moreover, Surface Plasmon Resonance (SPR) experiments revealed that the prototype trimers were efficient binders of CXCR4- and CCR5-tropic HIV-1 gp120 (estimated KD: lower micromolar range). Our findings support the interest of this novel family of anti-HIV agents and qualify them as potential novel microbicide lead compounds.



Acknowledgements: V. L. thanks the FSE and the JAE-Predoc programme for a predoctoral fellowship. This work has been supported by a grant of the Spanish CICYT (SAF2009-13914-C02-01), the CSIC-Intramural Programme (PIF08-022) and the K.U.Leuven (PF 10/018).

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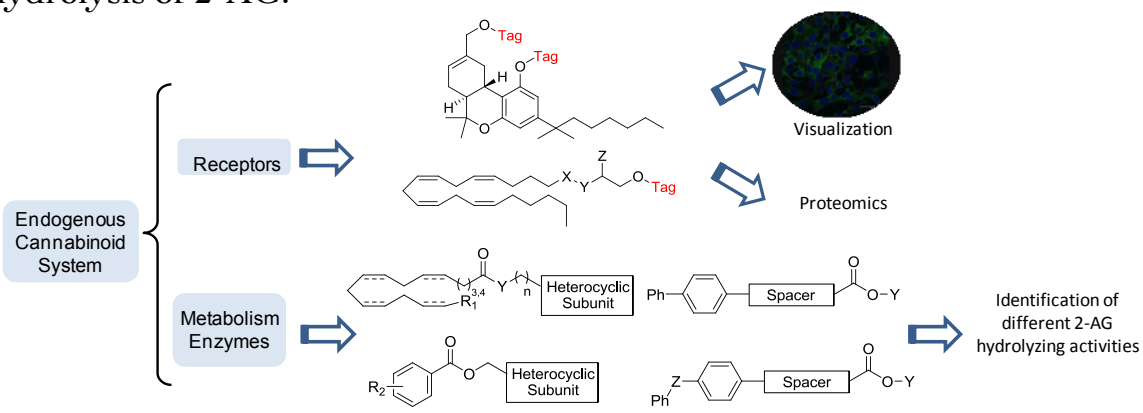
Silvia Ortega-Gutiérrez

Development of a chemical toolset for the study of the endogenous cannabinoid system

The endogenous cannabinoid system (ECS) has emerged as a promising system for the development of new drugs. Nonetheless, many basic questions remain unanswered. For example, endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2- AG) regulate cell functions independently of CB1 and CB2, fact that has led to hypothesize about the existence of other cannabinoid receptors (CBRs).[1] In addition, the inactivation pathways of both endocannabinoids are receiving increasing attention given the fact that chronic elevation of AEA or 2-AG produce profoundly different effects on animal behavior.[2]

In this context, we have started a project aimed at the development of a chemical toolset that facilitates the study of the ECS. We have focused our efforts on two aspects: i) the synthesis of molecular probes to study the CBRs and ii) the development of a series of inhibitors that aid the characterization of different 2-AG-hydrolyzing activities. We have developed a set of biotinylated probes based on the structure of different cannabinoid ligands that enable visualization of CB1 and CB2 receptors in native cellular systems.[3] In addition, the incorporation of a benzophenone as photocroslinking moiety makes them suitable probes for proteomic studies, experiments that are currently in course in our laboratory. With respect to the development of new inhibitors of the 2-AG inactivation, the synthesized compounds have enabled the identification of new enzymes involved in the hydrolysis of 2-AG.[4]



Acknowledgments: work supported by MICINN (SAF-2010/22198, FPU and FPI fellowships to L.M.C. and J.A.C. and Ramon y Cajal program to S.O.G.) and Comunidad Autónoma de Madrid (S-SAL-249-2006).

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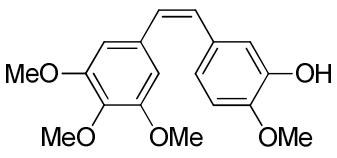
Rafael Peláez

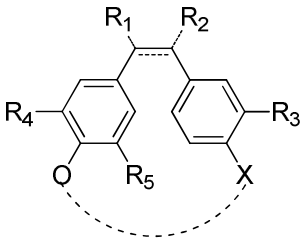
Conformationally restricted macrocyclic analogues of combrestatins

Stilbenes are present in a great number of organic compounds with application in different fields, thus making them highly studied substructures in organic chemistry. They display interesting biological activities, as for instance the anticancer agents combretastatins and resveratrol. Many efforts have been carried out improve their pharmacological activity and selectivity and thousands analogues have been prepared in order to study their structure-activity relationships. Combretastatins are antitumor natural products binding at the colchicine site of tubulin. Combretastatin A-4 is amongst the more potent inhibitors of tubulin polymerization and its prodrug Combretastatin A-4 phosphate appears as a good drug candidate, due to its antiangiogenic activity and higher water solubility, being at this moment in Phase II clinical trials.

Conformational restriction of open chain active models is a method for exploring the influence of molecular geometry on physico-chemical and biological properties and can be achieved by macrocyclization. This very interesting approach to modulate the activity-selectivity has not yet been applied to combretastatins and only recently we have published preliminary work on this subject. The compounds designed and synthesized to this purpose are stilbene and dihydrostilbene derivatives, conformationally blocked by the formation of macrocyclic structures.



Combretastatin A-4



General structure of macrocyclic combretastatin analogues

When compared with their open chain analogues, these macrocyclic compounds show conformational restrictions that have been analyzed by beans of molecular dynamics simulations and variable temperature NMR spectroscopy. Results on their cytotoxicity against different human tumour cell lines and on their tubulin polymerization inhibitory activities (TPI) will be presented.

Acknowledgments: Financial support came from Spanish AECID (PCI-Mediterráneo D/033593/10), Spanish MCINN (SAF2008-04242) and Junta de Castilla y León (SA067A09).

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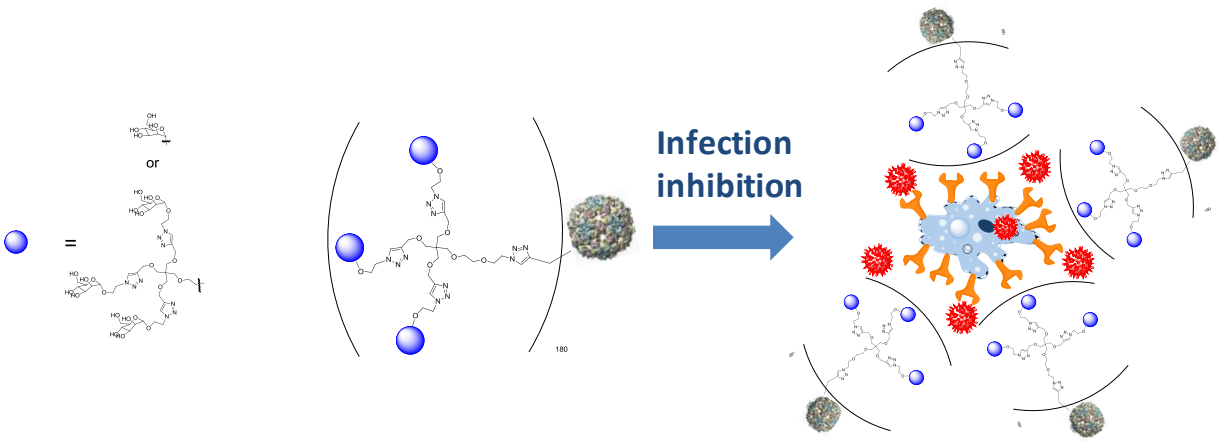
Renato Márcio Ribeiro-Viana

Glyconanoparticles: Virus-like particle construction and anti-viral activity

Protein-carbohydrate interaction is one of the most important biological events, found in many relevant processes such as pathogen infection, inflammation, signaling, etc. To increase the low affinity of the protein-carbohydrate interaction, nature uses the advantage of the multivalent presentation to enhance the strength and selectivity of these interactions. A better understanding of these processes can lead to a novel, effective and highly selective therapeutics.[1]

Virus-like particles (VLP) are attractive systems to build multivalent systems because they are often perfectly monodisperse in size and composition, ranging from the nano to the micrometer scale.[2] Some examples showing interesting biological activity have already been described.[3]

In this work, a VLP of the Qβ bacteriophage modified with 180 copies of alkynes was used as scaffold. Two glycodendrons with 3 and 9 copies of mannose functionalized with an azide group at the focal position were used as carbohydrate moiety. A Cu(I) catalyzed azide-alkyne 1,3-cycloaddition was used in the coupling step, affording fully functionalization and leading to particles with 540 and 1620 copies of mannoses. These VLP were tested in an infection model, using cells expressing DC-SIGN, which recognizes mannose, and a pseudo-typed Ebola virus. IC50s at nM-pM range were found for these glyconanoparticles.



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Hugo Gutiérrez-de-Terán

Structure-based ligand design on adenosine receptors

The new crystal structures of the A2A adenosine receptor now allow for accurate structure-based ligand design on this family of receptors with increasing pharmacological interest. We will here present how a combination of several computational techniques, including homology modeling, ligand docking, 3D-QSAR, molecular dynamics and free energy calculations, can be successfully used for understanding the structural reasons of ligand affinity and receptor selectivity. More importantly, these computational models actually guide different ligand design programs addressed at the adenosine receptors (ARs).

We have first modeled each of the four ARs in their inactive conformation, which were used as a basis for predictive computational models used in the design of selective antagonists at the A3AR.[1] The last applications of these computational models in the design of new scaffolds, with increased affinities at this receptor subtype, will be here presented.

The issue of agonist design is also addressed, on the basis of the last crystal structures of agonist-bound A2AAR.[2] The binding affinities of a new set of potent and selective A2A agonists[3] are analyzed in detail on the basis of free energy calculations, and the role of structural water molecules on ligand binding is elucidated.

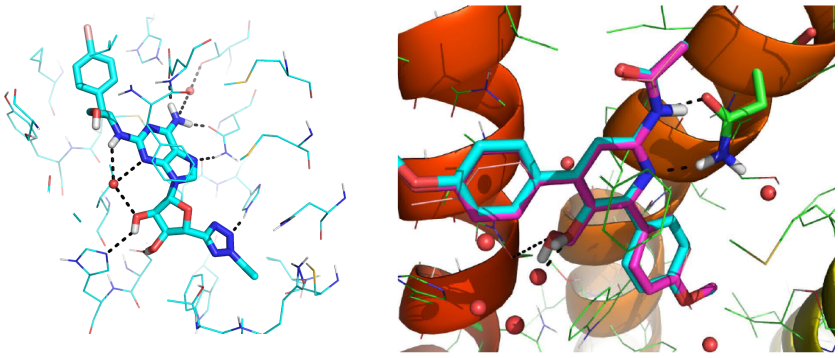

Fig 1: (Left) Binding mode of agonists3 at the A2AAR,as predicted from free energy calculations. (Right) New antagonists designed for the A3AR, bound as predicted from our model developed in ref 1.

Acknowledgements: This project is funded by Xunta de Galicia (PS09/63). Calculations were performed at CESGA, partially funded by ICTS-2011 program (MICINN).

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Pilar Serra

Molecular modeling studies for the design of new selective MMP2 inhibitors

Matrix metalloproteinases (MMPs) are a family of structurally related zinc containing enzymes, which mediate the breakdown of connective tissue. They play an important role in the progression of cancer, not only through their involvement in primary tumour growth, but also in other invasion processes, such as angiogenesis and metastasis. MMP2 has been reported as one of the MMPs with a major role in cancer.[1] The development of selective MMP2 inhibitors is of great interest, especially in relation to MMP9, the other metalloproteinase belonging to the gelatinase family, which is considered as an anti-target enzyme in patients with advanced disease.

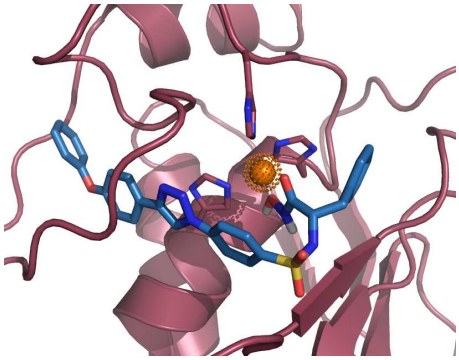

Figure 1

We have undertaken the study of the essential characteristics that define the pharmacophore of reported selective MMP2 hydroxamate-type inhibitors using Molecular Modeling techniques like docking (Figure 1), 3D-QSAR models and molecular dynamics simulations, among others. These studies allowed us to identify key interactions with exclusive MMP2 residues, and the selection of the most appropriate side chains in terms of selectivity.

A fragment-based drug design has also been undertaken combining the selected side chains with suitable ZBGs. These studies have allowed us to carry out the design design, synthesis and biological evaluation of a family of clicked MMP2 hydroxamate type inhibitors based on an α-sulphone, α-tetrahydropyrane scaffold, which have shown to be potent MMP2 inhibitors with an interesting selectivity profile.[2]

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