AQUAPORIN CHANNELS IN MEMBRANES: THERAPEUTIC TARGETS FOR CHRONIC DISEASES

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Introduction
Aquaporins (AQPs) belong to a highly conserved group of membrane proteins widely distributed in various tissues throughout the body involved in the transport of water and small solutes such as glycerol. AQPs are involved in many biological functions, including transepithelial fluid transport, cell migration and proliferation, brain oedema and neuroexcitation, adipocyte metabolism and epidermal water retention. AQPs have proved to be highly expressed in different tumor types, where they are involved in tumor invasion, metastasis and growth. In the last decade, the aquaporin field became a very hot area of research with increasing physiological and medical implications.

Objectives
To investigate AQPs as potential drug targets opening new perspectives to untangle mechanisms of disease.

Materials and Methods
Stopped-flow and fluorescence microscopy, molecular modeling, immunohistochemistry, cell toxicity and differentiation.

Discussion and Results
We have recently disclosed the potent and selective inhibition of human AQP3 by gold compounds. These compounds show a high selectivity for AQP3 with IC50 in the low-micromolar range, and no toxic effects to normal cells that would hamper their applicability. The effect of Auphen on AQP3 expressing cells was shown to induce blockage of cell proliferation, thus evidencing a targeted therapeutic effect on cancer types with large AQP3 expression. The specificity of Auphen towards aquaglyceroporins was confirmed by its inhibitory effect on AQP7, an aquaglyceroporin largely expressed in adipocytes and important in adipose tissue homeostasis and obesity. The high selectivity and low IC50 of these gold compounds makes them suitable drug leads for in vivo studies. In addition, our recent studies pointed to a role of AQP5 on adipocyte cell differentiation. Interestingly, we have detected aberrant expression of this same aquaporin in pancreatic tumors of high malignancy, suggesting it may be a potential tool for early diagnosis.

Conclusions
Our data clearly suggest AQPs as drug targets and point to the development of aquaporin modulators as therapeutic and diagnostic agents.