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AKR1C3 as prognostic biomarker, druggable target and more...

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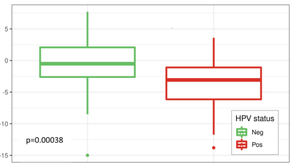
Aldo-keto reductase (AKR) 1C3 is a member of the AKR superfamily of proteins. It catalyzes the production of potent **androgen receptor (AR) ligands**, as testosterone (T) and 5α-dihydrotestosterone (DHT). AKR1C3 is also implicated in **prostaglandin** and **estrogen metabolism**, in regulating the trans-activation of various nuclear receptors, such as **AR**, **estrogen receptor (ER)**, and **peroxisome proliferator activated receptor gamma (PPARG)**. It is a suitable target in hormone-(in)dependent tumors. AKR1C3 is **overexpressed** in many cancer types and it is involved in tumor progression and in **chemo-hormone-radioresistance**.

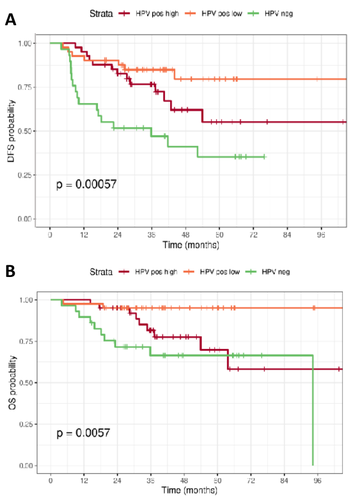
AKR1C3 is highly expressed in in HPV-negative oropharynx tumors (OPSCCs) and in a subgroup of HPV-positive OPSCCs.



Differential AKR1C3 expression determined using the -ΔCT method in an independent cohort of OPSCC samples (n = 111) according to HPV status.

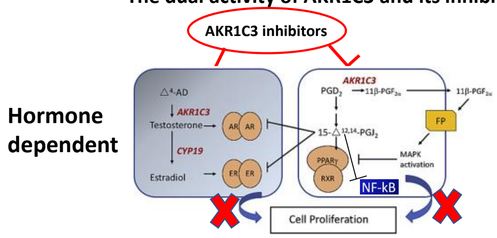
Gene set enrichment analysis (GSEA) revealed that the genes **down-regulated in HPV-negative samples** were mainly involved in **immune system**, whereas those **up-regulated** mainly in **glutathione derivative biosynthetic and xenobiotic metabolic processes.**

Its expression correlates with **worse prognosis**, independently of HPV-status.

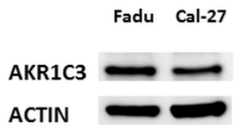


Kaplan-Meier curves for (**A**) disease-free survival and (**B**) overall survival, according to HPV-negative cases (green line), HPV-positive cases with high AKR1C3 expression (red line), and HPV-positive cases with low AKR1C3 expression (orange line).

The dual activity of AKR1C3 and its inhibition

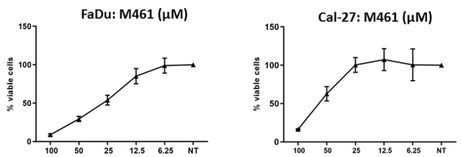


Adapted from Penning et al., AKR1C3: Roles in malignancy and endocrine disorders 2019, Mol Cell Endocrinol



AKR1C3 protein expression in two HPV-negative OPSCC cell lines

AKR1C3 is a target for therapy in OPSCCs. Its inhibition by MEDS461, a selective AKR1C3 inhibitor, **reduces cell proliferation** in AKR1C3 overexpressing OPSCC cell lines.



Dose-effect curves of MEDS461 (M461) in two OPSCC cell lines.

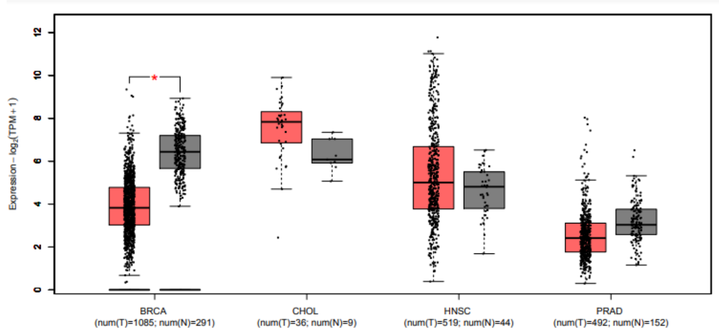
Pre-treatment with MEDS461 potentiates the effect of Cisplatin with an **enhancement factor** of 3.65 in AKR1C3 overexpressing cell line.

Cell line	Cisplatin IC50 (μM)	Pre-treatment 461 + Cisplatin IC50 (μM)	Cisplatin enhancement factor with pre-treatment	Cisplatin + 461 combination IC50 (μM)	Cisplatin enhancement factor in combination
Fadu	3.4	**0.93**	**3.65**	2.7	**1.26**

Cell line	Cisplatin IC50 (μM)	Pre-treatment 461 + Cisplatin IC50 (μM)	Cisplatin enhancement factor with pre-treatment	Cisplatin + 461 combination IC50 (μM)	Cisplatin enhancement factor in combination
Cal-27	3.9	11.52	**0.34**	5	**0.78**

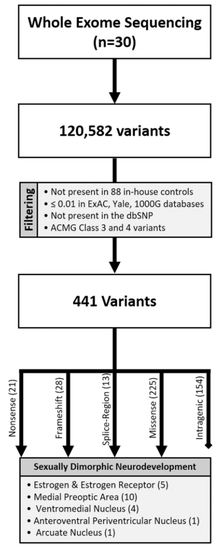
AKR1C3 is a suitable target in:

- **Prostate Cancer**, being a biomarker of poor prognosis in both androgen-dependent and castration resistant prostate cancer (CRPC). It is a **target** to overcome enzalutamide and abiraterone resistance.
- **Triple Negative Breast Cancer,** enriched for luminal androgen receptor (LAR). These tumors may respond to both **anti-androgen** and traditional **anti-estrogen** therapies and AKR1C3 could **counteract resistance** to such therapies
- **Cholangiocarcinoma,** an aggressive and orphan disease, in which AKR1C3 is overexpressed in tissues and cell lines.



Differential AKR1C3 expression between tumor (red) and normal (gray) tissues of breast cancer (BRCA), cholangiocarcinoma (CHOL), head and neck squamous carcinoma (HNSC), prostate adenocarcinoma (PRAD).

(http://gepia2.cancer-pku.cn/)



Relation	Gene	Location	Position^	Nomenclature
Estrogen & Estrogen Receptor	AKR1C3	10p15.1	5144369	c.A647G (p.Y216C)
	CDK12	17q12	37618361	c.G37C (p.G13R)
	PIK3CA	3q26.32	178917534	c.C409T (p.Q137X)
	PPARGC1B	5q32	149109981 149213068	c.C76T (p.Q26X) c.C1315T (p.R439C)

- AKR1C3 is involved in sexually dimorphic neurodevelopment;
- A rare variant is found in a cohort of transgenders

Adapted from Theisen, J. Graham et al., "The Use of Whole Exome Sequencing in a Cohort of Transgender Individuals to Identify Rare Genetic Variants". Scientific Reports. 9 (1), 2019. PMID 31882810

AKR1C3 is a biomarker and druggable target for oropharyngeal tumors. Peraldo-Neia C et al. Cell Oncol (Dordr). 2020 Nov 19.

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