МЕДИЦИНСКИ УНИВЕРСИТЕТ - ВАРНА
„Проф. д-р Параскев Стоянов“
Ул.“Марин Дринов“ 55, Варна 9002, България
Тел. : 052/ 65 00 57, Факс: 052/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

MEDICAL UNIVERSITY - VARNA
“Prof. Dr. Paraskev Stoyanov”
55, Marin Drinov Str., 9002 Varna, Bulgaria
Tel.: +359 52/ 65 00 57, Fax: + 359 52/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

Fund “Nauka” Project № 19029 Resume – Competition-Based Session 2019:

“Study of the effect of specific carboxylesterase inhibitors on the effectiveness of chemotherapy with Capecitabine”

Project leader: Prof. Petko Penkov Marinov, MD, PhD

Capecitabine is an antineoplastic *pro-drug*, representative of the fluoropyrimidine class. Once administered, the *pro-drug* is, *in vivo*, metabolised by a triad of enzymes into its active form (metabolite) - *5-Fluorouracil* (Fig. 1).

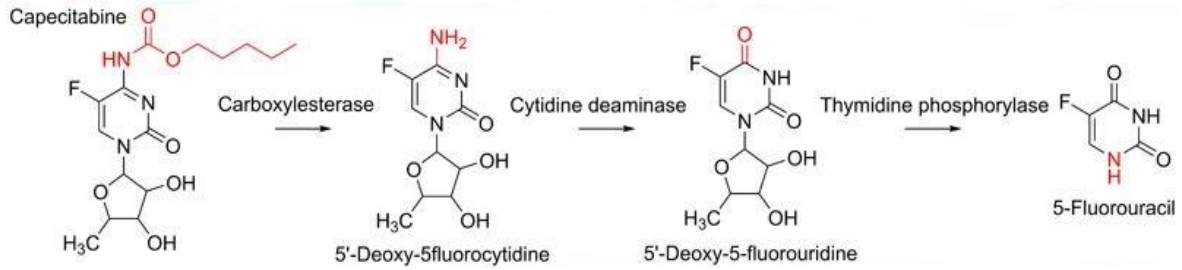

Figure 1. Three-step activation of Capecitabine

Both *5-Fluorouracil* and *Capecitabine* have been traditionally used in the treatment of multiple malignancies for years. Unlike *5-Fluorouracil*, however, *Capecitabine* is currently considered as a chemotherapeutic agent of first choice. Indeed, the clinical outcomes of *Capecitabine* treatment in terms of efficacy and side effects are more than acceptable.

A review of the medical literature has, however, shown that the number of studies related to enhancement of the *Capecitabine’s* theraupetic index is too limited.

The main strategies concern: the combination of *Capecitabine* with calcium folinate; the use of selective aminopeptidase-N (CD13; genomic) and dUTPase/ DPD inhibitors, as well as the use of nanostructured materials for drug delivery.

On the othe hand, the crucial role of several genetic alterations on *Capecitabine’s* theraupetic effciency has also been reported in several isolated reports. In this regard, the established relationships between CES2 and CES1 genes polymorphisms and the activity of the *pro-drug* in question have been considered as extremely intriguing.

These genes are known to affect the expression of CES2 and CES1 enzymes, responsible for the first stage of *Capecitabine* metabolism.

For the time being, however, there is no information about the activity of CES-inhibitors and their influence on the bioavailability of *Capecitabine*.

All these findings and questions highlightted the relevance of the present study, namely: To determine the effect of various CES inhibitors on the bioavailability of *Capecitabine* and its efficacy in the treatment of malignant tumors.

For the aim: The chemotherapeutic (antitumor) efficacy of *Capecitabine* in combination with CES-inhibitors was evaluated against Icr Albino Mice inoculated with Ehrlich-Lettre ascites cells.

The main **aim** of this study is: To generate of an innovative therapeutic approach/strategy for malignant tumors therapy – an approach bearing the traces of the modern pharmacological, phyto-, and nutritional therapy.

The current research can be viewed as interdisciplinary and focused on the priority scientific area - oncology and rare diseases.

Expected results:

- Enhancement of *Capecitabine* efficacy by increasing its therapeutic index; efficacy associated with the reduction of its total therapeutic dose and toxicity.
- To introduce innovative oncological therapy, hiding in itself the features of modern pharmaco-, phyto- and nutritional approaches.

Results:

The conducted experimental activities allowed us to analyze the possibilities for optimization of the antineoplastic therapy with Capecitabine in the presence of carboxylesterase inhibitors.

In this regard, an *in vivo* model of tumor disease was used. Experimental White Mice of the Icr Albino breed were peritoneally implanted with an Ehrlich tumor. The survival rate of the groups receiving combination therapy (carboxylesterase inhibitor + Capecitabine) was compared with the control groups (untreated or treated with antineoplastics only). In addition, an environmentally friendly procedure based on the protein precipitation method has been developed for the preparation of plasma samples from experimental animals treated with Capecitabine. An HPLC-based method for determining the analytes in question has also been successfully developed.

The analysis of the data showed that the survival rate of animals treated with Capecitabine and Isatin (carboxylesterase inhibitor) was 5% higher than that of the untreated control group, but did not exceed the effectiveness of antineoplastic monotherapy. On the other hand, the combination of Capecitabine and Loperamide (selective carboxylesterase-2 inhibitor) increased the survival rate of peritoneally implanted with Ehrlich tumor experimental animals by the highest percentage (twice as high as that of Capecitabine monotherapy).

The data obtained support the original hypothesis related to the possibility of increasing the effectiveness of Capecitabine therapy by inhibiting its extratumoral activation.

The present study should contribute to raising awareness of strategies for optimizing Capecitabine therapy in the presence of carboxylesterase-2 inhibitors. In addition, the protocols thus developed may be useful for other preclinical studies focused on the reduction of the toxic effects of antineoplastic therapy with the pro-drug studied.