Scientific and Technical Report

(2018 – 2021)

Competition:	**Complex Projects made in consortium CDI – PCCDI**
Contract no:	65PCCDI/2018
Research field:	Health
Title:	Advanced innovative approaches to predictive regenerative medicine
Acronym:	REGMED
Duration (months):	42
Total budget:	5.287.500 RON
- Component projects:	4861183,09 RON
- Management expenses:	368875 RON
- Checks:	57441,91 RON
Project Web page:	https://unibuc.ro/cercetare/promovarea-rezultatelor-cercetarii/proiecte-de-cercetare/proiecte-cu-finantare-nationala/65pccdi-2018/ https://unibuc.ro/cercetare/promovarea-rezultatelor-cercetarii/proiecte-de-cercetare/proiecte-cu-finantare-nationala/65pccdi-2018/?lang=en
Coordinating institution:	University of Bucharest
Project director:	Prof. Dr. Marieta Costache
Partner 1 complex project (P1):	University Politehnica of Bucharest (UPB)
partner 2 complex project (P2):	National Research and Development Institute in the field of Pathology and Biomedical Sciences "Victor Babeș" (IVB)
partner 3 complex project (P3):	Oncological Institute Prof. Dr. I. Chiricuța Cluj-Napoca IOCN
No of component projects:	4

Component projects	**Title of component project**	**Coordinating institution of component project**	**Involved institutions (CO,P1..Pn)**	**Budget of component project**
Component project 1	Osteoimmuno modulation as a predictive factor of bone tissue regeneration efficiency	University of Bucharest	CO, P1, P2	990645
Component project 2	Biocompatible system for assisting peripheral nerve regeneration	National Research and Development Institute in the field of Pathology and Biomedical Sciences "Victor Babeș"	CO, P1, P2	1311625

Component project 3	Cellular and molecular mechanisms involved in soft tissue regenerative processes	University of Bucharest	CO, P1, P2, P3	1134555,46
Component project 4	Modulation of the tumor microenvironment with intelligent systems for breast reconstruction	Oncological Institute Prof. Dr. I. Chiricuța Cluj-Napoca	CO, P1, P2, P3	1424357,63

1. **General presentation of the achievement of project objectives, highlighting the results and the degree of achievement of the objectives. The presentation must include explanations that justify the differences (if any) between the planned and the performed activities**

The project 65PCCDI / REGMED- "Advanced innovative approaches to predictive regenerative medicine" arose from the desire to unite efforts and expertise in the areas of bioengineering, biology and regenerative medicine in *a joint CDI program* to generate both *innovative biomaterial product*s with potential for use in tissue engineering and transfer in the economic environment, as well as *a consortium of specialists in the field of tissue engineering and regenerative medicine*.

The general goal of the project is to create *a consortium* with complementary research experience in the field of regenerative medicine, which will efficiently use human resources and modern research infrastructures newly created to implement innovative technologies, in order to develop and transfer to the economic environment. This consortium consists of *four partner institutions*, specializing in medical engineering, biology, pathology and medicine, as follows: (1) Coordinating Institution (IC) - University of Bucharest (Faculty of Biology, Department of Biochemistry and Molecular Biology), (2) University Politehnica of Bucharest, (3) National Research-Development Institute in the field of Pathology and Medical Sciences "Victor Babeș" and (4) Oncological Institute Prof. Dr. I. Chiricuța Cluj-Napoca. The general objective of the project is to *increase the institutional performance* of the research structures involved in order to address innovative techniques with applicability in regenerative medicine, in accordance with the priorities of public relevance and intelligent specialization in HEALTH (within the "National Strategy CDI 2014-2020 ").

At scientific level, the aim of the project is to obtain a series of innovative products such as controlled release systems for the regeneration of bone tissue, soft tissue, peripheral nerves and post-mastectomy breast tissue. REGMED addresses, through the component subprojects, the following topics: (1) Osteoimmunomodulation as a predictive factor of *bone tissue regeneration* efficiency (Project 1- BONE); (2) Biocompatible system to assist *regeneration of peripheral nerves* (Project 2- NERVE); (3) Cellular and molecular mechanisms involved in the *regenerative processes of soft tissues* (Project 3- SOFT); (4) Modulation of the tumor microenvironment with intelligent systems for *breast reconstruction* (Project 4- TUMOR).

The objectives proposed by the contract and assumed by the partner institutions of the consortium are: (i) the consolidation of a consortium with high specialization in Regenerative Medicine and sustainability through the development of a joint CDI program; (ii) creating and supporting 12 new jobs; (iii) obtaining new products - controlled release systems for the regeneration of bone tissue, soft tissue, peripheral nerves and post-mastectomy breast tissue; (iv) strengthening the capacity of institutions with possibilities to relaunch and training the human resources of the institutions involved in modern technologies through exchanges of experience; (v) improving the offer of research services offered on the erris.gov.ro platform; (vi) scientific input (min. 10 ISI articles, min. 20 papers at conferences) and (vii) exploration and development of possibilities to transfer the results of the project to the economic environment.

The objectives and activities were fully achieved according to the Additional Act no. 4/2021, and the result indicators were fully reached or exceeded. Thus, by the end of the project, the following were achieved: (i) a consortium of partners with high specialization in the field of bioengineering, tissue engineering and regenerative medicine was consolidated, a consortium validated by the results obtained *in vitro* and on animal models and the large number of publications in ISI-listed journals in the context of the project; the strengthening and continuation of collaborations between partners was done by applying projects in new financing competitions; (ii) 12 new jobs have been created for young researchers, supported by project funds and which will be further supported by other grants or own funds of the institutions; (iii) several innovative biomaterials-products have

been developed, at least one for each component project, for use in bone tissue engineering, peripheral nerve engineering, soft tissue engineering or breast reconstruction; (iv) resources were used for training and specialization of human resources at the consortium level by accessing 12 checks (10 type B checks and 2 type C checks); the new employees benefited from specialization courses at partners and abroad, insofar as no specific courses were organized for the respective techniques in Romania; (v) the offer of research services offered on the two-position ERRIS platform has been improved, namely the acquisition and analysis of confocal microscopy data (by upgrading the A1 / A1R Confocal Laser Microscope System) and the acquisition and processing of behavioral biology data (by acquisition of CatWalk ™ XT System); (vi) scientific contribution by publishing 22 ISI articles (in addition, another 4 are under review), 3 BDI articles, 3 book chapters in international publishing houses and 33 papers at conferences.

From a scientific point of view, all the proposed objectives have been fully achieved, as follows:

The central objective of project 1 was to optimize strategies for the evaluation and development of new clinically useful materials based on the concept of osteoimmunomodulation (ILO). The project aimed to investigate the impact of the biomaterial-induced immune microenvironment on osteogenesis and osteoclastogenesis, the results leading to the development of a new biomaterial with osteoimmunomodulatory properties for bone regeneration. The main objectives are: i) development of innovative strategies for manipulating the immune response for applications in bone regeneration, ii) analysis of the osteoimmune environment generated by the interaction between macrophages and biomaterial based on Mg, iii) analysis of the impact that the immune microenvironment created by biomaterial exerts on the process of osteogenesis and osteoclastogenesis *in vitro*, iv) optimization of the strategy for evaluating the *in vitro* osteogenic capacity of biomaterials for bone regeneration by establishing correlations between the effects of ILO *in vitro* and *in vivo* of biomaterial for bone regeneration. In the first three stages of the project, coatings were made and characterized on Mg alloy (AZ31) based on polycaprolactone fibers (Mg-PCL indicated and CPO) deposited by electrospinning, which were also subjected to functionalization with an active substance. - coumarin (Mg-PCL_coumarin also indicated in CPO_1) or with ZnO (Mg-PCL_ZnO also indicated in CPO_2) and with both compounds simultaneously (MgPCL_coumarin_ZnO also indicated in CPO_3). Also, hybrid polymer/natural polymer (PCL/chitosan) hybrid coatings were made consisting of three layers of synthetic polymer with glutaraldehyde used to crosslink the next layer containing natural polymer (PCL-GA-CS). In turn, the hybrid coatings were loaded with ZnO (PCL-GA-CS-ZnO). By evaluating the interaction between macrophages and biomaterial, but also the impact of biomaterial on the processes of osteogenesis and osteoclastogenesis, the most favorable results were obtained by coating the AZ31 alloy, with PCL films and functionalized with coumarin and/or ZnO. Also, these biomaterials were implanted subcutaneously in adult CD1 mice to highlight the inflammatory response, but also to monitor the level of regeneration induced in bone defects. This type of coating has demonstrated the potential for bone regeneration by providing the alloy with increased corrosion resistance, determining an appropriate inflammatory response, supporting the osteogenic process and reducing osteoclastogenesis.

Project 2 aims to create a new original variant of synthetic duct called Peripheral Nerve Regeneration Assistance System (SARN), which unlike those tested so far, is a duct based on biopolymers that mimics the components of the extracellular matrix, capable to deliver in a controlled manner two growth factors HGF- that stimulate the proliferation of Schwann cells and NGF that stimulate the migration of nerve fibers. Within the project, the synthesis and characterization of SARN was performed, enriched with different concentrations of nanodiamond particles. It was initially tested *in vitro* for biocompatibility. The results showed a good interaction between the cellular component and the material, so that the material with a concentration of 1% nanodiamond particles was selected to be further synthesized for *in vivo* studies. To this duct were added the two growth factors HGF and NGF, and in the third stage/2020, tests were performed to evaluate the potential of SARN to

support the regeneration of peripheral nerves *in vivo*, in animal models. The partial results obtained so far have demonstrated a slight inflammation and a regeneration process in the early stages, suggesting a good efficiency of SARN in peripheral nerve regeneration processes.

Project 3 aims to develop a complex strategy for regeneration of soft tissues damaged by accidents, burns, severe skin damage, deep wounds affecting the epidermis, dermis and hypodermis, based on intelligent materials with controlled release and the benefits of stem cells. The project is part of the current, modern trend of regenerative medicine, which combines the Bio approach (stem cells and inducing factors) with the Engineering (materials) approach. The specific objectives are (1) the synthesis and characterization of a controlled release system (SEC) for soft tissue regeneration; (2) *in vitro* evaluation of SEC biocompatibility and the ability to support stem cell differentiation in adipose tissue and (3) evaluation of the efficacy of SEC in soft tissue regeneration *in vivo* in animal models. The project proposes an alternative solution to the current methods of soft tissue reconstruction (with inert implants). In project 3, SECs were synthesized and characterized for soft tissue regeneration, based on synthetic polymers (poly (2-hydroxyethylmethacrylate), poly (2-acrylamido-2-methyl-1-propanesulfonic acid) (HEMA / AMPSA)) , natural polymers (fibroin and sericin), clays (montmorillonite (MMT) and double layered hydroxides (LDHs)) and active biomolecules (growth factors, adhesion factors and chemotreating factors). The biocompatibility and ability to support the differentiation of adipose tissue stem cells from HEMA/AMPSA/LDH-based materials were evaluated and confirmed. For the *in vivo* evaluation of the potential to induce soft tissue regeneration, the materials were improved and SEC was obtained consisting of HEMA/AMPSA/LDH, enriched with fibroin/sericin. The materials were implanted subcutaneously in the dorso-lumbar region of CD1 mice. The implanted area was excised 1 week and 3 weeks after implantation of the materials, for histopathological evaluation and molecular analysis, which demonstrated a good efficiency of this SEC for soft tissue regeneration.

Within project 4, 4 objectives were planned: (1) Characterization of the tumor and normal microenvironment in breast cancer; (2) Development of nanostructured materials loaded with anti-inflammatory and tissue regeneration therapeutic agents; (3) Evaluation of the *in vitro* effects of these uncontrolled release systems on epithelial cells, fibroblasts, immune stem cells and (4) Evaluation of the efficacy of these systems on animal models. In order to achieve these objectives, several experimental techniques and work protocols were developed and optimized. In the first stage, a biobank of tissues and cells was made by collecting biological samples, and the breast tumor microenvironment was evaluated compared to the normal one. Cellular and molecular changes of adipocytes and mammary epithelium were evaluated and new sets of cell differentiation gene markers were identified. Also, the immunological and post-transcriptional mechanisms activated in the soft tissue regeneration processes were evaluated. At the same time, several generations of porous materials (scaffold) were synthesized for breast reconstruction. After the physico-chemical characterization and biocompatibility testing of the materials, the optimal working compositions were established, namely those based on nanocellulose and pectin and gelatin and were subsequently enriched with different concentrations of anti-tumor drug (5-fluorouracil, paclitaxel). Their effect was evaluated *in vitro*, by quantitative and qualitative methods. An *in vivo* experimental model was obtained to evaluate the efficiency of breast adipose tissue reconstruction with the proposed functionalized fish gelatin systems. The degree of tissue regeneration was analyzed in the presence of the implant, at histological, protein and molecular level, by evaluating specific markers of the regeneration process. Therapeutic transport systems (STRs), such as liposomes with halofuginone and rhodamine, were synthesized, physico-chemically characterized and tested for toxicity. The therapeutic effects of STR and the functional changes caused by them were studied on *in vitro* and *in vivo* experimental models.

2. Common agenda (Deliverables/indicators)

Nr. crt.	The title of the component project Pn	Partner institutions	Planned objectives	Deliverables/ planned indicators (according to the Common Agenda)	Accomplished objectives	Accomplished deliverables/ indicators
1	Project 1 «Osteoimmunomodulation as a predictive factor of bone tissue regeneration efficiency»	IC – University of Bucharest P1 – University Politehnica of Bucharest P2 – National Research and Development Institute in the field of pathology and biomedical sciences "Victor Babes"	The project aims to systematically elucidate the impact of the microenvironment immune-induced biomaterials (BM) on osteogenesis and osteoclastogenesis, the results translating into protocols for *in vitro* evaluation of osteogenesis stimulated by materials with higher degree of prediction of behavior *in vivo*, and in the development of new biomaterials with osteoimmunomodulatory properties for bone regeneration. Thus, in the long run, the project has the potential to ensure a faster transfer to the clinic of newly developed materials and to reduce the costs of health care.	- 3 jobs created and supported by the project - 2 ISI articles - 3 scientific papers - 4 stage scientific reports -1 optimized protocol for the evaluation of biomaterials - 1 experimental model - complete the offer of services on the erris platform - elaboration of the necessary documentation for the patent application	The environmental impact of biomaterials on osteogenesis and osteoclastogenesis was analyzed and evaluation protocols were obtained. New biomaterials with osteoimmunomodulatory properties for bone regeneration have also been developed	-3 jobs created and supported by the project (Negrescu, Nica, Curti/Voicu) -4 scientific reports - 4 ISI articles -2 BDI articles -10 scientific communications -1 patent application A00556/16.09.2021 filed with OSIM -1 optimized protocol for standardized *in vitro* evaluation of the anti-microbial and anti-biofilm effect and of the cytocompatibility of biomaterials with osteoimmunomodulatory properties. -Development of the experimental protocol for evaluating the inflammatory response of macrophages to selected biomaterials - Development of the protocol for

						obtaining the AZ31 alloy coated with PCL fibers loaded with coumarin and ZnO, as well as the technological flow and material balance. - 1 experimental murine model for the *in vivo* study of bone regeneration - services completed on erris
2	Project 2 «Biocompatible system to assist peripheral nerve regeneration»	IC – National Research and Development Institute in the field of pathology and biomedical sciences "Victor Babes" P1 – University of Bucharest P2 – University Politehnica of Bucharest	The project aims to offer a new variant of synthetic duct called the Peripheral Nerve Regeneration Assistance System (SARN), which unlike those tested so far, will be a biopolymer duct that mimics the components of the extracellular matrix, being able to deliver in a controlled, sequential manner, and supported by two growth factors- HGF that stimulates proliferation of Schwann cells and NGF that stimulates nerve fiber migration. We anticipate that through the use of the latter	-4 jobs created and supported by the project - a research offer in the Erris platform - 1 research service - 1 OSIM patent application - 1 new product - Regeneration assistance system for peripheral nerves (SARN) with prospects of transfer to economic operator - 1 Improved product (databases) for transfer to economic operator -2 articles in ISI journals		-4 jobs created and supported by the project (Braescu, Olaret, Balahura and Selaru) -a research offer in the Erris platform (https://eeris.eu/ERIF-2000-000B-1724 CatWalk XT system) -1 research service on the locomotor capacity of animal models on the CatWalk XT system equipment (the service is available on the erris platform at https://eeris.eu/ERIF-2000-000B-1724) -1 patent application A00555/15.09.20

			discoveries in the field of peripheral nerve regeneration and biomaterials, we will be able to provide a reliable product of interest both for veterinary and human medicine.	-4 scientific reports		21 filed with OSIM -1 new product- Regeneration assistance system for peripheral nerves (SARN) with prospects of transfer to economic operator -1 Improved product (databases) transferred to IVB -6 articles in ISI journals -2 book chapters -10 scientific communications at conferences -4 scientific reports
3	Project 3 «Cellular and molecular mechanisms involved in the regenerative processes of soft tissues»	IC – University of Bucharest P1 – University Politehnica of Bucharest P2 – National Research and Development Institute in the field of pathology and biomedical sciences "Victor Babes" P3 – Oncological Institute Prof.Dr.I.Chiricuta Cluj-Napoca	1) Synthesis and characterization of a controlled release system (SEC) for soft tissue regeneration 2) *In vitro* evaluation of SEC biocompatibility and the ability to support adipose tissue stem cell differentiation 3) Evaluation of the efficiency of SEC in soft tissue regeneration *in vivo*, on animal models	-3 newly created jobs -4 scientific reports - 1 OSIM patent application - 1 new product - System with controlled release (SEC) with prospects of transfer to the economic operator - 2 ISI articles - 4 participation in conferences -1 protocol for culturing stem cells isolated	SEC was synthesized for soft tissue regeneration The *in vitro* biocompatibility of SEC and its ability to support adipose tissue stem cell differentiation was assessed The potential of SEC in soft tissue regeneration *in vivo* in animal models was evaluated	-3 newly created jobs (Ignat, Ciceu/Lazar, Bonci) -4 scientific reports -1 patent application A00550/15.09.2021 filed with OSIM -1 new product - System with controlled release (SEC) with prospects of transfer to the economic operator -5 ISI articles published and 2 ISI under evaluation

				from adipose tissue - 1 experimental model for studies of soft tissue regeneration		- 4 scientific communications at conferences -1 protocol for culturing stem cells isolated from adipose tissue - 1 murine experimental model for studies of soft tissue regeneration
4	Project 4 «Modulation of the Tumor Microenvironment with Intelligent Systems for Breast Reconstruction»	IC – Oncological Institute Prof.Dr.I.Chiricuta Cluj-Napoca P1 – University of Bucharest P2– University Politehnica of Bucharest P3– National Research and Development Institute in the field of pathology and biomedical sciences "Victor Babes"	1) Characterization of tumor and normal microenvironment in breast cancer 2) Elaboration of nanoconstruct materials loaded with anti-inflammatory therapeutic agents, able to stimulate tissue regeneration 3) Evaluation of the *in vitro* effects of these controlled release systems on epithelial cells, fibroblasts, immune stem cells 4) Evaluation of the efficiency of these systems *in vivo*, on animal models	- 2 new jobs created - 4 working protocols - development of the IOCN Biobank fund - 4 scientific reports - 3 scientific papers at conferences - 2 ISI articles - 1 experimental model for the study of breast reconstruction after tumor resection	Tumor and normal microenvironments in breast cancer have been investigated and characterized Nanoconstruct materials loaded with anti-inflammatory and tissue regeneration therapeutic agents were obtained. The *in vitro* effects of the systems on epithelial cells, fibroblasts, immune cells, stem cells were evaluated. The effect of these systems *in vivo* on animal models was evaluated	- 2 new jobs created (Morariu, Sur) - 4 working protocols - the IOCN Biobank fund was developed - 4 scientific reports - 9 scientific papers at conferences - 7 ISI articles published and 2 ISI under evaluation - 1 BDI article - 1 book chapter - 1 murine experimental model for the study of breast reconstruction after tumor resection

3. Dissemination of complex project results

Between 2018 and 2021, the results obtained from the complex project were disseminated within the consortium by organizing a consortium conference (May 23, 2018), as well as by organizing meetings and discussions on web platforms (skype, email). Within the complex project, on all four component projects, the

results obtained were disseminated by publishing **22 articles in ISI listed journals**, **3 articles in BDI journals**, **3 book chapters in international publishing houses**, **and 4 ISI articles are under review**. Also, the results were disseminated by presenting **33 papers at international/national conferences** in the form of posters and oral communications.

In addition, the results obtained within the complex project are included in a series of bachelor's, master's and doctoral theses carried out on the theme of the project - tissue engineering and regenerative medicine. Among them, we mention the doctoral theses in progress of the doctoral students: Filis Curti, Elena Olaret, Mirela Serban, Aida Șelaru, Simona Ignat, Andreea Lazar, Roxana Balahura, Negrescu Andreea.

The scientific results obtained, disseminated to the scientific community are presented in the table below.

Indicators	***Description/Name***	***No.***
Newly created research jobs (full time)	New researchers proposed	12
	New hired researchers	12
Strengthening the capacity of institutions with relaunch possibilities (checks):	Type B checks: training (research) and/or working visits (short duration)	10
	Type C checks: training for the newly hired human resource and for understanding new techniques and technologies	2
Research services provided (performed) by using the research infrastructure available for project implementation (checks):	Type A1 checks: research services offered between consortium partners	0
	Type A2 checks: research services provided by third party consortium partners	0
Articles published/ accepted/evaluated in ISI indexed journals	*Article title / Year of publication / Journal / Authors / Status (under evaluation /accepted /published)* [1] The effects of exogenous modulation on the peripheral nerve regeneration after injury and primary surgical repair /2018/ Biomed J Sci &Tech Res /Manole E., Bastian A., Ristoiu V., Zurac S., Neagu M./ **published** [2] Unveiling Ga (III) phthalocyanine – a different photosensitizer in neuroblastoma cellular model/2018/Journal of Cellular and Molecular Medicine/Constantin C., Lupu A.R., Fertig T.E., Gherghiceanu M., Pop S., Ion R.M., Neagu M/ **published** [3] Nanocomposite foams based on flexible biobased thermoplastic polyurethane and ZnO nanoparticles as potential wound dressing materials/2019/Materials Science and Engineering: C/Buzarovska A., Dinescu S., Lazar A.D., Serban M., Pircalabioru G.G., Costache M., Gualandi C., Averous L./ **published** [4] CXCL1 and CXCL2 inhibit the axon outgrowth in a time- and cell-type-dependent manner in adult rat dorsal root ganglia neurons/2019/ Neurochem Res /Deftu A.T., Ciorescu R., Gheorghe R.O., Mihailescu D., Ristoiu V./ **published** [5] Fabrication and biocompatibility evaluation of nanodiamonds gelatin electrospun materials designed for prospective tissue regeneration	26

	applications/2019/Materials/Selaru A., Dragusin D.M., Olaret E., Serafim A., Neth-Steinmuller D., Vasile E., Iovu H., Stancu I.C., Costache M., Dinescu S./ **published** [6] Efficiency of multiparticulate delivery systems loaded with flufenamic acid designed for burn wound healing applications/2019/Journal of Immunology Research/Dinescu S., Ignat S., Lazar A., Marin S., Danila E., Marin M., Udeanu D. I., Ghica M. V., Albu-Kaya M. G., Costache C/ **published** [7] Versatile biomaterial platform enriched with graphene oxide and carbon nanotubes for multiple tissue engineering applications/2019/Int J Mol Sci/Ignat S.R., Lazar A.D., Selaru A., Samoila I., Vlasceanu G.M., Ionita M., Radu E., Dinescu S., Costache M./ **published** [8] Hydrogels based drug delivery synthesis, characterization and administration/2019/ Pharmaceutics/Onaciu A, Munteanu RA, Moldovan AI, Moldovan CS, Berindan-Neagoe I./ **published** [9] Bioinspired 3D printable pectin-nanocellulose ink formulations/ 2019/Carbohydrate Polymers Cernencu A. I., Lungu A., Stancu I. C., Serafim A., Heggset E., Syverud K., Iovu H./ **published** [10] Molecular links between central obesity and breast cancer/2019/Int J Mol Sci/Zimta AA, Tigu AB, Muntean M, Cenariu D, Slaby O, Berindan-Neagoe I./ **published** [11] Inflammation and metabolism in cancer cell – mitochondria key player/2019/Frontiers in Oncology/ Neagu M., Constantin C., Popescu I.D., Zipeto D., Tzanakakis G., Nikitovic D., Fenga C., Stratakis C.A., Spandidos D.A., Tsatsakis A.M./ **published** [12] Release of the non-steroidal anti-inflammatory drug flufenamic acid by multiparticulate delivery systems promotes adipogenic differentiation of adipose-derived stem cells/2020/Materials/ Lazar A.D., Dinescu S., Albu-Kaya M.G., Gharbia S., Hermenean A., Costache M/ **published** [13] Connecting the missing dots: ncRNAs as critical regulators of therapeutic susceptibility in breast cancer/2020/Cancers/ Dobre E.G., Dinescu S., Costache M./ **published** [14] Novel Nanocomposites Based on Bacterial Polyester/LDH-SDS Clay for Stem Cells Delivery in Modern Wound Healing Management/ 2020/Materials/ Vasile E., Radu I.C., Galateanu B., Rapa M., Hudita A., Jianu D., Stanescu P.O., Cioflan H., Zaharia C./ **published** [15] In vitro macrophage immunomodulation by the PCL based-coated AZ31 Mg alloy/2020/Int. J. Mol. Sci./ Negresc A.M., Necula M.G., Gebaur A., Golgovici F.A., Nica C., Filis C., Iovu H., Costache M., Cimpean A./ **published** [16] The state of the art and prospects for osteoimmunomodulatory biomaterials/2021/ Materials/ Negrescu A.M., Cimpean A./ **published** [17] Nanocellulose-enriched hydrocolloid-based hydrogels designed using a Ca2+ free strategy based on citric acid/2021/Materials&Design/Lungu A., Cernencu A. I., Dinescu S., Balahura R., Mereuta P., Costache M., Syverud K., Stancu I. C., Iovu H./ **published** [18] Cellulose nanofiber-based hydrogels embedding 5-FU promote pyroptosis activation in breast cancer cells and support human adipose-derived stem cell proliferation, opening new perspectives for breast tissue engineering/2021/Pharmaceutics/ Balahura L.R., Dinescu S., Balas M., Cernencu A., Lungu A., Vlasceanu G.M., Iovu H., Costache M./ **published**	

	[19] 3D Bioprinting of biosynthetic nanocellulose-filled inks highly reliable for soft tissue-oriented constructs/2021/Materials/ Cernencu A.I., Lungu A., Dragusin D., Stancu I.C., Dinescu S., Balahura R., Mereuta P., Costache M., Iovu H/ **published** [20] Electrospinning fabrication and cytocompatibility investigation of nanodiamond particles-gelatin fibrous tubular scaffolds for nerve regeneration/2021/ Polymers/ Olaret E., Dragusin D.M., Serafim A., Lungu A., Selaru A., Dobranici A., Dinescu S., Costache M., Boerasu I., Vasile B.S., Steinmüller-Nethl D., Iovu H., Stancu I.C./ **published** [21] Gait Analysis Using Animal Models of Peripheral Nerve and Spinal Cord Injuries/ 2021/Biomedicines/ Isvoranu G, Manole E, Neagu M./ **published** [22] Fabrication and properties of alginate-hydroxyapatite biocomposites as efficient biomaterials for bone regeneration/2021/European Polymer Journal/Ocando C., Dinescu S., Samoila I., Ghitulica C.D., Cucuruz A., Costache M., Averous L./ **published** [23] In vitro and in vivo evaluation of HEMA/AMPSA/MMT hydrogels enriched with sericin and fibroin in the context of soft tissue engineering applications/2021/Nanomaterials/ Serban M., Ignat S., Dinescu S., Gharbia S., Herman H., Radu I., Zaharia C., Costache M., Hermenean A./ **under review** [24]Characterization and in vitro biocompatibility of HEMA/AMPSA/LDH designed for adipose tissue engineering/2021/Polymers/ Radu I., Zaharia C., Ignat S., Serban M., Dinescu S., Iovu H., Costache M./ **under review** [25] Application of bioprinted models to study of tumor microenvironment interaction/2021/ Jurj A., Berindan-Neagoe I., Braicu C./ **under review** [26] Cellular and molecular alteration of mammary epithelial cells by cellular reprogramming cell culture/ 2021/ Jurj A., Soritau O., Munteanu M., Groza M., Cojocneanu R., Zanaoaga O., Cismaru A., Braicu C., Berindan-Neagoe I./ **under review**	
Articles published / accepted/ under evaluation in BDI indexed journals	*Article title / Year of publication / Journal / Authors / Status (under evaluation /accepted /published)* [1] In vitro and in vivo biological performance of Mg-based bone implants/2020/Rev. Biol.Biomed. Sci./ Negrescu, A.M., Necula, M.G., Costache M., Cimpean A./ **published** [2] A biointerface growth at immersion of a biodegradable magnesium alloy in simulated body fluid/2020/UPB Sci. Bull/M-E. Voicu, F. Golgovici/ **published** [3] The interconnection between the inflammasome and breast cancer/2020/ Reviews in Biological and Biomedical Sciences/ Balahura L.R., Dinescu S., Costache M/ **published**	3
Book chapters in international publishing houses	[1] Theranostic Nanoparticles and Their Spectrum in Cancer, IntechOpen, DOI: 10.5772/intechopen.88097, 2019 [2] The Cellular and Molecular Patterns Involved in the Neural Differentiation of Adipose-Derived Stem Cells in "Advances in Experimental Medicine and Biology" book, Springer Nature, 2020; DOI: 10.1007/5584_2020_547 [3] Schwann cell plasticity in peripheral nerve regeneration after injury, In book: Schwann Cells, InTech Open, 2020, DOI: 10.5772/intechopen.91805	3

Participation in conferences	*Event name / Type / Title / Year* [1] Conferinta Internationala a SRBBM/Poster/ Effect of hydroxiapatite dopped with magnesium on the properties and biocompatibility of alginate materials in bone tissue engineering /2018 [2] Sesiunea de comunicari a Facultatii de Biologie/Comunicare orala/Studii preliminare de biocompatibilitate a unor materiale noi pe baza de chitosan si fosfat tricalcic, imbogatite cu magneziu, destinate regenerarii osoase/2018 [3] European Polymer Congress/Poster/ Nanofunctionalized electrospun gelatin fibers for peripheral nerve regeneration/2019 [4] 11th International Conference on Materials Science & Engineering/Poster/Deposition of a composite zinc oxide/PLGA coating on AZ31 Mg alloy for increased biocompatibility and antibacterial activity/2019 [5] 21th Romanian International Conference on Chemistry and Chemical Engineering/ Poster/Electrochemical behavior of magnesium alloy with and without polymeric coatings electrodeposited from ionic liquids/2019 [6] 21th Romanian International Conference on Chemistry and Chemical Engineering/ Poster/Magnesium alloy corrosion behavior by electrodeposition of bioactive calcium phosphate coating/2019 [7] 21th Romanian International Conference on Chemistry and Chemical Engineering/Poster/Development of 3D printed structures with controlled architecture for biomedical applications/2019 [8] Sesiunea de Comunicari Stiintifice a Facultatii de Biologie - Editia 2019/Comunicare orala/ Caracterizarea in vitro a performantei biologice a filmelor pe baza de acid polilactic pe un aliaj de magneziu/2019 [9] FEBS 2019/Poster/Novel thermoplastic polyurethane foams enriched with ZnO nanoparticles exhibit antibacterial effect for wound healing applications/2019 [10] 27th Annual Conference of the Polish Society for Biomaterials 'Biomaterials in Medicine and Veterinary Medicine/Comunicare orala/Plenary lecture: Naturally-derived hydrogels and nanocomposites as building blocks of scaffolds for tissue regeneration/2018 [11] European Society for Biomaterials 2019 (ESB2019) 30th Annual Conference of the European Society for Biomaterials, together with The 26th Annual Conference Of The German Society For Biomaterials (DGBM)/Poster/Nanocomposite electrospun gelatin fibers for peripheral nerve regeneration/2019 [12] European Polymer Congress/Poster/New coatings based on porcine gastric mucin with potential biomedical applications/2019 [13] FEBS Congress/Poster/Human adipose-derived stem cells behaviour and cytoskeleton development in contact with electrospun fibrous gelatin materials enriched with magnetic nanoparticles/2019 [14] FEBS Workshop Ageing and Regeneration (AGE-REG)/Poster/Scaffold-assisted neural regeneration initiated from mesenchymal stem cells/2019 [15] NANOTODAY/Poster/A Different View for Gallium (III) Phthalocyanine - Potential Bio-Application in Neuroblastoma Cellular Model/2019 [16] EUROTOX / Poster/ Bio-Inspired Nanoparticles in Neuroscience/2019 [17] RICCCE/ Poster/ Development of nanocomposite nerve guidance channels/2019	33

	[18] The Annual International Conference of the Romanian Society of Biochemistry and Molecular Biology/Poster/ Biocompatibility assessment of a HEMA/AMPS/LDH material for soft tissue engineering applications/ 2019 [19] Conferinta Internationala 21th Romanian International Conference on Chemistry and Chemical Engineering RICCCE/Poster/Nanocomposite hydrogels for tissue engineering applications/2019 [20] EMN Barcelona Meeting/Poster/ 3D printable nanocellulosepectin ink formulations/2018 [21] 21st Romanian International Conference on Chemistry and Chemical Engineering, RICCCE/Poster/ Porous Nanocellulosic Materials as Platforms for Drug Delivery,/2019 [22] Conferinta anuala de Imunologie si Imuno-Dermatologie/Comunicare orala/ Activation and involvement of inflammasome in tumor progression/2020 [23] Congresul national de oncologie. Provocarile anului 2020 in oncologie/Poster/ Cellular and molecular alterations of adipocytes and mammary epithelium by conditional reprogramming cell culturing 2020 [24] EMBO-FEBS Lecture Course ”Systems biology of cancer: promises of artificial intelligence”/Poster/ Molecular changes in breast cancer development during inflammasome activation/ 2020 [25] Sesiunea de comunicari a Facultatii de Biologie/Comunicare orala/ Evaluarea in vitro a potentialului imunomodulator al aliajului AZ31 acoperit cu biofilme pe baza de poli(ε-caprolactona)/2021 [26] Annual Scientific Meeting of Victor Babes Institute, The 12th National Pathology Symposium/Comunicare orala/ Biocompatibility analysis of HEMA/AMPS/LDH 3D bioconstructs designed for soft tissue reconstruction/ 2019 [27] 2nd World Congress on Smart Materials and Structures/poster/ HEMA/AMPSA hydrogel enriched with sericin and fibroin proved efficiency for soft tissue engineering applications/ 2021 [28] 45th FEBS Congress/poster/ 5-fluorouracil-enriched nanocellulose and pectin biomaterials determined inflammasome complex activation and ROS production in breast cancer cells/ 2021 [29] TRANSCOLONCAN COST Action – Workshop „Challenges of tumor profiling in translational research”/comunicare orala/ Smart biocomposites encapsulating methotrexate designed for cancer therapy/ 2021 [30] Sesiunea de comunicari a Facultatii de Biologie/Comunicare orala/ Efectul 5-fluorouracil asupra celulelor tumorale mamare cultivate in materiale tridimensionale pe baza de nanoceluloza/ 2021 [31] 5th ACTC- Advances in Circulating Tumor Cells "Liquid biopsy is its the best"/poster/ Adipocyte-derived exosomes promote the progression of triple negative breast cancer cells in vitro/ 2021 [32] 14th Göttingen Virtual Meeting/ poster/ The functioning of voltage gated (IKdr) K+ channels restores faster after a peripheral nerve lesion in the presence of a biocompatible nanomaterial support system/2021 [33] 14th Göttingen Virtual Meeting/ poster/ INav currents during sciatic nerve reconstruction guided by a Nerve Regeneration Assistance System (NerveRAS)/2021	

Patent applications filed nationally and internationally	*Patent title/Issuing authority/Date of filing* [1] Patent application no. A/00556 entitled "Process for obtaining fibrous composite materials used in the laminated coating of magnesium alloy AZ31" / OSIM / 16.09.2021 [2] Patent application no. A/00555 entitled "Process for obtaining multilumen fibrous tubular structures for the regeneration of peripheral nerves" / OSIM / 15.09.2021 [3] Patent application no. A/00550 entitled "Process for obtaining new bionanocomposites based on modified clays and polymers for soft tissue engineering" / OSIM / 15.09.2021 [4] Patent application no. A/00596 entitled "Procedure for obtaining and maintaining in culture epithelial cells from normal breast tissue" / OSIM / 30.09.2021	4
Patents obtained nationally and internationally	*Patent title/Issuing authority/Date of filing*	-
New or significantly improved products made and transferred to the economy	Name/Year	
New or significantly improved technologies developed and transferred to the economy	Name/Year	
New or significantly improved services performed and transferred to the economy	Name/Year	

Date: 30.09.2021

Complex Project Director,

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