

- Poller W, Kaya Z, Muche M, Kasner M, Skurk C, Kappert K, et al. High incidence of cardiac dysfunction and response to antiviral treatment in patients with chronic Hepatitis C virus infection. *Clin. Res. Cardiol.* 2017;1–6.
- Hagiwara S, Nishida N, Watanabe T, Sakurai T, Ida H, Minami Y, et al. Outcome of combination therapy with sofosbuvir and ledipasvir for chronic type C liver disease. *Oncology.* 2017;92 Suppl. 1:3–9.

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Neurosciences Plenary Session  
Saturday, September 16th, 14h00

### PS141

#### Paclitaxel-induced neuropathic pain: Unravelling the underlying mechanisms at the central nervous system

J. Ribeiro<sup>1,2,3,\*</sup>, J.T. Costa-Pereira<sup>1,2,3</sup>,  
I. Tavares<sup>1,2,3</sup>, I. Martins<sup>1,2,3</sup>

<sup>1</sup> Departamento de Biomedicina – Unidade de Biologia Experimental, Faculdade de Medicina da Universidade do Porto, Portugal

<sup>2</sup> i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal

<sup>3</sup> IBMC – Instituto de Biologia Celular e Molecular, Universidade do Porto, Portugal

E-mail address: [jribeiro504@gmail.com](mailto:jribeiro504@gmail.com)

(J. Ribeiro).

**Aim:** Here we studied the effects of the cytostatic paclitaxel on: (i) the development of nociceptive and aversive behaviors; (ii) noxious-evoked-activation of spinal dorsal horn neurons and (iii) on descending noradrenergic modulation, which is the main spinal nociceptive inhibitory system.

**Introduction:** Chemotherapeutic drugs are widely used for cancer treatment but they also cause numerous deleterious side effects. Chemotherapy-induced neuropathy (CIN) is one of the most common side effects. The mechanisms underlying CIN are starting to be uncovered namely the alterations induced by cytostatics at the peripheral nervous system but the effects of these drugs at the central nervous system are still poorly studied.

**Methods:** Male Wistar rats were injected with paclitaxel (Taxol, 2.0 mg/kg) or the vehicle solution dimethyl sulfoxide on four alternate days. Nociceptive and aversive behaviors were assessed by the von Frey and conditioned place aversion (CPA) tests, respectively. Noxious-evoked-activation of spinal dorsal neurons was achieved at one month after CIN by evaluating the expression of c-fos expression upon cold stimulation. To study the descending noradrenergic pain modulation we assessed the effects of the  $\alpha$ 2-adrenoreceptor agonist clonidine at 1 and 10  $\mu$ g administered intrathecally, on the von Frey test. We further assessed the expression of the  $\alpha$ 2-adrenoreceptor and dopamine- $\beta$ -hydroxylase (DBH), a nor-adrenaline biosynthetic enzyme expressed in noradrenergic fibers, at the spinal dorsal horn.

**Results:** Paclitaxel induced mechanical allodynia and aversive behaviors. c-fos and DBH expression were increased in paclitaxel-treated animals while  $\alpha$ 2-adrenoreceptor expression remained unaltered. Clonidine induced antinociception at both doses with more pronounced effects in paclitaxel-treated animals.

**Conclusion:** Paclitaxel-treated animals showed neuropathic like-behaviors and increased spinal neuronal activation. It remains to ascertain if DHB upregulation results in increased spinal nor-adrenaline levels, but the increase of  $\alpha$ 2-AR antinociceptive potency in paclitaxel-treated animals indicates the recruitment of

descending inhibition probably as a buffer to increased spinal sensitization.

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Oncology & Molecular Biology Plenary Session  
Saturday, September 16th, 14h00

### PS203

#### Is there horizontal transfer of the oncogene BCR-ABL mediated by extracellular vesicles released by chronic myeloid leukemia cells?

A. Teixeira<sup>1,2,3,\*</sup>, D. Sousa<sup>1,2,4</sup>, C.P.R. Xavier<sup>1,2</sup>,  
M.H. Vasconcelos<sup>1,2,4</sup>

<sup>1</sup> i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

<sup>2</sup> Cancer Drug Resistance Group, IPATIMUP – Instituto de Patologia e Imunologia Molecular da Universidade do Porto, Porto, Portugal

<sup>3</sup> ICBAS – Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal

<sup>4</sup> Department of Biological Sciences, FFUP – Faculty of Pharmacy of the University of Porto, Porto, Portugal

E-mail address: [alexandrat@ipatimup.pt](mailto:alexandrat@ipatimup.pt)

(A. Teixeira).

**Aim:** The aims are to verify if: (i) EVs released by CML cells carry BCR-ABL in their cargo and if that BCR-ABL is captured by recipient cells; (ii) EVs released by a CML drug resistant cell line, with mutant BCR-ABL, may transfer mutant BCR-ABL and a resistant phenotype to sensitive cells.

**Introduction:** BCR-ABL, the fusion gene originated by the t(9;22) translocation, is responsible for Chronic Myeloid Leukemia (CML). BCR-ABL codes for a constitutively active tyrosine kinase (TK), deregulating downstream pathways and promoting cell survival. Imatinib mesylate (Gleevec), a TK inhibitor, is the gold standard treatment for CML; nevertheless, resistance to this drug often arises, mostly caused by additional point mutations on BCR-ABL and representing a major clinical drawback. It was recently suggested that drug resistance might be horizontally transferred by EVs, from resistant to sensitive cells.

**Methods:** A pair of drug-sensitive BCR-ABL+ cell line (KBM5), and its drug-resistant counterpart (KBM5-STI, harboring mutated BCR-ABL) were used in this study. EVs were isolated by ultracentrifugation and characterized by Dynamic Light Scattering, Nanoparticle Tracking Analysis, Transmission Electron Microscopy and Western Blot. The resazurin assay was used to assess drug response of drug resistant cells, drug sensitive cells and of drug sensitive cells following co-culture with EVs released by drug resistant cells. BCR-ABL levels were analysed by Western Blot.

**Results:** A dose-response curve to imatinib was performed in both cell lines, to confirm their different responses to the drug. Regarding EVs characterization, they had between 10 and 1000 nm and presented several markers of EVs with no evidence of cellular contaminants. Interestingly, BCR-ABL protein was detected in the EVs.<sup>1–9</sup>

**Conclusion:** These results suggest that there is selective packaging of BCR-ABL into EVs, promoting oncogenic protein shedding. Ongoing work will clarify if the EVs released by the resistant cells have mutant BCR-ABL and if they confer drug resistance to recipient sensitive cells.

