INAUGURAL COURSE ON MOLECULAR TOXICOLOGY

EUROTOX - Molecular Toxicology Specialty Section

26-28 June 2019

Ege University, Izmir, Turkey

EUROTOX - Molecular Toxicology Specialty Section organised an inaugural course on molecular toxicology at Ege University, Izmir, Turkey, between 26 and 28 June 2019. Recent developments in science and feedback from various parties necessitated such an educational event in the field. Izmir hosted 14 invited lecturers and 32 course attendees from seven countries at the PhD and post-doc levels. Attendees and lecturers are pictured below.

The course was implemented with 32 attendees from Algeria, Australia, Belgium, Estonia, Poland, Serbia and Turkey. It started with an opening speech from the chair of the *Specialty Section* and *Organizing Committee*, Dr. Hilmi Orhan, on Wednesday 26 June. Subsequently, over two-and-a-half days, 14 lecturers gave 19 lectures (45 minutes each) under four main topics; *General Principles*, *Receptor-Mediated Toxic Outcomes*, *Targets, Cellular Responses and Interventions* and *Approaches to Toxicity Prediction*. As seen in the course programme, a majority of contemporary issues in molecular toxicology were covered and discussed by the attendees and invited lecturers in an interactive format. Several pictures taken during the course are shown below.

Among the various essential topics, three courses on predictive toxicology took place on the last day. The first two lectures were on an *Adverse Outcome Pathway* approach that can be defined as efforts to establish a plausible scenario of toxic pathway cascades for a particular agent at molecular levels. The last lecture was on *In Silico Molecular Modelling* that is an alternative/complementary approach to and/or interpretation of experimental laboratory studies.

COURSE PROGRAMME

DAY 1. JUNE 26TH, *Wednesday*

08:30-09:00	Opening and Introduction	*Hilmi Orhan*
09:00-11:45	***GENERAL PRINCIPLES***	
09:00-09:45	Structure-activity and dose-response relationships	*Hilmi Orhan*
09:45-10:30	Biotransformation reactions	*Miroslav Machala*
10:30-11:00	**Coffee break**	
11:00-11:45	Membrane lipid structure, cell surface receptors and cell-to-cell communication ……..…….....……	*Miroslav Machala*
11:45-12:45	**LUNCH**	
12:45-17:30	***RECEPTOR-MEDIATED TOXIC OUTCOMES***	
12:45-13:30	Xenoreceptors: PARP and CAR …….....	*Hartmut Jaeschke*

13:30-14:15	Xenoreceptors: PXR, KEAP and Nrf-2 …….....	*Hartmut Jaeschke*
14:15-15:00	AhR receptors …….....	*Jan Vondracek*
15:00-15:30	**Coffee break**	
15:30-16:15	THC receptors and novel mechanisms …….....	*Felix Carvalho*
16:15-17:30	Hormone receptor-mediated toxic outcomes ……..….....	*Hande Gürer Orhan*

DAY 2. JUNE 27TH, *Thursday*

09:00-17:45	***TARGETS, CELLULAR RESPONSES AND INTERVENTIONS***	
09:00-09:45	Fingerprints of carcinogens in tumour genomes …….....	*Mehmet Öztürk*
09:45-10:30	Physiological and toxicological functions of microRNAs ….....	*Brian Chorley*
10:30-11:00	**Coffee break**	
11:00-11:45	Modelling genetic susceptibility to disease	*Sinan Süzen*
11:45-12:30	Cellular responses to DNA damage …….....	*Bensu Karahalil*
12:30-13:30	**LUNCH**	
13:30-14:15	Calcium homeostasis and proteases …….....	*Metiner Tosun*
14:15-15:00	Protein modification and cellular responses …….....	*Angela Mally*
15:00-15:45	**Coffee break**	
15:45-16:15	Peptide and protein nanomaterials conjugates for biomedical interventions …….....	*Candan Tamerler*
16:15-17:00	Organelle-mediated toxic pathways	*Hilmi Orhan*
17:00-17:45	***a)*** Synthetic cannabinoids in the context of emerging addictive behaviours ***b)*** Epigenetics and cannabinoids addiction …….....	*Felix Carvalho*

DAY 3. JUNE 28TH, *Friday*

09:00-12:30	***APPROACHES TO TOXICITY PREDICTION***	
09:00-09:45	Adverse outcome pathways: focus on mitotoxicity …….....	*Mathieu Vinken*
09:45-10:30	Liver-based *in vitro* models: tools for molecular toxicology research	*Mathieu Vinken*
10:30-11:15	**Coffee break**	
11:15-11:45	Molecular modelling studies in toxicology …….....	*Atilla Akdemir*
11:45-12:30	**Break**	
12:30-14:00	**LUNCH**	
14:00-16:30	**Multiple choice exam**	
20:00-	**Group Dinner**	

DAY 4. JUNE 29TH, *Saturday*

09:00-16:00	**Visiting Ephesus and city excursion**

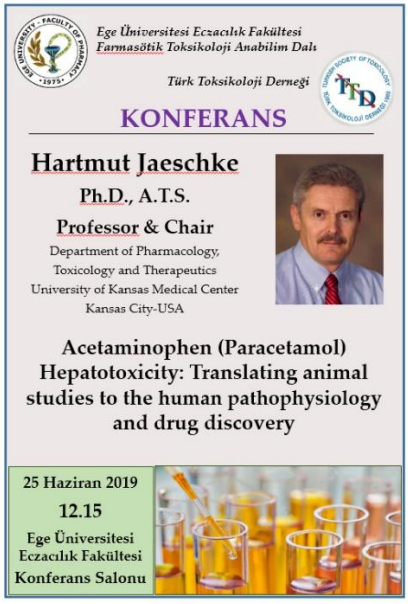
After the two-and-a-half-day course, there was a multiple-choice exam to assess the efficiency of the course. Subsequently, certificates were sent to the attendees. One scene from the classroom during the exam is pictured below.

A course dinner that combined the lecturers and attendees was organised on the evening of Friday 28 June, and the social programme was finalised with a visit to *House of Mother Mary* and then the antique city *Ephesus* on Saturday 29 June.

During the course, PhD students and PhDs from different countries and various disciplines had an intense interaction with each other and found an opportunity to discuss and share scientific topics covered or not covered by the course as well as personal experiences with the lecturers. Several collaborations were also established.

The feedback we received from face-to-face chats, telephone and e-mail messages from the attendees (and later the lecturers) were enthusiastic and encouraging towards organising similar courses in molecular toxicology. As the management of the Specialty Section, we began such preparations.

The day before the course started, a conference was given by one of the lecturers, Prof. Dr. Hartmut Jaeschke. Dr. Jaeschke is the chair of the Department of Pharmacology, Toxicology & Therapeutics of Kansas University Medical Centre in Kansas City, Kansas, USA. He is known for his long-standing studies on acetaminophen (paracetamol)-induced hepatic toxicity and liver injury caused by various agents.



The title of the conference was "*Acetaminophen (Paracetamol) hepatotoxicity: Translating animal studies to the human pathophysiology and drug discovery*". The rector of Ege University, Prof. Necdet Budak, opened this conference series that was originally planned as lectures given by eminent scientists from various disciplines in particular areas. Subsequently, Dr. Orhan introduced the scientific and social aspects of the speaker.

Dr. Jaeschke summarised the emergence and development of paracetamol as a drug. He stressed that, although paracetamol has largely been considered as the safest antipyretic and analgesic even in pregnant women and babies, it may not pass current criteria for drug approval because of its high risk of hepatic damage as well as kidney damage (although that occurs less frequently). Dr. Jaeschke summarised the studies conducted by his research group over the years to clarify the hepatotoxic mechanism of the drug. Lastly, he finished his conference with the novel potential antidote, 4-methylpyrazole (fomepizole), against hepatic damage induced by paracetamol overdose. Fomepizole is an antidote against methanol toxicity; it inhibits aldehyde dehydrogenase and prevents the toxic formic acid formation from methanol. Nevertheless, the studies conducted in the speaker's and others' laboratories revealed that fomepizole also inhibits CYP2E1, the major enzyme responsible for the toxic paracetamol metabolite (N-acetyl-p-benzoquinone imine), as well as c-Jun N-terminal kinase (JNK) activation and translocation into hepatocyte mitochondria. This process is one of the initial steps that commences cell death and eventually results in massive hepatic damage in paracetamol overdose.