



## About 30 years of organising international meetings cholinesterases and related enzymes

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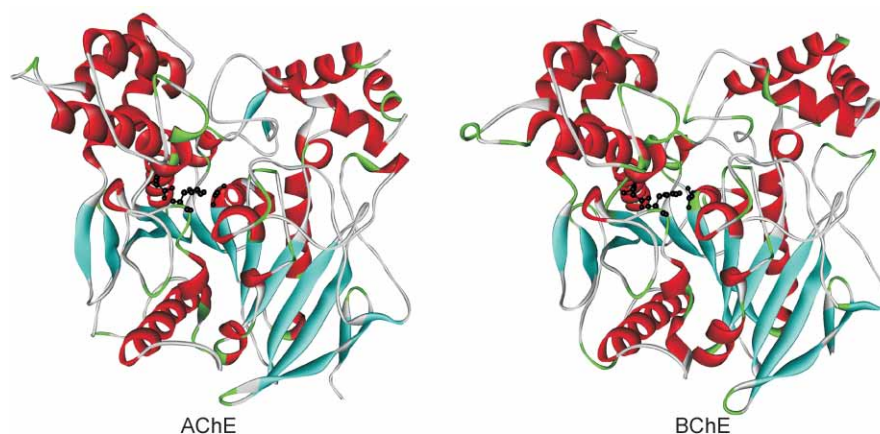
This paper summarizes a series of international meetings on cholinesterases and related enzymes initiated by the Institute for Medical Research and Occupational Health (IMI) over the past decades.

Since their discovery in the 1930s, the enzymes belonging to the cholinesterase family (ChEs), acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8), have been in focus of many studies in biochemistry, physiology, biomedicine and toxicology. AChE and BChE own their enzyme activity to the catalytic triad serine-histidine-glutamic acid, positioned at the bottom of the active site enzyme gorge (Figure 1). The physiological role of AChE is to hydrolyse acetylcholine (ACh) released into the synapse as a neurotransmitter. The hydrolysis of released ACh must occur before the next released ACh reaches the cholinergic receptor, because accumulation of ACh in the synapse is toxic. The physiological role of BChE is not yet fully clarified. However, BChE can hydrolyse ACh and many xenobiotics. Organophosphorus (OP) compounds are potent inhibitors of ChEs because they bind covalently to the serine of the catalytic triad. Inhibition of ChEs by OPs is therefore toxic. OP compounds are used as pesticides, some compounds also as drugs, but some are being misused as warfare nerve agents (Figure 2). Enzymes related to cholinesterases, named paraoxonase and DFP-ase, hydrolyse OP compounds and thereby act as antidotes against OP poisoning.

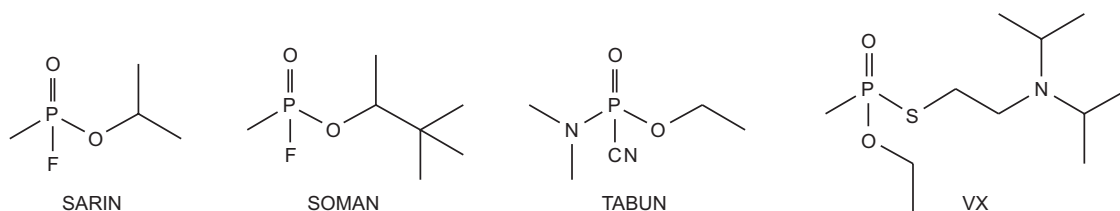
Way back in 1975, we organised the first meeting on cholinesterases that also included cholinergic mechanisms. The meeting was held in Split. Participation was by invitation only, and 45 participants from 13 countries convened. The meeting created considerable interest and resulted as the beginning of two series of international meetings being held up to the present date. Since Split, participation was not limited to invitations only. ChE meetings take place in different countries and on different continents thereby creating »a family« of participants that is continually growing and hopefully helping fruitful collaboration and advances in the field.

The list of cholinesterase meetings is given in Table 1a and the list of published proceedings is given in Table 1b. The 11<sup>th</sup> ChE meeting is planned to be held in Kazan, Russia, in June 2012. Meetings on cholinergic mechanisms developed as a separate series. The 13<sup>th</sup> meeting was in Foz du Iquacu, Parana, Brazil in August 2008, and the next is planned to take place in Kyoto, Japan, in September 2012.

The threat of misusing OP compounds stimulated us to start in parallel a separate series of meetings on enzymes hydrolysing these compounds. The list of the first three meetings on esterases reacting with



**Figure 1.** Schematic presentation of AChE and BChE structures with indicated  $\beta$ -sheets (blue-green) and  $\alpha$ -helices (red). Amino acids of the active site catalytic triad (Ser-His-Glu) are indicated in dark gray (AChE PDB code 3LII, BChE PDB code 2PM8). (Prepared by Goran Šinđo, IMI, Zagreb).



**Figure 2.** Structure of four organophosphorus warfare nerve agents.

organophosphorus compounds is given in Table 2a and the list of published proceedings is given in Table 2b. All three meetings were planned to take place in the Inter-university Center in Dubrovnik, however, due to the war against Croatia, the second meeting was held in Italy thanks to the kind help obtained from Marcello Lotti (Padova, Italy).

One topic discussed during these meetings was the classification of enzymes hydrolysing OPs and thereby detoxifying these compounds. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology accepted our recommendation concerning the classification (W. N. Aldridge, F. C. G. Hoskin, E. Reiner, C. H. Walker (1989) Suggestions for a nomenclature and classification of enzymes hydrolysing organophosphorus compounds. *In*: E. Reiner, W. N. Aldridge, F. C. G. Hoskin (Eds.) *Enzymes Hydrolysing Organophosphorus Compounds*. Ellis Horwood Limited, Chichester, England, pp 246–253), and since 1992 these enzymes are classified as phosphoric triester hydrolases EC 3.1.8 with two subgroups: paraoxonase EC 3.1.8.1 and DFP-ase EC 3.1.8.2 (Enzyme Nomenclature, Recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (prepared by E. C. Webb). Academic Press, Inc., San Diego, USA, 1992, p. 336). This series of meetings is also continuing to the present date, but focusing mostly on paraoxonases. The numbering of meetings that continued, however, started again from No. 1. The 4<sup>th</sup> meeting was held in La Pineda, Catalonia, Spain,

in September 2010, and the next meeting has been announced, but place and date not yet decided.

The 10<sup>th</sup> ChE was for us a jubilee meeting not only because it was the 10<sup>th</sup> but because the meeting venue was again in Croatia. The meeting coorganiser was the Croatian Society of Biochemistry and Molecular Biology, and the meeting was held under the auspices of the Croatian Academy of Science and Arts. The meeting was attended by 204 participants from 28 countries. The programme covered a broad range of topics beginning with basic structure of cholinesterases, molecular and cell biology, mechanisms of interactions, up to the newly debated alternative (noncholinergic) functions of cholinesterases. The meeting also covered topics on enzymes hydrolysing OP compounds as well as diseases, Alzheimer and Parkinson disease, linked to the ChE activity. For the first time the programme included a 3D-session for the presentation of structural aspects of enzymes in stereoscopic 3D technique. The proceeding (Table 1b, ref. (10)) comprises 80 manuscripts from oral and poster presentations given at the 10<sup>th</sup> ChE meeting. The plenary lecturer Palmer Taylor (San Diego, USA) summarised the major achievements since the Split meeting in a lecture entitled »From Split to Šibenik: The tortuous pathway in the cholinesterase field« giving thereby a historical background to the ChE meetings (Table 1b, ref. (10) pages 3–9).

We hope that the series of meetings will continue supporting worldwide advancements in research, fruitful collaboration and lasting friendships.

**TABLE 1a**

List of international meetings on cholinesterases.

Meeting	Year	Place	Main Organizers	Proceedings reference
1 <sup>st</sup>	1975	Split, Croatia	Elsa Reiner (Croatia)	(1)
2 <sup>nd</sup>	1983	Bled, Slovenia	Miro Brzin (Slovenia)	(2)
3 <sup>rd</sup>	1990	La Grande Motte, France	Jean-Pierre Toutant (France)	(3)
4 <sup>th</sup>	1992	Eilat, Israel	Avigdor Shafferman (Israel) Baruch Velan (Israel)	(4)
5 <sup>th</sup>	1994	Madras, India	A. Balasubramanian (India) Bhupendra P. Doctor (USA)	(5)
6 <sup>th</sup>	1998	La Jolla, USA	Palmer Taylor (USA)	(6)
7 <sup>th</sup>	2002	Pucon, Chile	Nivaldo Inestrosa (Chile)	(7)
8 <sup>th</sup>	2004	Perugia, Italy	Vincenzo N. Talesa (Italy)	(8)
9 <sup>th</sup>	2007	Suzhou, China	Karl W.K. Tsim (China)	(9)
10 <sup>th</sup>	2009	Šibenik, Croatia	Elsa Reiner (Croatia) Zrinka Kovarik (Croatia)	(10)

**TABLE 1b**

List of proceedings references.

No.	Proceedings references
(1)	Cholinesterases and Cholinergic Receptors <i>Eds.</i> : E. Reiner; <i>Subeds.</i> : M. Škrinjarić-Špoljar, V. Simeon <i>Croatica Chemica Acta</i> 47 (1975) 163–506 Croatian Chemical Society, Zagreb, Croatia
(2)	Cholinesterases, Fundamental and Applied Aspects <i>Eds.</i> : M. Brzin, E. A. Barnard, D. Sket Walter De Gruyter, Berlin, New York, USA (1984) pp 1–526
(3)	Cholinesterases: Structure, Function, Mechanism, Genetics, and Cell Biology (ACS Conference Proceedings Series) <i>Eds.</i> : J. Massoulié, E. Barnard, A. Chatonnet, F. Bacou, B. P. Doctor, D. M. Quinn American Chemical Society, Washington, USA (1991) pp 1–414
(4)	Multidisciplinary Approaches to Cholinesterase Functions <i>Eds.</i> : A. Shafferman, B. Velan Plenum Press, New York, USA (1992) pp 1–293
(5)	Enzymes of the Cholinesterase Family <i>Eds.</i> : A.S. Balasubramanian, B. P. Doctor, D. M. Quinn, P. Taylor Plenum Press, New York, USA (1995) pp 1–534
(6)	Structure and Function of Cholinesterases and Related Proteins <i>Eds.</i> : B. P. Doctor, P. Taylor, D. M. Quinn, R. L. Rotundo, M. K. Gentry Plenum Press, New York, USA (1998) pp 1–630
(7)	Cholinesterases in the Second Millennium: Biomolecular and Pathological Aspect <i>Eds.</i> : N. Inestrosa, E. O. Campos P. Universidad Católica de Chile – FONDAPE Biomedicina, Chile (2004) pp 1–384
(8)	Proceedings of the VIII International Meeting on Cholinesterases <i>Guest Eds.</i> : V. N. Talesa, C. Antognelli <i>Chemico-Biological Interactions</i> – Special Issue 157–158 (2005) 1–434 Elsevier Ireland Ltd.
(9)	Proceedings of the IX International Meeting on Cholinesterases <i>Guest Eds.</i> : K. W. K. Tsim, B. P. Doctor, N. L. Siow <i>Chemico-Biological Interactions</i> – Special Issue 175/1–3 (2008) 1–430 Elsevier Ireland Ltd.
(10)	Proceeding of the 10th International Meeting on Cholinesterases <i>Guest Eds.</i> : E. Reiner, J. Massoulié, T. Rosenberry, P. Eyer, G. Amitai, Z. Radić, Z. Kovarik; <i>Assistant to Guest Eds.</i> : M. Katalinić <i>Chemico-Biological Interactions</i> – Special Issue 187/1–3 (2010) 1–446 Elsevier Ireland Ltd.

**TABLE 2a**

List of international meetings on esterases reacting with organophosphorus compounds.

Meeting	Year	Place	Main Organizers	Proceedings reference
1 <sup>st</sup>	1988	Dubrovnik, Croatia	Elsa Reiner (Croatia) W. Norman Aldridge (UK) Francis C. G. Hoskin (USA)	(1)
2 <sup>nd</sup>	1992	Salsomaggiore, Italy	Elsa Reiner (Croatia) Marcello Lotti (Italy)	(2)
3 <sup>rd</sup>	1998	Dubrovnik, Croatia	Elsa Reiner (Croatia)	(3)

**TABLE 2b**

List of proceedings references.

No.	Proceedings references
(1)	Enzymes Hydrolysing Organophosphorus Compounds <i>Eds.</i> : E. Reiner, W. N. Aldridge, F. C. G. Hoskin Ellis Horwood Limited, Chichester, England (1989) pp 1–266
(2)	Enzymes Intereacting with Organophosphorus Compounds <i>Guest Eds.</i> : E. Reiner, M. Lotti; <i>Associate Guest Eds.</i> : M. K. Johnson, V. Simeon, A. Moretto; <i>Consulting Ed.</i> : E. Hodgson <i>Chemico-Biological Interactions</i> – Special Issue 87 (1993) 1–476 Elsevier Scientific Publisher Ireland Ltd.
(3)	Esterases Reacting with Organophosphorus Compounds <i>Guest Eds.</i> : E. Reiner, V. Simeon-Rudolf, B. P. Doctor, C. E. Furlong, M. K. Johnson, M. Lotti, I. Silman, P. Taylor <i>Chemico-Biological Interactions</i> – Special Issue 119–120 (1999) 1–620 Elsevier Science Ireland Ltd.