

## AGE-RELATED MACULAR DEGENERATION (AMD): FROM METABOLOMICS APPROACH TO THE INHIBITION OF PDK AS A NEW THERAPEUTIC TARGET

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Metabolomics is one of the most recent technologies in the world of Omics sciences. It aims at studying metabolome, which is composed of small molecular weight organic molecules (called metabolites) of a cell, an organism or a biological system. This approach gives rise to a growing number of applications in many areas, such as biomarkers discovery, clinical studies, drug efficacy and toxicity evaluation, diagnostic tools, quality control. One of the most interesting features of metabolomics is its capability to extract biochemical information reflecting biological events and then to be a powerful tool in the knowledge of the aetiology of some pathologies. Indeed, it is clear that every disease could alter more or less drastically the metabolic profile of the patients. Then a metabolomics approach could highlight the biochemical pathways affected and could allow the identification of new putative therapeutic strategies or targets that could be useful in a new drug discovery strategy. As proteomics, metabolomics approach represents a new and powerful tool for Medicinal Chemistry.

Age-related Macular Degeneration (AMD) is a leading cause of vision loss in the western world among people aged 50 or older. 90% of all vision loss due to AMD results from the exudative form, which is characterized by choroidal neovascularization (CNV). Age-related changes that induce pathologic CNV are incompletely understood. A successful application of anti-VEGF approaches in the clinic is obviously a turning point in AMD treatment. Nevertheless, despite such important advances, critical issues remain to be addressed. To better understand the aetiology of this pathology, we used and improved a murine model of laser-induced choroidal neovascularization and applied a <sup>1</sup>H NMR metabolomics study.<sup>1</sup>

This approach leads to the emergence of different putative biomarkers and to the validation of the CNV model for an experimental study of AMD. Among these “biomarkers”, lactate appears to be clearly involved in the development of AMD. The modulation of their plasma concentration by treatment of the animals with synthetic compounds and more specifically Pyruvate Dehydrogenase Kinase inhibitors (PDK) significantly decrease the impact of laser induced CNV. Starting from these results, the development of new PDHK inhibitors could open the way to innovative treatment opportunities in AMD disease.

### References

1. Lambert, V.; Lecomte, J.; Hansen, S.; Blacher, S.; Gonzalez, M. L. A.; Struman, I.; Sounni, N. E.; Rozet, E.; De Tullio, P.; Foidart, J. M.; Rakic, J. M.; Noel, A. Laser-induced choroidal neovascularization model to study age-related macular degeneration in mice. *Nature Protocols* **2013**, 8, 2197-2211.