



PRINCIPE FELIPE  
CENTRO DE INVESTIGACION

## The Future of Biomedical Research Lecture Series

### Targeting necroptosis and ferroptosis in experimental disease models, therapeutic perspectives

Speaker: **Dr. Peter Vandenabeele**<sup>1,2</sup>

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Date: **15/06/18- 12:30h**

Place: Sal3n de Actos CIPF

**Abstract:** There are many ways by which cells can die depending on the stimulus and the cellular context. To classify different types of cell death, the term “regulated cell death” was introduced to discriminate it from “accidental cell death”. Regulated cell death involves the activation of genetically encoded molecular machinery, while accidental cell death occurs in response to physical or chemical insults and occurs independently of molecular signalling pathways. Apoptosis, the best understood form of regulated cell death involves the activation of cysteine proteases, caspases. The necrotic cell death modalities share the activation of different plasma membrane destabilizing mechanism during the execution phase: phosphorylated MLKL in necroptosis, caspase-1-cleaved gasdermin D in pyroptosis, caspase-3-cleaved DFNA5/gasdermin E in secondary necrosis (following apoptosis) and accumulation of peroxidized phospholipids in ferroptosis. The role of cell death is twofold: loss of barrier and consecutive infiltration of microbes, and release of Damage Associated Molecular Patterns (DAMPs) and chemokines from dying cells, which could contribute to inflammation.

Necroptosis is a form of regulated cell death that can be triggered by activation of death receptors, T cell receptor Toll-like receptors and by viral infection. Necroptosis involves the kinases RIPK1 and RIPK3 which affect death decisions through both their kinase activity and protein-protein interactions independent of their kinase activity. RIPK1 kinase activity is involved in autophosphorylation allowing the recruitment and activation of RIPK3. RIPK3 on its turn phosphorylates and activates MLKL. Novel drugs and known drugs have been identified in cellular phenotypic screenings which block necroptosis. These drugs are effective in blocking inflammatory, degenerative and infectious experimental diseases. Altogether data illustrate the crucial role of RIPK1 kinase activity in homeostasis and pathologies, and provide profound therapeutic perspectives for its targeting in Crohn’s disease, rheumatoid arthritis, psoriasis..

Ferroptosis is a new type of regulated necrosis, which is characterized by overwhelming iron-catalyzed lipid peroxidation leading to cell death. It has been identified that loss of activity of the lipid repair enzyme glutathione peroxidase 4 (GPX4) and blocking GSH synthesis, makes the cell vulnerable for ferroptosis induction. I will discuss the molecular insights in ferroptotic cell death and how this could be translated in therapeutic strategies.

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