Pharmacological Strategies for the Treatment of Neurodegenerative Disorders: From Current Therapies to Novel Targets

| ORGANIZER(S) | Dr. Giuseppe Caruso, Senior researcher, Department of Drug Sciences  
Viale Andrea Doria, 6, 95125, Catania, Italy  
forgiuseppecaruso@gmail.com |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ECTS</td>
<td></td>
</tr>
<tr>
<td>SUMMARY</td>
<td>The aim of this course is to discuss recent evidence on the neurobiology of Alzheimer’s disease (AD) including the role of amyloid, neuroinflammation, oxidative stress, and neurotrophic factors in the pathogenesis of AD. I will then examine the pharmacology of cholinergic system, the current pharmacological treatment of AD as well as the new disease-modifying drugs developed to prevent the transition from mild cognitive impairment (MCI) to AD. I will also analyze the novel approaches in drug discovery in AD field and in particular the therapeutic potential of the natural dipeptide carnosine. Finally I will discuss the pathogenesis of Parkinson’s disease with a focus on oxidative stress and the novel pharmacological strategies in the treatment of this disease.</td>
</tr>
<tr>
<td>COURSE LEVEL</td>
<td>Intermediate; Basic knowledge on Biology, Biochemistry, and Physiology needed</td>
</tr>
</tbody>
</table>
| COURSE DATES | • September 29 – October 1, 2020  
• Always 9:30-12:00 and 13:00-15:30 |
| LOCATION | The course can be followed online; the zoom link will be sent to registered participants only. The live course takes place at CMU Geneva, room C07.1732.a (7th floor). The access to the floor is restricted; please ring the doorbell “Secretariat” or dial 022-3795400 to enter. |

Note: Dr. Caruso will also give a talk entitled “Fluoxetine and vortioxetine reverse depressive-like phenotype and memory deficits induced by amyloid-β(1-42) oligomers in mice: implication of transforming growth factor-β1 and oxidative stress” on September 28 at 16h30 in Lausanne (zoom meeting ID: 940 7189 8638; passcode:645866). |

| CONTENT OF COURSE SESSIONS | September 29: Neurobiology of neurodegenerative disorders: focus on Alzheimer’s disease (AD)  
- Amyloid beta  
- Neuroinflammation  
- Oxidative stress  
- Microglia activation/polarization  
- Neurotrophic factors |
September 30: Pharmacological treatment of AD
- Current strategies
- Disease-modifying drugs: focus on immunotherapy
- Drug discovery in AD: the therapeutic potential of the natural dipeptide carnosine

October 1: Parkinson’s disease (PD)
- Pathogenesis of PD: focus on oxidative stress
- Novel pharmacological strategies

The course session on October 1 will end with a talk of Giuseppe Caruso @ 14:30 open to the neuroscience community. Please see below for details. For remote listening to the talk, please go to: https://unil.zoom.us/j/98033963907

**COURSE MATERIALS**
Reading and course materials are stored in the LNDS moodle system, to access:
- go to "https://moodle2.unil.ch"
- log in with your institutional address (unil, unige, epfl)
- click on "Faculté de Biologie et de Médecine" > "Ecole doctorale / doctoral school" > "Lemanic Neuroscience Doctoral School"
- course materials and papers are stored under "Pharmacological strategies for the treatment of neurodegenerative disorders"

**EVALUATION**
In the end of the course all students will be asked to write a critical report (1-2 pages) regarding the topics discussed during the course. Please submit the report by November 15, 2020, to lnds@unil.ch.

**REGISTRATION**
Register before September 20, 2020, by writing a mail to lndscourses@gmail.com (with your supervisor in copy) and stating the course title as subject.

*Talk @ CMU on October 1: “Carnosine negatively modulates pro-oxidant activities of M1 peripheral macrophages and prevents neuroinflammation induced by amyloid-β in microglial cells”.*

Carnosine is a natural dipeptide widely distributed in mammalian tissues and exists at particularly high concentrations in skeletal and cardiac muscles and brain. A growing body of evidence shows that carnosine is involved in many cellular defense mechanisms against oxidative stress, including inhibition of amyloid-β (Aβ) aggregation, modulation of nitric oxide (NO) metabolism, and scavenging both reactive nitrogen and oxygen species. Different types of cells are involved in the innate immune response, with macrophage cells representing those primarily activated, especially under different diseases characterized by oxidative stress and systemic inflammation such as depression and cardiovascular disorders. Microglia, the tissue-resident macrophages of the brain, are emerging as a central player in regulating key pathways in central nervous system inflammation; with specific regard to Alzheimer’s disease (AD) these cells exert a dual role: on one hand promoting the clearance of Aβ via phagocytosis, on the other hand increasing neuroinflammation through the secretion of inflammatory mediators and free radicals.

The activity of carnosine was tested in an in vitro model of macrophage activation (M1) (RAW 264.7 cells stimulated with LPS + IFN-γ) and in a well-validated model of Aβ-induced neuroinflammation (BV-2 microglia treated with Aβ oligomers). An ample set of techniques/assays including MTT assay, trypan blue exclusion test, high performance liquid chromatography, high-throughput real-time PCR, western
blot, atomic force microscopy, microchip electrophoresis coupled to laser-induced fluorescence, and ELISA aimed to evaluate the antioxidant and anti-inflammatory activities of carnosine was employed.

In our experimental model of macrophage activation (M1), therapeutic concentrations of carnosine exerted the following effects: 1) an increased degradation rate of NO into its non-toxic end-products nitrite and nitrate; 2) the amelioration of the macrophage energy state, by restoring nucleoside triphosphates and counterbalancing the changes in ATP/ADP, NAD+/NADH and NADP+/NADPH ratio obtained by LPS + IFN-γ induction; 3) a reduced expression of pro-oxidant enzymes (NADPH oxidase, Cyclooxygenase-2) and of the lipid peroxidation product malondialdehyde; 4) the rescue of antioxidant enzymes expression (Glutathione peroxidase 1, Superoxide dismutase 2, Catalase); 5) an increased synthesis of transforming growth factor-β1 (TGF-β1) combined with the negative modulation of interleukines 1β and 6 (IL-1β and IL-6), and 6) the induction of nuclear factor erythroid-derived 2-like 2 (Nrf2) and heme oxygenase-1 (HO-1).

In our experimental model of Aβ-induced neuroinflammation, carnosine: 1) prevented cell death in BV-2 cells challenged with Aβ oligomers; 2) lowered oxidative stress by decreasing the expression of inducible nitric oxide synthase and NADPH oxidase, and the concentrations of nitric oxide and superoxide anion; 3) decreased the secretion of pro-inflammatory cytokines such as IL-1β simultaneously rescuing IL-10 levels and increasing the expression and the release of TGF-β1; 4) prevented Aβ-induced neurodegeneration in primary mixed neuronal cultures challenged with Aβ oligomers and these neuroprotective effects was completely abolished by SB431542, a selective inhibitor of type-1 TGF-β receptor.

Overall, our data suggest a novel multimodal mechanism of action of carnosine underlying its protective effects in macrophages and microglia and the therapeutic potential of this dipeptide in counteracting pro-oxidant and pro-inflammatory phenomena observed in different disorders characterized by elevated levels of oxidative stress and inflammation such as depression, cardiovascular disorders, and Alzheimer’s disease.