Proposal Title	**Biomonitoring of cytotoxic effects of statins using cytological and biochemical biomarkers**
Keywords	**Biomonitoring, Biomarkers, Statins, Cytotoxity, Cytotoxity tests**
FRASCATI classification	**3. Medical sciences and Health** **301 Basic medicine (Cytology, Biochemistry, Toxicology Medical genetics)** **308 Public health and health protection** **- Health ecology, Health indicators**

Abstract (max 250 words)

Introduction: Biological monitoring is a set of activities which can confirm the toxic effects of different substances present in the body, using the qualitative (cytological or histopathological) or quantitative methods (by determining the concentrations of different substances and their metabolites in biological media such as blood, urine, serum, specific tissues, etc.). In addition, biomonitoring can confirm or exclude the cytotoxic or genotoxic effect of various physical and chemical agents present in the body, especially in the conditions of its chronical exposure. It means that various chemical agents or pharmaceuticals as drugs administered into the body in increased concentrations for a long time may have toxic or carcinogenic effect. In the human biomonitoring, different specific bioindicators (markers) are used, which can confirm the presence of various chemical agents in the body and their effects on cells or molecules.
The term "marker" means any substance or change in the cells or tissues that can be identified or measured.
The most commonly used biological medium for human biomonitoring is blood.

Project goals: This is a fundamental research that can be found in further clinical practice becaouse the project goal is biomonitoring of the cytotoxic effects of statins (chemical agents used in patients with dyslipidemia), as an effective therapy for lowering the concentration of cholesterol in the blood.

Patients and methods: The study will include subjects, mainly patients of different ages, who are on therapy with statins for a long time.

- Biochemical markers will be monitored, such as hepatic enzymes (serum transaminases) and other enzymes (such as creatine kinase) in correlation with the dose of statins;
- Cytological biomarkers will be monitored to confirm the cytotoxic effect of statins on the cells;
- We will compare the values of hepatic and other enzymes in the body with the dose of statins and others values as BMI, biochemical and hematological parameters that indicate certain pathophysiological changes in the organism (myalgia, hepatic changes, renal insufficiency etc.).

Expected results: We expect that in the subjects who have been treated for a long time, statins will induce the following changes:

- increased values of certain liver enzymes (such as serum transaminases) and other enzymes (creatine kinase) as important biochemical biomarkers for the cytotoxicity of these drugs;

- cytological changes as important biomarkers that indicate cytotoxicity in the organism according to the duration and dose of statins;
- the same changes will be correlated with other biochemical and genotoxicological biomarkers and others pathophysiological changes in the organism.

Research Project

1. Aim of the research

The aim of this project is to conduct biomonitoring of the cytotoxic effect of statins in subjects (patients) with dyslipidemia using biochemical and cytological biomarkers. We expect to confirm the scientific knowledge that statins have a cytotoxic effect if they are administered in the body for a long time, especially in high dose. We assume that cytotoxicity of statins will be different in different subjects according to their age, duration of therapy, sensitivity and other physiological parameters.

2. Patients

In this project will be included a group of subjects of different ages with confirmed dyslipidemia, with increased concentration of cholesterol in the blood and who are on therapy with statins, in order to reduce the risk of cardiovascular diseases as a consequence of their increased concentration of cholesterol in the blood. All participants will be informed of the nature and purpose of the research. Only those participants who give written consent will be included in the study.

3. Methods

a) Laboratory analysis

The biomonitoring of the cytotoxic effects of statins will be conducted by evaluating of:
- biochemical markers, mainly liver enzymes (serum transaminases) or other enzymes (creatine kinase) and
- cytological biomarkers (morphological and structural cellular changes, the appearance of micronuclei and apoptosis)
as important indicators or parameters for evaluating the cytotoxic effect of certain chemical agents, in our study, statins.

b) Statistical data processing

The results that will be obtained from this research will be statistically processed using a statistical package i.e. statistically appropriate tests.

4. Timeline of the research

The proposed research is planned to last for two years, and the activities will be allocated as follows:

First year of research

a) First quarter

Organization and coordination of the whole research team involved in the project. Distribution of activities to all participants in the project.
Search of literature and comparison with similar research in the field of genotoxicology.

b) Second quarter

Full organization and standardization of the necessary conditions need for this study.

c) Third quarter

Coordination with all participants.
Filing of statements for voluntary participation in the project and completion of questionnaire.
Summing up all the questionnaires and their proper documentation and separation.

d) Fourth quarter

Preparation and monitoring of all subjects involved in the research.

Second year of research

a) First quarter

Qualitative and quantitative biochemical and cytogenetic analysis.

b) Second quarter

Summary of all the results and their statistical processing.
Analysis of the final results.
Preparation of the results for publication.

c) Second half of the year

Presentation of project results at national and international conferences.
Preparation of the final report of the Project.