

Immunobiology Laboratory

The Immunobiology Laboratory starts as a new unit in the 2000 year, having its origins in the former Immunochemistry Laboratory founded in 1973 by a group of researchers from the previous Immunology Laboratory. The main activities performed by the Immunobiology Laboratory are related to immunochemistry, humoral immune response, immunomodulation and immunoregulatory domains. On the whole, the activity of the Immunobiology Laboratory is focused on fundamental research to which has been increasingly adding a significant applicative side.

The Immunobiology Laboratory has been conducted first by Dr. Victor Ghetie (1972-1986) followed by Dr. Alexandru Bancu (1986-2000) and Dr. Monica Neagu (2000-present).

In the 1970 - 1980 decade due to an international milieu biased to molecular study of humoral components of the immune system, the laboratory activities has been directed to the structure and function elucidation of immunoglobulins:

- Obtaining and purification of the IgG fragments;
- The IgG interaction with membrane receptors;
- Modulation of IgG functions by isolated fragments of the *Staphylococcus aureus* Protein A;
- Isolation and purification of the serum and secretory IgA;
- Isolation and purification of IgM;
- Obtaining of a specific anti-immunoglobulins antiserum;

In the same decade, the former Immunochemistry Laboratory has been obtaining for the first time at national level the anti-IgG4 antiserum. Also, as a result of the collaboration with the National Institute of Hematology, it was developed the methodology for obtaining of a C1 inhibitor enriched preparation very efficient in angioneurotic oedema therapy.

Starting with 1980, the Immunochemistry Laboratory activity has been focused on obtaining and testing of the *Ricinus communis* - based immunotoxin, both as whole molecule and as cytotoxic chain. The encouraging results have lead to an international recognition of the laboratory as an Immunotoxins Laboratory, granted subsequently by UNESCO funds.

Between the 1986-1999 years, the Laboratory has maintained its research area in Immunochemistry field mainly by:

- Obtaining of a specific anti-C4 human serum;

- Isolation and biological evaluation of *some specific* lectins;
- Evaluation of a placenta extract to be used as diagnosis reagent in tumor proliferative processes, along with elucidation of the underlying reaction mechanisms;

In addition, in the same period the laboratory team has enlarged its research area according to the international tendency, studying the following topics:

- The *in vivo* effect of *Ricinus*-based immunotoxins with normal and attenuated cytophilic activity upon murine tumor cells in experimental cytotoxicity models;
- The exploitation of the *Ricinus*-based immunotoxins and of homologous and heterologous antibodies such as, or associated with adjuvant treatments, in murine lymphoid tumors therapy;

Starting with 2000 year, along with activities focused especially on intracellular mechanisms elucidation, the Immunobiology Laboratory start to be involved in different national and international grants. Thus, the research activity has been focused on:

- The effects of intra- and extracellular ions concentrations upon human normal granulocytes functions;
- Functional parameters of peripheral granulocytes isolated from patients with rheumatoid arthritis;
- The interplay between the tumor process and the inflammatory process in an experimental murine model;
- Investigation of the peripheral granulocytes and lymphocytes functionality in patients with myocardial infarction, unstable angina and atheromatous disease;
- Study of the immunomodulatory effect of the low weight molecular heparins (LWMH) for prevention and therapy of the cardiovascular diseases;
- Monitoring of the transmembrane calcium wave changes upon toxic doses of opioids in cellular suspensions experimental models;
- Experimental model for the *in vitro* antitumor testing of the porphyrins in cancer photodynamic therapy;
- Immunomodulatory signals delivered by the opioids receptors in patients with rheumatoid arthritis;

The recognition and background of the laboratory has contributed to the enrolment in some prodigious international collaborations and clinical trials, namely:

- 1980-1985: collaboration with the University from Uppsala, Sweden, regarding the study of *Staphylococcus aureus* Protein A structure and its interaction with IgG. One of the main results of the collaboration was the developing of a national patent regarding Protein A purification;
- 2003-2004: a bilateral cooperation with University of Athens, Greece was carrying out in order to investigate the immunomodulatory effects of prothymosin-alpha and its component fragments in cellular culture models;
- 2003-2005: the laboratory team was involved in a Clinical Trial phase III, double blind, multicenter, randomized study in chemo-naïve patients with locally advanced or metastatic pancreatic cancer;
- 2006-2008: membership in COST D39 Chemistry and Molecular Sciences and Technologies Metallo-Drug Design & Action

In the last 5 years our team was involved in the following research directions: biomarker discovery in cancer, immune-related mechanisms favouring neoplastic transformation, innovative immune-detection in infectious diseases and nano-drugs for controlled delivery.

In the *biomarkers discovery* domain we have published several original results, namely the importance of immune markers in the diagnosis, prognosis and therapy monitoring of cutaneous melanoma. The published papers emphasized that skin melanoma has a powerful immunological basis and that immune-markers, whether circulatory or teamed up with the tumoral/sentinel lymph node tissue are to be registered in the larger panel of biomarkers that monitor the early diagnosis, development, metastasis and therapy efficacy in cutaneous melanoma. The published results showed that in melanoma bearing patients a CD4⁺ immune response is elicited, response that unfortunately is maintained by an immune-suppressor subpopulation CD4⁺CD25⁺FoxP3⁺. Therefore, a down-regulation immune-mediated mechanism was found hindering the specific anti-tumoral CTL response. Analyzing various immune arms we found a possible compensatory mechanism between innate and adaptive cellular responses in these patients. Our last 5 years experience in immune markers tested in melanoma patients showed that there is a direct link between therapy efficacy and the immune status of the melanoma bearing patient, link emphasized when immune-based therapies, like interferon and/or melanoma vaccinations are used. As the mentioned subject is continuously evolving, we have additionally enlarged the studies of biomarker discovery by identifying in cooperation with Bio-Rad Biomarkers Centre, Malvern, USA a panel of plasma future

prognostic biomarkers that presently are in the identification stage through cooperation with Omics Centre, King's College London. The results obtained by our team were recognized by the involvement in the Editorial Board of the journal *Recent Patents in Biomarkers*, *Bentham Science Publishers*. The future of the domain lies within the link established between the proteomic biomarkers discovered and their genetic counterparts as to further develop an enlarged personalized set of markers applicable in melanoma patient's personalized medicine.

In the domain of *innovative immune-detection in infectious diseases* through the cooperation developed between us and University of Tübingen and Athens we have established a complete new testing approach for early bacterial infection testing. In the last 4 years we have published the relation between the in vitro and in vivo bacterial infection and the release of a C-terminal prothymosine peptide. This year we have developed a modified competitive chemiluminescence method for detection in biological fluids of the mentioned peptide as early as 2 hours post-infection. The possibility to detect as early as 2hrs post-infection a marker by means of chemiluminometric testing is a major breakthrough in this domain. The future of these results will be the development of an original international patent.

In the domain of *nano-drugs for controlled delivery*, in the last 4 years through a long lasting collaboration with the National Institute for Chemistry we have developed several classes of photosensitizing compounds with anti-tumoral effect. In this domain, besides publications, several patents were accomplished and the internationally recognized value was recognized by awards. The patent entitled "Tetra-sulphonated porphyrin application for producing a dermatologic therapy – photosensitizer". received Gold medal at Brussels Innova 2008, Special Prize of Rudy Demotte, Minister President of the Walloon Government, Gold medal at The 37th International Exhibition of Inventions of Geneva 2009 and Special Prize of the Ministry of Education of Russia, 2009; Gold medal at The International Fair for Innovation, Moscow, 2009. Recognition of the long-standing work performed by us in this domain in the last 10 years, resides in our affiliation to the international networks: COST D39 *Metallo-Drug Design & Action* (2006-2010); COST TD1002 *European network on applications ...in NanoMedicine and Life Sciences* (2011-2015). Through cooperation with the University of Lisbon, Chemistry Department, we have developed several classes of nano-compounds intended to be intracellular trackers in tumor cells. The future of this research direction lays in increasing the nano-drug specificity with emphasis in targeting tumour receptors and tissue markers for not only a controlled delivery in time but as well in space.

The personnel dynamics in our team is remarkable, namely we have a mean age of 44.2 years and equilibrated between young researchers and more experienced senior researchers. The knowledge up-grading of our team is continuous such as each of the team members attends international courses on up-to-date technologies. We have constant young Bachelor of Science degree personnel that perform their diplomas in the framework of the mentioned domain.

National research grants (*selection*)

Title	Duration
Projects PN 09.33 - 01.01 Serum protein biomarkers for cutaneous melanoma monitoring	2009-2011
PNII 62-074 Development of irradiation protocols with coherent optical radiation multiple fractionated (SIFROC) used for photodynamic therapy with methyl aminolevulinate (MAL-PDT) in premalignant and malignant non-melanocytic cutaneous pathologies	2008-2011

International Research Grants

Project	Duration	Stage
Bilateral Cooperation Romania-China (511/2011) Biomarker discovery in digestive tract cancer and skin melanoma using proteomic approaches <i>China partner</i> Beijing Institute of Genomics, Chinese Academy of Science	2011-2012	On-going
COST TD1002 European network on applications of Atomic Force Microscopy to NanoMedicine and Life Sciences	2011-2015	On-going
POSDRU nr. 58819. „Training platform for implementing high technology in the health care system”	2010-2013	On-going
POS CCE Proteomics Technologies For Cancer Biomarkers Discovery	2010-2013	On-going
POSDRU nr. 31081, 1.2 University for future “Dermato-oncology development as multidisciplinary domain for medical training and international cooperation”	2010-2012	On-going
MNT-ERA NET (MNT 7030/2010, acronym <i>Biomark</i>) Tetrapyrrole nanostructures towards fluorescent molecular markers for biomedicine	2010-2012	On-going
NATO SfP 982838/2007 Development of a novel immunoassay for the very early detection of Biothreatening bacterial infections	2007-2012	On-going

FP7-PEOPLE-IRSES-2008 Natural antidiabetic & antihypertensive drugs	2008-2011	Finalized
COST D39 Chemistry and Molecular Sciences and Technologies Metallo-Drug Design & Action	2006-2008	Finalized
LOR/VIR/PO3/002 – firma Lorus, Canada Clinical Trial phase III, double blind, multicenter, randomized study in chemo-naïve patients with locally advanced or metastatic pancreatic cancer to compare a combination therapy of Virulizin® plus Gemcitabine versus placebo plus Gemcitabine; optional second-line therapy may include continuation of Virulizin® or placebo, alone or in combination with 5-Fluorouracil	2003-2005	Finalized
Bilateral Cooperation Romania-Greece 7285/02 “Victor Babes” National Institute – University of Athens Immunomodulating potential of prothymosin alpha and its fragments on lymphocyte functions in vitro. Analysis of the mechanisms of action of the polypeptide and specific peptides spanning its primary structure.	2003-2004	Finalized

Other achievements

Members of the team are co-inventors for several patents

- OSIM Nr. 00489/25.06.2008 **Patent entitled:** *Tetra-sulphonated porphyrin application for producing a dermatologic therapy - photosensitizer*
The Patent was awarded:
Gold Medal at Brussels Innova 2008, Special Prize of Minister President of the Walloon Government Rudy Demotte.
Gold Medal at 37-th International Fair Inventika Genève 2009 and Special Prize of Education and Research Ministry of Russia.
Gold Medal at The International Fair for Innovation, Moscow, 2009.
- OSIM Nr. RO-BOPI2/2009 **Patent entitled** “Tetrapirolic compound asymmetrically substituted – synthesis and biological evaluation”
- OSIM A/00351/2019 / 21.04.2010 **Patent entitled** “Equipment and procedure for microwave irradiation in *in vitro* models with concomitant registration of biological behavior in a fluorescence microscope”

Members of the team have received the **First Prize** of the Romanian National Authority for Research on Health Domain in 2008 for the project entitled “*Photochemotherapy innovative methods with nanostructured photosensitizer – from synthesis to clinical trial*”.

The laboratory is affiliated to the *National Platform for Nanomedicine*

The Laboratory has hosted in the last year PhD students in the framework of the international collaborations: Margarita Skopeliti and Pinelopi Samara from the University of Athens.

Neagu Monica is a member of the [Commission for Advanced Therapies – European Medicine Agency](#)

Perspectives

- **The Laboratory will join the Early Detection Research Network: Biomarker Developmental Laboratories** chaired by National Institutes of Health (NIH) (<http://www.nih.gov/>) and National Cancer Institute (NCI) (<http://www.cancer.gov/>)

Publications

- Monica Neagu. Editorial [Hot Topic: Transcriptomic Biomarkers in Cancer Diagnosis, Prognosis and Therapy Monitoring (Guest Editor: Monica Neagu)] *Recent Patents on Biomarkers*, Volume 2 (2), Pp.73-74 May 2012; <http://www.benthamscience.com/contents-JCode-RPBM-Vol-00000002-Iss-00000002.htm>
- Monica Neagu and Daniel Boda. Transcriptomics in Cancer - Stages Toward Patents in Biomarkers? *Recent Patents on Biomarkers*, Volume 2 (2), Pp.75-82 May 2012
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The Immunobiology Laboratory staff:

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2. Dr. Carolina Constantin, PhD, Biochemist, Senior Resercher III
3. Georgiana Dumitrașcu, Faculty of Medicine Student, research assistant
4. Mariana Caralicea, medical assistant
5. Mariana Pisiță, laboratory technician



Monica Neagu, PhD, Senior Researcher III, Head of the Immunobiology Laboratory



Carolina Constantin, PhD, Senior researcher III



Georgiana Dumitrașcu, Faculty of Medicine Student, research assistant



Mariana Caralicea, Medical assistant



Mariana Pisiță, Laboratory technician

Alumni

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Bostan Marinela, Biochemist
Catargiu Cristina, Biologist
Călugaru Anca, Biologist
Cealăcu Valentin, Biologist
Dima Silvia, Biologist
Dumitrescu Rodica, MD
Gabor Doru, Biologist
Gagheș Marinela, Biologist
Gheție Maria-Ana, Biochemist

Hristescu Sanda, Biologist
Kosma Ecaterina, Biologist
Laky Mariana, Biochemist
Livescu Alexandra, Biochemist
Manda Gina, Physicist
Marcheş Radu, Biochemist
Mărgineanu Ilca, Physicist
Medeşan Cornel, Chemist
Mihăescu Silvia, Biochemist
Moţa Gabriela, Biologist
Neagoe Ionela, Chemist
Olosz Ferencz, Biochemist
Onică Doina, Biochemist
Roman Viviana, Biologist
Stanciu Cristina Luminita, Biologist
Stănescu Theodor, Biologist
Tănase Cristiana, MD
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Voinea Anca Cristina, MD
Voinea Liviu, MD
Waller Mariana, Biologist
Zamfir GeŃiana, Biologist

link pictures



Margarita Skopeliti during her stage in the Immunobiology Laboratory (right)



Pinelopi Samara during her stage in the Immunobiology Laboratory (left)

