

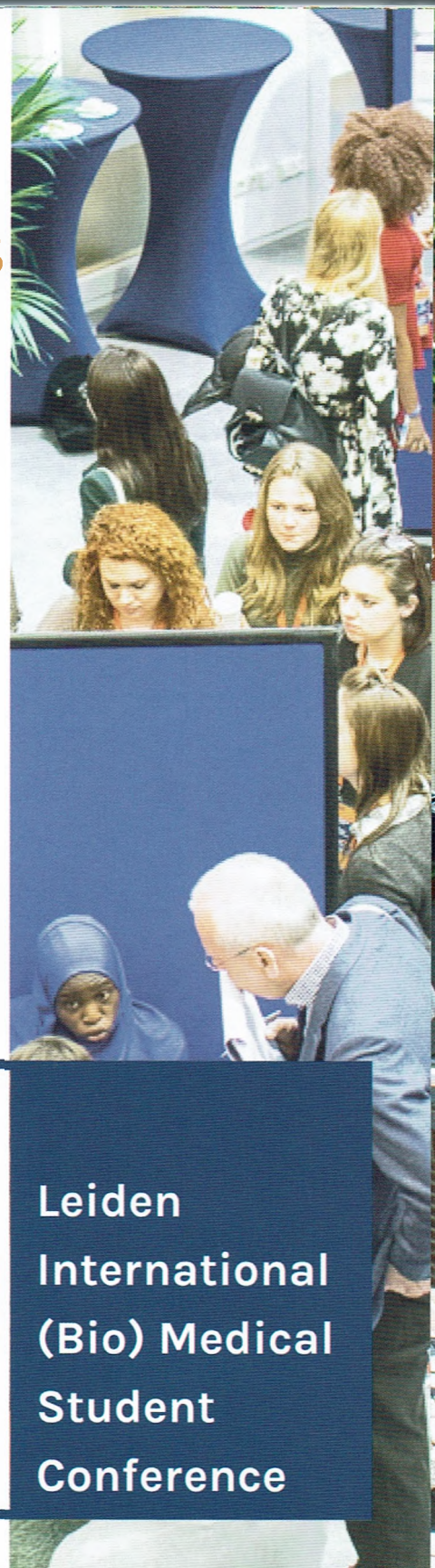
BOOK OF ABSTRACTS

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LEIDEN,
THE NETHERLANDS



Leiden
International
(Bio) Medical
Student
Conference



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INVESTIGATION OF TUMOR INHIBITORY EFFECTS OF 17 NOVEL TAMOXIFEN ANALOGUES ON DIFFERENT TUMOR CELL TYPES

Name: Márton Kalabay

Co-authors: Marton Kalabay, Zsolt Szasz

Project Supervisor: Laszlo Kohidai, MD, PhD

Institution: Semmelweis University

The selective estrogen receptor modulator Tamoxifen is a well known anti-tumor compound; however, it can modulate multiple cellular physiological processes (e.g. anti-angiogenic, proapoptotic, inhibitor of PKC), too. Previous investigations of the drug documented that structural modifications of the parent molecule may result in significantly diverse (increased and decreased) activity in different models. In the present work our objective was to study whether presence of ferrocene residue, heterocycles or halogenation can improve the anti-tumor effects of the drug. Our aims were (i) to study the anti-tumor effects of 17 novel tamoxifen analogues on tumor cells with different origin; (ii) to investigate the mechanism of their cytotoxic effect, as well as (iii) to describe structure-activity relationships in order to find an ideal analogue for targeted tumor therapy.

Tamoxifen and 17 analogues were investigated in 4 tumor model cell lines (PANC-1: human pancreatic cc.; COLO205: human colorectal adenocarc.; A2048: human metastatic melanoma and EBC-1: human lung squamous cell cc.; MCF7: human estrogen-positive breast cc.). The antiproliferative/cytotoxic effects (IC₅₀) were evaluated by impedimetry (xCELLigence SP) as well as colorimetric AlamarBlue assay. The cell cycle arrests elicited by the analogues were measured by a propidium iodide based assay in flow cytometry. Statistical analysis of data was performed by ANOVA and statistical routines of RTCA 2.0 were applied to analyse impedimetry data.

Tamoxifen performed antitumor effects in each cell line (IC₅₀: PANC-1 – 33.7 µM, COLO205 – 12.0 µM, A2048 – 13.5 µM, EBC-1 – 8.2 µM). Incorporation of ferrocene (e.g. T15) as well as halogenation of tamoxifen (e.g. T6) resulted in significantly increased anti-tumor effect in PANC-1 (IC₅₀: T15 – 15.0 µM, T6 – 29.6 µM) and in COLO205 (IC₅₀: T15 – 2.5 µM, T6 – 9.9 µM) cells. Cytotoxic responses of EBC-1 cells proved to be in general more sensitive to the tamoxifen analogues than PANC-1 or A2048 cell line. Tamoxifen and the ferrocene containing derivatives could elicit weaker toxic effects in the estrogen receptor positive MCF-7 cells than in the estrogen receptor negative cell-lines. Halogenation could increase the anti-tumor effects even in the MCF-7 cells. Tamoxifen analogues containing heterocycle with nitrogen and oxygen showed lower cytotoxic activity than tamoxifen on all investigated tumor cell line. Cell cycle study confirmed that presence of ferrocene residue (subG1: 40.7%) can enhance the basic apoptotic character of tamoxifen (subG1: 7.9%), while the ferrocene containing derivative (T6) resulted in an arrested cell cycle in G2/M phase in PANC-1 cells.