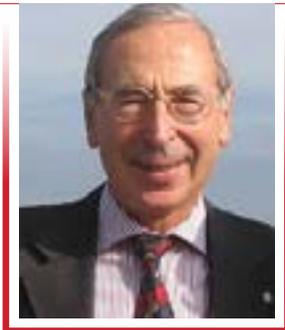


Keynote Forum | Day 1

November 20-21, 2019 | Berlin, Germany

Tsetlin V, J Chem Tech App 2019, Volume 3



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ANALYTICAL CHEMISTRY IN RESEARCH ON NICOTINIC RECEPTOR INTERACTIONS WITH NEUROTOXIC PEPTIDES AND PROTEINS

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BIOGRAPHY

Tsetlin V did his Ph D Degree in Chemistry (1973) at the Shemyakin-Ovchinnikov Institute; Head of the Department for molecular neuroimmune signaling; Professor (1996); Corresponding Member of the Russian Academy of Sciences (2006). He was honored with Russian State Prize in Science and Technology (1985) and the Humboldt Prize (1992). He is an Invited Scientist at Imperial College, London (1983-1984), Institute of Protein Research, Osaka (1992-1993), Free University of Berlin (1993-1994). He is the author of over 250 papers, including those in *PNAS*, *Neuron*, *Nature Str. Mol. Biol.*, Member of the *FEBS J* Advisory Board (2000-2011), *Biochem. J.* (2013 - present). His Citation Index is 4280 and Hirsh index 34.

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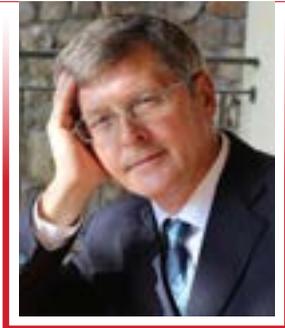
Authors work is in the field of neurobiology and neurochemistry, close to the analytical chemistry, the topic of this conference. Their main targets are nicotinic acetylcholine receptors (nAChR). Invaluable instruments for nAChR research are snake venom, α -neurotoxins and in proteomic studies of venoms they recently found a new variant ($\alpha\delta$ -bungarotoxin) of classical α -bungarotoxin which inhibits muscle-type and neuronal $\alpha 7$ nAChRs, but more reversibly. Another result of proteomics was covalently bound dimeric α -cobratoxin. Computer modelling, peptide synthesis, analytical chemistry and mass-spectrometry's allowed as to obtain α -conotoxin PnIA analogues which for the neuronal $\alpha 7$ nAChR had a 50-fold higher affinity than PnIA itself. Neurotoxic peptides and proteins interacting with nAChRs provide information about their binding sites necessary for drug design against neurodegenerative diseases, pain and inflammatory processes. For understanding physiological processes and drug design, of great importance are human proteins having the same three-finger folding as snake venom α -neurotoxins. Some of them, like Lynx1 and SLURP-1, are localized in the brain and in the immune system close to nAChRs and modulate their assembly and functioning. An illustration of matching the analytical chemistry with other modern approaches is our recent work with Australian researchers who prepared SLURP-1 (81 amino-acid residues, 5 disulfides) by total chemical synthesis. It had the same NMR structure as recombinant SLURP-1 (having an extra N-terminal Met residue), but by combination of radioligand analysis, calcium imaging and electrophysiology they demonstrated that this difference resulted in the selectivity shift from $\alpha 7$ to $\alpha 9/\alpha 10$ nAChR.

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BIOGRAPHY

Anatoly Verenchikov is currently the Director of "Mass Spectrometry Consulting Ltd." Bar, Montenegro and served as the Founder for the company from 2007-2016. In 2015, he received the Golden medal of the Russian Society of Mass Spectrometry for outstanding achievements in mass spectrometry, Moscow, Russia. He also received the Golden award of Pittsburg Conference for Pegasus MRTOF, USA in 2011. He is the author of over 50 patents, more than 200 papers and conference presentations.

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TRACE ANALYSIS WITHIN RICH AND VARIABLE MATRICES USING GC-MS WITH HIGH RESOLUTION MULTI-REFLECTING TOFMS

GC-MS remains an important part of analytical armory and is indispensable in forensic, environmental and food control area. While major components are detected with low cost single quadrupoles (GCQ), trace analyses of minor components require MS tandems like 3Q or Q-TOF to reduce matrix interferences. Matrices of volatiles in GCMS, though are less diverse than those in LC-MS, still contain thousands of compounds particularly, in food, clinical and biological samples. Matrix diversity grows roughly proportional to the analysis depth. To detect minor traces (fg levels) within rich matrices, it takes both sensitivity and specificity; a combination which is not yet available in existing commercial instruments. Although the detection limit of detection (LOD) of GCQ in SIM mode to pure samples is in the 1-10fg range, matrix interferences limit the working LOD to 10-100pg. 3Q and Q-TOFs then step in to allow LOD in 100fg range. With GC-3Q instrument MRM methods are developed to find fragmentation channels which do differentiate analytes from the matrix. However, a limitation is that whenever matrix varies the original MRM methods have to be requalified or redeveloped. GC-3Q data alone are insufficient for court cases and GC-3Q is a poor choice when searching unknowns (spices, poisoning etc.). GC-MRTOF is a joint effort of two companies, MSC and QTek, who developed GCQ Maestro™ and GC-Mini™, both delivering LOD around 1-3fg for pure samples. GC-Mini™ is a compact multi-reflecting TOF (MRTOF) benchtop system with moderately high-resolution $R=30,000$. This resolution is sufficient to separate isobaric interferences corresponding to such elemental replacements as C/H_{12} (95mDa), C_2H_6/NO (88mDa), C_2H_8/O_2 (55mDa), CH_4/O (36mDa) and CH_2/N (12mDa) for GC-MS small mass ions up to 500amu. The GC-MRTOF instrumental configuration provides: The specificity comparable to existing GC-3Q and GC-QTOF; much cleaner chromatographic traces by resolving out isobaric interferences; NIST identifiable spectra are obtained at 10-100fg loads, and molecular ions can be detected

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at 1-10fg loads. GC-Mini™ can do everything that 3Q and QTOF can do, and provides many other analytical opportunities: Recording of panoramic (full mass) spectra. This provides non-filtered complete information, where post-analysis may be either choosing MRM channels of 3Q methods, or flexibly selecting channels with reduced matrix interference (Judged by relative peaks intensity and by retention time correlation of the traces); MRM methods for 3Q could be verified, adjusted or developed to overcome the method variations, caused by matrix or chromatography variations; Accurate masses of fragments improve the identification confidence and may be serving as a court proof; data can be treated after acquisition when searching for unknowns; Identification and detection limits improve vs 3Q, since GC-MRTOF records fragments produced within the EI source and avoid losses associated with parent selection and fragmentation. Though the GC-MRTOF instrument may be potentially extended to GCxGC-TOF or to GC-Q-TOF, author do not see this as beneficial: GC-MRTOF already provides strong specificity to separate low fg traces within complex matrices; GCxGC would further improve specificity, but would slow down analyses; GC-Q-TOF would also improve specificity but would deteriorate LOD and LOQ with selection of single precursor and by splitting the precursor intensity into multiple fragments. The talk will present on the analysis of matrix composition and analytical examples of GC-MRTOF analyses within complex matrices.