

Kafka M.<sup>1</sup>, Temml V.<sup>2</sup>, Mayr F.<sup>2</sup>, Bouchal J.<sup>3</sup>, Kharraishvili G.<sup>3</sup>, Klocker H.<sup>1</sup>, Bektic J.<sup>1</sup>, Stuppner H.<sup>2</sup>, Eder I.E.<sup>1</sup>

<sup>1</sup>Medical University Innsbruck, Urology, Innsbruck, Austria, <sup>2</sup>University Innsbruck, Pharmacy/Pharmacognosy, Innsbruck, Austria, <sup>3</sup>Palacky University, Clinical and Molecular Pathology, Olomouc, Czech Republic

**Introduction & Objectives:** Prostate Cancer (PCa) is a common malign neoplasm in men with an incidence of over 200 in 100,000 men worldwide. Curative treatment at early stages is usually possible, whereas therapy of progressed PCa still poses a challenge. Since tumor development and progression are largely dependent on androgens, the gold standard therapy for advanced PCa is androgen deprivation therapy (ADT). Even if good treatment response can be achieved initially, a subsequent conversion to castration resistant PCa (CRPC) is frequently observed after 18 to 36 months. There is evidence that aldo-keto reductase family 1 member C3 (AKR1C3) is involved in this progress by supplying intratumoral androgens via de novo steroidogenesis. Furthermore, novel data suggests that resistances to clinically used drugs (e.g. enzalutamide) may be overcome by the inhibition of AKR1C3. In this study, we tested the effects of novel dihydrochalcones, which were isolated from the plant *Melodorum fruticosum* and which exhibited inhibitory activity towards AKR1C3.

**Materials & Methods:** The effects of different dihydrochalcones were investigated in various PCa cell lines using a cell viability assay (CellTiter-Glo®). AKR1C3 expression was explored by real-time qPCR and Western blot analysis in cell lines and by immunohistochemistry in human clinical specimens.

**Results:** AKR1C3 was significantly elevated in PCa compared to benign prostate tissue with a significant association to higher Gleason score and metastatic disease (N-stage). Its expression was heterogeneous among various PCa cell lines tested with highest levels in CWR22Rv1 and two enzalutamide resistant PCa cell lines that were previously established in our lab (LAPC4\_EnzaR, DuCaP\_EnzaR). We then tested the growth-inhibitory effects of various concentrations (0.2 – 100 µM) of three dihydrochalcones with potential inhibitory activity towards AKR1C3 in CWR22Rv1 PCa cells. MF-15 emerged as the most potent compound with over 50% reduction of cell viability with an applied concentration of 10µM. Similarly, MF-15 significantly inhibited the two enzalutamide resistant cell lines comparable to the known AKR1C3 inhibitor indomethacin.

**Conclusions:** With our analysis we could illustrate that AKR1C3 plays a significant role in PCa and in enzalutamide resistance in particular. Moreover, we showed that MF-15, a novel dihydrochalcone is effective in inhibiting enzalutamide resistant PCa cell lines in vitro. Since there is data suggesting that an additional potent inhibition of AKR1C3 might overcome drug resistances we are confident that our data could be clinically relevant.