

**MicroRNA-205 driven rewiring of cholesterol biosynthesis identifies therapeutic windows in aggressive prostate cancer**

Eur Urol Suppl 2019;18(8):e3089

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**Introduction & Objectives:** Due to its rising incidence, prostate cancer (PCa) has become a worldwide challenge for uro-oncologists. PCa is characterized by heavy reliance on the androgen receptor pathway in many stages of the disease, as mirrored to increased uptake, synthesis and usage of cholesterol, which serves as the starting metabolite for steroid and therefore testosterone synthesis. In this work, we aimed at correlating key enzymes of cholesterol biosynthesis to microRNA-205, a miR previously described as down-regulated in advanced PCa by our study group.

**Results:** We show here that overexpression of SQLE, a rate-limiting enzyme of the cholesterol synthesis pathway and PCa-related gene, is linked to advanced tumour stages and worse prognosis in PCa tissue cohorts. Moreover, we demonstrate that SQLE is an essential target gene of microRNA-205 and that its regulation through tetracycline-inducible microRNA-205 overexpression or competitive inhibition with terbinafine is capable of regulating cholesterol synthesis and downstream androgen receptor activity in a plethora of in-vitro PCa progression models. Furthermore, we show that orally administered terbinafine is able to delay biochemical progression in an incurable PCa patient with liver metastases. On-going in-vivo experimentation will test whether competitive inhibition of SQLE via terbinafine is able to block tumour growth and metastasis in an orthotopic PCa mouse model.

**Conclusions:** Taken together, our results highlight the importance of cholesterol biosynthesis inhibition as an innovative therapeutic tool for aggressive PCa, which should be evaluated in clinical trials.