A recent acquisition in the field of thyroid hormone signaling is the discovery (2004) that one of its metabolites, 3-iodothyronamine (T1AM), may represent an independent chemical messenger. T1AM has been detected in virtually every tissue in rodents, as well as in human blood. Tissue concentrations are in the nanomolar range (pmol/g), i.e. on the same order of magnitude as tissue thyroid hormone concentration. While the biosynthetic pathway responsible for T1AM production is still incompletely understood, in vivo T1AM is a substrate for several enzymes, and in most cell types its major metabolite is 3-iodothyroacetic acid (TA1).

T1AM is not a ligand for nuclear thyroid hormone receptors, but stimulates with nanomolar affinity trace amine-associated receptor 1 (TAAR1), a G-protein coupled membrane receptors. Notably, TAAR1 is activated by amphetamines and other psychotropic drugs, while the TAAR1 gene maps in a chromosomal region which has been associated to the susceptibility to schizophrenia or bipolar affective disorder. However, T1AM is regarded as a multi-target ligand, since it also interacts with other aminergic receptors, amine transporters, and ionic channels of the transient receptor potential class.

Administration of exogenous T1AM to experimental animals caused a wide array of functional responses. While several effects occurred at pharmacological concentrations, metabolic and neurological effects were observed at lower dosages, which increased endogenous tissue levels of about one order of magnitude. It is therefore likely that T1AM may play a physiologic role in the central nervous system. Evidence for a cross-talk between TAAR1 and dopaminergic signaling has been reported, while systemic or i.c.v. T1AM administration in mice elicited pro-learning and anti-amnestic effects, stimulated locomotor activity, modulated alimentary behavior and reduced non-REM sleep.

The group meeting will be organized as follows:
- Riccardo Zucchi will summarize the basic features of T1AM/TAAR1 signaling and introduce the on-going research projects.
- Grazia Rutigliano will present her work on the analysis and functional characterization of TAAR1 variants in patients with mental disorders.
- Annunziatina Laurino will show her results on the cognitive and neuroprotective effects of T1AM and TA1.
- Grazia Chiellini will deal with the potential pharmacological exploitation of this system, discussing the design, synthesis and evaluation of novel T1AM analogues / TAAR1 agonists.

**Martedì 19 Febbraio 2019, alle ore 17.15**
**Aula Magna, Scuola Medica**