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Conferencia: Building Defined Protein-Drug Conjugates for Targeted Cancer Therapy

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10/10/14

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Aula de Seminarios do CIQUS

9:30 h

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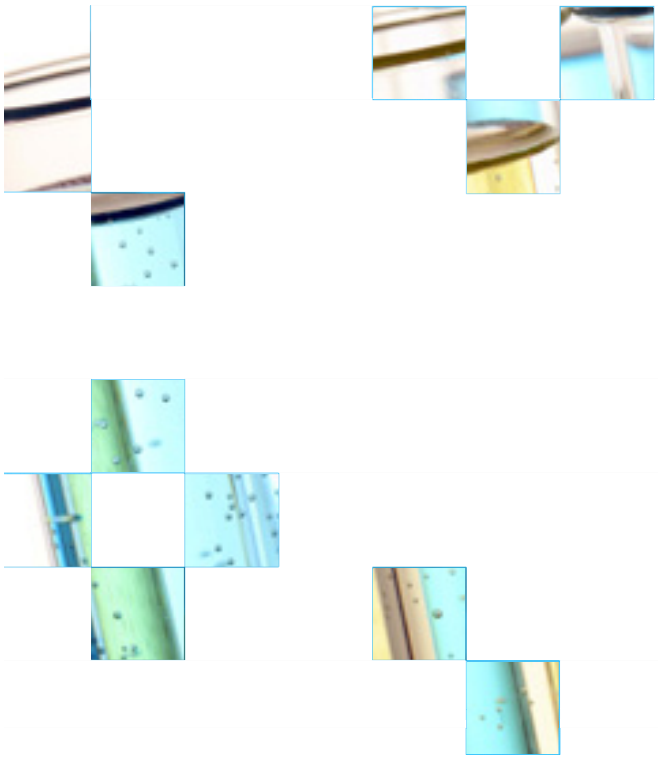

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BUILDING DEFINED PROTEIN-DRUG CONJUGATES FOR TARGETED CANCER THERAPY

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The targeted delivery of effector molecules into diseased tissues has emerged as a promising strategy for the treatment of cancer and other serious conditions. Linking a therapeutic effector (e.g. cytotoxics, proinflammatory cytokines or radionuclides) to a ligand specific to a marker of disease results in preferential accumulation of the effector molecule at the target tissue. This offers the double benefit of increased effective concentrations at the intended site of action and low concentrations in healthy tissues, thus reducing side effects. Our work explores the interplay between effector molecules, targeting ligands and site-selective protein conjugation chemistry to create safer, more selective and efficient cancer therapeutics.
This lecture will cover recent examples of emerging areas in our group in (i) targeted drug conjugates construction with an emphasis on traceless antibody-drug conjugates and (ii) use of carbon monoxide (CO) as a immunomodulator signalling molecule for applications in cancer therapeutics.
(i) A new non-internalizing antibody-drug conjugate (ADCs) that cures cancer in immunocompetent mice bearing tumours will be presented.[1,2] This ADC was built using of a robust site-selective disulfide conjugation protocol.[3] Using this protocol we were able to systematically investigate how the therapeutic efficacy of a traceless, vascular targeting ADC is affected by the length of a spacer introduced between the antibody's globular fold and the site of drug attachment.[4] (together with Prof. Dario Neri)
(ii) We are exploring the immunomodulatory effects of CO for cancer therapeuty.[5] A new CORM conjugate is able to ablate the expression of the pro-inflammatory cytokines TNF-α and IL-6 , and of the chemokine, IL-8, which are involved in tumour progression and metastasis. In an immunocompetent mouse model of colon carcinoma that is not cured by the standard-care-of therapy 5-fluorouracil (5-FU), the new CORM conjugate can elicit a strong-anti-tumour activity.[Unpublished results]

References

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2. E. Perrino, M. Steiner, N. Krall, G.J.L. Bernardes, F. Pretto, G. Casi, and D. Neri, Cancer Res. doi:10.1158/0008-5472.CAN-13-2990 (2014).
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4. M. Steiner, I. Hartmann, E. Perrino, G. Casi, S. Brighton, I. Jelesarov, G.J.L. Bernardes*, and D. Neri, Chemical Science, **4**, 297-302 (2013).
5. S. García-Gallego, G.J.L. Bernardes*, Angew. Chem. Int. Ed. doi:10.1002/anie.201311225 (2014).

Dr Bernardes is a Group Leader at the University of Cambridge, UK. He is also Director of the Chemical Biology and Pharmaceutical Biotechnology Unit at the Instituto de Medicina Molecular, Portugal. After completing his D.Phil. degree in 2008 at the University of Oxford, UK, he undertook postdoctoral work at the Max-Planck Institute of Colloids and Interfaces, Germany, the ETH Zürich, Switzerland, and worked as a Group Leader at Alfama Lda, Portugal. His research interests focus on the development of new chemoselective reactions for the modification of biomolecules and their use to understand and influence human disease. His research efforts have resulted in >35 publications and 5 patents. He was recently awarded the EFMC prize for a Young Medicinal Chemist in Academia and was distinguished by the Portuguese Ministry of Health (MH) of Portugal for relevant services to Public Health and Medicine.