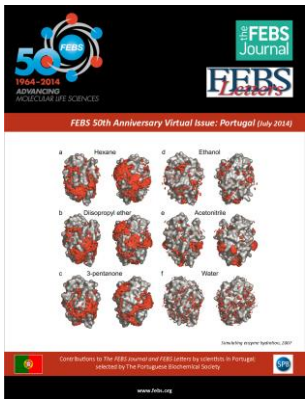
FEBS 50th Anniversary Virtual Issue: Portugal



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Editorial

This celebratory Virtual Issue for the 50th anniversary of FEBS (2014) highlights the high quality and diversity of biochemistry research carried out in Portugal. Up to 2013, 303 articles were published in *FEBS Letters* and *The FEBS Journal* / *European Journal of Biochemistry* with at least one author having Portugal as an address. While during the past 20 years the average number of publications has been approximately 10 per year, the number of citations has been steadily increasing from 150 in 1995 to 550 in 2013, an indication of the improvement in the quality of Portuguese science during the past two decades. The average number of citations of all articles is 23.15 per article. On a methodological note concerning the selection of works to include in this issue, we focused only on original contributions and, as far as possible, have avoided repetition of works coming from the same laboratory. The selection criterion applied was the impact on the scientific community as indicated by the overall count of citations or, for more recent works, the number of citations per year. Nevertheless, some degree of

subjectivity is unavoidable and we apologize to the authors of high-quality research whose work was not included in this celebratory issue.

Among the 12 papers selected for this issue, two are in the area of bioinorganic biochemistry. In fact, many more could have been chosen: this is a very strong field in Portuguese biochemistry, as António Xavier was a pioneer in this area not only in Portugal but worldwide. One of these papers is focused on cytochrome c3, a member of the electron-transfer sulfate respiratory chain found in anaerobic sulfate-reducing bacteria *Desulfovibrio gigas*, and in general in the genus *Desulfovibrio*. Being a multihaem protein it shows complex redox behaviour, which was characterized by NMR (Santos, H. et al., 1984). Haem–haem interacting potentials that depend on pH and cover a range from –50 mV to +60 mV were found, justifying the multitude of redox partners that were subsequently attributed to cytochrome c3 (Santos, H. et al., 1984). For supposedly a strict anaerobe, *Desulfovibrio gigas has a remarkable resistance to molecular oxygen, which had been attributed to oxygen reduction by components of the* dissimilatory sulfate-reducing pathway. However, a true canonical respiratory chain capable of reducing oxygen was identified, and in particular the terminal component of this chain was identified to be a member of the cytochrome *bd* family (Lemos, R.S. et al., 2001).

Three papers focused on the quantitative analysis of metabolic fluxes were selected. One such paper applies *in vivo* non-invasive ^{13}C-NMR to investigate glycolytic flux changes in a lactic acid bacteria strain deficient in lactate dehydrogenase, which has a lower NAD^+/NADH ratio (Neves, A.R. et al., 2000). Instead of a higher flux through acetolactate, an increase in mannitol 1-phosphate formation was observed in order to regenerate NAD^+. This observation has potential industrial implications as mannitol is

used as a sweetening agent, and reinforces the concept that to redirect microbial metabolic fluxes an integrative view of metabolism is essential. The other two articles are centred on secondary metabolism. In one work, hydrogen peroxide catabolism and respective fluxes through antioxidant enzymes were quantified in Jurkat T-cells, including the estimation of gradients formed between cellular compartments (Antunes, F. and Cadenas, E., 2000). Rather than supporting the common view of a freely diffusible species, the observations support the concept that local pools of hydrogen peroxide can be maintained due to the permeability barrier imposed by biomembranes. The third work describes how cells cope with the unavoidable formation of the potentially toxic metabolite methylglyoxal, which originates non-enzymatically from triose phosphate glycolytic intermediates and reacts with macromolecules to form advanced glycation end-products (Martins, A.M.T.B.S. et al., 2001). This paper demonstrated a quantitative relationship between glycolytic flux and methylglyoxal formation and the high importance of the glyoxalase pathway for methylglyoxal detoxification.

A third area of interest in this FEBS Virtual Issue is theoretical biochemistry. This is a field with high relative strength in Portugal, with several groups working on the topic. The area is exemplified here by a work in which molecular dynamics simulation is applied to address the hydration of enzymes in non-aqueous solvents and whether the enzyme activity can be predicted from the content of water present for both polar and non-polar solvents (Micaêlo, N.M. et al., 2007). It provides a detailed mechanism of how protein water solvation depends on the polarity of the solvent, as shown in the cover figure of this celebratory issue, and concludes that for polar solvents water activity and enzyme activity may not correlate.

Two works on genetics were included in the article selection, as a fourth area of impact in Portugal. The first work reports the creation of a frataxin knockin mouse. Frataxin is a mitochondrial protein involved in iron homeostasis and its deficiency results in Friedreich ataxia, a genetic disease characterized by damage to the nervous system and movement problems. The knockin mouse was crossed with frataxin knockout mice to generate mice expressing 25–36% of wild-type frataxin levels, which do not show any noticeable phenotype changes (Miranda, C.J. et al., 2002). The second work concerns the identification of the microRNA-143 as an agent that shows anti-proliferative action in HCT116 colon cancer cells, and sensitizes these cells to 5-fluorouracil, a drug commonly used in treatment of colorectal cancer (Borralho, P.M. et al., 2009) .

One work on plant biochemistry was picked out, as a fifth area of interest in this selection. The paper is focused on glycochemistry and identified for the first time the presence of the human Lewis^{a} type determinant in glycoproteins secreted by plant cells, more specifically in a peroxidase from *Vaccinium myrtillus (Melo, N.S. et al., 1997).* This type of determinant is involved in the metastasis of human cancer cells and the identification of molecules containing these motifs may result in new potential anti-cancer drugs.

Finally, three of the articles included in this issue fall within the scope of what today is termed ‘smart specialization’. Familial amyloid polyneuropathy (FAP), also called Corino de Andrade's disease after the Portuguese neurologist who first identified the disease, is a neurodegenerative disease that is endemic in the Portuguese fishing cities Póvoa de Varzim and Vila do Conde. This disease is characterized by generalized amyloidosis, with the amyloid fibrils being constituted by variants of transthyretin, a homo-tetrameric protein found in cerebrospinal fluid and in plasma. Two of the selected

articles address transthyretin aggregation dynamics. In the first, it is shown that not only is the stability of the tetramer of transthyretin important to avoid amyloid fibril formation, but also amyloid variants of transthyretin show a higher tendency for their monomers to aggregate as high-molecular weight complexes that form the fibrils (Quintas, A. et al., 1997). The second paper is a recent work where three natural polyphenols – curcumin, nordihydroguaiaretic acid and (−)-epigallocatechin gallate – were found to impair transthyretin aggregation by either stabilizing the tetramer or inhibiting the tendency of transthyretin variants to aggregate as amyloid fibrils, raising the perspective of using these compounds as new lead therapeutic agents (Ferreira, N. et al., 2011) .

The third article that falls within smart specialization concerns the purification and characterization of two new aspartic proteinases – cardosin A and cardosin B – from flowers of *Cynara cardunculus* L., which are used as milk-clotting enzymes in the Portuguese cheese industry (Veríssimo, P. et al., 1996). Subsequently, potential pharmacological actions including anti-tumoural actions were attributed to these enzymes.

Putting it all together, this issue gives a general snapshot of molecular bioscience studies performed in Portugal and their contribution to the development of this research area. It is clearly a fact that FEBS journals have been excellent channels to the dissemination of high-quality science. Political will from Portuguese authorities to support science should be maintained, in order that the trend observed during the last two decades of a persistent improvement in the quality of biochemistry research in Portugal continues.