WORKSHOP ON
DRUG DISCOVERY AND NANOMEDICINE

Porto Alegre
March 29 to 30, 2016

Federal University of Rio Grande do Sul
Institute of Chemistry
Av. Bento Gonçalves, 9500
Amphitheatre (43111, A212)
Federal University of Rio Grande do Sul is pleased to host the Workshop on Drug Discovery and Nanomedicine
President: Prof. Carlos Alexandre Netto
Vice President: Prof. Rui Vicente Oppermann

Center of Nanoscience and Nanotechnology
Director: Prof. Silva S. Gutteres
Vice Director: Dr. Naira M. Balzaretti

Institute of Chemistry
Director: Prof. Nadya Pesce da Silveira
Vice Director: Dr. Henri Stephan Schrekker

Newton Fund/UK Deputy: Ms. Fernanda Silva

Workshop on Drug Discovery and Nanomedicine
Coordinators:
Prof. Adriana R. Pohlmann (UFRGS)
Dr. Nicholas Holliday (Univ. Nottingham)

Mentors:
Dr. Rafael Roesler (UFRGS)
Prof. Steven Charlton (Univ. Nottingham)

Our goal is to bring together a UK and Brazilian cohort of early career researchers to take part in a workshop focusing on building links for future collaboration and enhancing the researchers’ career opportunities. The workshop content is centred on drug discovery and nanomedicine.
PROGRAM
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<tr>
<td>8:30</td>
<td>Opening Ceremony</td>
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<tr>
<td>9:00</td>
<td>Conference 1 Prof. Steven Charlton (University of Nottingham, UK)</td>
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<td><em>The importance of target binding kinetics in drug discovery</em></td>
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<td>9:45</td>
<td>Lecture 1 Dr. Brian Hudson (University of Glasgow, UK)</td>
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<td><em>Unlocking the Therapeutic Potential of the FFA4 Long Chain Fatty Acid Receptor</em></td>
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<td>10:15</td>
<td>Lecture 2 Dr. Dyeison Antonow (PUC-RS, Brazil)</td>
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<td><em>Drug Delivery Systems: Targeted Therapies based on Antibody-Drug Conjugates (ADCs)</em></td>
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<td>11:10</td>
<td>Pharmacology 101 – session 1</td>
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<td>Lecture 3 Dr. Sophie Bradley (Medical Research Council Toxicology Unit, UK)</td>
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<td><em>Targeting the M1 muscarinic acetylcholine receptor in neurodegeneration</em></td>
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<td>12:20</td>
<td>Discussion</td>
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<td>Lunch</td>
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<td>Conference 2 Dr. Rafael Roesler (UFRGS, Brazil)</td>
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<td><em>Gastrin-releasing peptide receptors in the central nervous system: role in brain function and as a drug target</em></td>
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<td>Lecture 4 Dr. Margaret Cunningham (University of Strathclyde, UK)</td>
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<td><em>A multidisciplinary approach to thrombin receptor research: Targeting proteinase-activated receptors as an antiplatelet strategy</em></td>
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<td>3:15</td>
<td>Lecture 5 Dr. Marcelo Bispo de Jesus (UNICAMP, Brazil)</td>
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<td><em>Cellular Mechanisms in Nanomaterial Internalization, Intracellular Trafficking, and Toxicity</em></td>
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<td>4:10</td>
<td>Pharmacology 101 – session 2</td>
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<td>Return to the Hotel</td>
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### Wednesday, March 30th

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<tr>
<td>9:00</td>
<td>Conference 3 Prof. Adriana R. Pohlmann (UFRGS, Brazil)</td>
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<td><em>Polymeric nanocapsules as promising nanocarriers in therapeutics</em></td>
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<td>9:45</td>
<td>Lecture 6 Dr. André Luís Branco de Barros (UFMG, Brazil)</td>
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<td><em>Radiolabeled nanoparticles as alternative tool for cancer diagnosis</em></td>
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<td>10:15</td>
<td>Lecture 7 Dr. Irene Clemes Kulkamp Guerreiro (UFRGS, Brazil)</td>
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<td><em>Antifungal and antiretroviral drugs nanoencapsulation: Could it be</em></td>
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<td><em>an efficient strategy to improve actual therapy?</em></td>
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<td>11:10</td>
<td>Pharmacology 101 – session 3</td>
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<td>11:50</td>
<td>Lecture 8 Dr. Javier Hernández Gil (Imperial College London, UK)</td>
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<td><em>Tumour-Targeted and Matrix Metalloproteinase-Responsive Iron Oxide</em></td>
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<td><em>Nanoparticles for Theranostic Applications</em></td>
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<td><em>fluorescence complementation and imaging approaches</em></td>
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<td>2:45</td>
<td>Lecture 9 Dr. Elizabeth Rosethorne (University of Nottingham, UK)</td>
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<td><em>Using Phenotypic Assays to Explore Ep4 Agonism in Airway Remodelling</em></td>
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<td>3:15</td>
<td>Lecture 10 Dr. Ana Rosa Lopes Pereira Ribeiro (INMETRO, Brazil)</td>
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<td><em>Biomineralization of Anatase Nanoparticles and its Implications in</em></td>
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<td><em>Bone cells Survival</em></td>
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<td>4:00</td>
<td>Group competition – due diligence exercise and Final remarks</td>
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<td>Return to the Hotel</td>
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COORDINATORS AND MENTORS
Coordinators
Associate Prof Nicholas D Holliday
Dr Nick Holliday was appointed Associate Professor of Molecular Pharmacology in 2013, after previously holding a Lectureship (since 2011) and a five year research fellowship in the School of Life Sciences at Nottingham. Following first class honours from the University of Cambridge (1994), Nick carried out his PhD studies at King’s College London (1998), supported by a prize AJ Clark PhD studentship from the British Pharmacological Society. It was during subsequent postdoctoral work in London that his interests in peptide messengers regulating appetite and metabolism became focused on molecular mechanisms underlying the signalling and regulation of their receptors, which led to the Nottingham appointment. Since then, Dr. Holliday has built a research group investigating these and other G protein coupled receptors (GPCRs), the largest class of drug targets in man. He has specialised in quantitative pharmacological and signalling assays based on novel fluorescence techniques and automated imaging for use in drug discovery, with 14 primary papers since 2010. His particular expertise in bimolecular fluorescence complementation methods to study signalling partner interactions arose initially through Medical Research Council funding establishing assays for GPCR association with arrestin proteins, and to quantify pharmacology of defined receptor oligomers (Kilpatrick et al. (2010) Br J Pharmacol; Watson et al (2012) Mol Pharmacol; Kilpatrick et al. (2015) Mol Pharmacol). Dr Holliday also pioneered developments of this technology necessary to study signalling complexes using advanced imaging methods such as fluorescence correlation spectroscopy (Kilpatrick et al (2012) Biochimica Biophysica Acta Mol Cell Res), and adaptation of these techniques to membrane transporters and transcription factors (Evans et al (2011) Nuc Acids Res; Haider et al (2011) PloS ONE; Alqahtani et al (2014) Open Biol; Wong et al (2015) Biochimica Biophysic Acta, in press). This work was recognised by the prize award of the 2011 Bill Bowman lectureship from the British Pharmacological Society, together with several invited reviews (e.g. Kilpatrick & Holliday (2012) Methods Mol Biol; Sivertsen et al (2013) Br J Pharmacol; Stott et al (2015) Biochem Pharmacol in press). It continues to support high calibre international academic collaborations (e.g. Mountford et al (2014) Org Biomol Chem; Valentin-Hansen et al (2015) J Biol Chem), including as UK lead for CAPES Drug Discovery Award held by Prof Roesler, together industrial funding (e.g. GSK, AstraZeneca, NovoNordisk). Dr Holliday leads undergraduate pharmacology modules in pharmacy and neuroscience, and has trained 9 PhD students since 2009, three of which have won prize studentships or presentation prizes at international conferences. He is on the editorial board of Pharmacology Research and Perspectives, and also has been actively involved in public engagement, including an arts crossover project to explain the use of imaging in pharmacology (“Hijacking Natural Systems”), funded by the Wellcome Trust.

Prof. Adriana R. Pohlmann
Adriana R. Pohlmann, Full Professor of Organic Chemistry at the Chemistry Institute of the Universidade Federal do Rio Grande do Sul in Porto Alegre, Brazil, received her Graduation in Pharmacy (1985) and Master in Chemistry (1991) at UFRGS, and Doctorate Degree in Therapeutic Chemistry at the University of Paris V, France (1997). In 1998, she received the prestigious Roussel-Uclaf award for her Dissertation and a Laureate Diploma from the College of Pharmaceutical and Biological Sciences, University of Paris V, France. She served as Head of the Department of Organic Chemistry (1999-2001), as First Director of the Center of Nanoscience and Nanotechnology at UFRGS (2006), as member of the Committee of the Postgraduate Program in Chemistry (2001-2003; 2009-2011), Coordinator of the Post-Graduate Program on
Pharmaceutical Nanotechnology (2013-2015) and as Vice-Director of the Institute of Chemistry (2003-2007). She also served as the Vice-Director of the Brazilian National Nanotechnology Network, and Coordinator of an international collaborative IBSA project between India, Brazil and South Africa both supported by the Brazilian Ministry of Science and Technology. She is a recognized researcher at the National Council for Scientific and Technological Development (CNPq/Brazil) leading the group: Micro- and nanoparticles for therapeutics. She currently advises Graduate and Post-Graduate students in Chemistry, Pharmaceutical Sciences and Pharmaceutical Nanotechnology. Her main research is focused on the organic chemistry applied to drug nanocarriers, including polymeric nanocapsules and nanospheres, with the view of understanding and controlling their sizes, shape, surface and physico-chemical properties. She has published more than 200 peer-reviewed articles, 3 books and 19 book chapters. Her research group holds 50 patents and transferred 7 products to a Brazilian Company, reaching the market since 2009. She currently serves as Ad-hoc reviewer for more than 25 International Scientific Journals, for Brazilian Agencies to support scientific research, and as Associate Editor of the Journal of Nanoscience and Nanotechnology and the Journal of Colloid Science and Biotechnology, Editorial Board member of the Journal of Nanopharmaceutics and Drug Delivery and the Journal of Biomedical Nanotechnology (American Scientific Publishers). She is also a member of the Brazilian Association of Pharmaceutical Scientists and of the Brazilian Chemical Society.

Mentors
Prof Steven Charlton
Prof Charlton has recently joined the University of Nottingham where he is Professor of Molecular Pharmacology and Drug Discovery. Prior to that he spent 16 years in the pharmaceutical industry, both at SmithKline Beecham and Novartis. At Novartis he was Director of Molecular Pharmacology in Respiratory Diseases, leading an assay development and compound profiling team of 30 scientists providing expert opinion and support for GPCR, ion channel and enzyme projects. He has broad drug discovery experience, ranging from target validation through to leading full lead optimisation programmes to successful clinical proof of concept. He is interested in all aspects of the quantitative assessment of ligand-receptor interactions, with a particular interest in the kinetics of ligand binding and signalling. Prof Charlton serves as an editor of the British Journal of Pharmacology and is actively engaged in training new pharmacologists, working closely with the British Pharmacological Society to organise scientific symposia and teaching workshops. Prof Charlton was awarded Novartis Leading Scientist in 2007.

Associate Prof Rafael Roesler
Dr. Rafael Roesler, Associate Professor in the Department of Pharmacology, Institute for Basic Health Sciences, Federal University of Rio Grande do Sul has published more than 190 articles, 11 book chapters and holds 6 patents. Head, Cancer and Neurobiology Laboratory, University Hospital Experimental Research Centre (CPE-HCPA) focuses his research interest on biology and pharmacology of neurotransmitter and neuropeptide receptors; neurobiology and neuropharmacology of synaptic plasticity and memory; brain tumour biology and pharmacology; cell signalling in brain function, brain disorders, and cancer.
ABSTRACTS
The importance of target binding kinetics in drug discovery
Prof Steven Charlton, Molecular Pharmacology and Drug Discovery, University of Nottingham

Optimizing the receptor binding kinetics of new drugs can have significant benefits, ranging from improved duration of action to enhanced efficacy through the insurmountable antagonism of dynamic physiological systems. It is also becoming apparent that binding kinetics plays a role in the phenomenon of biased agonism. Despite this, the kinetics of new receptor ligands are rarely measured early in the drug discovery process, largely because current assays are technically difficult and relatively low-throughput.

This talk will introduce the potential clinical benefits of optimising binding kinetics and review the current methods for measuring kinetic parameters. It will then describe the development of a novel approach using time-resolved FRET in continuous read mode that is capable of simultaneously measuring the kinetics of hundreds of compounds. This offers the potential for placing a kinetics assay at the top of a screening cascade, negating the need to first run “IC50 curves” to assess affinity at the receptor. It also presents the opportunity to screen fragment libraries at receptors in a kinetic mode. Finally, the talk will end with a discussion on the concept of “micro pharmacokinetics” and how the local drug concentrations around the receptor must be taken into consideration when interpreting the kinetics of new receptor ligands.

Selected publications


Unlocking the Therapeutic Potential of the FFA4 Long Chain Fatty Acid Receptor

Dr Brian Hudson, Leadership Fellow, Institute of Molecular Cell and Systems Biology, University of Glasgow
http://www.gla.ac.uk/researchinstitutes/biology/staff/brianhudson/

Abstract: I am interested in the link between the fats obtained through diet and our health. In particular, long chain fatty acids derived from dietary fats regulate two G protein-coupled receptors: FFA1 and FFA4. My research focuses on building our understanding of these receptors, in particular FFA4, in order to better understand how to target them for metabolic disease. This has led to the identification of the first potent and selective FFA4 agonist, detailed characterization of its pharmacology, and defining the molecular basis for its interaction with FFA4. To further refine our understanding of the therapeutic potential of FFA4, my current focus is on developing biosensor technologies, based primarily on bioluminescence resonance energy transfer, to assess complex aspects of FFA4 pharmacology; including: ligand binding kinetics, receptor activation kinetics, active receptor conformations, and signaling bias. My long-term goal is to use these biosensors to identify the optimal properties for FFA4 targeting therapeutics.

Selected publications (FFA4 related marked with *):


Drug Delivery Systems: Targeted Therapies based on Antibody-Drug Conjugates (ADCs).

Dr. Dyeison Antonow: Associate Professor at the Faculty of Medicine – PUCRS.

http://lattes.cnpq.br/2698938968819675

Abstract: Biological agents such as therapeutic technologies based on monoclonal antibodies (mAbs) are established in the pharmaceutical market, especially in oncology. Trastuzumab (Herceptin®) and cetuximab (Erbitux®) are good examples of this class of targeted therapies against cancer. Therapeutic mAbs are selectively active against a variety of tumour types and considerably less toxic when compared with cytotoxic agents from standard chemotherapy. However, these biological agents may have problems related to resistance and are associated with a number of other challenges in the clinical setting. An exciting development in the targeted therapy is the move towards antibody-drug conjugates (ADCs). In general, ADCs are complex drug-delivery systems made of three main components: mAb, linker (which can be self-immolative), and the drug itself, often called the “payload”. While biologically-inactive themselves, these “warheads” or “payloads” can be released from the therapeutic antibody to form potent cytotoxic compounds at the antibody-targeted tumour site. The first ADCs used molecules such as the enediyynes or maytansinoids that suffer from significant drawbacks including high molecular weight and limited availability from natural sources. Even so, a number of ADCs have made to the clinic and they are advancing rapidly through pharmaceutical industries pipelines. For example, in 2011 the FDA granted accelerated approval to brentuximab vedotin (Adcetris®, Seattle Genetics) for two types of lymphoma. More recently the FDA has approved ado-trastuzumab emtansine (Kadcyla®, Genentech/Roche), for patients with HER2-positive metastatic breast cancer who had previously received treatment with trastuzumab. Importantly, ADCs still have a number of regulatory challenges and is a very active area of research. Highly innovative aspects of ADC-based therapies make them particularly attractive for entrepreneurial initiatives and a number of companies have been exploring the ADC technology towards clinical benefits. In this session, Dr. Antonow (PUCRS, Brazil) will discuss the use of natural products as payloads, linker strategies, and basic aspects for the generation of ADCs as candidates for clinical development.

Recommended reading:

http://onlinelibrary.wiley.com/doi/10.1111/cbdd.12085/abstract;jsessionid=858C80080E0CD46D279B35BB52A266A2.f01t02


http://pubs.acs.org/doi/abs/10.1021/cr100120f
Targeting the M₁ muscarinic acetylcholine receptor in neurodegeneration

Dr. Sophie Bradley, Career Development Fellow, MRC Toxicology Unit, Leicester

**Abstract:** Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's, and the less-common prion diseases, are characterized by progressive neuronal atrophy and cognitive dysfunction. Muscarinic acetylcholine receptors (mACHRs) regulate an array of CNS processes, including cognitive, behavioural and motor functions. The M₁ mACHR subtype is widely expressed post-synaptically in the cortex and the hippocampus (areas known to be important in learning and memory) and here we show that M₁ deficient mice have a deficit in hippocampal-dependent learning and memory. In this study, we have used a well-established mouse model of neurodegeneration to further explore the therapeutic potential of M₁ mACHR ligands in restoring cholinergic function and cognition in AD.

Prion-infected tg37 mice develop early pathological changes at 7 weeks post infection (wpi) with Rocky Mountain Laboratory (RML) scrapie prion. At 9 wpi, mice display a decline in burrowing behaviour and an abrupt reduction in synaptic proteins, rapidly followed by neurodegeneration, with 50% loss of hippocampal pyramidal neurons by 10 wpi (Moreno *et al.*, 2012). Choline acetyltransferase levels in the hippocampus of prion-infected mice are reduced from 9 wpi, indicating degeneration of cholinergic neurons. However, M₁ mACHR expression and G-protein coupling at 9- and 10 wpi is maintained. Prion-diseased mice display reduced fear conditioning responses at 9 wpi. This impairment in learning and memory is rescued by xanomeline, an M₁ and M₄ orthosteric agonist, and also by BQCA and BQZ12, M₁-specific allosteric agonists. Furthermore, we show that xanomeline modulates postsynaptic activity and AMPA receptor phosphorylation in the hippocampus of prion-diseased mice.

In conclusion, prion-infected mice undergo cholinergic degeneration in the hippocampus, which is accompanied by a significant reduction in fear learning and memory. We show that targeting muscarinic receptor activity, with both orthosteric and allosteric ligands, can rescue the cognitive deficit in prion-diseased mice.

Selected publications:


Gastrin-releasing peptide receptors in the central nervous system: role in brain function and as a drug target
Prof. Rafael Roesler, Department of Pharmacology, Institute for Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil; Cancer and Neurobiology Laboratory, Experimental Research Center, Clinical Hospital (CPE-HCPA), Porto Alegre, RS, Brazil

Abstract: Neuropeptides act as signaling molecules that regulate a range of aspects of brain function. Gastrin-releasing peptide (GRP), a mammalian neuropeptide homolog of the amphibian peptide bombesin, acts by binding to the GRP receptor (GRPR, also called BB2), a member of the G-protein coupled receptor (GPCR) superfamily. GRPR signaling modulates memory formation, serving as a component of the set of neurobiological systems underlying the enhancement of memory storage by emotionally arousing information. In addition, some alterations in the GRP/GRPR system have been described in patients with neurological disorders or brain tumors. Findings from preclinical models are consistent with the view that drugs acting on the GRPR might ameliorate cognitive and social deficits associated with neurological diseases and reduce the growth of brain cancer.
A multidisciplinary approach to thrombin receptor research: Targeting proteinase-activated receptors as an antiplatelet strategy.

Dr Margaret Cunningham, Chancellor Research Fellow, University of Strathclyde


Abstract: The focus of our research is identifying targets for the development new or improved antiplatelet therapies. One target of interest is the GPCR family called proteinase-activated receptors (PARs), which are known to regulate thrombin activity in hemostasis and thrombosis. We have employed a variety of approaches to identify regulatory pathways that could be exploited to target members of the PAR family and limit the pro-thrombotic activity of thrombin. These approaches include SILAC mass spec-based quantitative proteomics to identify PAR-protein and variant PAR-protein interacting complexes. Recently we have identified patients harboring a novel PAR4 variant with defective receptor trafficking that result in inhibition of platelet aggregation, activation and a mild bleeding phenotype. Follow-up proteomic analysis has revealed critical changes in the variant PAR4 interactome and highlighted potentially new paradigms for GPCR regulation which we are currently investigating. In addition to this, we are currently screening new (and existing) synthetic modulators of PARs to assess their pharmacology and determine their use as inhibitors of platelet activation and aggregation. The plan is to test these further on a recently customized multi-panel biomimetic microfluidic thrombosis device (IC50-on-a-chip).

Selected publications (PAR starred):

* Cunningham, M.R., McIntosh, K.A., Bushell, T.J., Sloan, G., and Plevin, R. (2016) Proteinase-activated receptors (PARs) as targets for antiplatelet therapy. Biochemical Society Transactions. DOI: 10.1042/BST20150282 Accepted 05/02/2016 (Review)


Cellular Mechanisms in Nanomaterial Internalization, Intracellular Trafficking, and Toxicity

Dr Marcelo Bispo de Jesus, Associate Professor of Biochemistry, University of Campinas

https://scholar.google.com.br/citations?user=PGvSnuQAAAAJ&hl=en

Abstract: Nanomaterials are expected to have a significant impact on medicine, although they still need to overcome several challenges before they are widely used. Understanding the molecular interaction of nanomaterials in the context of the cellular environment is crucial for the successful applications of nanomaterials. Therefore, the groups’ primary research goals are directed towards understanding the molecular basis of interactions between nanomaterials and eukaryotic cells (animal and plants). More specifically we are interested in intracellular delivery of contents (e.g., gene delivery) and toxic effects of nanomaterials to cells (nanotoxicity). In the past years we were acting on the following topics: endocytosis and intracellular trafficking of nanoparticles, nanotoxicology (in vitro and in vivo), solid lipid nanoparticles and non-viral transfection systems (gene delivery).

Selected publications:

Research articles:


Solid lipid nanoparticles as nucleic acid delivery system: Properties and molecular mechanisms. de Jesus MB, Zuhorn IS. Journal of Controlled Release, 2015. PMID: 25578828


Book chapter:

Polymeric nanocapsules as promising nanocarriers in therapeutics

Prof. Adriana Raffin Pohlmann, Institute of Chemistry, Federal University of Rio Grande do Sul

Abstract: Biodegradable nanocarriers have been studied as a promising alternative to therapeutics. The control of size distribution, by using self-assembly methods of preparation, affects the drug biodistribution and release. Some advantages of the nanoparticulate systems are related to the drug targeting reducing side effects and increasing therapeutic index. The presentation addresses the aspects of the synthesis of lipid-core nanocapsules, an original type of carrier useful to encapsulate poorly water-soluble drugs, as well as their surface functionalization by organometallic complex formation at the surface of multi-wall nanocapsules. Examples of physico-chemical characterization and biological applications of surface-functionalized lipid-core nanocapsules are discussed: i) LDL(-) molecular recognition aiming atherosclerosis prevention, and ii) enzyme replacement therapy in pre-clinical model of Mucopolysaccharidosis type I. (CNPq, CAPES, FAPERGS)

Selected publications:


Radiolabeled nanoparticles as alternative tool for cancer diagnosis and therapy
Dr. Andre Luis Branco de Barros, Assistant Professor of Radiopharmacy, Universidade Federal de Minas Gerais

Abstract: Our group focuses on the development of new nanoplatforms for detection and treatment of cancer. In this specific field, we have been working with radiolabeled nanoparticles (liposomes, micelles, solid lipid nanoparticles) as theranostic probes. In these sense, we have developed new formulations to reduce side effects and improve antitumoral activity of drugs, moreover these formulations are able to monitor tumor extent by scintigraphic images. For example, we have developed pH-sensitive liposomes for specifically delivery the radiopharmaceutical (\(^{99m}\text{Tc-HYNIC-} \cdot \text{Al}-\text{bombesin}_{[7-16]}\)) to tumor sites. This approach have improved tumor uptake leading to high quality images, which may help in the diagnosis of this malignancy. In another study, we develop radiolabeled Solid Lipid Nanoparticles (SLN) loading doxorubicin as a theranostic probe. Tumor could be visualized by scintigraphic images and SLN improve the efficacy of the treatment. Other nanoparticles have been studied in our group with promising results in diagnosis and/or treatment of cancer.

Selected publications (NPY starred):

Antifungal and antiretroviral drugs nanoencapsulation: Could it be an efficient strategy to improve actual therapy?

Dr Irene Clemes Külkamp Guerreiro, Federal University do Rio Grande do Sul
http://lattes.cnpq.br/9385103078887175

Abstract: The focus of our research group is to understand how the nanoencapsulation could improve in fact the therapy of fungal and HIV infections. Besides the promises related to the applications of nanotechnology to drugs, we need proofs of the better action of the nanoencapsulated drugs. We aimed to find the enhancement of the therapy of fungal infections, mainly related to drug action and microorganisms resistance. We have also been working on the development of pharmaceutical dosage forms suitable for children use. We have been using different approaches to prepare and characterize nanotechnological formulations, and to prove the therapy enhancement reached by the nanoencapsulation. As examples, we can highlight the improvement of ketoconazole and fluconazole drug action, overcoming fluconazole resistance, and the nanoencapsulation of saquinavir reaching a liquid formulation with taste masking.

Selected publications:


Tumour-Targeted and Matrix Metalloproteinase-Responsive Iron Oxide Nanoparticles for Theranostic Applications

Dr Javier Hernández-Gil, Research Associate, Department of Chemistry, Imperial College London
http://www.imperial.ac.uk/people/j.hernandez-gil

Abstract: The application of nanotechnology in medicine offers extraordinary opportunities to yield advances in the diagnosis and treatment of cancer. To achieve these goals, inorganic nanoparticle (iNPs) have attracted considerable interest due to their unique and versatile electronic, optical, plasmonic and magnetic properties. Nowadays, it seems clear that modern iNPs can be more than just “imaging” or “therapeutic” probes and, combine both features to enable detection and treatment of disease in a single procedure (“theranostic” agents). However, these iNP-based systems still need to tackle issues such as insufficient sensitivity, limited spatial and temporal resolution, efficient tumour targeting, undesirable off-target activities and, simple preparation/purification before being real candidates for clinical translation. Through a “multimodal imaging” approach, nanoparticles can help to overcome the intrinsic limitations of each imaging modality towards diagnosing/staging the disease. On the other hand, through a “multimodal therapy” design, nanoparticles can exhibit a synergistic cancer cell killing effect by exploiting different complementary drug payloads, cellular targets and “off-target” effects. At the workshop, I will present our last efforts to develop a “theranostic” agent that upon an enzyme-controlled stimulus offers the possibility of dual-modality imaging and drug release in cancerous tissue.

The oral presentation will start introducing our initial proof-of-concept in this regard: two sets of superparamagnetic iron oxide NPs that selectively aggregate in the presence of cancer-specific matrix metalloproteinases (MMP). The self-assembled nanoclusters induce a magnetic resonance (MR) signal amplification and therefore in vivo cancer detection. Then, I will discuss ongoing results on developing the second-generation system that aims to overcome detected limitations from the original design such as large hydrodynamic size, sub-optimal coupling rates and, insufficient PEG length. The new nanoconstructs can be also easily radiolabelled with $^{68}$Ga for positron emission tomography (PET). The dual-mode MR-PET probe can enable high spatial resolution (MR) and extreme sensitivity (PET) in a single unit, improving tumour detection and in vivo tracking. Finally, I will show our strategy to provide the constructs with therapeutic properties. Through surface functionalization, one set of iNPs will contain gatekeepers that specifically respond to the other set of iNPs upon the MMP-triggered self-assembly process and therefore, leading to on-demand release of therapeutic molecules. I believe these nanoconstructs hold considerable promise as new delivery vehicles for developing more selective and/or efficient materials for drug delivery.

Selected publications (initial proof-of-concept starred):
Shedding light on G protein coupled receptor pharmacology using fluorescence complementation and imaging approaches

Dr Nick Holliday, Associate Professor of Pharmacology, University of Nottingham
http://www.nottingham.ac.uk/life-sciences/people/nicholas.holliday

Abstract: Our group focuses on the mechanisms driving the signalling, intracellular trafficking and ligand pharmacology of GPCRs for peptides such as neuropeptide Y and ghrelin, and nutrients such as free fatty acids – all of which are implicated in the control of appetite, body weight and insulin secretion. We use a variety of approaches, especially high content fluorescent imaging and quantitative analysis of fluorescent ligand binding, receptor endocytosis and receptor interaction with associated signalling proteins. Recently for example, we have applied bimolecular fluorescence complementation (BiFC) to study interactions between GPCRs and signalling partners known as arrestins, and also to examine the function of particular receptor homo- and heterodimers. This is a route to explore the pharmacology of particular receptor heterodimers selectively and quantitatively (for example, the NPY Y1/Y5 dimer proposed to regulate appetite), and it has also allowed investigation of key signalling complexes using advanced imaging methods such as fluorescence correlation spectroscopy.

Selected publications:


Use of phenotypic assays to explore $G_s$-coupled receptor agonism in airway remodelling.

Dr Elizabeth M Rosethorne, Snr Research Fellow, University of Nottingham

Abstract: One of the major research themes in our group is the use of human primary cells to explore GPCR pharmacology. My specific interests include the use of phenotypic assays to identify novel targets for disease, the exploration of biased signalling and the role of signalling kinetics in determining agonist efficacy. My current research is focussed on the role of the second messenger cAMP in the inhibition of the airway remodelling observed in respiratory diseases such as pulmonary fibrosis and severe asthma. The reason for this is that in addition to the acute bronchoconstriction observed in patients with asthma, there are a number of studies demonstrating that severe, persistent asthma is selectively associated with increased airway smooth muscle and fibroblast accumulation resulting in pathological airway remodelling. Here we have used isolated primary human cells to investigate the potential for $G_s$-coupled receptor agonists to inhibit the proliferation and differentiation of airway smooth muscle cells and fibroblasts. We have also demonstrated that the anti-proliferative effects of $G_s$-coupled receptors may not be solely dependent on global cAMP accumulation. This highlights the importance of monitoring the kinetics and localisation of intracellular signals, as well as multiple intracellular signalling pathways when profiling novel compounds, as endpoint population second messenger assays may not always predict phenotypic outcomes.

Selected peer reviewed publications:


Biomineralization of Anatase Nanoparticles and its Implications in Bone Cells Survival

Dr Ana Ribeiro, Researcher Scientist, Metrology Division Applied to Health Sciences, National Institute of Metrology Quality and Technology

**Abstract:** Dentistry and orthopedics are undergoing a revolution in order to provide more reliable, comfortable and long-lasting implants to patients. Titanium (Ti) and titanium alloys have been used in dental implants and total hip arthroplasty due to their excellent biocompatibility. However, Ti-based implants in human body suffer surface degradation (corrosion and wear) resulting in the release of metallic ions and solid wear debris (mainly titanium dioxide) leading to peri-implant inflammatory reactions. Unfortunately, our current understanding of the biological interactions with titanium dioxide nanoparticles is still very limited. Taking this into consideration, this study focuses on the internalization of titanium dioxide nanoparticles on primary bone cells, exploring the events occurring at the nano-bio interface. In the complex biological environment, anatase nanoparticles form bio-complexes (mixture of proteins and ions) resulting in a kind of Trojan horse that facilitates their internalization by cells.

**Selected publications:**


Execution:

Support: