XIIth International ChE Meeting/VI the International Paraoxonase Meeting – Closing Remarks

by Israel Sisman.

Unless a meeting ends in the evening, people have either left in the morning, or are impatient to leave as soon as possible, so I will try to be mercifully brief!

First, although this was likely said by somebody else at the Gala Dinner, I would like to thank our hosts, Eugenio, Jorge and Miguel Angel, for putting together such a successful meeting in such a delightful setting, as well as the very helpful and efficient administrative staff. It was a real achievement to implement such a dense program, while sticking to the schedule almost all of the time.

I do not intend to drag you through the whole program, but just to mention a few main issues, and, for me, individual highlights.

One main issue was that of the approaches to treatment of organophosphate (OP) poisoning, whether in a military or a civilian context, using either conventional treatments or bioscavengers. This was actually covered at a roundtable yesterday. Combinations of the two approaches will obviously be the way forward, but one controversy that remains to be settled is the added value to be anticipated from oxime reactivators that can penetrate the blood brain barrier.

Mona Soreq's keynote address exposed us to the world of the micro-RNAs (miRNAs). Little over a decade ago they were only just emerging, but by now they have totally changed our understanding of how translation is regulated, whether for cholinesterases (ChEs), paraoxonases (PONs), or any other protein. The

presentation of Dr Xie, from Beijing, who showed that two miRNAs which bind to human AChE messenger RNA are up-regulated by dioxin, is a striking example of the unanticipated directions in which this line of research can lead us.

Although Clem Furlong's title was more general, the main message that I took away from his keynote lecture, and I think that that was indeed his intention, is that however valuable studies of polymorphisms may be, the bottom line is the level of activity of a given PON that is measured.

John Casida's lecture was not a keynote lecture, but it had the air of one. His survey of the various types of enzymes, including lipases, that are targets of OPs served to remind us that there are many others, in addition to ChEs and PONs, including, as we heard this morning, carbxoylesterases. John told me that he, too, had worked, like Elsa Reiner, in the lab of Norman Aldridge, who pioneered the approach to identification of multiple OP targets, including NTE, that found its expression in the meetings organized by Elsa.

Finally, at the Gala Dinner, we heard from Rick Rotundo about the intricate and prolonged process of AChE biosynthesis, and how it can be speeded up by molecular chaperones. Perhaps only now, the AChE that was coming off our ribosomes at breakfast has finally become fully folded and active!

Those are some of the major issues, but I will mention a few interesting points that caught my eye and ear, though I make no attempt, nor do I have the time, to be comprehensive.

I found the study of the action of tariquidar on P-glycoprotein, from the TNO, a novel and promising complementary approach to reduction of OP-induced seizures.

The observation by Brazzolotto and colleagues that the pig BChE inhibited by V agents displays spontaneous reactivation is a fascinating example of how unanticipated species differences can be.

Dr Zhang, in Shanghai, has long been investigating the possible association of AChE with apoptosis, and its possible DNAse activity. Although this is a complex experimental system, and many artefacts need to be considered, the complementary findings of Dr Campoy and his colleagues in Murcia lend support to the overall phenomenon.

Unfortunately, Steve Brimijoin could not join us. But we heard from Oksana about his new and fascinating data concerning octanoyl-ghrelin as a substrate for BChE and its link to aggression in mice. The role or roles of BChE have been elusive, and this is a novel and unexpected one.

I found Dr Nalivaeva's presentation on cross-talk between AChE and APP full of new and unanticipated findings, including the correlation between shedding of Aβ and of AChE. Also, impressive progress is being made in understanding the biological roles of APP itself, and the complexities of the APP transcriptome.

I also was impressed by the insights yielded by Jonah Cheung's presentation of his structural studies on a mutant hAChE in which aging of the OP conjugate had been retarded, and its turnover increased. In particular, the increased size of the gorge that resulted from mutation

of larger to smaller residues may enhance productive access of reactivators to the OP moiety.

Finally, I would like to note the separation of the developmental role of NTE from its catalytic activity demonstrated by our hosts at Elche.