Androgen receptor; a tale of two cancers

Prostate cancer and breast cancer share similarities as hormone related cancers with a wide range of heterogeneous settings. Macklin, as early as 1954, provided evidence for a significantly higher frequency of prostate cancer among relatives of breast cancer patients and proposed for the first time that prostate cancer may be the male equivalent of some female breast cancers. Androgen receptor (AR) is a member of the steroids receptor family and is involved in both reproductive and anabolic actions in both men and women. AR signaling has an important role in initiation and progression of many hormone related cancers. Typically, androgen receptor antagonists are used for the treatment of prostate cancer (PC) but unfortunately the currently used ones are not strong enough and in some cases they cause resistance and fail to inhibit the AR.

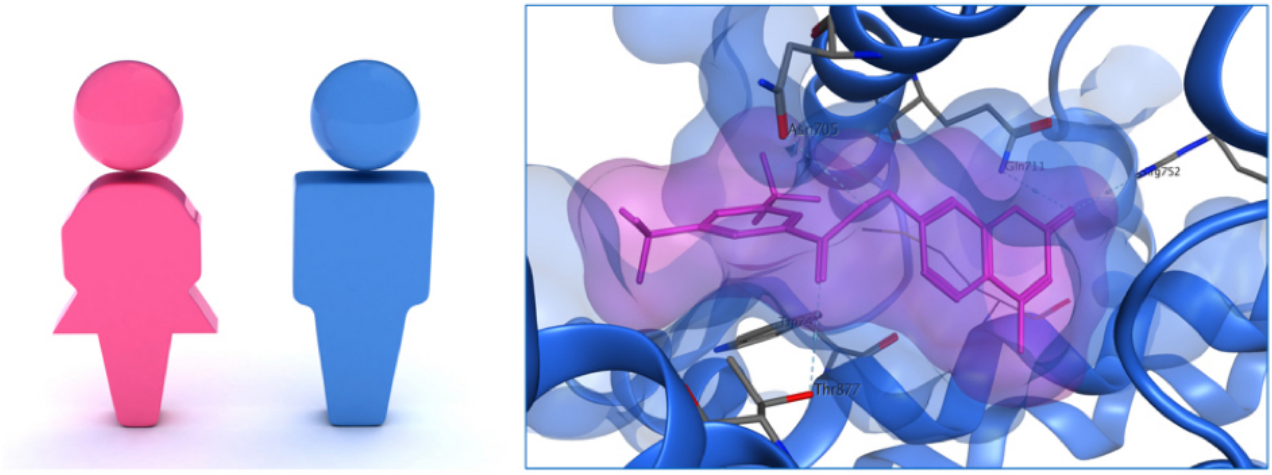

Fig. 1. Umbelliferone derivative (pink) interacting with androgen receptor (blue) showing promising in vitro activity against human breast cancer (MCF-7) and human prostate cancer (22Rv1) cell lines.

In addition to the substantial role of antiandrogens in the treatment of PC, there has been growing evidence that the androgen signaling pathway can play a critical role in breast cancer (BC). The AR is occurring in up to 90% of primary tumours and 75% of metastases. The tumour AR expression level was shown to be inversely associated with the survival of BC patients. Triple negative breast cancers (TNBC) are characterised by aggressive tumour biology resulting in a poor prognosis. The androgen receptor (AR) is reported to be a newly emerging biomarker in TNBC.

In two independent and recently published studies, a computer aided drug discovery platform was used to identify alternative chemical architectures of AR antagonists. Interestingly, both of these studies came up with similar chemical entities featuring umbelliferone core structures. Umbelliferone is a widespread natural product and its name comes from the *umbelliferae* family of

plants, which was named for their umbrella shaped inflorescences, carrots and coriander are members of this family.

The findings of these two independent studies were interesting for us to start lead optimisation strategy, where modification of the structure of the umbelliferone core has been carried out to prepare a series of twenty nine compounds. Our compounds were tested *in vitro* against human breast cancer (MCF-7) and human prostate cancer (22Rv1). One of our compounds shown in Fig.1 displayed a 50 fold improvement of the activity profile compared to the clinically used AR antagonist (bicalutamide). We also used established computer models to explain the correlation between the chemical structure and our observed biological activity.

In summary, through lead optimisation approach, we have prepared 29 umbelliferone derivatives. They were tested *in vitro* against the human prostate cancer (22Rv1). One of these derivatives proved to have the structural features that lead to 50 fold improvement over the clinically used bicalutamide. Interestingly, this compound demonstrated even better activity against the human breast cancer (MCF-7). These findings provide a basis for further development of umbelliferone derivatives for the potential treatment of human AR related cancers.

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