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PROTEIN DESIGN AS A TOOL FOR SPECIFIC AND MORE POTENT POLYPEPTIDE-BASED DRUGS

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Luis Serrano did his PhD at the CBM in Madrid, Spain working on the structure and function of the Tubulin dimer. He did a posdoc. At Prof. A.R. Fehrst at the MRC in Cambridge, UK working in the field of protein Folding. He became a Group Leader at the EMBL and started a new activity related to Protein design. He was promoted to Senior Scientist and appointed head of the Structural & Computational Biology programme. His group was one of the pioneers in the field of systems and synthetic biology. After 14 years at the EMBL he moved back to the CRG as head of Systems Biology and vice-director. His group is currently focused on Synthetic Biology. Dr. Serrano has been involved in the creation of several Biotech. Companies (Diverdrugs, Cellzome , TRISKEL).

PROTEIN DESIGN AS A TOOL FOR SPECIFIC AND MORE POTENT POLYPEPTIDE-BASED DRUGS

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In recent years we have seen a progressive increase in the use of peptide and protein-based drugs for human therapies. This mainly has applied to extracellular targets but with new delivery systems and vectors it is quite conceivable that in the future we could see the same happening for intracellular targets. One of the advantages of protein and peptide-based drugs is the possibility of targeting protein-protein interactions which are difficult to target by conventional small compounds. The use of polypeptide-base drugs requires in many cases the manipulation of their sequence in order to increase stability, solubility, specificity and other properties. This can be achieved by automatic protein design tools which have reached maturity. Now provided we have a good structure of a complex it is possible to engineer different properties with a good chance of success. Here I will discuss different applications of protein design to the family of tumour necrosis ligands which have a broad range of possible applications in different therapies.

AGONISTS, INVERSE AGONISTS, AND ALLOSTERIC MODULATORS OF G PROTEIN-COUPLED RECEPTORS

Leonardo Pardo

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Leonardo Pardo received his Ph.D. in Physical Chemistry from the Autonomous University of Barcelona, Spain, in 1986, and subsequently held Post-Doctoral Fellow and Research Assistant positions at the Department of Physiology and Biophysics in the Mount Sinai School of Medicine, New York. He is a Professor of Biostatistics at the Autonomous University of Barcelona and Head of its Laboratory of Computational Medicine within the School of Medicine. His group applies bioinformatic tools to dissect the molecular details of G protein coupled receptor function. During the last years his research has focused on the design of new therapeutic ligands targeting serotonin receptors; and the study of the structure and function of biogenic amine, chemokine, and glycoprotein hormone receptor families.

AGONISTS, INVERSE AGONISTS, AND ALLOSTERIC MODULATORS OF G PROTEIN-COUPLED RECEPTORS

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G protein-coupled receptors (GPCRs) are one of the most prevailing protein families in the human genome. GPCRs are receptors for sensory signals of external origin such as odors, pheromones, or tastes; and for endogenous signals such as neurotransmitters, (neuro)peptides, hormones, and others. These proteins are key in cell physiology, and their malfunction is commonly translated into pathological outcomes. Thus, GPCRs constitute one of the most attractive drug targets.

In the ligand-free basal state, GPCRs exist in equilibrium of conformations, each stabilized by a network of intramolecular interactions. Ligand binding at the native (or orthosteric) site modulates receptor function by stabilizing new interaction networks and establishing new conformational equilibria. Activating ligands, or agonists, stabilize conformational changes in cytoplasmic domains that increase receptor signaling. Conversely, inverse agonists decrease the basal, agonist-independent level of signaling by stabilizing different conformational changes. In addition, ligand binding to an allosteric site (that is topographically distinct from the orthosteric site) might modulate the signalling of the orthosteric ligand. Positive allosteric modulators enhance the response of orthosteric agonists, while negative allosteric modulators decrease the effect.

We will show, combining the latest information about GPCR structure with chemical synthesis, site-directed mutagenesis, biophysical experiments and computational modeling, how the binding of the ligand to the allosteric or orthosteric site influences this equilibrium of conformations.

DISCOVERY OF α-7 NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS. VIRTUAL SCREENING, SYNTHESIS AND BIOLOGICAL PROFILING

Laura Maccari

Molecular Informatics Department
Siena Biotech, Siena, Italy

2001: *Degree in Medicinal Chemistry at University of Siena.*
2001 – 2004: *PhD at University of Siena in Computational Methods applied to various fields including anti-hypertensive and anticancer drugs. Stage on QSAR methods at the Centre for Molecular Design at University of Portsmouth.*
2005 – Present: Siena Biotech, Drug Design Unit. Project Leader and Team member in several drug discovery projects.

Scientific interests are focusing on application of computer aided drug design techniques to drug discovery. In particular, 3D QSAR, homology modeling, docking, pharmacophore generation, and virtual screening cascade. Recently working on the strategy for compound collection enrichment and chemical space exploration including ADME aspects.

DISCOVERY OF α-7 NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS. VIRTUAL SCREENING, SYNTHESIS AND BIOLOGICAL PROFILING

Laura Maccari (1), Hendrick Bothmann (1), Chiara Ghiron (1), Adam Gilbert (2), Arianna Nencini (1), Iolanda Micco (1), Alessandro Padova (1), Silvia Papini (1), Joanna Quinn (1)

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α-7 nicotinic receptors are highly expressed in brain and have proven to facilitate neuronal synaptic transmission. α-7 receptors have a primary function in cognition, memory and neurodegeneration and have been implicated in a range of diseases including schizophrenia and Alzheimer's syndrome[1]. α-7 modulators are therefore of interest as potential therapies.

A number of α-7 agonists and positive allosteric modulators (PAMs) were identified via virtual screening of compounds from both commercially available sources and our in house collection. The approach involved generating a compound set using a series of CNS criteria, followed by both pharmacophore and docking screening. The pharmacophore model was derived from known endogenous and synthetic α-7 ligands whilst the docking approach was based on a homology model derived from the α-7 human receptor sequence modelled onto an AChBP x-ray.

Selected compounds were then tested in a FLIPR-based calcium-flux assay affording several novel hits, including some interesting series of PAMs belonging to diverse chemical classes. The structure-activity relationships derived from the FLIPR data were subsequently rationalised via a molecular field analysis.

Among identified agonist compounds a series of aminoalkyl benzimidazoles were selected for further optimisation[2]. Virtual libraries, addressing multiple objectives simultaneously, were enumerated based on commercially available building blocks. In particular, a series of analogues were designed around original agonist hits and their properties calculated to improve the likelihood of synthesizing brain-penetrant molecules. The resulting set was synthesized and screened leading to the identification of low micromolar compounds, which formed the starting point for compound optimisation via interactive cycles of design, synthesis, screening and physico-chemical profiling.

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THE DESIGN AND SYNTHESIS OF PAN-5-HT$_{1A/B/D}$ ANTAGONISTS FOR THE TREATMENT OF DEPRESSION

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UNIVERSITY EDUCATION

University of Leeds (1980-1986)

FIRST DEGREE:

B.Sc. First Class Honours in Chemistry

HIGHER DEGREE:

PhD in Synthetic Organic Chemistry (Prof. Peter Sammes)

PROFESSIONAL AFFILIATIONS

CChem FRSC

POSITIONS

Sept 2007 - date	*Neurosciences CEDD, GSK, Harlow, UK*
Aug 2001 - Sept 2007	*Psychiatry-CEDD, GSK, Verona, Italy*
1987 - 2001	*SmithKline Beecham, Harlow, UK*
1986 - 1987	*Courtaulds Ltd., Coventry, UK*

Currently Senior Research Leader in the Schizophrenia and Cognitive Disorders Discovery Performance Unit within the Neurosciences Centre of Excellence for Drug Discovery (CEDD). Extensive international CNS drug discovery experience having led medicinal chemistry and cross-matrix Programme teams for over 12 years. I have delivered multiple drug candidates into development for a variety of indications (up to Phase III) and authored over 80 publications

THE DESIGN AND SYNTHESIS OF PAN-5-HT$_{1A/B/D}$ ANTAGONISTS FOR THE TREATMENT OF DEPRESSION

Steven Mark Bromidge

GlaxoSmithKline, Neuroscience Centre of Excellence for Drug Discovery, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

A wealth of pre-clinical and clinical evidence has confirmed a link between extracellular levels of serotonin (5-HT) and a plethora of psychiatric indications, in particular anxiety and depression[1]. In particular, enhanced serotonergic neurotransmission has become the unifying mechanism of action of modern day antidepressants and the selective serotonin reuptake inhibitors (SSRIs) have become established as the most effective antidepressant agents in clinical use. Despite the success of SSRIs, one undesirable characteristic is long latency to therapeutic onset which is hypothesized to be due to the requirement for desensitisation of 5-HT$_1$ autoreceptors in order to maintain increased 5-HT levels[2].

5-HT$_1$ autoreceptors are widely distributed in the brain and in addition to serotonin transporters (SerT) are known to have a major role in the control of synaptic 5-HT levels. Blockade of 5-HT$_{1A/B/D}$ autoreceptors, with or without concomitant SerT inhibition, rapidly increases brain 5-HT levels and should provide a fast onset of antidepressant/anxiolytic action relative to current therapies[3].

We have disclosed several series of potent 5 HT$_{1A/B/D}$ receptor antagonists both with and without concomitant hSerT reuptake inhibitory activity including **1** (SB-649915)[4]. More recently we discovered series of 6- and 8-[2-(4-aryl-1-piperazinyl)ethyl]-2H-1,4-benzoxazin-3(4H)-ones (e.g. **2** and **3**) with excellent *in vitro* and *in vivo* profiles in different animal models of anxiety and depression[5]. This presentation will describe the further optimisation and evolution of these series culminating in a new clinical candidate. Key medicinal chemistry breakthroughs from this series will be highlighted including overcoming hERG liability and addressing metabolic instability.

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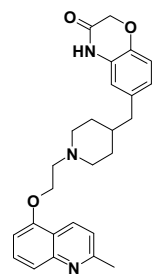
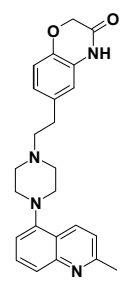


1 (SB-649915)



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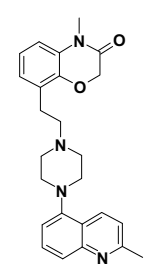


3

IDENTIFICATION OF POTENT DUAL OREXIN RECEPTOR ANTAGONISTS

Paul J. Coleman

Department of Medicinal Chemistry, Merck Research Laboratories

West Point, PA

Paul joined the Medicinal Chemistry Department, Merck Research Laboratories in 1996 as a Senior Research Chemist and was subsequently promoted to positions of increasing responsibility; he is currently Senior Director of Medicinal Chemistry and oversees several program teams focused on developing novel CNS therapeutics. He has led groups that have identified clinical candidates for the treatment of osteoporosis, cancer, infectious diseases, and sleep disorders. Paul's group has developed potent peptidomimetics ($\alpha v\beta 3$ integrin antagonists); allosteric enzyme inhibitors (kinesin spindle protein), protease inhibitors (HCV protease), ion channels blockers, and GPCR antagonists (orexin receptors). Paul holds a B.A. in Chemistry (1987) from the University of Chicago and a Ph.D. from Indiana University (1994). He was a NIH postdoctoral fellow at Harvard University from 1994-1996.

IDENTIFICATION OF POTENT DUAL OREXIN RECEPTOR ANTAGONISTS

Paul J. Coleman (1), John D. Schreier (1), Christopher D. Cox (1), Michael J. Breslin (1), David B. Whitman (1), Anthony J. Roecker (1), Michael J. Bogusky (1), Rodney A. Bednar (1), Wei Lemaire (1), Joseph G. Bruno (1), George D. Hartman (1), Georgia B. McGaughey (1), Duane R. Reiss (2), C. Meacham Harrell (2), Scott M. Doran (2), Susan L. Garson (2), Richard L. Kraus (2), Yuxing Li (2), Thomayant Prueksaritanont (3), Chunze Li (3), Christopher J. Winrow (2), Kenneth S. Koblan (2), and John J. Renger (2)

(1) Department of Medicinal Chemistry, Merck Research Laboratories, (2) Department of Depression and Circadian Disorders, Merck Research Laboratories, (3) Department of Drug Metabolism, Merck Research Laboratories

Orexins are neuropeptides secreted by hypothalamic neurons that project into regions of the brain that modulate sleep and arousal. Antagonism of the orexin (or hypocretin) system has been identified as a novel approach for the treatment of insomnia, and several drug candidates have entered clinical development. This presentation will describe a series of potent, dual orexin receptor antagonists containing novel central scaffolds that were discovered following a high throughput screening effort. The synthesis, structure-activity relationships, and pharmacological activity of these potent orexin receptor antagonists will be described.

AN ANTEDRUG APPROACH TO PDE4 INHIBITORS FOR THE TOPICAL TREATMENT OF PSORIASIS

Jordi Gràcia

Laboratorios Almirall

Jordi Gràcia is Senior Section Head of Medicinal Chemistry at Laboratorios Almirall. He received his doctoral degree in Organic Synthesis and Medicinal Chemistry from the University of Barcelona where he worked with Josep Bonjoch and Joan Bosch on the total synthesis of indole alkaloids. After postdoctoral work on the synthesis of bryostatins in the group of Jim Thomas at the University of Manchester, he joined the Medicinal Chemistry Department of Laboratorios Almirall as a research scientist. He has been the chemistry leader of several drug discovery projects mainly in the respiratory and autoimmune fields and gained experience in the design of drugs, not only for oral dosing, but also for topical dermal and inhaled routes of administration.

AN ANTEDRUG APPROACH TO PDE4 INHIBITORS FOR THE TOPICAL TREATMENT OF PSORIASIS

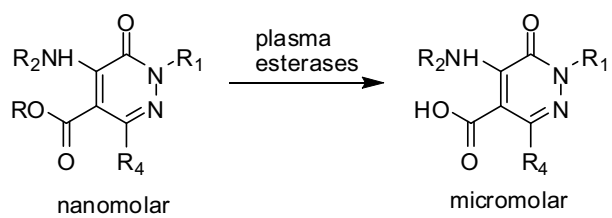
Jordi Gràcia

Laboratorios Almirall S.A.

Phosphodiesterase 4 (PDE4) is a cAMP-specific phosphodiesterase which is predominantly expressed by immune and pro-inflammatory cells. PDE4 inhibition has shown beneficial effects in animal models mimicking certain aspects of asthma and COPD, as well as inflammatory bowel disease, atopic dermatitis, psoriasis and rheumatoid arthritis. However, despite significant progress in this area, most development candidates have been discontinued so far because of lack of efficacy and/or dose-limiting side effects, mainly nausea and vomiting which severely restrict their potential therapeutic utility.

A research effort was initiated at Almirall for the identification of novel PDE4 inhibitors for the topical treatment of psoriasis based on an antedrug strategy, aimed at achieving high local efficacy in the skin whilst decreasing the overall PDE4 inhibitory systemic exposure and hence increasing the therapeutic window.

The objective of the talk is to present all the SAR and optimization studies around these pyridazinone carboxylate antedrugs, not only concerning potency modulation but also the achievement of low plasma stability whilst maintaining chemical stability to ensure formulability and stability in skin cells to ensure in vivo efficacy. These efforts have led to the identification of several compounds with the desired profile in terms of efficacy and emetic window and to the selection of a compound for advanced preclinical studies.



THE DISCOVERY OF JNJ37822681 AS A POTENTIAL NOVEL TREATMENT OF SCHIZOPHRENIA

José Manuel Bartolomé-Nebreda

Neuroscience Chemistry, Johnson & Johnson Pharmaceutical Research and Early Development (Europe), Jarama 75, 45007 Toledo, Spain

1993 *B.S. in Organic Chemistry. Universidad Autónoma de Madrid, Spain.*
1998 *Ph. D. in Organic Chemistry (Cum Laude). "A Novel Class of Potent and Highly Selective Cholecystokinin CCK-A Receptors Antagonists: 2-substituted 5-Boc-Tryptophylamino-1,3-dioxoperhidropirido[1,2-c]pyrimidines and Related Analogues". Medicinal Chemistry Institute, Consejo Superior de Investigaciones Científicas, Madrid, Spain.*

J&JPRD CAREER:

1997 *Incorporation at J&JPRD Toledo site as Medicinal Chemistry Scientist*
2002 *Promoted to Senior Scientist.*
2008 *Promoted to Principal Scientist.*

Involved in 13 different Drug Discovery programs at J&JPRD in different therapeutic areas: Pain, Gastrointestinal, Neurology and specially Psichiatry.
Delivery of 4 NME candidates.

PUBLICATIONS, PATENTS AND COMMUNICATIONS:

Co-author of 13 peer-reviewed articles.
Co-inventor of 14 patent applications.
Co-author of more than 15 communications (Posters & oral) to international conferences.

AWARDS:

Janssen-Cilag Award, VII Summon of the Spanish Medicinal Chemistry Society Awards for Novel Researchers. "Approaches Towards the Bioavailability Improvement of IQM-95,333, Potent and Highly Selective CCK-A Receptors Antagonist"

THE DISCOVERY OF JNJ37822681 AS A POTENTIAL NOVEL TREATMENT OF SCHIZOPHRENIA

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Atypical defines an antipsychotic with low extra-pyramidal syndrome (EPS) liability. In 2001 Kapur and Seeman[1] postulated the hypothesis that fast dissociation from the dopamine D_2 receptor makes an antipsychotic atypical. Following this hypothesis a drug discovery program was initiated at J&JPRD with the goal to identify potential new atypical antipsychotic agents by screening compounds based on their rate of dissociation from D_2 receptors. Furthermore, an additional goal was to combine such a fast-dissociating profile with high specificity for D_2 receptors, in order to avoid the unwanted side-effects associated with the multiple receptor profile of current atypical antipsychotics (i.e. weight gain and type II diabetes, sedation, orthostatic hypotension and cardiovascular side effects).

An indirect dissociation assay with [^{3}H]-spiperone, was employed to determine the rate of dissociation for a large set of D_2 antagonists selected from our chemical library. A total of 4 distinct chemical series were identified and then further explored in an initial Hit-to-Lead chemistry program to develop preliminary SAR and SPR of the various chemotypes.

A subsequent LO program focused around 2 chemical series to optimize the SAR with respect to activity, selectivity, ADMET and CV safety profiles was initiated. SAR data from the medicinal chemistry program will be presented together with the optimization process and strategy which led eventually to the identification of JNJ37822681, a candidate that provides an optimized combination of D_2 affinity, fast-dissociating D_2 antagonism, selectivity, CyP450 2D6 interaction and low hERG inhibition. Furthermore, initial data shows that JNJ37822681 behaves as an atypical antipsychotic in preclinical species. This suggests that this fastdissociating D_2 profile with low EPS liability can be achieved without binding to receptors other than dopamine D_2 and further validates our approach to select new antipsychotic agents.

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THE DISCOVERY OF HIGHLY SELECTIVE NaV1.8 MODULATORS WITH GOOD PHARMACOKINETIC PROPERTIES FOR CHRONIC MIXED PAIN

Mark Kemp

Pfizer, Sandwich, UK

B.Sc. Southampton University (1991) followed by a Ph.D. with Prof. Richard Whitby on zirconocene mediated synthesis of heterocycles (1994). I joined Pfizer in 1994 and have worked in a variety of therapeutic areas, most recently on targets for the treatment of pain.

THE DISCOVERY OF HIGHLY SELECTIVE NaV1.8 MODULATORS WITH GOOD PHARMACOKINETIC PROPERTIES FOR CHRONIC MIXED PAIN

Mark Kemp

Pfizer, Sandwich, UK

Biological evidence suggests that selective Nav1.8 modulators will provide an efficacious and safe treatment for inflammatory and/or neuropathic pain. This presentation describes the discovery of two related series of Nav1.8 modulators, starting from a common non-selective lead. Both series were optimised in terms of potency, selectivity and pharmacokinetics to produce two candidates which were progressed to rat models of pain. The electrophysiology, *in vivo* efficacy, pharmacokinetics and rat toxicological findings for these two compounds are also presented.

SELECTIVE SIGMA-1 RECEPTOR (σ_1R) ANTAGONISTS: AN EMERGING TARGET FOR THE TREATMENT OF NEUROPATHIC PAIN

José Luis Díaz Fernández

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José Luis Díaz (1973) was born in Barcelona (Spain) and studied chemistry at the University of Barcelona, where he specialized in organic chemistry receiving his BSc (1996), MSc (1997) and PhD (2001).

In the period 2001-2004, he worked as a postdoctoral fellow for Almirall Prodesfarma in the Pharmacology and Therapeutic Chemistry department at the Faculty of Pharmacy, and in the Biomedical Research Institute (IRBB) at the Scientific Park of Barcelona (PCB), under the supervision of Prof. R. Lavilla. He was involved in the field of Multicomponent Reactions (MCRs) methodologies searching for novel NADH analogues, and in the synthesis of different heterocyclic scaffolds for medicinal chemistry projects.

In 2004, he joined Esteve, where he is, since 2006, the Head of Medicinal Chemistry Department. In Esteve his research has been focused in CNS disorders and pain projects.

SELECTIVE SIGMA-1 RECEPTOR (σ_1R) ANTAGONISTS: AN EMERGING TARGET FOR THE TREATMENT OF NEUROPATHIC PAIN

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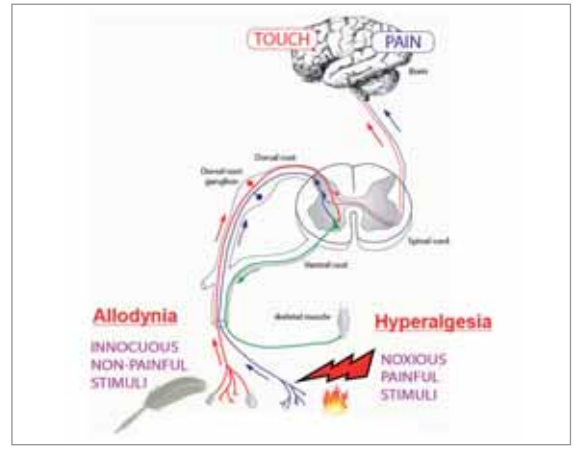
A large number of therapeutic roles have been proposed for σ_1 receptors (σ_1Rs), but their involvement in non-acute pain had not been well explored up to now. Precedents in modulation of opioid analgesia, expression of σ_1Rs in key areas for pain control, and *in house* development of σ_1R knock-out (KO) mice, offered us the possibility to investigate the role of σ_1R in nociception.

We have synthesized several σ_1 antagonists which have shown very promising results in animal models of neuropathic pain. Herein, we present the rational basis of this approach, synthesis, structure-activity relationships and pharmacological results of different chemical series[1]. Functional data in pain models are presented providing evidence to consider selective σ_1 receptor antagonists as an innovative approach for treating neuropathic pain[2].



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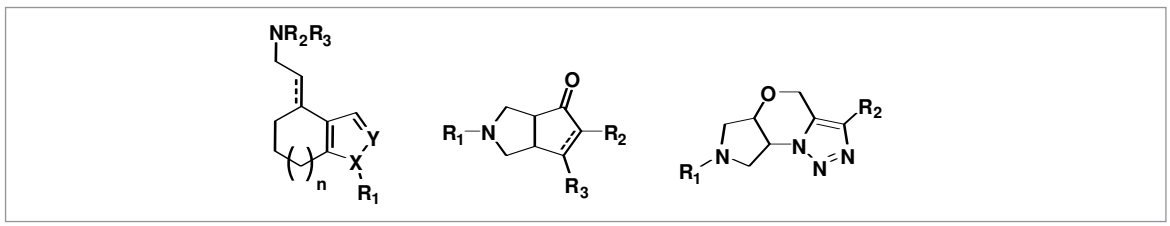
2. J. L. Díaz, D. Zamanillo, J. Corbera, J. M. Baeyens, R. Maldonaldo, M. A. Pericàs, J. M. Vela, A. Torrens, *Central Nervous Agents in Medicinal Chemistry*, **2009**, *in press*.



NEW PURINERGIC $P2X_3$ RECEPTOR LIGANDS AS USEFUL TOOLS IN THE MANAGEMENT OF PAIN

Gloria Cristalli

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Gloria Cristalli graduated in Chemistry and Technology of Drugs in 1974 at the University of Camerino (UNICAM, IT).

Her scientific activity has been carried out at the Department of Chemical Sciences of UNICAM, at the University of Cambridge (UK), and at Temple University, Philadelphia (USA).

In 1994 she became Full Professor of Medicinal Chemistry at the University of Modena and in 1997 at UNICAM, where since 2008 she is in charge as Dean of the Pharmacy Faculty. She is also Director of the EFMC accredited school ESMEC (IT). Her scientific experiences are related mainly to the synthesis and biological evaluation of heterocycles and nucleoside/nucleotide analogues. As results of her research she published over 180 scientific papers, filed 10 international patents, and presented about 250 communications to meetings.

NEW PURINERGIC $P2X_3$ RECEPTOR LIGANDS AS USEFUL TOOLS IN THE MANAGEMENT OF PAIN

Gloria Cristalli and Rosaria Volpini

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Extracellular nucleotides like ATP interact with the ionotropic P2X and the metabotropic P2Y receptors, modulating physiological functions like neurotransmission, muscle contractility, neural and endocrine secretion, immune cell regulation or cell proliferation[1]. In particular, $P2X_3$ receptors are specifically expressed on pain relevant sensory afferent neurons, and their activation is believed to be involved in a number of chronic pain conditions including neuropathic pain and migraine. On these bases, this P2X receptor subtype is considered as a potential target for the development of new analgesic drugs.

Recently, a new series of acyclic-nucleotides (**a**), based on the adenine skeleton and bearing in 9-position a phosphorylated four carbon chain, has been synthesized and evaluated for their biological activity on rat $P2X_3$ receptors. The results suggest that they are endowed with modest partial agonism on $P2X_3$ receptors[2]. This is an interesting property, as the new acyclic-nucleotides are able to persistently block, by desensitization, $P2X_3$ receptor activity after a brief, modest activation, yet leaving the ability of sensory neurons to mediate responses to standard painful stimuli via a lower level of signalling.

Furthermore, taking into account the structure of recently reported non-nucleotide $P2X_3$ antagonists having a 2,4-diaminopyrimidine scaffold[3], new 2,6-diaminopurine derivatives have been designed and synthesized (**b**), by utilizing poly-substituted benzyl groups as substituents in 9-position. Biological studies demonstrated that the new purine derivatives behave as $P2X_3$ receptor antagonists, being able to inhibit the α,β-meATP evoked current.

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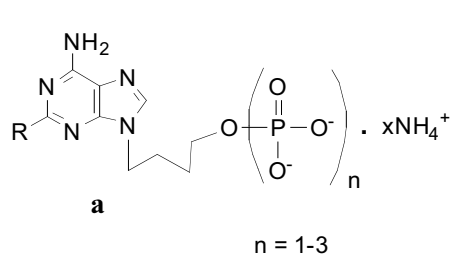
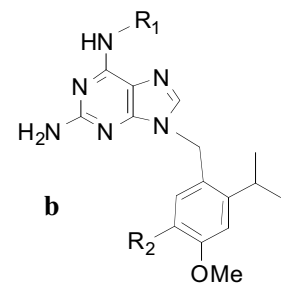


a

n = 1-3



b

INVITED SPEAKERS – IS.11

THE DISCOVERY OF AN A_1 ADENOSINE RECEPTOR PARTIAL AGONIST FOR THE TREATMENT OF TYPE II DIABETES

Jeff Zablocki

Gilead Sciences, Inc.

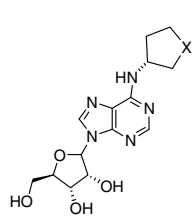
Jeff is a Senior Director and Head of Cardiovascular Chemistry at Gilead Sciences, Inc. Jeff Zablocki served as the Head of Chemistry at CV Therapeutics for 11 years. The CVT Chemistry team under his direction generated 4 compounds for development: Lexiscan® (A_{2A} agonist, approved as pharmacological stress agent), CVT-6883 (A_{2B} antagonist, asthma, Phase II), CVT-3619(Partial A1 Agonist, Type II diabetes, Phase I), and CVT-10216 (ALDH-2, drug addiction, Development). Jeff's strong passion for drug discovery is exemplified by his being an inventor/author on over 145 patents, publications, and presentations. Jeff is the Program Chair of the Medicinal Division of the American Chemical Society.

THE DISCOVERY OF AN A_1 ADENOSINE RECEPTOR PARTIAL AGONIST FOR THE TREATMENT OF TYPE II DIABETES

Jeff Zablocki (1), Elfatih Elzein (1), Rao Kalla (1), Xiaofen Li (1), Thao Perry (1), Tim Marquart (1), Malcolm McGregor (4), John Shryock (2), Lin Wu (2), Yuzhi Wu (2), Dewan Zeng (2), Nancy Chu (3), Dan Soohoo (3), Kwan Leung (3), Xuegong Wang (4), Justus Bingham (4), Peter Staehr (4), Arvinder K. Dhalla (2)

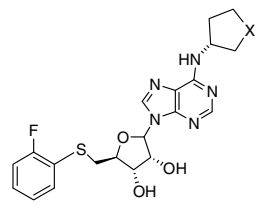
(1) Department of Medicinal Chemistry, (2) Department of Drug Research and Pharmacological Sciences, (3) Department of Pre-clinical Develoment, (4) Clinical Pharmacology, Gilead Sciences, Inc., 3172 Porter Drive, Palo Alto, CA 94304, USA, 5Accelrys Inc. San Diego, CA USA

A_1 adenosine receptor (AdoR) partial agonists have the potential for treatment of Type II diabetes due to their propensity to increase insulin sensitivity by lowering circulating non-esterified free fatty acids (NEFA) by an inhibiting lipolysis in adipocytes. Partial A_1 AdoR agonists retain efficacy to reduce plasma NEFA but do not have the cardiovascular side effects of full A_1 AdoR agonists, including heart rate. To discover a partial A_1 AdoR agonist we replaced the 5'-hydroxyl group of the full agonists N-6-cyclopentyladenosine **1** (CPA) and Tecadenoson **2** with 5'-(2-fluorophenylsulfide) group as illustrated in **3** and **4**. Both compounds retained affinity for A_1 AdoR and selectivity over other AdoR subtypes. Further structural modification of **3** through the incorporation of a 2-hydroxyl group on the cyclopentyl ring of **3** led to **4** and **5** (CVT-3619) that were partial agonists with respect to their A-V nodal effects in the heart (Langendorff, guinea pig). Compound **5** has been demonstrated to inhibit forskolin induced NEFA release from adipocytes in a partial manner relative to **1** (Fatholahi JPET 2006). The pharmacokinetic (PK) outcomes for **5** following oral and IV dosing in rat and dog included good oral bioavailability (rat – 18-27%, dog – 65%) and favorable half-life (rat – 4.0-5.4 h, dog-4.3 h). Compound **5** demonstrated a dose-dependent decrease in NEFA levels (maximum -55%) and triglycerides (maximum -55%) following oral dosing *in vivo* (Sprague-Dawley fasted awake rat, 1 – 10 MPK, time point 1 h post dosing). Furthermore, compound **5** lowered NEFA levels (maximum -57%) in a Zucker diabetic fatty (ZDF) rat model following an oral dose (5 MPK, 10 min – 1 h, Dhalla Diabetes, Obesity, and Metabolism 2009). In a hyperinsulinemic euglycemic clamp study in mice (C57BL/J6) fed a high-fat (HF) diet for 12 weeks, glucose infusion rate was decreased significantly in HF mice compared with chow-fed mice (Dhalla Am J Physiol Endocrin Metab 2007). Treatment with compound **5** 15 min prior to the start of the clamp study significantly ($P < 0.01$) increased glucose infusion rate to values similar to that for chow-fed mice. We have discovered a partial A_1 agonist **5** that lowers NEFA levels and enhances insulin sensitivity with no effect on heart rate, thus providing a tissue selective A_1 AdoR mediated effect. Recently in a Phase I trial in healthy volunteers, **5** lowered circulating NEFA levels in a dose dependent manner with an ED_{50} of approximately 335 mg. CVT-3619 (**5**) was safe and well-tolerated in doses up to 1800 mg with no significant changes in heart rate, blood pressure or PR interval.



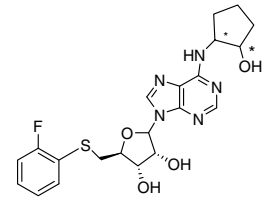
1 CPA X = CH_2
A_1 K_{iH} = 1 nM

2 X = O
A_1 K_{iH} = 3 nM



3 R = CH_2
A_1 K_{iH} = 122 nM

4 R = O
A_1 K_{iH} = 842 nM



5 (R, R)
A_1 K_{iH} = 55 nM

6 (S, S)
A_1 K_{iH} = 94 nM

BIOLOGY ORIENTED SYNTHESIS

Herbert Waldmann

Herbert Waldmann Max-Planck-Institut für molekulare Physiologie, Department of Chemical Biology, Otto-Hahn-Str. 11, D¬44227 Dortmund, Germany, and TU Dortmund, Fachbereich 3, Chemische Biologie
Herbert.waldmann@mpi-dortmund.mpg.de

Prof. Dr. Waldmann was born in Neuwied, Germany. He studied chemistry at the University of Mainz where he received his Ph.D. in organic chemistry in 1985 under the guidance of Horst Kunz. After a postdoctoral appointment with Professor George Whitesides at Harvard University, he completed his habilitation at the University of Mainz in 1991. In 1991 he was appointed as Professor of Organic Chemistry at the University of Bonn, then in 1993 was appointed to full Professor of Organic Chemistry at the University of Karlsruhe. In 1999 he was appointed as Director of the Max-Planck-Institute of Molecular Physiology Dortmund and Professor of Organic Chemistry at the University of Dortmund.

He is a recipient of the Otto Bayer Award, the Max Bergmann Medal and the GSK Award for Outstanding Achievements in Chemical Biology. He is Member of "Deutsche Akademie der Naturforscher Leopoldina, Halle/Saale", the "NRW Akademie der Wissenschaften und der Künste" and since 2005 he is a Fellow of the Royal Society of Chemistry.

BIOLOGY ORIENTED SYNTHESIS

Herbert Waldmann

Herbert Waldmann Max-Planck-Institut für molekulare Physiologie, Department of Chemical Biology, Otto-Hahn-Str. 11, D¬44227 Dortmund, Germany, and TU Dortmund, Fachbereich 3, Chemische Biologie
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Relevance to nature is one of the most important criteria to be met by compound classes for chemical biology and medicinal chemistry research. The underlying frameworks of natural products (NPs) provide evolutionary selected chemical structures encoding the properties required for binding to proteins, and their structural scaffolds represent the biologically relevant and prevalidated fractions of chemical space explored by nature so far.

Biology oriented synthesis (BIOS) builds on these arguments. It employs core structures delineated from NPs as scaffolds of compound collections and creates focussed diversity around a biologically prevalidated starting point in vast structural space. BIOS, therefore, builds on the diversity created by nature in evolution and aims at its local extension in areas of proven biological relevance. Consequently BIOS offers a conceptual alternative to other guiding strategies for library design which for instance are based on mechanistic considerations, sequence or structure homology or on the creation of chemical diversity.

In the lecture the trains of thought leading to the BIOS concept will be detailed, including the development of a Structural Clustering of Natural Products (SCONP) in a tree-like arrangement and its combined use with Protein Structure Similarity Clustering (PSSC) as hypothesis generators for the development of NP-derived and -inspired collections, the chemical feasibility of their synthesis on the solid phase and in solution and the investigation of these compound collections in selected biochemical and biological assays.

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6. S. Wetzel, K. Klein, S. Renner, D. Rauh, Tudor I. Oprea, P. Mutzel, H. Waldmann, Nat. Chem. Biol., **2009**, in press.

FROM RATIONAL LIGAND DESIGN TO TARGET VALIDATION: DEVELOPMENT OF CHEMICAL PROBES FOR THE CNS

Silvia Ortega-Gutiérrez

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Avda. Complutense s/n, E-28040 Spain

After finishing my bachelor´s degree in Biochemistry at Complutense University (Madrid, Spain), I joined the Medicinal Chemistry Laboratory leaded by Prof. María L. López-Rodríguez in the Organic Chemistry Department of the same university. Under her supervision, I completed my PhD in the area of medicinal chemistry working in the field of endocannabinoids. In particular, we developed a series of inhibitors of the anandamide uptake that enabled us to establish some of the basis of this mechanism as well as to evaluate its therapeutic potential.

Afterwards, I worked as a postdoctoral research associate at The Scripps Research Institute (La Jolla, California, USA) with a MEC-Fulbright scholarship under the supervision of Prof. Benjamin F. Cravatt. During this period I acquired experience in the fields of chemical biology and proteomics.

In 2008 I was appointed research associate as Ramón y Cajal scholar in the Organic Chemistry Department at Complutense University (Madrid, Spain), which is my current position.

My areas of interest include medicinal chemistry and chemical biology. At this moment I am involved in several research lines in the fields of the endogenous cannabinoid system (monoacylglycerol lipase, cannabinoid receptors), cancer (fatty acid synthase, isoprenylcysteine carboxyl methyltransferase) and the development of chemical probes for the study of G protein-coupled receptors.

All this work has been published in more than twenty research and review articles in peer reviewed high impact scientific journals as well as in two international patents, one of which has been recently transferred to the pharmaceutical industry. Additionally, I am actively involved in the pre- and postgraduate chemistry and biology programs as well as in the supervision of several graduate students.

FROM RATIONAL LIGAND DESIGN TO TARGET VALIDATION: DEVELOPMENT OF CHEMICAL PROBES FOR THE CNS

Silvia Ortega-Gutiérrez (1), Henar Vázquez-Villa (1), Mar Martín-Fontecha (1), Lidia Martín-Couce (1), Arnau Cordomí (2), Leonardo Pardo (2), Bellinda Benhamú (1), and María L. López-Rodríguez (1)

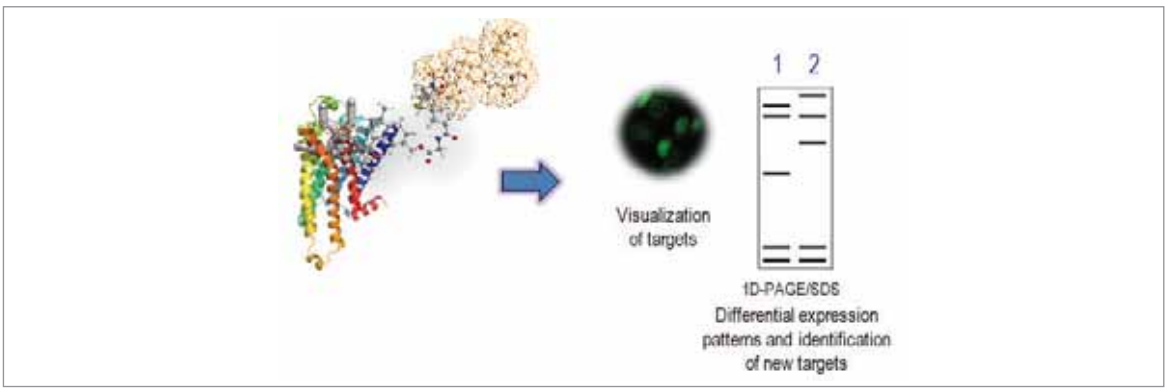
(1) Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Avda. Complutense s/n, E-28040 Madrid; (2) Laboratori de Medicina Computacional, Unitat de Bioestadística, Facultat de Medicina, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Barcelona, Spain

Functional proteomics and activity-based protein profiling (ABPP) have emerged as powerful chemical proteomic strategies to characterize enzyme function directly in native biological systems on a global scale. Simultaneously, the development of activity-based probes (ABPs) has boosted the identification of enzymes associated with a wide range of diseases. However, to date, the huge potential of this platform has been limited basically to enzymes[1]. Hence, development of probes to cover other fractions of the proteome currently constitutes an important challenge. In this context, no probes have been developed so far for the study of G protein-coupled receptors (GPCRs), which constitute almost the 50% of the druggable genome[2]. Therefore, in our research group we have started a project aimed at the development of a set of chemical probes bearing different tags that enable visualization, isolation, enrichment and/or identification of GPCRs.

Among the several hundreds of known GPCRs, we have focused our initial efforts on serotonin and cannabinoid receptors, due to their clinical significance and our previous experience[3]. However, if this approach is successful it should be feasible to extend it to other GPCRs of interest in order to address relevant questions that enable us to improve our understanding of the endogenous system of interest, its physiology and its therapeutic potential.

Using β_2 adrenergic-based homology models of the corresponding GPCR under study in complex with the selected scaffolds, we have identified those regions in the molecule where the different tags can be introduced. The chemical probes will enable the direct visualization, isolation and/or identification of the labelled targets.

Here, we will show our latest results towards this objective focused on the serotonin 5-HT_{1A} and 5-HT_6 receptors and in CB_1 and CB_2 cannabinoid receptors. We have already identified some labelled compounds able to bind the target receptors and therefore they are suitable candidates for their further development in biological systems[4]. These experiments are underway in our research laboratory.



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2. Lagerström, M. C. *et al. Nat. Rev. Drug Discov.* **2008**, *7*, 339.
3. (a) López-Rodríguez *et al. J. Med. Chem.* **2005**, *48*, 2548. (b) Medina, R. A. *et al. J. Med. Chem.* **2009**, *52*, 2384. (c) de la Fuente, T. *et al. J. Med. Chem.* Submitted.
4. Martín-Couce, L. *et al. J. Am. Chem. Soc.* Submitted.

THE DISCOVERY OF THE HEDGEHOG ANTAGONIST GDC-0449 FOR THE TREATMENT OF SOLID TUMORS

Dan Sutherlin

Department of Discovery Chemistry, Genentech, Inc.

Dan Sutherlin received his BS in chemistry from Eckerd College in 1991. He then began graduate work with Robert Armstrong at UCLA and received a PhD in Organic Chemistry in 1996, focusing on synthetic and combinatorial chemistry. Dan then performed postdoctoral research in Peter Schultz's labs at UC Berkeley, where he increased his exposure to biology. In 1999, he started at Genentech, located in South San Francisco and has since worked on a variety of enzyme and protein small molecule targets directed towards the treatment of Cardiovascular, Oncology, and Immunology diseases. Following his work as a member Hedgehog Antagonist team, Dan has worked with another team to discover a novel compound for oncology that is currently in phase I clinical trials and served as a project leader for two kinase projects.

THE DISCOVERY OF THE HEDGEHOG ANTAGONIST GDC-0449 FOR THE TREATMENT OF SOLID TUMORS

Dan Sutherlin (1), Kirk Robarge (1), Shirley Brunton (2), Georgette Castanedo (1), Yong Cui (1), Michael Dina (1), Richard Goldsmith (1), Stephen Gould (3), Oivin Guichert (3), Janet Gunzner (1), Jason Halladay (1), Wei Jia (1), Cyrus Khojasteh (1), Michael Koehler (1), Karen Kotkow (3), Hank La (1), Rebecca LaLonde (1), Kevin Lau (1), Leslie Lee (1), Derek Marshall (1), James Marsters Jr (1), Lesley Murray (1), Changgeng Qian (3), Lee Rubin (3), Laurent Salphati (1), Mark Stanley (1), John Stibbard (3), Savita Ubhayaker (1), Shumei Wang (1), Susan Wong (1), Minli Xie (1)

(1) Genentech, Inc., (2) Evotech, (3) Curis, Inc.

Cellular pathways involved in cell differentiation and embryonic development have recently been implicated in cancer. In particular, the hedgehog pathway has been shown to be activated in BCC (basal cell carcinoma), some medublastomas, and a number of other epithelial cancers. Hedgehog ligands bind to the trans-membrane protein Patched (PTCH) which releases Smoothened (SMO) to transmit signals to the nucleus, resulting in the transcription of a number of proteins including the transcription factor Gli. Organic compounds, such as the plant derived cyclopamine, have been shown to block this signal transduction cascade by binding to SMO. Herein we report the discovery of a potent and efficacious small molecule inhibitor of the hedgehog pathway, identified via a systematic structure-activity process with an emphasis on superior pharmaceutical properties. The compound, GDC-0449, is currently being developed by Genentech as a novel cancer therapeutic and has advanced to Phase II clinical trials in patients with BCC, colorectal and ovarian cancers.

MOLECULAR RECOGNITION OF ANTITUMOUR DRUGS BY PROTEIN RECEPTORS. A 3D VIEW BY USING NMR

Jesús Jiménez-Barbero

Chemical and Physical Biology, Centro de Investigaciones Biológicas, C.S.I.C., Madrid, Spain

DEGREES *Ph. D. in Organic Chemistry, University Autónoma Madrid, 1987*
BSc in Chemistry, Madrid, 1982

EARLY RESEARCH ACTIVITY *CERMAV-CNRS, Grenoble, France, 1986*
Dept.of Chemistry, University of Zurich (Switzerland), 1988
National Institute for Medical Research, Mill Hill (UK) 1988
Carnegie Mellon Univ., Pittsburgh, USA; 1990-1992

POSITIONS IN ACADEMY *Full Professor, CSIC, Centro de Investigaciones Biológicas, 2002-*
Senior Research Scientist, CSIC, Inst. Quím. Org., 1996–2002
Tenure Scientist, CSIC, Instituto Química Orgánica, 1988–1996

VISITING PROFESSORSHIPS *ENS (Paris; 2004); UPMC (Paris; 2008); Milano Biccoca (2009-)*

AWARDS *Spanish Royal Society of Chemistry Janssen-Cilag Award in Organic Chemistry, 2003*
Spainsh Royal Society of Chemistry-Bruker Award in NMR, 2008

RESEARCH TOPICS *Over 300 papers and 13 PhD Theses supervised Molecular recognition. Interactions of ligands and inhibitors with receptors and enzymes, Protein-Carbohydrate Interactions, Biomolecular structure. NMR methods*

OTHER

- *Secretary General, Royal Society of Chemistry of Spain, 2004-.*
- *Member of the Editorial Boards of:* Chem. Eur. J. *2001-,* Org. Biomol Chem *2007-,* Carbohydr. Res. *2001-,* J. Carbohydr. Chem. *2002-,* Glycoconj. J *2008-,* Eur. J. Org. Chem. *2009- Scientific responsible: 4 national research grants (3 years) from academy and 4 from industry. 4 other from Comunidad de Madrid*
- *Participation in European Programmes: 6 TMR and RTN projects from the V, VI and VIIth Framework Programmes. COST actions: participation in 4 actions.*
- *More than 70 Invited or Plenary talks at international scientific conferences and institutions. More than 50 Invited or Plenary talks at National conferences and institutions*
- *Member of the Scientific and/or Organizing Commitees of more than 15 Symposia (Nat and Internat). Index h=34*
- *Research web: http://www.cib.csic.es/es/grupo_publicaciones.php?idgrupo=40*

MOLECULAR RECOGNITION OF ANTITUMOUR DRUGS BY PROTEIN RECEPTORS. A 3D VIEW BY USING NMR

Jesús Jiménez-Barbero

Chemical and Physical Biology, Centro de Investigaciones Biológicas, C.S.I.C., Madrid, Spain

Molecular recognition by specific targets is at the heart of the life processes. In recent years, it has been shown that the interactions between carbohydrates and proteins mediate a range of biological activities, starting from fertilization, embryogenesis, and tissue maturation, and extending to such pathological processes as tumor metastasis. The elucidation of the mechanisms that govern how saccharides are accommodated in the binding sites of receptors is a topic of major interest. In this context, the determination of the structural factors, which govern the molecular recognition of these molecules, as well as the knowledge of the physicochemical features of these processes, is of paramount importance for structure based drug design. The chemical nature of sugar-protein interaction has been a matter of debate for years. Due to the amphipatic character of the saccharide, different kind of forces may be involved in its recognition by receptors. The presence of the hydroxyl groups and the presence of water obviously makes possible their involvement in intermolecular hydrogen bonds to side-chains of polar aminoacids. Nevertheless, not only polar forces are involved in carbohydrate recognition. NMR and X-Ray diffraction data have shown that depending on the stereochemistry of the saccharide, the presence of a number of apolar C-H groups constitute patches that interact with the aromatic residues of protein side chains. We present an in-depth study of the origin of the intermolecular interaction between sugars and aromatics, with particular emphasis in its relationship with cancer processes. A comparison with the features deduced for the recognition of microtubule stabilizing drugs by assembled tubulin will also be presented.

FROM SINGLETON TO A SUCCESSFUL LEAD CLASS: A CASE STUDY OF KSP INHIBITORS

Peter Ettmayer

Department of Medicinal Chemistry, Boehringer Ingelheim, Vienna, Austria

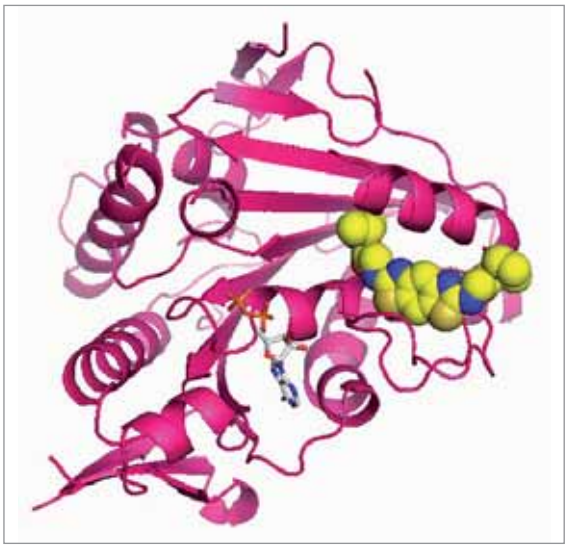
Peter Ettmayer graduated at the Vienna University of Technology, Austria, in synthetic organic chemistry and received his doctoral degree there in 1990 (sub auspiciis praesidentis). After a postdoctoral stay at the Christian Doppler Laboratories for Chiral Compounds & Chemical Synthesis he joined the Novartis Research Institute in Vienna as a laboratory head in the antiviral therapy area in 1991. In 1996 Peter worked one year at the Novartis research facility in New Jersey where he also received training in solid phase chemistry at Pharmacopeia, Princeton. His main research areas are in the areas of oncology, immunopathology and virology, covering many fields of medicinal chemistry, e.g. peptidomimetics, combinatorial chemistry and prodrugs. From 1999 to 2005 he was chairman of the medicinal chemistry section of the Austrian Chemical Society. Since October 2005 Peter heads the Lead Generation group at Boehringer Ingelheim Austria GmbH in the field of Oncology. He is the author of numerous publication and patents and acted as chairperson for the 2005 JMMC and 2008 EFMC-ISMC in Vienna.

FROM SINGLETON TO A SUCCESSFUL LEAD CLASS: A CASE STUDY OF KSP INHIBITORS

Ulrich Reiser, Gerd Bader, Peter Ettmayer, Lars Herfurth, Oliver Krämer, Dorothea Rudolph, Renate Schnitzer, Otmar Schaaf, Peter Sennhenn, Walter Spevak, Andreas Zöphel, Ulrike Tontsch-Grunt

Departments of Medicinal Chemistry, Exploratory Research and New Chemical Entities Pharmacology, Boehringer Ingelheim, Vienna, Austria

Mitosis is a fundamental process during cell division. The interest in mitotic kinesins as drug targets goes back to the discovery of Monastrol as a selective inhibitor of Kinesin spindle protein (KSP) also termed Eg5. KSP is a molecular motor essential for proper separation of the spindle poles during mitosis. Disruption of KSP function leads to the formation of monopolar spindles and prolonged mitotic arrest, triggering the apoptotic pathway in tumor cells. KSP inhibitors therefore have potential as antiproliferative agents useful for the treatment of cancer that might be devoid of side effects such as the neurotoxicity that is frequently observed with microtubules or tubuline targeting drugs. This talk will describe the structure-based optimization of an allosteric KSP inhibitor with a novel binding mode towards in-vivo efficacy in mice. The presentation will highlight the importance of the right balance of physicochemical properties to achieve potency, microsomal stability, solubility and to minimize P-glycoprotein efflux and ion channel activities.



SMALL-MOLECULE INHIBITORS OF HIV-1 REPLICATION TARGETING REVERSE TRANSCRIPTASE (RT) DIMERIZATION

María José Camarasa

Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3, 28006 Madrid, Spain

María José Camarasa received her Ph.D. degree in Chemistry from Madrid Complutense University. After a two-year post-doctoral stay at the Medicinal Chemistry Department of the University of Birmingham (U.K.), she returned to the Medicinal Chemistry Institute (IQM-CSIC), where in 1987 she became Tenured Scientist and succesively promoted to Senior Research Scientist (1995) and since 2002 to Research Professor (Full professor). She was head of the Chemotherapy department of the Institute of Medicinal Chemistry-CSIC and Vice-director of the Institute (1992-2002). She is head of the group of nucleosides and analogues (http://www.iqm.csic.es/paginas/nucleosidos/nucleosidos.html). She was President of the Spanish Society of Therapeutic Chemistry (SEQT) (2004-2007, http://www.seqt.org). She was on the executive board of the Chemistry Area of ANEP (2005-2008). She is a member of the executive board (Co-cordinator) of the Chemical Science and Technologies area of the CSIC. She is a member of International Advisory and Editorial Boards of Nucleosides, Nucleotides and Nucleic Acids (since 1998), Current Topics in Medicinal Chemistry (since 2005), ChemMedChem (since 2005), Current HIV Research (since 2006). Invited Editor for Special Issue of Current Topics in Medicinal Chemistry (2004).

Her main research interests are always oriented in the field of Medicinal Chemistry and particularly, in the design, synthesis and evaluation of novel sugars, nucleosides, heterocycles and peptides as enzymatic inhibitors with potential anticancer, antifungal and antiviral activity, specially against the human immunodefiency virus (HIV-1). She is recipient of several awards and prizes, including two international (UK) prizes. In 2001 she received the highly competitive and prestigous René Descartes Prize for Scientific and Technological Excellence through European collaborative research.

Her scientific contributions so far are among others ca. 170 papers in medicinal chemistry (in international peer-reviewed journals), reviews, book chapters and patents.

SMALL-MOLECULE INHIBITORS OF HIV-1 REPLICATION TARGETING REVERSE TRANSCRIPTASE (RT) DIMERIZATION

María José Camarasa

Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3, 28006 Madrid, Spain

In the third decade of the AIDS pandemic, this disease remains as one of the most important challenges for chemotherapy in the 21st century. The main pitfalls in the treatment of the disease are the relatively low selectivity of current drugs that is translated into many undesired side-effects and the development of drug-resistance that in turn is the major hurdle to ensure long-term suppression of the virus. Consequently, there remains an urgent need to devise and develop alternative treatment options, ideally directed towards novel targets or towards currently validated targets but through mechanisms that are different from those employed by the clinically used drugs.

There is a novel approach that exploits a new strategy, in terms of mechanism of inhibition of HIV-1 reverse transcriptase (RT) (an enzyme that plays a key role in the life cycle of HIV-1 replication). That is, the discovery and development of low-molecular-weight molecules able to disrupt the crucial protein-protein interaction taking place between p66 and p51 subunits in HIV-1 RT. The dimeric form of the enzyme is an absolute requirement for all enzymatic activities and the dimerization is essential for a fully functional RT. The development of inhibitors targeting RT dimerization thus represents a highly promising alternative antiviral strategy.

Figure 1. Binding mode of a Small-molecule, developed in our labs., to the p66(blue)/p51(pink) HIV-1 RT dimer interface

Targeting protein-protein interactions (PPIs) instead of catalytic sites with small drug-like molecules can be considered as a paradigm shift in drug discovery. Developing small molecules that modulate PPIs is difficult, owing to the lack of well-defined binding pockets. Till very recently, it has been considered that PPIs were the result of the sum of numerous low energy punctual interactions. However, it is now commonly accepted that just a few of these contributions are crucial for the protein-protein interaction. A significant contribution to the binding energy is localized in small regions that are designated as "hot spots".

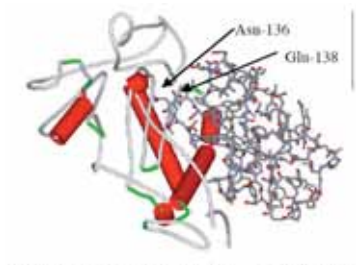


Figure 2. Detail of HIV-1 RT p66/p51 heterodimer

In the last few years our research group concentrated on the discovery of alternative HIV-1 RT dimerization inhibitors focussing on a dimerization "hot spot" of p51 subunit of HIV-1-RT that we have identified. The results of these efforts will be presented.

DISCOVERY OF THE MACROCYCLIC HCV PROTEASE INHIBITOR TMC435

Pierre Raboisson

Tibotec BVBA, Belgium

HCV Disease Area Chemistry Leader & Research Fellow at Tibotec (a division of Johnson & Johnson).

Pierre joined Tibotec in 2004. One of the major achievements was the discovery of TMC435, a protease inhibitor currently being evaluated in phase 2b clinical trials. Prior to this date, Pierre worked at Johnson & Johnson Springhouse and ArQule in the US. Pierre obtained his PhD, Master, and Pharmacist diplomas in Strasbourg (France) in the laboratory of Professor C.G. Wermuth. Pierre is the author and co-inventor of over 100 peer-reviewed scientific papers and patent applications.

DISCOVERY OF THE MACROCYCLIC HCV PROTEASE INHIBITOR TMC435

Pierre Raboisson (1), Kristof Van Emelen (1), Tse-I Lin (1), Herman de Kock (1), Sandrine Vendeville (1), Oliver Lenz (1), Åsa Rosenquist (1), Magnus Nilsson (2), Lotta Vrang (2), Wim Van de Vreken (1), David McGowan (1), Lili Hu (1), Abdellah Tahri (1), Frederic Delouvroy (1), Ismet Dorange (1), Piet Wigerinck (1), Bertil Samuelsson (2), Kenneth Simmen (1)

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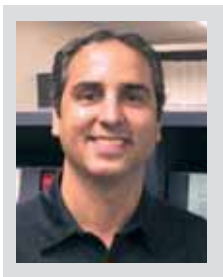
Hepatitis C virus (HCV)-encoded NS3/4A protease is essential for viral replication and represents an attractive target for therapeutic intervention in HCV-infected patients. Recent studies demonstrated that NS3/4A protease inhibitors are able to decrease HCV viremia, either as monotherapy or in addition to the current standard of care therapy. Lead optimization of a novel series of cyclopentane-containing macrocyclic NS3/4A serine protease inhibitors resulted in the discovery of the clinical candidate TMC435, a potent and specific inhibitor of HCV replication in genotype 1 replicon cells with an EC50 value of 8 nM and a selectivity index (SI) over 2000. Furthermore, TMC435 was found inactive across a representative panel of RNA and DNA viruses and exhibited synergistic effect with interferon-α (IFN-α) in reducing HCV replicon RNA and suppressing the emergence of drug resistant replicon colonies. Pharmacokinetic and safety pharmacology assessment prompted the selection of TMC435 as the lead candidate. This compound is currently in phase 2b clinical evaluation in HCV-Genotype 1 infected patients.

TELAPREVIR: DISCOVERY, HOMOLOGUES AND CLINICAL UPDATE



Youssef L. Bennani

Vertex Pharmaceuticals, 130 Waverly Street, Cambridge MA 02139

Youssef L. Bennani obtained his PhD degree in chemistry from the Universite de Montreal under Prof. S. Hanessian's guidance, followed by a postdoctoral stint at The Scipps Research Institute with Prof. K. B. Sharpless. He has been practicing medicinal chemistry in the areas of infection, immunology, oncology, CNS and metabolic diseases for over 15 years. He is currently Vice-President of Drug Innovation at Vertex Pharmaceuticals.

TELAPREVIR: DISCOVERY, HOMOLOGUES AND CLINICAL UPDATE

Youssef L. Bennani

Vertex Pharmaceuticals, 130 Waverly Street, Cambridge MA 02139

Hepatitis C is a viral infection (HCV) of the liver affecting an estimated 180 million people Worldwide. Current treatments include lnterferon and Ribavirin regimen lasting 48 weeks and resulting in an average 40-45% success rates. Telaprevir is an HCV protease inhibitor currently in phase 3 human clinical trials. The discovery, synthesis, pre-clinical profiling and SAR of Telaprevir, will be presented. Attempts to enhance its pharmacokinetic profile, through the synthesis of homologues and a clinical update will be presented.

INVITED SPEAKERS – IS.20

DRUG POLYPHARMACOLOGY IN COMPLEX DISEASES

Jordi Mestres

Chemogenomics Laboratory, Research Unit on Biomedical Informatics, Municipal Institute of Medical Research and University Pompeu Fabra, Barcelona, Catalonia (Spain)

Jordi Mestres was born in Girona, Catalonia (Spain) in 1967. He received a PhD in Computational Chemistry from the University of Girona in 1996. After a post-doctoral stay at Pharmacia&Upjohn (Kalamazoo, Michigan, USA), in 1997 he joined the Molecular Design & Informatics department at N.V. Organon (Oss, The Netherlands) and in 2000 he was appointed as Head of Computational Medicinal Chemistry at Organon Laboratories (Newhouse, Scotland, UK). In 2003, he took on his current position as Head of Chemogenomics at the Municipal Institute of Medical Research (Barcelona, Catalonia, Spain). His current research interests focus on the use of chemistry to probe biology and its applications to drug discovery.

DRUG POLYPHARMACOLOGY IN COMPLEX DISEASES

Jordi Mestres

Chemogenomics Laboratory, Research Unit on Biomedical Informatics, Municipal Institute of Medical Research and University Pompeu Fabra, Barcelona, Catalonia (Spain)

Systematic screening of drugs across multiple targets has revealed that their level of target promiscuity is higher than traditionally accepted[1], the most recent compilation of experimental data indicating average polypharmacology levels of 6 targets per drug[2]. The main message emerging from these data is that therapeutic efficacy in a compound is often linked to complex pharmacologies and although it may have been lately pursued through selective interaction with a protein target, it can be also attained with relatively weak perturbations on multiple targets[3,4]. The design of ligands binding efficiently to multiple targets is thus emerging as a new paradigm in drug discovery[5-7].

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6. Morphy, R. and Rankovic, Z. (2007) Fragments, network biology and designing multiple ligands. *Drug Discov. Today* 12, 156-160.
7. Mestres, J. and Gregori-Puigjané, E. (2009) Conciliating binding efficiency and polypharmacology. *Trends Pharmacol Sci.* 30, 470-474.

IMPACT OF DRUG TRANSPORTERS IN ABSORPTION, DISTRIBUTION AND ELIMINATION

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Neuropsychopharmacology of Drug Addictions
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Jean-Michel Scherrmann is professor of Pharmacokinetics, Faculty of Pharmacy, University Paris Descartes. He currently leads the Neuropsychopharmacology Unit at the French Institute of Health and Medical Research (INSERM) and the National Center of Scientific Research (CNRS).

He has made major contributions in the development of drug radioimmunoassay, drug detoxification by immunotherapy and drug redistribution concepts in pharmacokinetics.

He pionneered the first clinical application of colchicine immunotherapy in acute colchicine overdoses and is now focusing his research on the role of drug transporters in neuropharmacokinetics. His work has resulted in two patents, 290 scientific articles, 35 books chapters and more than 250 presentations. He has been a recipient of the 1992 Americal Academy of Clinical Toxicology Award and the 1999 French National Academy of Medicine Achievement Award. He is a Fellow of the American Association of Pharmaceutical Scientists and a member of the French National Academy of Pharmacy. He has been visiting Professor of Tohoku University (Japan) Graduate School of Pharmaceutical Sciences in 2008.

IMPACT OF DRUG TRANSPORTERS IN ABSORPTION, DISTRIBUTION AND ELIMINATION

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Neuropsychopharmacology of Drug Addictions

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Pharmacokinetics have been defined as the study of drug absorption, distribution, metabolism and excretion (ADME). Most of the molecular processes responsible for the fate of a drug in the body were attributed to the passive crossing of the bilayer cell membranes. Several drug descriptors like molecular weight, degree of ionization, and solubility were used to explain how a drug crossed biological membranes.

Pharmacokinetics is now challenged by the growing importance of transporters, a relatively new factor in drug ADME. There is no single mechanism by which drugs permeate through the membranes. The presence at membranes of transporters that facilitate the movement of solutes into cells – influx (import) transporters, and of transporters that remove substances from the cytosol of cells – efflux (export) transporters, modulates the traditional theory of "diffusional pharmacokinetics" towards "vectorial pharmacokinetics" in which ADME processes are more deterministically governed.

All these transporters have polyspecific transport properties. A wide range of drugs and metabolites, from conventional organic anions, cations and zwitterions to oligopeptides, can be simultaneously transported by one or more transporters. These transporters are also ubiquitous within the cells of all mammalian organs, including the intestine, liver and kidney, where they play key roles in the absorption and elimination of drugs. Their presence at all physiological blood-barriers make them critical components for regulating the tissue distribution of drugs. Drug transporters are also clinically important. They can modulate the pharmacological activity of drugs and are key players in drug-drug interactions.

21ST CENTURY DRUG METABOLISM

Russell J. Mortishire-Smith

Johnson & Johnson PR&D, Beerse, Belgium

Russell Mortishire-Smith did his doctoral studies on molecular recognition by natural products at the University of Cambridge, UK, and was a NATO postdoctoral fellow at the Scripps Research Institute, La Jolla where he worked on the structures of a variety of transcription-regulating proteins. Between 1993 and 2006, he was employed at Merck Sharp and Dohme's Neuroscience Research Centre in the UK supporting drug discovery projects by the application of the analytical sciences to a wide variety of challenges including structure elucidation, conformational analysis, metabonomics, and drug metabolism. In 2006 he joined the ADME/Tox department at Janssen Pharmaceutica in Belgium, where he is currently responsible for delivery of functional in vitro *and* in vivo *ADME data to the Research and Early Development unit.*

21ST CENTURY DRUG METABOLISM

Russell J. Mortishire-Smith

Johnson & Johnson PR&D, Beerse, Belgium

The reasons for characterising drug metabolites are well established in both the research and development phases of a project or compound's trajectory. Until relatively recently, approaches for identifying drug metabolites were based largely on predefined assumptions about the likely metabolic fate of a compound and its collisionally induced dissociation pathways. These assumptions necessarily limit the nature of the metabolites which will be found. The interpretation of mass spectrometric data, especially CID data, was largely a qualitative science residing in the realm of the expert. Newer approaches using the power of generic high resolution LC/MS methodology, together with systematic data analysis and interpretation algorithms have dramatically increased both the rate at which biotransformation data can be fed back into projects, and the value of the data which is thus provided. In particular *in vivo* drug metabolism studies can be performed without the need for radiolabels. The scope and future of available tools for data analysis will be covered, together with examples of how these new strategies have been used to best effect.

DRUGGING THE "UNDRUGGABLE"

Gregory L. Verdine

Harvard University, USA

Greg Verdine is the Director of the Program in Cancer Chemical Biology at the Dana-Farber Cancer Institute, and is the Erving Professor of Chemistry at Harvard University. He holds academic appointments at Harvard in the Department of Stem Cell and Regenerative Biology (SCRB, primary), Chemistry and Chemical Biology (CCB, voting), and Molecular and Cellular Biology (MCB, affiliate). His Dana-Farber research effort aims to discover entirely new molecular classes of drugs to tackle so-called "undruggable" targets, while his work in the Harvard Faculty of Arts and Sciences focuses on understanding fundamental aspects of DNA damage recognition and repair. Verdine is a senior advisor to Third Rock Ventures and the Texas Pacific Group, and has founded, co-founded or re-founded six biopharmaceutical companies.

DRUGGING THE "UNDRUGGABLE"

Gregory L. Verdine

Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University and Chemical Biology Initiative and Program in Cancer Chemical Biology, Dana-Farber Cancer Institute

One of the most vexing problems in life science is that of "undruggability," the difficulty of targeting certain biological macromolecules in vivo using existing drug or ligand discovery technologies. It has been estimated that as many as 80-90% of all potential targets, including many that have been extensively validated in humans and in animal models, are undruggable. The Verdine laboratory is developing powerful new chemistry-based platform technologies to address these undruggable targets. Specifically, the lab is developing "synthetic biologics," molecules that, like biologics, possess the ability to target large flat surfaces, but that, like small molecules, are fully synthetic and hence can be modified at will. Progress on the development of one class of synthetic biologics – hydrocarbon-stapled alpha-helical peptides – will be reviewed in this talk.