Scientific report for the project PN-II-ID-PCE-2011-3-0571, between april 2012 – december 2015, Stages I, II, III, IV, cumulative

Activities of each stage:

Stage I, 2012

1. Experiments to get more biological data to be used in mathematical modeling. New data on the apoptosis, proliferation and the transfer of thymocytes between main subpopulations, and the dynamics of medullary and stromal cells of the thymus.
2. Generation of a mathematical model of the first stages of thymus regeneration and the inverted CD4+ single-positive/CD8+ single-positive ratio in the regenerated thymus.

Stage II, 2013

1. Finishing the mathematical model of the first stages of thymus regeneration and the inverted CD4+ single-positive/CD8+ single-positive ratio in the regenerated thymus.

Stage III, 2014

1. Modeling the inverted CD4+single-positive/CD8+single-positive thymocyte ratio in the regenerated thymus.
2. Modeling the apoptosis of thymocytes in the involuting and regenerating thymus under the influence of glucocorticoids.

Stage IV, 2015

1. The dynamics of the main four thymocytes populations în the diabetic thymus and the thymus thatwhich involutes and regenerates under the influence of dexamethasone.
2. Obtaining experimental data on the dynamics of eicosanoid mediators in the thymus which involutes and regenerates.
3. Obtaining experimental data Prezentarea datelor experimentale referitoare la dinamica acizilor grași nesaturați în timusul care involuează și se regenerează.

Objectives:

Stage I - to publish two ISI-indexed papers from these results with members of the project as principal authors;

Stage II – to publish one ISI-indexed, impact factor paper, from these results with members of the project as principal authors;

Stage III - to publish one ISI-indexed, impact factor paper, from these results with members of the project as principal authors;

Stage IV - to publish at least one ISI-indexed, impact factor paper, from these results with members of the project as principal authors;

Results:

Stage I, 2012

Papers

1. In this stage we submitted to publication a paper that we got eventually approved on the dynamics of macrophages in the diabetic thymus. The main authors are members of the project.

Accumulation of tissue macrophages and depletion of resident macrophages in the diabetic thymus in response to hyperglycemia-induced thymocyte apoptosis.

Barbu-Tudoran L, Gavriliuc OI, Paunescu V, Mic FA.

Journal of Diabetes and its Complications. 2013 Mar-Apr;27(2):114-22.

2. We have completed and submitted to publication (at **Molecular Systems Biology)** another paper that deals with the mathematical modeling of glucocorticoid-induced thymus involution and regeneration. All authors are members of the project.

Mathematical modeling with perturbation functions of the drug's mechanism of action on thymocyte populations during glucocorticoid-induced thymus involution and regeneration.

Daniela Zaharie , Radu Dumitru Moleriu, Lavinia Cristina Moleriu, Ioan Nicolae Casu, Alexandra Teodora Gruia, Ani Aurora Mic Virgil Paunescu, Felix Aurel Mic.

Conferences, Workshops

1. We have presented a paper at SYNASC 2012, the 14th International Symposium on Symbolic and Numeric Algorithms for Scientific Computing, held at Universitatea de Vest Timisoara, Romania, between 26-29 september, 2012. All three authors are members of the project.

- Stability analysis and its impact on the parameters estimation for a logistic growth model.

Lavinia Moleriu, Radu Moleriu and Daniela Zaharie

2. We have presented a paper at "The 13th International Conference on Mathematics and its Applications ICMA2012", Politechnica University of Timisoara, Romania, section Probability and Statistics. Applications in Health and Clinical Research, held in Timisoara, november 1-3, 2012. The author is a member of the project.

Inferring evolution models from experimental data on populations of thymocytes.

Lavinia Cristina Moatar-Moleriu

Stage II, 2013

Papers

1. We published a paper in the conference volume of the Genetic and Evolutionary Computation Conference, Amsterdam, The Netherlands, july 6-10, 2013 (http://www.sigevo.org/gecco-2013/). The first two authors are members of the project. The paper is indexed in the main databases and is available at http://dl.acm.org/citation.cfm?doid=2463372.2463408

Particularities of Evolutionary Parameter Estimation in Multi-stage Compartmental Models of Thymocyte Dynamics.

Daniela Zaharie, Lavinia Moatar-Moleriu, Viorel Negru

Conferences, Workshops

1. We published a paper in the conference volume of the 9th International Conference on"Large-Scale Scientific Computations"June 3-7, 2013, Sozopol, Bulgaria. The first and the last authors are members of the project.

Evolutionary Estimation of Parameters in Computational Models of Thymocyte Dynamics.

Lavinia Cristina Moatar-Moleriu, Viorel. Negru, Daniela Zaharie

Stage III, 2014

Papers

1. We published a paper in the Journal of Theoretical Biology that shows a mathematical model of the involuting and regenerating thymus, which addresses the role of apoptosis in these events and explains the mechanism of the inverted ratio of CD4+single-positive/CD8+single-positive thymocytes in the regenerated thymus. All authors are members of the project.

Insights into the mechanisms of thymus involution and regeneration by modeling the

glucocorticoid-induced perturbation of thymocyte populations dynamics.
Moleriu RD, Zaharie D, Moatar-Moleriu LC, Gruia AT, Mic AA, Mic FA.
J Theor Biol. 2014 May 7;348:80-99.

2. We have resubmitted a revision of our manuscript to the journal Differentiation in which we document the involvement of trogocytosis in the interactions between mesenchymal stem cells from thymus and thymocytes in vivo. All main authors are members of the project.
Trogocytosis supports the viability and differentiation of thymocytes in autologous co- cultures with mesenchymal stromal cells .
Seyed Mohammad Reza Azghadi, Maria Suciu, Alexandra Teodora Gruia, Lucian Barbu-Tudoran, Mirabela Iustina Cristea, Ani Aurora Mic, Virgil Paunescu, Danina Muntean, Felix Aurel Mic.
Differentiation, DIFF-D-14-00074R1

3. We have submitted a manuscript to Molecular and Cellular Endocrinology that is currently Under Review, that deals with the molecular mechanism of glucocorticoid's action on thymocyte homeostasis in the diabetic thymus. All main authors are members of the project.
Corticosterone perturbs the apoptotic gene machinery of thymocytes in the diabetic thymus leading to persistent organ involution.
Ani A. Mic, Alexandra T. Gruia, Maria Suciu, Seyed Mohammad Reza Azghadi, Oana I. Gavriliuc, Valentin L. Ordodi, Virgil Paunescu, Felix A. Mic.
Molecular and Cellular Endocrinology, MCE-D-14-00600

4. We have submitted a manuscript to Comparative Medicine that shows in mouse the detailed changes in the thymocyte subpopulations during thymus involution in diabetes and the mechanisms by which they occur. All main authors are members of the project.
Diabetes impairs thymocyte proliferation and causes thymocyte apoptosis with subsequent thymus involution.
Ani A. Mic, Oana I. Gavriliuc, Alexandra T. Gruia, Maria Suciu, Valentin L. Ordodi, Virgil Paunescu, Felix A. Mic.
Comparative Medicine - CM-14-000127

5. We have finished the experimentation and the Gompertzian modeling for another manuscript in which we model the apoptosis of thymocytes and the dynamics of thymocyte populations in the pre-natal and post-natal thymus in mice. We intend to submit the manuscript to Journal of Immunology and all authors on it are members of the project.

Gompertzian modeling of thymocyte homeostasis in the murine thymus shows that post-natal thymus is independent of the inflow of bone marrow progenitors.
Daniela Zaharie, Moleriu Radu Dumitru, Moleriu Lavinia Cristina, Felix Aurel Mic

Conferences, Workshops

1. We have presented two posters at the EMBO Workshop „Complex Systems in Immunology", Singapore, december 2-4, 2013.

- **Insights into the mechanisms of thymus involution and regeneration by modeling the glucocorticoid-induced perturbation of thymocyte populations dynamics.**

Moleriu RD, Zaharie D, Moatar-Moleriu LC, Gruia AT, Mic AA, Mic FA.

- **Gompertzian modeling of thymus evolution** reveals **different dynamics of thymocyte generation in pre- and post-natal periods.**

Daniela Zaharie, Radu Dumitru Moleriu, Lavinia Cristina Moatar-Moleriu, Alexandra Teodora Gruia, Ani Aurora Mic, Felix Aurel Mic.

2. We have presented two posters at the Young Researchers in Biosciences (International Symposium) Cluj Napoca, july 23-27, 2014.

- **Stromal macrophages dynamics in diabetic thymus.**

Alexandra Teodora Gruia, Lucian Barbu-Tudoran, Ani Aurora Mic, Valentin Laurentiu Ordodi, Oana Isabella Gavriliuc, Maria Suciu, Virgil Paunescu, Felix Aurel Mic.

- **Membrane Communication of MSCs and Thymocytes in Autologous Co-culture Generates Mature T-cells in vitro.**

Seyed Mohammad Reza Azghadi, Alexandra Teodora Gruia, Lucian Barbu-Tudoran, Ani Aurora Mic, Valentin Laurentiu Ordodi, Maria Suciu, Virgil Paunescu, Felix Aurel Mic.

3. We have presented an oral communication at the National Conference of the Romania Society of Cell Biology, Targu-Mures, Romania, june 4-7, 2014.

Components of the inflammatory and stress reaction cause thymus involution in experimental

diabetes.

Suciu Maria, Alexandra Teodora Gruia, Seyed Muhammad Reza Azghadi, Oana Gavriliuc, Ani Aurora Mic, Valentin Ordodi, Virgil Paunescu, Felix Aurel Mic.

Stage IV, 2015

Papers

1. We published în the Annals of the Romanian Society for Cell Biology a paper which showed the dynamics of the mouse thymocytes populations in the diabetic thymus. All authors are members of the project.

Title - Diabetes impairs thymocyte proliferation and causes thymocyte apoptosis with subsequent thymus involution in mouse

Authors - ANI A. MIC, ALEXANDRA T. GRUIA, MARIA SUCIU, SEYED MOHAMMAD REZA AZGHADI, FELIX A. MIC.

Journal - Annals of the Romanian Society for Cell Biology, Vol. XIX, Issue 3, 2015, pp. 21 – 33

http://www.annalsofrscb.ro/numar%20in%20curs/19%203/index%2019%203.html

2. We published a paper in Chemico-Biological Interactions, IF-2.5, în which we investigated the dynamics of the enzymes of the lipid metabolism and eicosanoids during the acetaminophen-induced liver damage and regeneration. Five of the six authors (the first and the last authors) are members of the project

Title - Acetaminophen-induced liver injury: Implications for temporal homeostasis of lipid metabolism and eicosanoid signaling pathway.

Authors - Suciu M, Gruia AT, Nica DV, Azghadi SM, Mic AA, **Mic FA**.

Journal - Chem Biol Interact. 2015 Oct 30;242:335-344.

http://www.ncbi.nlm.nih.gov/pubmed/26522476

3. We published a paper in Journal of Cellular Physiology Molecular, IF-3.8, in which we investigated the structure and function of lipid droplets in rat mesenchymal stem cells differentiating to adipocytes. Out of the ten authors, six (and all main authors) are members of the project.

Title - Mesenchymal Stromal Cells Differentiating to Adipocytes Accumulate Autophagic Vesicles Instead of Functional Lipid Droplets.

Authors - Gruia AT, Suciu M, Barbu-Tudoran L, Azghadi SM, Cristea MI, Nica DV, Vaduva A, Muntean D, Mic AA, **Mic FA**.

Journal - J Cell Physiol. 2015 Sep 1. doi: 10.1002/jcp.25177.
http://www.ncbi.nlm.nih.gov/pubmed/26332160

4. We have a manuscript submitted to Histochemistry and Cell Biology (HCB-3314-15-Drenckhahn) that deals with the interaction between mesenchymal stem cells (as part of the thymic micro-environment) and thymocytes. This manuscript is about to be re-submitted after the reviewers requested some minor changes în order to be accepted. There are good chances that this manuscript will be accepted. Four out of the six authors (and all main authors) are members of the project.
Title - Trogocytosis supports the viability and differentiation of thymocytes in autologous co-cultures with mesenchymal stromal cells.
Authors - Seyed Mohammad Reza Azghadi, Maria Suciu, Alexandra Teodora Gruia, LucianBarbu-Tudoran, Mirabela Iustina Cristea, Ani Aurora Mic, Danina Muntean, Dragos VasileNica, **Felix Aurel Mic.**

5. We have submitted to Journal of Immunology (15-00408-FLR) a revised version of a manuscript which describes the dynamics of thymocyte populations in the pre-natal and post-natal mouse thymus, based on our experimental findings. Since april 2015 we have perfomed experiments to address the issues raised by the reviewer. All authors are members of the project.
Title - The thymocyte populations of the post-natal mouse thymus could develop in the absenceof bone marrow progenitors - a mathematical model
Authors - Daniela Zaharie, Radu D. Moleriu, Felix A. Mic

Conferences, Workshops
1. **Mic Aurel Felix** presented a poster with the title **„Gompertzian modeling of the pre-natal and post-natal thymus formation and the analysis of its dependence of bone marrow progenitors”,** authors Daniela Zaharie, Radu Dumitru Moleriu, **Felix Aurel Mic**, at the conference Cellular Dynamics & Models, 3rd - 6th March 2015, organized by Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA;
2. **Mic Aurel Felix** participated with the oral presentation called **„Gompertzian modeling of thymocyte populations formation the pre-natal and post-natal murine thymus and its relationship with the bone marrow progenitors”** at the **2nd Symposium on Complex Biodynamics & Networks, 11-13th May 2015, Tsuruoka, Japan;**
3. **Mic Ani Aurora** presented a poster with the title **„Diabetes impairs thymocyte proliferation and**

causes thymocyte apoptosis with subsequent thymus involution in mouse”, authors **Ani A. Mic**, Alexandra T. Gruia, Maria Suciu, Seyed Mohammad Reza Azghadi, Felix A. Mic, at the National Conference of the Romanian Society for Cellular Biology with international participation and the XXXIII Annual Scientific Session of the RSCB, june 11-14-th, 2015, Baia Mare, Romania;

4. **Seyed Mohammad Reza Azghadi** presented a poster with title **„BMSCs-derived adipocytes are not structurally and functionally similar with adipocytes from the adipose tissue”,** authors Alexandra Teodora Gruia, **Seyed Mohammad Reza Azghadi**, Maria Suciu, Ani Aurora Mic, Felix Aurel Mic, at the International Symposium Young Researchers in BioSciences, july 22 – 25-th 2015, Cluj Napoca, Romania.

Project manager, Dr. Mic Aurel Felix