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INTERNATIONAL SYMPOSIUM AT FACULTY OF MEDICAL SCIENCES
“Current achievements and future perspectives in medical and biomedical research”

SCIENTIFIC PROGRAM
November 24, 2015 - Stip

Registration

Rector / Vice rector/Dean

SESSION 1

Chair: Prof. Emilija Janevik Ivanovska

Co-chair: Ass. Prof. Elena Drakalska

Ass. Marija Darkovska Serafimovska
Macedonian agency of drug and medical devices, Director
University Goce Delcev Stip
Republic of Macedonia

Step forward of Macedonian agency for medicines and medical devices, establishment and strategic plan for development

Assoc. Prof. Zorica Arsovska Sarafinovska
Institute of Human Health, Skopje,
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Adherence to Therapy: A Modern Pharmacotherapeutic Approach

Prof. Biljana Gjorgjeska
University Goce Delcev Stip
Republic of Macedonia

Use of disinfectants and antiseptics in the health institution in Republic of Macedonia

Assoc. Prof. Bistra Angelovska
University Goce Delcev Stip
President of Pharmaceutical Chamber of Macedonia. Republic of Macedonia

Code of Ethics for Pharmacists – Pharmaceutical Chamber of Macedonia

Coffee break

Poster presentation

SESSION 2

Chair: Prof. Milka Zdravkovska

Co-chair: Ass. Prof. Darinka Gjorgieva Ackova

Prof. Neven Zarkovic
Rudjer Boskovic Institute, Croatia

4-Hydroxynonenal – major bioactive marker of lipid peroxidation

Assoc. Prof. Tatjana Ruskovska University Goce Delcev Stip Republic of Macedonia

Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes

Prof. Rubin Gulaboski University Goce Delcev Stip Republic of Macedonia

New insights into the chemistry and functions of Coenzyme Q

Assoc. Prof. Darko Bosnakovski
University Goce Delcev Stip
Republic of Macedonia

Genetically modified systems to study muscular dystrophies

Coffee break

Poster presentation

Chair: Assoc. Prof. Cena Dimova
Co-chair: Ass. Prof. Nevenka Velickova

Prof. Lia Rimondini
Università del Piemonte Orientale,
Novara, Italy

*Counteracting microbial biofilm formation
onto dental materials*

Prof. Elizabeta Zisovska
Agency for Quality and Accreditation of
Healthcare Institutions, Skopje,
Republic of Macedonia

*The endless potential of the umbilical cord
blood for investigation, research and treat-
ment*

Ass. Misko Milev
University Goce Delcev Stip
Republic of Macedonia

*The cytokinesis-blocked micronucleus assay:
Good choice for detection and evaluation of
genotoxicity in human cells*

Prof. Lence Miloseva
University Goce Delcev Stip
Republic of Macedonia

*Multiple predictive model for clinical and
subclinical depression in adolescence*

Coffee break

Poster presentation

SESSION 4

Chair: Assoc. Prof. Darko Bosnakovski
Co-chair: Ass. Prof. Katarina Smilkov

Prof. Adriano Duatti
University of Ferrara, Ferrara, Italy

*Molecular imaging and radionuclide therapy
of prostate cancer*

Assoc. Prof. Vaso Taleski
University Goce Delcev Stip
Republic of Macedonia

*Where Nanotechnology and Nanomedicine
meet – Applications and Potential Risks*

Dr. Aleksandar Cvetkovski
University Goce Delcev Stip
Republic of Macedonia

*The role of molecular cocrystals in drug devel-
opment*

Prof. Emilija Janevik Ivanovska
University Goce Delcev Stip
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*Drug development based on radiolabeled
antibodies*

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- 3. Case Report : Oligoasthenoteratozoospermia, treatment with acupuncture**
Authors: Jihe Zhu, Blagica Arsovska, Dance Vasileva, Andrijana Sterjovska-Aleksovska, Kristina Kozovska;
- 4. Treatment of cervical spondylosis with acupuncture**
Authors: Kristina Kozovska, Jihe Zhu, Blagica Arsovska, Andrijana Sterjovska-Aleksovska;
- 5. Effect of kinesitherapy on static and dynamic balance in patient after vertebro-basilar system stroke**
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- 6. Malignant pleural effusions in lung cancer: the condition during the disease**
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- 7. Systemic fungal infections in hematological malignancies**
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- 8. Morbidity and mortality of malignant neoplasms in Macedonia**
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- 20. Analysis of clinical features and complications in patients with β -thalassemia in the region of Strumica**
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- 28. Alveolar socket preservation and shaping using temporary prosthetic construction – case presentation**
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Achievements and perspectives in formulation of stable immunoconjugate of the HER2-targeting trastuzumab – potential for rapid labelling with Gallium-68

Marija Sterjova¹, Predrag Dzodic², Katarina Smilkov¹, Darinka Gorgieva-Ackova¹, Emilija Janevik-Ivanovska¹

¹ University 'Goce Delcev', Faculty of Medical Sciences – Stip, R. Macedonia,

² University of Nis, Faculty of Medicine, Department of Pharmacy – Nis, Serbia

Abstract

Objectives: To synthesize and evaluate the immunoconjugate of the HER2-targeting trastuzumab with Gallium – 68 using already established method of freeze dried kit formulation.

Introduction: Trastuzumab (Herceptin®) is a humanized IgG1 monoclonal antibody which is approved for therapy of HER2 positive breast cancer. Good clinical results and improvement of the patient's general condition makes it interesting for further conjugation, in order to increase the therapeutic effect of trastuzumab.

With the development of radiopharmacy many efforts are made for formulation of stable conjugates with various bifunctional chelators, further labelled with radioisotopes (α , β and γ emitters). According to the literature, successful conjugation of trastuzumab is achieved with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), TCMC (1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane), HYNIC (succinimidyl-6-hydrazino-nicotinamide) and DTPA derivate 1B4M-DTPA (2-(4-isothiocyanatobenzyl)-6-methyl-diethylene-triaminepentaacetic acid).

Significant radiopharmaceuticals based on peptide and antibody for diagnostic and therapeutical purpose used different radioisotopes (^{99m}Tc/¹⁸⁸Re, ⁶⁷Ga, ¹⁷⁷Lu, ⁹⁰Y, ¹³¹I).

Several studies have shown that already existing radiolabeled formulations, using beta and alpha emitters (⁹⁰Y-DTPA-trastuzumab, ⁸⁶Y-DTPA-trastuzumab, ¹⁷⁷Lu-DOTA-trastuzumab, ²²⁷Th-DOTA-p-benzil-trastuzumab, ²²⁵Ac-trastuzumab) are potent against HER2 positive breast cancer.

Our already **obtained and published results** related to the method for ready to use production of freeze dried kit formulation of Rituximab immunoconjugates for labeling with Lu-177 and Y-90 including preclinical assessment of three immunoconjugates (p-SCN-Bn-DOTA, p-SCN-Bn-DTPA and 1B4M-DTPA) including chemical characterization, animal imaging, biodistribution and toxicological studies, were good reason to have an indication to introduce the same approach for labeling HER2-targeting trastuzumab using ⁶⁸Ga³⁺ under mild conditions without subsequent purification for PET imaging.

Work progress towards objectives and achievements

Progress results and research outcomes critical to work progress and achievements are listed under our project milestones, and referenced to project aims.

Milestone 1: Standardize previously established method used for freeze dried kit formulation of Rituximab immunoconjugates for HER2-targeting trastuzumab immunoconjugates.

Milestone 2: Conjugation of bifunctional chelators to targeting for HER2-targeting trastuzumab, and radiolabeling with Ga-68 (define the most appropriate immunoconjugate).

Milestone 3: In vitro characterization and in vivo biodistribution of ⁶⁸Ga-labeled conjugates.

Significance: Already established method for freeze dried kit formulation of conjugated Rituximab antibody ready for labeling with Lutetium-177, Yttrium-90 for therapeutical purpose that is under

the final phase of the evaluation provide good information to introduce the same method for labeling of for HER2-targeting trastuzumab.

The simplicity and efficiency of labelling and the possibility of kit-based ^{68}Ga tracer production without complex automated synthesis typical of multistep PET radiochemistry will greatly increase ^{68}Ga PET access to hospitals, expanding the use of the ^{68}Ga generator.

In the same time give opportunity to work on the same or similar kit formulation using with Lu-177 for therapy.

Keywords

bifunctional chelators, breast cancer, immunoconjugates, radioisotopes, trastuzumab.