MANUNET ERA-NET Project

Full Proposal[1]

Project Acronym: BioTiDent

CONTENT

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1 SUMMARY

Acronym/Short name	BioTiDent				
Proposal Full Name	Advanced dental implants from a high biocompatible beta Ti alloy with functionalized surface				
Project Coordinator	Leire Valentín			Email	leire.valentin@mugape.com
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Organisation	MUGAPE S.L.			Region/Country	Basque Country/Spain
Total project costs (€)	712,300			Requested funds (€)	342,890
Planned starting date[1]	01.01.2017	Duration (in months)	24	Total person/months	115
Topics[2]	Other technologies/products related to the manufacturing				

Title and brief description of project, to be published in case of recommendation for funding (up to 10 lines)

The project “Advanced dental implants from a high biocompatible beta Ti alloy with functionalized surface” has the objective to design an innovative dental implant by means of the development of a new superelastic beta Ti alloy with superior mechanical properties. Besides, implants can be provided with bioactive and antibacterial properties by their surface functionalization with multifunctional coatings composed by oxides doped with Ca, P and fluorides, using plasma electrolytic oxidation technology. These biocompatible coatings will also supply to the implants better corrosion and wear resistance due to their excellent protective properties. As a result of the project, a more resistant dental implant in terms of mechanical, corrosion and tribological properties will be obtained with better osseointegration and antibacterial features, which will result in an improved quality of life for the patient.

Project Summary

The BioTiDent Consortium consists of 4 members from two countries: 3 Small Medium Enterprises (SMEs) interested in industrial implementation of project outcomes, one from the **Basque Country** (MUGAPE/MUG-specialized in surface coatings) and two from **Romania** (TEHNOMED Impex Co/Teh-implant producer and R&D Consulting and Services/RD-specialized in Ti alloys synthesis and thermo-mechanical processing), 1 research unit from Romania (University of Bucharest /UB, Department of Biochemistry and Molecular Biology) and also one subcontracted technological centre from the Basque Country (IK4-TEKNIKER/TEK) for development of surface tailored solutions and characterization of performance of the Ti-coated materials.
The **main objective** of BioTiDent is to develop advanced dental implants from a high biocompatible β Ti alloy with bioactive and antibacterial functionalized surface for good osseointegration and infection preventing.
The **specific objectives** are:
- development of the new β superelastic Ti alloy for implant body and the technologies for its synthesis and thermo-mechanical processing;
- design of novel implant from the new Ti alloy and the development of its manufacturing technology at the Romanian implants producer SME partner;
- development of the technology for bioactive and antibacterial implant surface coating at Basque SME partner.

In the project, the new coatings will be applied on the new developed beta superelastic titanium alloy, and the mechanical, corrosion and wear properties, and corrosion-wear synergy will be studied. Additionally, the antibacterial properties needed to avoid infection and the osseointegration capability will be assessed.
The **project innovation** regarding the current state of the art consists of:

-a new safer biocompatible β Ti alloy containing non-toxic elements, with improved characteristics compared to commercial Ti alloys in respect to the corrosion resistance and mechanical properties (superelasticity, higher strength, wear and fatigue resistance) and better machinability, avoiding implant manufacturing flaws;
-new plasma electrolytic oxidation (PEO) coating applied on the new beta Ti alloy consists of Ti oxide layers doped with bioactive (Ca and P) and anti-microbial (fluorine) agents, in order to generate biocompatible, osseoconductive, antibacterial, wear and corrosion resistant surfaces;
-implant with improved characteristics compared to the commercial dental implants in term of biocompatibility, corrosion resistance, mechanical properties, osseointegrative and antibacterial abilities due to advanced coatings, leading to a better reliability and improved quality of life for the patients.
The proposal need is challenged by the market requirement for advanced safer dental implants with long term stability. Although new systems mainly based on polymeric and ceramic materials have been introduced in the market during the last years, currently, around 70% of the commercialized dental implants are based on metallic materials. This situation is not expected to change in the near future, essentially because of the high strength, toughness and durability offered by the metallic materials. Regarding dental implants, most are made of Ti and Ti-based alloys. It is widely accepted that when used as dental implant material, the surface properties of Ti play an essential role in the interaction with jaw-bone tissue. Consequently, surface modification strategies in the last years are focused on functionalization, providing specific bioactive characteristics. In fact, the interaction of the material with the living bone tissue depends on its bioactivity, surface energy, surface topography (roughness, porosity and texture at micro- and nano-level), chemical composition, structure, corrosion resistance and tribological properties.
Although in the last years, the use of titanium implants became a common implantology practice, a significant number of failures are still being reported. Among other factors, failure of dental implants strongly depends on the implant/bone interfacial mechanical properties and on the biological events occurring at the interface, including the formation of microbial biofilms (for which is necessary antibacterial protective coating), fibrous tissue and/or the presence of wear debris or corrosion products. Micro-movements between the implant and the bone are unavoidable leading to the formation of debris and release of metal ions, causing an adverse cellular response, which can result in implant loosening and pain. In the same way, during surgery, the implant is screwed into place at a precise torque and wear debris can be created. Consequently, the tribological properties of the surface of the implants are important.
BioTiDent will have as outcomes new products (new beta Ti superelastic bioalloy with high biological and mechanical compatibility; new advanced Ti implant, with bioactive and antibacterial coatings for improved osteointegration and infection preventing) and the afferent manufacturing technologies (synthesis of new bulk β Ti bioalloy, its thermo-mechanical processing, implant manufacturing, bioactive and antibacterial surface coatings). The market acceptance will depend on the high quality of the developed dental implants.
The implementation of these results will enable the participating companies to widen their competences and acquire the experience necessary in order to design and produce in an effective and economical way novel innovative and competitive advanced dental implants. At the same time, the participation in this proposal will put them into contact with other European companies, enabling to strengthen business collaboration links on international market.
The transnational cooperation and implementation of project expected outcomes will bring benefits for all project partners. The main benefit of the industrial partners is the development of their companies by the enlargement of production profile with the new dental implants with good chances in the market. Participating in the project, they will benefit of free rights to implement the developed technologies (based on IPRs allocation stated in Consortium Agreement). The Basque partner MUG will implement protective, bioactive and antibacterial implant surface coating. Romanian partner Teh will enlarge its production profile with the new advanced dental implants developed in the project. The new bioalloy synthesis and thermo-mechanical processing technologies developed by RD will be transferred to the Romanian Ti alloys producer (ZIROM), which in the future could be supplier for Teh and other clients from European Market, including the Basque country. The improved technical performances and market competitiveness will increase companies turn-over for medium and long term and their employees' number. The research units will benefit of the developed knowledge through the transfer to industry, dissemination and increased visibility in the scientific community.

2 CONSORTIUM DESCRIPTION

CONSORTIUM OVERVIEW				
Partner name	Coordinator: MUGAPE S.L.	Partner 2: R&D Colsulting and Services	Partner 3: TEHNOMED Impex Co	Partner 4: University of Bucharest
Legal Status[1]	SME	SME	SME	UNI
Region/ Country	Basque Country	Romania	Romania	Romania
Company registration number [3]	B95543625	J40/10684/2004	J40/6402/2001	4505502/16.08.1993
Size (number of employees)	62	5	18	2568
Turnover (€)	6,000,000	187,600	117,500	76,000,000
Person months in the project	61	30	12	12
Total person months in the project			115	
Contact person in the company	Leire Valentín	Doina Stanciu	Sorin Croitoru	Anisoara Cimpean
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Person contacted for funding programme[4]	Cristina Ugarte	Nicoleta Dumitrache	Nicoleta Dumitrache	Nicoleta Dumitrache
Funding programme[5]	Basque Country - H	Romania - Internatior	Romania - Interna	Romania - Internation

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Partner's qualification in the field of Manufacturing

- **Consortium and project management**

The project objective, in line with the MANUNET topic *"technologies and products related to the manufacturing field*" is *to obtain advanced dental implants from a new superelastic Ti alloy with functionalized surface, having high biological and mechanical compatibility*.

For achieving this objective the ***Consortium*** gathers a multi-disciplinary scientific team from one Romanian university (Bucharest University/**UB**, Department of Biochemistry and Molecular Biology), one subcontracted technological centre from the Basque Country (IK4-TEKNIKER/**TEK**) and three industrial partners, experienced in the approached manufacturing fields and also in research activity, interested in industrial implementation of project outcomes (MUGAPE/**MUG**, Basque Country; R&D Consulting and Services/**RD**, Romania and TEHNOMED Impex Co/**Teh**, Romania).

The partners assigned as *project coordinator* the SME MUG, high experienced in the field of surface functionalization in which is involved in the project, but also with management expertise gained in national projects and also in coordination of some industrial cooperation initiatives.

- **Role of each partner in the project**

Coordinator – Partner 1 – MUGAPE S.L. (MUG)

MUG is a Basque SME, whose main industrial activities involve the application from conventional coatings to the most advanced technologies in surface engineering for a wide range of industries such as machine-tools, wind energy, aeronautics, automotive, capital goods, household electrical goods, bathroom accessories, engineering, decoration, *medical*, space. MUG applies different types of surface treatments (anodizing, phosphating, passivating) by means of metal electrodeposition over the substrate that must be protected, having a huge experience in anodic treatments on Al and Ti parts, producing strongly adhesive layers of oxides. The applied coatings are functional, providing to the part corrosion resistance, wear resistance as well as an aesthetic feature, because of the possibility of applying matt and bright finishes. MUG is member of Euskadi´s automotive Cluster (ACICAE). For improving the competitiveness and all customers' satisfaction, this company has got the certification of Quality Management System UNE-EN-ISO 9001, UNE-EN-ISO-TS 16949 (for automotive field) and is committed to implement an Environmental Management System according to ISO 14001. MUG has a proactive behaviour, focused on the customers' requirements, collaborating on the solution´s search to achieve the required surface properties. Research and innovation is a constant factor in MUG development and its technological basis for creation of new business opportunities. MUG has proven experience in coordinating different national projects as Gaitek programs. Previously, in cooperation with TEK, MUG performed a project for the development of protective coatings on Mg alloys for medical application. *Recently, MUG has setup an experimental micro-arc oxidation treatment installation in view to apply this technique for implants surface coating and consolidate its market position in the medical field, where now the company is not totally established. The possibility to cooperate with companies involved in dental sector using new Ti bioalloys and performing surface treatments for dental implants, will improve the exploitation opportunities of the developed technologies.*

Role in the project: MUG will be the project coordinator and will be involved in the project with the development of the technology for titanium implant surface treatment with bioactive and antibacterial coatings. The process conditions (electrolyte composition and PEO parameters) established by TEK at laboratory scale will be implemented in MUG experimental installation for their optimization at a higher scale. MUG will coat the implant, demonstrator product, and will perform a deep characterization of the coatings in collaboration with TEK. TEK's help for the study of the deposition conditions, types of electrolyte, layers characterization will be a real advantage to reach the project objective and to reduce the gap between research and production, making easier for MUG the further exploitation. MUG will participate with own funds to project co-financing.

The Subcontractor of Basque SME - Fundación IK4-TEKNIKER (TEK)

TEK is a technological centre experienced in research and innovation in coatings for a wide range of industries, mainly automotive, aeronautics and biomedical devices. During 5 years, TEK has been the Spanish Representative of the COST 533 Action of Biotribology, and now participates in the biomaterials team of the EU Platform EUMAT. In the medical field, TEK has been very active participating in many European and national projects, where it studied different coating depositions as PVD for knee prosthesis, DLC for hip prosthesis, accompanied by different characterizations as friction and wear properties of synovial liquid, mechanical characteristics of scaffolds for bone implants (strength, elastic, plastic, impact and wear properties). It has a huge experience in the development of PEO treatments on Al and Mg alloys for different applications (3 national projects). For this project, TEK will use its PEO lab equipment; for the complete characterization of the coating layers, will use its *modern equipment* as Friction and wear testing machines-CETR, Falex, SRV, corrosion and tribocorrosion testing machines, Universal Static Machines, SEM-EDS,

Hardness, goniometer for wettability tests, GDOES, scratch tests, calotest, nanoindenter and a microbiological laboratory.

Role in the project: TEK will develop new Plasma Electrolytic Oxidation (PEO) coatings with outstanding resistance to corrosion and wear on the new β Titanium alloy to be applied on dental implants. It will be responsible with the study of PEO coatings deposition conditions and layers characterization. TEK will use its PEO lab equipment in order to apply the oxidized layers, will design a specific electrolyte appropriate for titanium alloys and will test it varying the composition and will experimentally establish the deposition conditions (voltage/current and time, mainly) for achieving the most promising oxide films in terms of surface properties, including composition, roughness, hydrophilicity/hydrophobia grade, texture and morphology. TEK will characterize all performed coatings by itself and by MUG by means of microstructural, physical and chemical analysis, tribological, tribocorrosion and corrosion tests and antibacterial study.

The knowledge about the process will be transmitted to MUG in order to apply the technology on its experimental installation and scale up the process.

Partner 2 - SC R&D Consulting and Services SRL (RD)

RD is a Romanian SME, having as main field of activity research and development in material science, mainly in new advanced alloys synthesis for medical and industrial use. It offers consultancy, technical assistance and technical-economic analyses for new projects and new business. The company is carrying out experimental research and industrial development and it was/is involved in 36 research projects (8 European: 7 ERA Net, 1 FP7), concerning biomaterials, shape memory alloys, alloys for high temperature operation in corrosive environments, etc. Company personnel have a long experience in design, synthesis and thermo-mechanical processing of metallic biomaterials, especially Ti alloys for dentistry and orthopaedic applications. Some scientific results were presented in over than 30 papers published or communicated at national and international conferences. In the project domain, RD has five patents/patent applications regarding high biocompatible alloys for medical devices. The company has specialized endowment for alloys melting, casting, thermo-mechanical processing and alloys characterization. Relevant for the project are induction melting furnace with cold crucible (levitation furnace) for metallic material synthesis, treatment furnace and press for thermo-mechanical processing, chemical, structural and mechanical characterization equipment (X ray spectrometer, optical microscope, static and dynamic test machine, micro-hardness tester), and equipment for raw materials and metallographic sample preparation.

Role in the project: RD will be involved in the project with the design of new high biocompatible superelastic Ti bioalloy composition, design and experiments of synthesis and thermo-mechanical processing technologies, obtaining bioalloy samples and test lot for other partner's activities, chemical and mechanical characterization and finally, technical economic analysis for the assessment of project results applicability and implementation. RD will participate with own funds to project co-financing.

Partner 3 - **TEHNOMED Impex Co (Teh)**

Teh is a Romanian SME having as main field of activity the production of medical devices, mainly dental implants, from Ti and Ti alloy Ti6Al4V and afferent implantation instruments (kits), based on its own *6 patents*. It is one of the main Romanian implant producers, well quoted on the domestic market. Their quality integrated management system for medical devices production is certified: SR EN ISO 9001 (quality), 14001 (environment), OHSAS SR EN ISO 1801 (occupational security), SR EN ISO 13485 (medical devices suppliers). Its end-products are registered as medical devices and certified by Romanian Health Ministry. Teh has specialized endowment for precision machining, implants sterilization. The company is interested in increasing the market position through implants quality improvement as answer to the newest tendencies and market requirements. Having a long experience in implant production, the company has qualified personnel in design and precision machining. The team involved in the project, specialized in Ti and Ti alloys machining, participated in the last 5 years in many national research projects, as well as in 4 European projects in the field of new medical devices, dental and orthopaedic implants, (1 EUREKA and 3 ERA NET).

Role in the project: Teh will be involved with the design of dental implant from the new bioalloy, design and experiment of bioalloy machining technology for implants obtaining, and will produce the dental implants lot for the demonstrator product that will be coated by MUG. Teh will supply the necessary data for the technical feasibility study performed by RD in the last project stage and will participate with own funds to project co-financing.

Partner 4 - University of Bucharest - Department of Biochemistry and Molecular Biology (UB)

UB is well-known for its specialists in the fields of human cell cultures, molecular and cell biology, biochemistry, etc. UB has a modern and competitive infrastructure. Its laboratories are endowed with equipment to support the project specific research, such as laminar flow cabinets, incubators, phase contrast microscope with epifluorescence system and video camera, laser scanning confocal microscope, etc. The team involved in this project has worked at the forefront of research into the biocompatibility of materials used

in medical devices since 2004. Within this period, it participated in over 25 projects, in national and international programs including ERA Net to evaluate the cell response to implantable materials. The team members acquired a high qualification and relevant experience in investigating the behaviour of different cell types on new biomaterials in terms of: cytotoxicity, cell adhesion, spreading and morphology, cell proliferation and differentiation, expression of proteins associated with osteoblastic phenotype and inflammatory activity. They published more than 50 ISI papers in the fields of cell cultures, cell biology and biochemistry.
Role in the project: UB will perform *in vitro* testing of biocompatibility according to ISO 10993-5. Furthermore, the osseointegration abilities of the newly developed biomaterials will be assessed with MC3T3-E1 pre-osteoblasts in terms of cellular survival, adhesion, morphology, proliferation and differentiation potentials of the cells grown in contact with the analyzed surfaces.

- **Scientific and technological expertise of the Consortium as a whole**

The Consortium structure will promote the convergence of national research programmes from the Basque Country and Romania towards collaborative research in transnational research MANUNET projects, for efficient use of project partners' scientific knowledge related to the approached topic, balancing the research costs and risks. Each partner contribution will represent an added & synergistic value to project objective achievement.
Project goal involve scientific and technological research activities in view to obtain market oriented new products (advanced dental implants) and their manufacturing technologies. The project complexity requires a multidisciplinary specialization of Consortium members, best assured by a transnational cooperation joining the innovative capabilities of the Basque Country and Romania partners with high level specific qualification and expertise in the approached research and/or production field. Their specializations, covering the following fields necessary for achieving the proposed targets are: *metallic materials science* (for new bioalloy obtaining, its thermo-mechanical processing including chemical and mechanical characterizations-the partner RD, Romania), *physics and physical chemistry* (for surface functionalization with osseointegrative and antibacterial coatings-MUG and its subcontractor TEK, Basque Country, for surface characterization and corrosion testing-TEK, Basque Country), *metallic materials processing* (for implants obtaining through new bioalloy machining-Teh, Romania), *biology* (for biocompatibility testing -UB, Romania and antibacterial testing-TEK, Basque Country) and *economics* (for technical-economic assessment of project results applicability and implementation in each country-RD, Romania and TEK, Basque Country). This complementary experience of the proposers, their geographical distribution, and the critical mass in human and financial resources, give the Consortium the added value necessary to achieve the project objectives.
In such a structure, the Consortium has the scientific, technical, organizational and financial capability to finalize the project with the expected result: *a complete technologies chain for advanced dental implants manufacturing, starting with new high biocompatible superelastic Ti alloy synthesis, its processing (thermo-mechanical and machining) and surface coating for osseointegrative and antibacterial abilities.*
Another favourable premise of Consortium successful work is partners' past or ongoing cooperation in national and European projects (i.e. RD with UB, Teh and TEK, MUG with TEK).

- **Brief presentation of the relevant researchers**

MUG - *Leire Valentín*, Technical Chemical Engineer, she has been working in surface treatment since 2004 in different fields such as lab, quality and process engineer. Among the treatments that she has experience are plating (copper, nickel and chromium over zamak, steel and aluminium), chromic and sulphuric anodizing, a wide range of phosphating over steel and passivations over aluminium and stainless steel and so on. It is remarkable her collaboration with HENKEL for the industrial development of the PEO (Plasma Electrolytic Oxidation) process ALODINE EC2, which is been applied over aluminium parts to withstand extreme conditions. *She will be the project manager*.
- *Vanesa Marcilla*, Degree in Chemistry, she has been working in surface treatment since 2009 in different fields such as lab, quality and process engineer. Among the treatments that she has experience are plating (copper, nickel and chromium over zamak, steel and aluminum), chromic and sulphuric anodizing, a wide range of phosphating over steel and passivations over aluminium and stainless steel and so on. *She will participate in the integration of PEO technology for demonstrator product in MUG facilities.*
- *Itziar Gonzalo*, Technical Chemical Engineer, she has been working in surface treatment since 2015 in different fields such as lab, quality and process engineer. Among the treatments that she has experience are plating (copper, nickel and chromium over zamak, steel and aluminium), chromic and sulphuric anodizing, a wide range of phosphating over steel and passivations over aluminium and stainless steel and so on. *She will participate in the integration of PEO technology for demonstrator product in MUG facilities.*
- *Alfonso Gallo*, Industrial Engineer and Master in Quality Management, since 1993 has been working for several companies as production and quality manager. He also has experience in a wide range of industries

such as automotive, aeronautical, electrical appliance and so on. Nowadays he is the Quality Manager of MUGAPE S.L. *He will check the good quality of the parts treated with PEO process.*

- *Ana Ledo,* Technical Chemical Engineer, she has been working in surface treatment since 2005. Among the treatments that she has experience are plating (copper, nickel and chromium over zamak, steel and aluminum). Her main field is quality; she has a wide experience in customer requirements for surface treatments. *She will participate in the integration of PEO technology for demonstrator product in MUG facilities.*

- *Arcangel Navarro,* Technical Industrial Engineer started her activity in MUGAPE in 1997, before that he has been working in other surface treatment companies and testing laboratories. He created for MUGAPE the chrome plating business line where he has a huge experience in new process design and getting approvals for different industries such as automotive, aeronautical, medical, and so on. *She will participate in the integration of PEO technology for demonstrator product in MUG facilities.*

TEK - *Virginia Sáenz de Viteri*, *PhD.,* MsC in Chemistry, specialized in Polymers area, PhD since January 2016 in the area of "Development of protective coatings to improve the Ti6Al4V alloy behavior in orthopedic applications". She is researcher in TEK Tribology Unit, with proven experience in Tribology (friction, wear and lubrication), biotribology, biomechanics, materials engineering, mechanical characterization of polymeric materials and biomaterials. She has participated in European projects, mainly focused on biomaterials and she has a large number of publications to Congresses. *In the project, she will perform the PEO surface treatment on the selected super-elastic Ti alloy by formulating different electrolytes and processing conditions and will participate to the coating layers characterization. She will be the responsible for the project at TEK level.*

- *Raquel Bayón*, PhD, PhD in the area of "Corrosion-wear behavior of novel surface coatings developed by means of advanced techniques", is experienced in the field of materials science, surface treatments, tribology, corrosion and tribocorrosion. She has coordinated the role of TEK in several European projects in different programs and in more than 10 Spanish ones. She is member of the Spanish Materials platform (Materplat), PESI (Spanish Platform of Industrial Security) and AENOR committee C112 about corrosion. She is author of 27 papers and has participated in more than 45 international conferences. In the project, s*he will be involved in the corrosion and tribocorrosion study of developed protective coatings and designed Ti bioalloy.*

- *Gemma Mendoza*, Technical Industrial Engineer in TEK Tribology Unit, specialized in the application of LCA (Life Cycle Assessment) in different fields (lubricants, light materials, coatings, green machining processes) with the aim of implementing environmentally friendly product or processes. She has participated and led several National and European projects on these areas, where improved tribological solutions for different applications have been developed. She is also the responsible of the bacteriological laboratory specialized in the performance of biodegradability and toxicity tests on lubricants, industrial fluids, coatings and polymers. *In the project, she will perform the antibacterial analysis of the implant coating and developed Ti bioalloy.*

RD - *Doina Stanciu*, chemical engineer, senior researcher, is specialized in biomaterials field; her research interest was focused on metal based materials synthesis, design of environmental friendly technologies, scale up of research results for industrial implementation, especially for development of new bioalloys for medical devices, with improved biological and mechanical characteristics as well as their synthesis and processing technologies, process engineering design. She participated in many national and European projects in biomaterials field, as project leader and/or member of research team. *In the project she will participate to the design of the experimental models for development of new technologies, laboratory analyses for chemical* characterization, design and development of eco-friendly technologies and will participate to the technical analysis in view to project implementation. She will be the responsible of RD research team.

- *Steliana Ivanescu*, material science engineer, senior researcher, is specialized in the field of alloys synthesis and thermo-mechanical processing. Her research interest was focused on alloys for medical and industrial use, especially Ti alloys. She participated in many national and European projects in biomaterials field, as project leader and/or member of research team. *In the project she will design the new alloy composition to obtain improved biocompatibility and mechanical characteristics and the synthesis process. She will perform the analysis of experimental results and structural characterization.*

- *Ioan Dan*, technological equipment engineer, senior researcher is specialized in equipment for metallic alloys synthesis, especially in levitation melting furnace, thermo-mechanical processing, mechanical characterization (static and dynamic testing) and technical-economic studies. He participated in many national and European projects in biomaterials field, as project leader and/or member of research team. *In the project he will design the thermo-mechanical processing technology, will be responsible for the synthesis and thermo-mechanical processing of the new Ti alloy and mechanical characterisations. He will participate to the technical-economic analysis regarding the future implementation of project results.*

Teh - *Sorin Mihai Croitoru* PhD, associate professor at faculty of Engineering and Management of Technological Systems IMST, University POLITEHNICA of Bucharest, is specialized in machine tools and integrated systems of machine tools. He participated in many national and European projects in biomaterials field, as project leader and/or member of research team. *In the project, he will design the technology of new Ti bioalloy machining for implant manufacturing and will be Teh project responsible.*
- *Popovici Ion Alexandru*, PhD in dental implantology with Master in Oral Implants and Prosthesis rehabilitation, is specialized in dental surgery and osseointegration of oral implants. *In the project he will participate to the design of the dental implant, demonstrator product, based on the actual tendencies and requirements for advanced dental implants.*
UB - *Anisoara Cimpean***,** PhD, Professor at the Faculty of Biology, University of Bucharest Department of Biochemistry and Molecular Biology (UB-DBBM), has a vast experience in the cell biology field, especially on animal cell cultures and their applications in biomedical engineering being intensively involved in didactic and research activities. She participated as project coordinator, project responsible and/or member of research team in many national and European projects in biomaterials biological assessment. *In the project she will be in charge with biological testing of coated and uncoated Ti bioalloy and will be UB project responsible.*
- *Valentina Mitran***,** PhD**.** with Master of Biochemistry and Molecular Biology, focused her research activity on the evaluation of metallic implants' biocompatibility, being specialized in *in vitro* studies for unravelling the complexity of cell–material interactions and for evaluating the biocompatibility of implant materials, by highlighting cellular survival, proliferation, differentiation and extracellular matrix turnover. *In the project, she will participate to the in vitro biological assessment of the coated Ti bioalloy.*

Competences, past experiences in the field of the proposal
The consortium partners gathered together based on their special competence, complementarities in above mentioned specialization, the past experience and expertise in their research and/or production domain related to the project. All of them have specialized personnel with high qualification gained through long lasting national research activity and international cooperation. They also have suitable infrastructure with advanced modern endowment, appropriate for allocated project activities. *From Romania*, RD is specialized in the synthesis and thermo-mechanical processing of metallic materials for medical devices, mainly Ti alloys, and also in alloys characterization (chemical, mechanical/static and dynamic, structural), with participation in many national and European projects, finalized with 4 patents/patent applications. Teh is an implants producer, mainly dental, based on its own patents, with a good position on the Romanian market, specialized in Ti and Ti6Al4V machining. It participated with co-financing in many national and 4 EU projects. The Biology Department of UB is specialized in biocompatibility evaluation of metallic biomaterials, including Ti alloys, having long experience in many national and European projects. *From the Basque Country*, MUG is a company specialized in coatings and has participated in innovation and development projects inspired by various public organizations, collaborating with companies and research centres across the country, including in medical devices fields. Their subcontractor, TEK, is a prestigious technological centre experienced in coating deposition research on different substrates, including on medical devices, and afferent surface and antibacterial characterization. TEK is a referent in the field of Tribology at European level. Focused on innovation, TEK participated in many national and European projects related to coatings on medical devices. The Consortium units TEK, UB and RD have disseminated their scientific and technical results, most of them in project field, through published papers and participation to conferences.

- **Project management capacity of the coordinator**

The partners assigned the project management to MUGAPE S.L. from the Basque Country (Spain), which has great experience in management and execution of complex projects. MUG has participated in some national research projects in the field of biomaterials.
The project coordinator, with certificated Quality Management System UNE-EN-ISO 9001, has the necessary logistics and expertise for an efficient management of the allocated resources (human, technical and financial) and has the methodology for monitoring and control of the activities and project results. It has specialized personnel in risk management, which will follow-up the project progress, identifying the possible risks connected to the expected outcomes and time schedule, in view to corrective measures, if necessary.
The project manager, Leire Valentín, designated by MUGAPE S.L. has technical and scientific qualification in the project field, and has proven her expertise and experience in project management. Her technical competence covers the domains of surface treatment of metallic alloys for different application fields, allowing her to have a general view on the project concept and achieving ways in each partner charge. The project manager's background and experience, are the guarantee of its capability to perform a good management in all its four components (scientific, financial, organizational and administrative), for a successfully implementation of the project. She has the necessary competence for the coordination, control and analysis of

the obtained results and to set the necessary measures for the achievement of the proposed project objectives in the scheduled time.
The project manager demonstrated that she is able to act for assuring a good work atmosphere in a project team and inter-personal communication for stimulating the individual and collective creativity, also assuring the links of the research team with other organizational structures from inside and outside the project, conducting the project development and permanently maintaining an equilibrium between the exigencies regarding the technical-scientific content, costs and implementation terms.

- **Outline of the Consortium Agreement**

The project partners will sign the Consortium Agreement if the project will be accepted for funding, before concluding the financing contract. It will mandatory contain the following data, accepted by all Consortium members: *project data (title, acronym etc.); data concerning the project partners organization (type of organization, role and representation); entry into force, duration and termination; specific objectives of the partnership; technical and administrative responsibilities during the project; liabilities; management structure (project coordinator, work package leaders, management support team and methods); financial provisions; IPRs (background, foreground allocation and protection, dissemination); miscellaneous (work plan, planning of expenses, communication, language, applicable low, major force, settlement of disputes).* From the proposal stage, the partners agreed a draft of Consortium Agreement related to the main of the above issues.
Each partner will use in the project as background its previous knowledge for carrying out the allocated tasks and generation of the new innovative knowledge. *The IPRs allocation* between the partners *will be based on their contribution to each result achievement, the foreground being owned by those who generated it.* The innovative results which could be commercialized for industrial application will be patented and the other will be disseminated for increasing research team visibility in the scientific community.

3 PROJECT MERITS

3.1 Current state of the art

In EU, the growing elderly population with edentulism risk, and the incidence at old and young people of gingivitis, trauma injury, congenital defects, root canal failure, and excessive wear and tear, require new or improved solutions in dentistry. A major reason of loss of teeth in all age groups includes poor oral health and periodontal disease. The health and wellness policies established by EU Commission are sustained through research programs focused on *technologies and products (*i.e. medical devices) *related to the manufacturing field*. Dental implants are medical devices, consisting of artificial tooth or a tooth root embedded surgically into the upper or lower jawbone without disturbing the adjacent healthy teeth, (Persistence, 2014) being the best treatment for missing teeth in most of cases. Dental implants must be durable, stable, strong and support for securing other bridges or dentures, if attached well, thus making life more comfortable for the patient, offering a very natural look.(Persistence, 2014)

Today, the specific survival rate of dental implants ranges from 90% to 96.5% (Y. Kirimanidou, 2016) and well over 95% of the placed dental implants are of Ti and Ti alloy (P.A.Balogh, 2015) as Ti6Al4V ELI and Ti6Al7Nb. Despite the quite satisfactory survival rate of implants, failures still exist. (Y. Kirimanidou et al., 2016)

The selection of dental implant material depends on different factors, such as biocompatibility, corrosion resistance, mechanical strength, wear resistance and low elastic modulus (Paredes et al. 2015) and strength-to-weight ratio. The development of new biomaterials for dental implants application is challenging due to the necessity for improvement of the actual materials characteristics, in view to avoid the implants loosening caused by corrosion cracks, fracture, metal fatigue that occurs when it is subjected to repeated applied loads as mastication.(K. Semetov-Yona, 2015)

Due to the negative effect of aluminium, related to Alzheimer, and the toxic character of vanadium, there is much effort currently dedicated to replace these metals from commercial Ti and Ti bioalloys (Ti6Al4V ELI and Ti6Al7Nb) with safer alloying elements, providing better mechanical properties, reducing elastic modulus, while retaining high strength in the new alloys (M.Niinomi et al, 2011). Nb, Ta and Zr are now considered to be the safest, non-toxic alloying elements for Ti alloys, being demonstrated through research studies the higher cell viability, corrosion resistance, tissue compatibility and non-allergic properties (C.Y.Cui et al, 2009).

Ongoing researches have in view to develop new Ti alloys with different ratio of these safe metals (Nb, Zr, Ta), studying the obtaining of a good mechanical compatibility with the human bone (high tensile strength, ductility, wear properties, low Young modulus and functionalities), as actually require the implant application fields. (M.Niinomi et al, 2011) There were developed Ti alloys V free with α + β structure, but with high elasticity modulus (N. Sakaguchi, et al., 2006, Titaniuminfogroup, 2011) and more recently, Al free Ti alloys with β structure and lower elasticity modulus (C.Y.Cui et al, 2009, N. Sakaguchi, et al., 2006, Titaniuminfogroup, 2011).

The most commercially available Ti-based implant biomaterials exhibit much higher Young's modulus (over 100 GPa) than that of human bones (around 30 GPa or less). Recently, a new commercial Ti alloy (with 13-17%wt Zr) for narrow diameter dental implants (Roxolid®, Straumann) has been introduced. It has been claimed that it exhibits better tensile and fatigue strength compared to CpTi and Ti-6Al-4V. The exact data on its elastic modulus is still missing (R.B. Osman et al., 2015). The mismatch of Young's modulus between the Ti-based implants (110GPa for Ti-6Al-4V) and bone is unfavourable for bone healing and remodelling. (V. Mitran et al., 2015). Especially the β-Ti alloys obtained through addition of β-stabilizing elements (Mo, Nb, Ta, Fe, Si) and neutral elements as Zr, Hf, Sn, exhibit a substantially lower modulus and superelasticity (Niinomi 2002-2003a,b). Based on the selection of non-toxic alloying element, the β titanium alloys recently reported are in binary systems (Ti-Nb, Ti-Mo, Ti-Ta, Ti-Zr), ternary (Ti-Ta-Zr, Ti-Nb-Hf, Ti-Nb-Ta, Ti-Nb-Zr, Ti-Nb-Mo, Ti-Nb-Sn), as well as quaternary (Ti-Nb-Ta-Zr) and so on. (Y.Yang, 2015) Furthermore, the high corrosion resistance and biocompatibility of these new alloys will limit implant failure due to fatigue fractures and adverse reactions of the released ions.(Y. Kirimanidou et al., 2016) Mechanical properties could be improved not only through an appropriate alloy composition design, but also through thermo-mechanical processing, which allows the obtaining of uniform structure with fine grains, which improves both mechanical properties (lower elastic modulus and higher strength) and corrosion resistance. The used thermo-mechanical processing methods are common (forging, rolling, extrusion) or advanced (different severe plastic deformation). (Y.Yang, 2015)

Most of dental implants have three pieces (Fig. 1 and 2): the implant that goes in the jaw-bone, the abutment which holds the tooth and the ceramic crown tooth that attaches to the abutment. The actually used implants and abutments are made entirely of titanium/Ti alloy or zirconia (ZrO_2). The abutment could be zirconia "hybrid", which has a zirconia body luted in the laboratory to a short titanium connection not visible through the tissue, to provide a titanium interface with the titanium implant platform. Both materials, titanium and zirconia, can be integrated with bone with equal success, provided certain protocols are followed, but titanium has a much longer history, being patients with titanium implants still functioning after 20-35 years (P.A.Balogh,

2015). The quality of the clinical studies regarding *in vivo* zirconia implants behaviour, available in the literature, is more recent and questionable. (R.B. Osman et al., 2015)

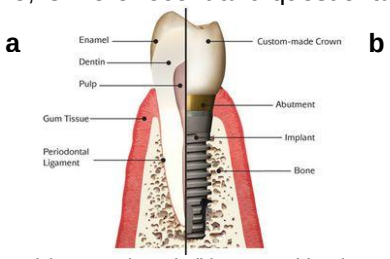


Fig. 1 (a) Natural tooth (b) Inserted implant

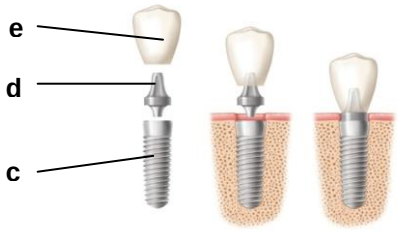


Fig. 2 Dental implant components: (c) Implant screw; (d) Abutment; (e) Crown.

Regarding the abutments, the titanium ones are commonly used in all regions of the mouth, because of their robustness and versatility. Zirconia abutments offer aesthetic advantages that are particularly beneficial to cases in the anterior maxilla. The medium-term survival of zirconia abutments in posterior regions was comparable with that of Ti ones, but long-term evaluations are needed to confirm this finding (D.Lops et al., 2013). *In vitro* study and testing the fracture strength and accelerated fatigue reliability of titanium and zirconia abutment systems showed that strength and reliability were significantly higher for the titanium abutments compared to the zirconia abutments."(J.Gordon 2010)

Although much progress has been made in the dental implants field, there are still many improvements to be achieved, including in what it concerns the fabrication methods and their parameters, which appear to play a pivotal role on the mechanical properties, corrosion resistance, surface porosity(Y. Kirimanidou et al., 2016)

Therefore, the new generation of biomaterials used for dental implants must resolve the problems related to: the improvement of biocompatibility by removing the toxic elements, of mechanical properties (decreased elastic modulus and higher strength) by β fine grain structure and of corrosion resistance in biological environment. Besides alloy chemical composition and fine structure, it is necessary the use of implant surface treatment in order to develop protective coatings for increasing implant corrosion resistance and strong cell adherence of osteoblasts, essential for successful osseointegration. Nowadays, surface treatments such as shot peening, shot peening + acid etching, anodizing, addition of bioactive substances, Ti plasma spraying, are being used for dental implants.

Ti alloy treatment by plasma electrolytic oxidation (PEO) technique facilitates the creation of a ceramic protective matrix on its surface, having in chemical composition elements from the alloy and the electrolyte. In comparison with other oxidation techniques (such as thermal oxidation or conventional anodic oxidation), the PEO coatings exhibit higher porosity and increased bioactivity, improving the osseointegration; are thicker and harder with a higher wear resistance (S. Park, et al., 2006). Additionally, they have an excellent bonding strength with the substrate, avoiding the delamination. The obtained ceramic coatings with this technique not only prevent the wear, but also provide excellent corrosion resistance. PEO is an economic, environmental friendly, quick and easy process, able to coat complex surface geometries with uniform thickness.

The biological response to titanium depends on the surface chemical composition and the ability of titanium oxides to absorb molecules and incorporate certain elements (A. Letic-Gavrilovic, et al., 2000). Surface topography plays a fundamental role in regulating cell behaviour, e.g. the shape, orientation and adhesion of cells (F. Ravanetti, et al., 2010). Concerning the pore size, values between 1 and 20 μm are suitable for cell adhesion (J.S. Temenoff and A.G. Mikos, 2008). Also, the presence of Ca has been reported to be advantageous to cell growth, and "*in vivo*" data show that implant surfaces containing both Ca and P enhance bone apposition on the implant surface (H.Y. Wang, et al., 2014), because both elements are present in hydroxyapatite, the principal inorganic bone component.

Due to the possibility to introduce different elements by PEO technique, it is possible to provide the coatings with antibacterial properties doping the electrolyte with biocide elements, like Ag, Cu, I or F (B.S. Necula, et al., 2011; B.S. Necula, et al., 2012; Y. Ando, et al., 2010; W. Zhu, et al., 2013; K. Venkateswarlu, et at., 2013). This property could help to avoid after implantation infections.

The main drawback of the actual commercial dental implants revealed by the state of the art analysis is the incidence of implants or abutments failure due to material inappropriate mechanical characteristics (elastic modulus, strength, fatigue, wear resistance) and the unfavourable biological response of the tissue due to the presence of toxic elements in alloy composition (V, Al), when released through corrosion in the biological fluids. Corrosion (galvanic, pitting, fatigue) and wear (debris), influenced by the alloy and implants manufacturing technology, decrease implant and abutment stability reducing their life time.

3.2. Originality and/or innovation of the proposed approach

The originality of the proposed project consist of the combined approach of the most recent innovation tendencies in the field of dental implants, having as objective to get *novel advanced dental implants with improved biocompatibility and mechanical characteristics, with surface coating that will facilitate the osseointegration and will avoid bacterial infection for preventing implant failure*. This project objective, which is in accordance with the European and worldwide research directions and market requirements in the field of dental implants, will be achieved through the transnational interdisciplinary cooperation, based on the partners' background and state of the art achievements. For this goal will be approached innovative solutions related to the obtaining of new advanced implants capable of connecting structurally and functionally with human bone. The approach, proposed in the project for the development of a new eco-friendly low-cost integrated manufacturing technologies chain for advanced dental implants, is referring to:

-design and development (by RD) of *new high biocompatible superelastic beta bioalloy* with nontoxic elements in the system Ti-Nb-Ta-Zr, with original composition, better mechanical properties (low elastic modulus and superelasticity, high mechanical, fatigue and wear strength), and better corrosion resistance in biological environment than pure Ti or other commercial Ti alloys; design and development of its synthesis technology using *the modern top level levitation melting technique,* suitable for synthesis of alloys with alloying elements having high melting temperatures and different densities; by intensive mixing, rapid cooling and controlled inert atmosphere, it allows the obtaining of alloy high chemical and structural homogeneity of the cast alloy;

- design and development (by RD) of a suitable thermo-mechanical treatment for obtaining fine grains microstructure, which enhance the mechanical characteristics and corrosion behaviour of the cast Ti alloy;

- design and development (by MUG and TEK) of multifunctional coating applied on the new beta Ti alloy, consisting of Ti oxide layers doped with bioactive and anti-microbial agents, in order to generate biocompatible, osseoconductive, antibacterial, wear and corrosion resistant surfaces, to promote the integration of metallic implants with bone tissue and stimulate implant direct attachment to bone for a firm anchoring, and for avoiding bacterial infection such as peri-implantitis; design and development of the coating technology, using the modern plasma electrolytic oxidation (PEO) technique tailored for the new Ti alloy surface and the complex coatings to be deposited;

- design and development (by Teh) of novel low-cost, optimized, validated manufacturing technology at lab scale for the implants, through machining of thermo-mechanically processed bioalloy; the proposed implants manufacturing technology will be adapted to the new bioalloy mechanical characteristics and to the partner specific endowment, and also to the implant geometry which, due to the alloy superelastic property, could be more supple but strong.

The proposed manufacturing technologies chain will take into account all the necessary process steps, starting with the implant bioalloy obtaining (synthesis and thermo-mechanical processing), implant fabrication from the non-toxic novel material, ending with its multifunctional coating and will be validated through the obtaining of the demonstrator product and its characteristics evaluation (physical, mechanical and biological)

The assessment of the new bio-alloy and its coating characteristics along the technology chain will be performed by the project partners with their modern endowment as follows:

-chemical and mechanical (static and dynamic) characterization of the new bio-alloy will be in RD charge;

-structural characterizations of the new bio-alloy, advanced coating characterization and corrosion resistance tests will be performed by MUG in collaboration with TEK, which will also carry out the antibacterial test, analyzing the antimicrobial activity and efficacy;

-in vitro evaluation of biocompatibility for bulk and coated bio-alloy for validation of the new alloy and coating, using the proliferation, differentiation and cytotoxicity test, will be in UB charge. These results will be the concept basis for the "in vivo" tests, which will be the following step on the way towards implants certification for the market;

-in the last stage of the project is provided a technical-economic analysis (by RD and TEK), for the assessment of project outcomes implementation, defining the following necessary steps.

The project progress beyond the state of the art consists of:

-implant bioalloy: a new safer biocompatible β Ti alloy containing non-toxic elements, with improved characteristics compared to commercial Ti alloys in respect to the corrosion resistance and mechanical properties (superelasticity, higher strength, wear and fatigue resistance) obtained due to the designed chemical composition and applied thermo-mechanical treatment. The alloy improved mechanical characteristics will provide a better machinability, avoiding implant manufacturing flaws;

-coating: new plasma electrolytic oxidation treatments will be applied on the surface of superelastic Ti bioalloy. By means of PEO, elements such as Ca and P will be incorporated into the oxides coating and its micro-topography can be varied through the adjustment of electrolyte chemical composition, and electrochemical

process conditions. As well, biocide agents (as fluorine) will be incorporated in the surface coating;
-dental implant: improved characteristics compared to the commercial dental implants in terms of biocompatibility, corrosion resistance, mechanical properties, osseointegrative and antibacterial abilities, due to advanced coating, leading to a better reliability and improved life quality for the patients.

3.3 Market analysis

The project need is challenged by the market requirement for advanced safer dental implants with long term stability. The main factors driving the growth of this market are the rising incidences of dental caries and other periodontal diseases among the baby booming population, the growing aging population (which is more prone to tooth loss). (Research and Markets, 2016). The global dental implants market is expected to reach $10,427.7 million by 2020, with a growing rate of 7.2% during the period of 2015 to 2020.(Research and Markets, 2016). In 2014, Europe was the largest market for the global dental implants & prosthetics market, with a share of 39.8%. (Markets and Markets, 2016) Besides the big companies leading in the dental implants market, small producers have the opportunity to be active in their national markets. They compete mainly on price, having in view that the competitiveness of a new product and the optimum quality/price rate help to penetrate the market. So, with the new improved characteristics, the implants developed in the project have good chance to penetrate Romanian and Basque Country markets, as well as of other European countries, being high competitive with respect to the best implants existing now. It's evident that the market is ready to receive the new products resulting from project. In Romania, the project partner Teh, implants producer, is already an important player in the national dental implants market, interested to implement the project results for manufacturing the new more competitive products with good chances to be well appreciated by the dental surgeon. In the Basque Country, a potential user of project results could be REINER Dental, a Basque SME specialized in the manufacture of high-precision parts for the healthcare market and in particular for the dental market. The company manufactures dental abutment, titanium screws, implant analogues, attaches/dental interfaces and healing caps. They could be interested in the new coatings, and in the future in the superelastic Ti alloy developed within this Manunet project.

The increased focus on better quality dental care and the rising of the awareness among patients are further expected to propel the demand of tooth restorative techniques and products like dental implants. However, limited dental insurance coverage and reimbursement in many countries could hinder the growth of this demand to a certain extent. (Markets and Markets, 2016) Now, the Ti implants segment, with good biocompatibility and corrosion resistance, accounted for the largest share (98% in 2015) of the dental implants market.(Markets and Markets, 2016). The overall adoption of dental implants is greater than that of dental prosthetics due to the better aesthetics and hygiene associated with the use of dental implants (Markets and Markets, 2015). Despite of zirconia implants attractiveness for the patients in the last years, the titanium implants remain the most used due to their proven better reliability.
On the other hand, the actual titanium dental implants have still many issues to be solved. The dental surgery may be critical as there is high incidence of infections in gingival tissue when implantation is done. Another challenge for the dental surgeons is achieving implants osseointegration (Research Moz, 2015) and long term mechanical stability.
It is relevant the clinical investigation at Technion-Israel Institute of Technology. There were examined 100 discarded dental implants under a scanning electron microscope and found that more than 60% of them have had cracks and other flaws, due to metal fatigue (localized structural damage that occurs when a metal is subjected to repeated applied loads), which causes many of the implant-related fractures. (K. Semetov-Yona, 2015) The Cp-Ti implants have been found with more cracks than those from Ti alloy. The manufacturing flaws can develop up to full cracks as effect of wear after long time daily use and subsequently lead to the ultimate failure of the implant materials. Metal fatigue, leading to its degradation, is caused by unavoidable repeated loading through mastication.(K. Semetov-Yona, 2015)
The proposal aim is to overcome some of the technical challenges revealed by above market surveys and clinical investigations that showed the necessity of increasing the implant material biocompatibility (Ti alloy chemical composition with nontoxic alloying elements), improvement of mechanical compatibility with jaw-bone (low elastic modulus, superelasticity and high strength, wear and fatigue resistance) for avoiding material fracture, increasing the corrosion resistance responsible of cracks. The uniform fine grain structure obtained through the thermo-mechanical processing improves both mechanical and corrosion resistance properties. The dental implant surface coating with bioactive and antibacterial agents will act as corrosion barrier, facilitating the osseointegration and preventing the post implantation infections.
The developed technologies from the entire fabrication chain will avoid the manufacturing flaws and will be environmental friendly with low energy consumption and without dangerous effluents and scraps.

4 DESCRIPTION OF WORK

4.1 Project structure

The total duration of the project is 24 months. The defined project stages have in view the deadlines when could be obtained consistent outcomes to be reported, based on the carried out research activities. The logical sequence of the stages and of delivery terms are established even from the project proposal phase. It was stated a *clear tasks schedule*, considering their complexity, sequence and the necessary time (i.e. the biological testing strongly requires several months). To avoid un-fulfilment of project objectives will be analysed the intermediate outcomes, in order to take corrective measures, if necessary, and to assure the framing in the initial deadlines.

Six Work Packages are planned in the project, covering research and development activities, management and exploitation, as follows:

WP1 – *Product requirements & Development approaches*
WP2 – *Superelastic alloy development: synthesis and thermo-mechanical processing*
WP3 – *Surface treatments development*
WP4 – *New implant development*
WP5 – *Technologies integration for demonstrator product obtaining*
WP6 – *Management. IPRs. Dissemination and exploitation*

There is 1 transversal WP, WP6 that includes the management activities, IPRs, dissemination and exploitation of the project results. The WPs are interconnected as shown in PERT diagram.

The analysis of the process approaches and the definition of the products specification (WP1) is the first step of the work and will be based on the experience gained by all partners of the Consortium, taking also in account the most recent medical and market requirements. The participation of all partners in this WP will guarantee the definition of process specifications compatible with a realistic development of the proposed manufacturing process. Based on these requirements, the material (new Ti bioalloy) will be designed, produced (WP2) and samples delivered for the development of technologies for surface coating (WP3) and implant manufacturing (WP4). WP5 will be dedicated to the integration of the developed technologies and obtaining of the demonstrator product. In WP2, WP3 and WP5 will be performed the necessary characterization and testing of samples, test lots and demonstrator product, including mechanical, tribological, corrosion, tribocorrosion, *in vitro* citotoxicity and antibacterial behaviour testing, for the validation of the developed technologies, proving the obtaining of advanced implants with targeted characteristics.

4.2 Work packages

WP no: ***1***	*WP title:* ***Product Requirements & Development Approaches***	
Leader: Teh	*Partners involved: Teh, MUG, RD, UB*	*Start/End Month: M1/M3*
Objectives: ***O1.1*** *To detail the requirements of the dental implants targeted to be developed within the BioTident project.* ***O1.2*** *To establish the development approaches to be done, the characterization and testing protocols.*		
Description of work: **Task 1.1** Product Requirements (M1) (*Teh*) Dental implant requirements will be identified as well as the implant type that will be considered as reference one. **Task 1.2** Development approaches (M3) (RD, MUG) Different approaches for the development of the new superelastic Ti bioalloy, thermo-mechanical processing and surface treatments will be considered. A*ssessment of main risks for each process from the implant manufacturing chain, providing the mitigation measures.* **Task 1.3** Definition and setting up of testing methods/protocols (M3) (RD, MUG, UB) Partners will define the characteristics and characterization/testing methods/protocols and afferent equipment that will be used during the project: RD for bioalloy chemical and mechanical characterization; MUG for surface coating characterizations in terms of porosity level, pore size, roughness, and chemical composition, tribological, corrosion, tribocorrosion and antibacterial testing; UB for citotoxicity testing.		
Deliverables: ***D1.1*** *(M1) Specification for implants (Teh);* ***D1.2*** *(M3) Report on development approaches and characterization/testing methods (RD, UB);* ***D1.3*** *(M3) Report on development approaches and characterization/ testing methods (MUG)*		
Milestones:		

WP no: ***2***	*WP title:* ***Superelastic alloy development: synthesis and thermo-mechanical processing***	
Leader: RD	*Partners involved: RD, MUG*	*Start/End Month: M4/M10*

Objectives: ***O2.1*** *Design and experiment of new Ti bioalloy synthesis.* ***O2.2*** *Design and experiment of Ti bioalloy thermo-mechanical processing*
Description of work: **Task 2.1 Design of new superelastic Ti alloy composition** (M4)(RD) RD will design the composition of the new high biocompatible Ti bioalloy for implant body, in the system TiNbTaZr, with a original rate of the alloying elements which confer suitable mechanical properties for advanced dental implants, as superelasticity, low Young modulus, high strength, wear and fatigue resistance. **Task 2.2 Design and experiment of TiNbTaZr superelastic alloy synthesis technology** (M4-M5) (*RD*). *RD* will design the lab-technology for alloy synthesis; will design and realize *the laboratory experimental model* for alloy synthesis in cold crucible furnace (levitation melting) with controlled Ar atmosphere; will perform the synthesis experiments obtaining alloy samples. **Task 2.3 Design and experiment of the technology for thermo-mechanical processing of TiNbTaZr alloy** (M6-8) (*RD*). *RD* will design the laboratory technology for thermo-mechanical processing of the cast alloy, necessary for its structure refining in view to improve the mechanical properties and corrosion resistance; will design and realize *the laboratory experimental model* for alloy processing; will perform deformability study and processing experiments, obtaining processed alloy samples. **Task 2.4 Alloy synthesis and thermo-mechanical processing experiments for test lot 1** (M8) (*RD*) Using the developed process flow for synthesis and thermo-mechanical processing, RD will produce the test lot 1 from *TiNbTaZr* alloy. **Task 2.5 Characterization of the obtained samples and test lot 1** (M4-8) (*RD*). Samples and test lot 1 of as-cast and thermo-mechanically processed alloy will be mechanically characterized (micro-hardness, ultimate tensile strength, 0.2% yield strength, elongation); chemical characterization will be made for the as cast alloy. **Task 2.6 Corrosion resistance testing of thermo-mechanically processed alloy** (M9-M10) (*MUG by TEK*). The corrosion resistance in simulated physiological solution will be tested for the thermo-mechanically processed alloy test lot 1 by means of potentiostast and the electrochemical monitoring.
Deliverables: ***D2.1*** *(M4) Documentation for alloy synthesis technology (RD);* ***D2.2*** *(M5) Experimental model for alloy synthesis (RD);* ***D2.3*** *(M6) Documentation of alloy thermo-mechanical processing (RD);* ***D2.4*** *(M6) Experimental model for alloy thermo-mechanical processing (RD);* ***D2.5*** *(M8) Test lot1 of processed TiNbTaZr alloy with characterization report (RD).*
Milestones: M1-Test lot 1 of thermo-mechanically processed alloy(M8)

WP no: ***3***	*WP title:* ***Surface treatments development***	
Leader: MUG	*Partners involved: MUG, UB*	*Start/End Month: M4/M14*
Objectives: ***O3.1*** *Design and development of an optimal coating/treatment by plasma electrolytic oxidation technique for achieving coating with desired properties (micro-structural characteristics, biocide and bioactive features).* ***O3.2*** *Complex characterization of multifunctional coated surface.*		
Description of work: **Task 3.1 Design and experiment of surface treatment method** (M4-M7) (MUG by TEK) In this task, PEO coating process tuning will take place at laboratory scale. TEK will design and experiment the PEO coating method controlling the process parameters like applied current, processing time and electrolyte which is the most important factor in the coatings finish and quality. A new electrolyte will be developed changing its composition and doping with different elements as Ca, P, F... that provides to the coating the desired properties. Once the electrolyte is designed, the activity related to the PEO process will be carried out, taking into account different currents and times. **Task 3.2 Design and experiment of surface treatment technology** (M8-M11) (*MUG*) MUG will implement the surface coating technology based on PEO, developed in task 3.1, on its experimental installations. For this purpose, several preliminary tests with the defined electrolyte will carry out. The tuning will be associated with the study of the effect of several parameters, like voltage/current control, the reverse of the polarity or the frequency (from 0 Hz to 5000 Hz), and the effect of the modification of the maximum voltage (up to 500 V) and current density (up to total 500 A). Besides, it can be studies the effect of the temperature (from 0 ºC to 60 ºC) and the duration of the process. After the experiment and optimization of the process parameters MUG will obtain the test lot 1 of bioactive and antibacterial coated Ti alloy. **Task 3.3 Characterization of multifunctional coated surface** (M5-M12) *(MUG by TEK)* All surfaces developed by plasma electrolytic oxidation will be detailed characterized in terms of micro-structural analysis, tribological and corrosion tests, investigation of biofilm colonization and in vitro biocompatibility. ***Subtask 3.3.1. Micro-structural characterization*** (*MUG by TEK)* The holistic characterization will be		

performed by means of using SEM technique, GDOES, XRF and EDS chemical characterization, wetting experiments and thickness measurements.

Subtask 3.3.2. Tribological, tribocorrosion and corrosion tests (*MUG by TEK)* Tribological tests will be carried out in order to study the wear and friction properties of developed treatments. Testing conditions will be close to real conditions. Concerning corrosion, electrolytes (artificial saliva) will be analyzed by ICP technique in order to study the permeability properties of coatings by means of measuring removed elements from the substrate to the electrolyte during the corrosion tests. As well, some tribometers will be equipped with a potentiostat in order to allow electrochemical (corrosion) monitoring and/or control for tribocorrosion measurements, where the synergism between tribological and corrosion phenomena will be studied.

Subtask 3.3.3. Antibacterial tests (*MUG by TEK)* Standard test to probe the biocide activity of the most promising developed films requires growth of bacteria (*E. Coli, S. aureus*) in a culture. A culture is the growing of microbial populations in a controlled way, in an artificial environment. The bacterial activity for the bacterial cells is estimated by relative number of bacteria survived calculated from the number of viable cells which form colonies on the nutrient agar plates.

Task 3.4. Testing of *in vitro* **cellular response to uncoated and coated beta-type Ti alloy with bioactive layer** (M9-M14) (*UB*) For *in vitro* biological testing, UB will comparatively assess the biocompatibility and bioactivity of the uncoated Ti bioalloy and coated with bioactive layer.

Subtask 3.4.1 Standardized in vitro evaluation of biocompatibility according to ISO 10993-Part 5/2009 through study of cell morphology, cell viability, cellular proliferation in MEM with 10% serum.

Subtask 3.4.2 In vitro analysis of the behaviour of osteoblast-like cells*:* evaluation of cellular survival and proliferation, cell attachment, spreading and morphology, osseoinductive abilities (alkaline phosphatase activity, extracellular formation of mineralized nodules of calcium deposits, expression levels of proteins associated with the osteogenic phenotype).

Deliverables: ***D3.1*** *(M7) Report on the study of PEO process parameters (MUG by TEK)*
D3.2 *(M9) Experimental model for PEO coating (MUG);* ***D3.3*** *(M11) Documentation for PEO coating technology (MUG);* ***D3.4*** *(M12) Test lot 1 of coated processed TiNbTaZr alloy with characterization report (MUG).*
D3.5 *(M14) Report on osteoblast response to the uncoated and plasma-coated Ti bioalloy (UB)*

Milestones: M2 – In vitro testing report of uncoated and coated alloy (M14.)

WP no: ***4***	*WP title:* ***New implant development***	
Leader: Teh	*Partners involved: Teh*	*Start/End Month: M8/M12*

Objectives: ***O4.1*** *Design and experiment of new Ti bioalloy machining technology.* ***O4.2*** *Design and manufacturing of the new implant.*

Description of work:

Task 4.1 Design and experiment of machining technology tailored for the new superelastic alloy (M8-M9) (*Teh*) *Teh* will design the machining technology tailored for the mechanical properties of the new Ti alloy, establishing the process conditions based on a machining study.

Task 4.2 Design of the implant from the new Ti alloy (M10) (Teh). *Teh* will design the new implant with improved geometry, taking into account the mechanical properties of the new alloy.

Task 4.3 New implant manufacturing (M11-M12) (*Teh*). *Teh* will apply the developed technology and will obtain the test lot 1 of implants which will be assessed through dynamic tests

Deliverables: ***D4.1*** *(M9) Documentation for machining technology (Teh);* ***D4.2*** *(M9) Implant design (Teh);*
D4.3 *(M12) Implant test lot 1 (Teh);*

Milestones:

WP no: ***5***	*WP title:* ***Integration of technologies for demonstrator product obtaining***	
Leader: MUG	*Partners involved: RD, Teh, MUG*	*Start/End Month: M13/M20*

Objectives: ***O5.1*** *Demonstration of the functionality of the technologies from the manufacturing chain*

Description of work:

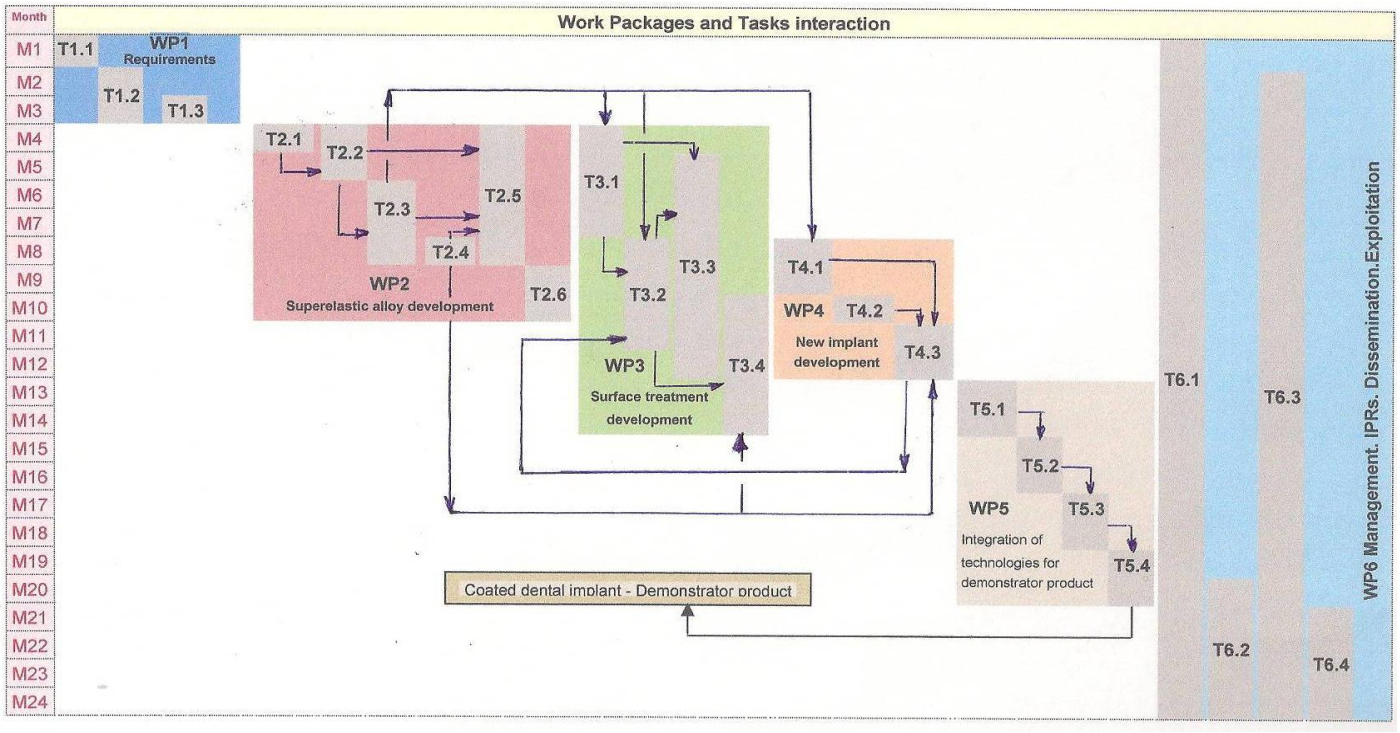
Task 5.1 Demonstration of Ti alloy synthesis technology; obtaining of test lot 2 (M13-M14) (RD) RD will demonstrate the functionality of TiNbTaZr alloy synthesis technology through process parameters and product characteristics reproducibility and will obtain the test lot 2 which will be chemically and mechanically characterized.

Task 5.2 Demonstration of thermo-mechanical processing technology; obtaining of test lot 2 (M15-M16)

(RD) RD will demonstrate the functionality of TiNbTaZr alloy thermo-mechanical processing technology through process parameters and product characteristics reproducibility and will obtain the test lot 2 of processed Ti alloy, which will be mechanically characterized and supplied to The for implants manufacturing. **Task 5.3 Demonstration of implant manufacturing technology from the processed TiNbTaZr alloy; obtaining of test lot 2** (M17-M18) (*Teh*). *Teh* will demonstrate the functionality implant manufacturing technology through process parameters and product characteristics reproducibility and will obtain the test lot 2 of dental implants, dynamically tested, which will be supplied to MUG for bioactive and antibacterial surface coating. **Task 5.4 Demonstration of multifunctional surface treatments technology; obtaining of demonstrator product** (M19-M20) (*MUG*). *MUG* will demonstrate the functionality implant surface coating technology through process parameters and product characteristics reproducibility and will obtain the demonstrator product of coated advanced dental implants, which will be physic-chemically characterized by non-destructive testing (microstructural, chemical analysis...).
*Deliverables: **D5.1** (M14) Technology for new Ti alloy synthesis (RD); **D5.2** (M16) Technology for thermo-mechanical processing of the new Ti alloy (RD); **D5.3** (M18) Technology for implants manufacturing (Teh); **D5.4** (M20) Technology for PEO surface coating (MUG); **D5.5** (M16) Test lot 2 of processed TiNbTaZr alloy with characterization report (RD). **D5.6** (M18) Test lot 2 of implants from the processed Ti alloy with characterization report (Teh). **D5.7** (M20) Demonstrator product: coated implant with characterization report (MUG).*
Milestones: M3- Demonstrator product – implant with bioactive and antibacterial coatings (M20)

*WP no: **6***	*WP title: **Management. IPRs. Dissemination and exploitation Technical feasibility analysis***	
Leader: MUG	*Partners involved: MUG, RD, Teh, UB*	*Start/End Month: M1/M24*
*Objectives: **O6.1** Scientific, technical and administrative management of the Project. **O6.2** IPRs allocation and protection of RTD project results. **O6.3** Dissemination of project innovative scientific results.*		
Description of work: **Task 6.1 Project management** (M1-M24) (*MUG, RD, Teh, UB*) The project will be coordinated by MUG by the project manager and an Executive Board will supervise its implementation. For each partner, the administrative and financial management will be the liability of its responsible, member of Executive Board. Starting from the proposal preparing stage, a judicious schedule was stated regarding the tasks and responsibilities of each involved partner and research team member, for achieving all proposed objectives. Each WP has a leader (Teh – WP1, WP4, RD – WP2, MUG- WP3, WP5, WP6), in charge to fulfil the tasks included in that WP. **Task 6.2 Protection of RTD results** (M20-24) (*MUG, RD*) For intellectual property protection, the main actions will be in accordance with the Consortium Agreement signed prior the project start. For the generated foreground, it is stated that the IPR is owned by those who generated it. Based on the evaluation of the project technical and scientific outcomes will be identified and allocated the innovative scientific results, selecting the results which could be patented. *One patent application* will be registered. **Task 6.3 Dissemination of the project results** (M2-24) (*MUG, RD, UB*) The strategies for results dissemination, prepared by ach partner, will be included in the Dissemination Plan. The novel scientific results will be communicated at conferences and published in journals (with high impact index) or in proceedings. The partners will participate to the dissemination of the non-confidential project's results in project web-page, informing by this way the target groups. Public information will make industry aware of this project for a future industrial exploitation. **Task 6.4 Exploitation of the project results** (M12, M21-M24) (*MUG, RD, Teh*) The project manager will appoint the *project exploitation responsible, one from each participating country*, charged with elaboration of Exploitation Plan (including information/data regarding the homologation of the products for medical application), preparing patent application, papers for publication, coordination the measures for the future exploitation of innovative results obtained in the project. A Life Cycle Assessment (LCA) will be carried out by TEK in order to determine the environmental impact of the new developed dental implant in comparison with the reference one. A cost-benefit analysis will be performed by the SME companies involved in the project, in the frame of technical feasibility studies regarding the future industrial application potential.		
*Deliverables: **D6.1** (M12, M24) Two periodic reports (MUG, RD, Teh, UB); **D6.2** (M24) Final report of the project (MUG, RD, Teh, UB). **D6.2** (M24) One patent applications (MUG) **D6.3** (M21) Two paper for publication in ISI journals (MUG, UB); **D6.4** (M20) One communication at national/ international conferences (MUG); **D6.5** (M12, M23-updated) Exploitation Plan (MUG, RD); **D6.6** (M23) LCA report (MUG); **D6.7** (M24) Technical feasibility studies (MUG, RD, Teh).*		
Milestones: M4 - Final Exploitation Plan agreed between partners (M23)		

PERT diagram



4.3 Timing

GANTT diagram

WP Task		2017												2018											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
WP 1	***Product Requirements & Development Approaches***																								
T1.1	Product Requirements																								
T1.2	Development approaches																								
T1.3	Definition and setting up of testing methods/protocols																								
WP 2	***Superelastic alloy development: synth and thermo-mec. proc.***																								
T2.1	Design of new superelastic Ti alloy composition																								
T2.2	Design and experiment of TiNbTaZr alloy synthesis technology																								
T2.3	Design and experiment of thermo-mec processing technology																								
T2.4	Alloy synthesis and thermo-mechanical processing of test lot 1																								
T2.5	Characterization of the obtained samples and test lot 1																								
T2.6	Corrosion resistance testing of processed alloy																								
WP 3	***Surface treatments development***																								
T3.1	Design and experiment of surface treatment method																								
T3.2	Design and experiment of surface treatment technology; test lot 1																								
T3.3	Characterization of multifunctional coated surface																								
T3.4	Testing of *in vitro* cellular response to uncoated and coated alloy																								
WP 4	***New implant development***																								
T4.1	Design and experiment of machining technology of new alloy																								
T4.2	Design of the implant from the new Ti alloy																								
T4.3	New implant manufacturing; test lot 1																								
WP 5	***Integration of technologies for demonstrator product obtain.***																								
T5.1	Demonstration of Ti alloy synthesis technology; test lot 2																								
T5.2	Demonstration of thermo-mech. process. technology; test lot 2																								
T5.3	Demonstration of implant manufacturing technology; test lot 2																								
T5.4	Demonstration of surface treatment technology; *demonstrator prod*																								
WP 6	***Management. IPRs. Dissemin&exploitation Techn. feasib anal***																								
T6.1	Project management																								
T6.2	Protection of RTD results																								
T6.3	Dissemination of the project results																								
T6.4	Exploitation of the project results																								

5. COST CALCULATION

Total project costs per partner and per year[2]

	Costs Year 1 (Months 1-12)	Costs Year 2 (Months 13-24)	Total Costs	Requested Funding
Partners role	€	€	€	€
Coordinator MUG*	241,725	234,575	476,300	142,890
Partner RD	60,000	56,000	116,000	95,000
Partner Teh	30,000	40,000	70,000	55,000
Partner UB	20,000	30,000	50,000	50,000
Total	**351,725**	**360,575**	**712,300**	**342,890**

(*) Including Subcontractor TEK

	Personnel	Overheads	Travel & Subsistence	Material & Supply	Equipment	Subcontract	Other
Partners role	€	€	€	€	€	€	€
Coord. MUG	286,000	42,900	2,000	48,000	0	95,400	2,000
Partner RD	66,000	23,200	1,500	25,300	0	0	0
Partner Teh	30,600	10,950	1,500	11,700	15,250	0	0
Partner UB	30,000	10,000	1,500	8,500	0	0	0
Total	412,600	87,050	6,500	95,500	15,250	95,400	0

5.1 Personnel cost

Partner MUG (Coordinator): Allocated human resources for MUG tasks are 61 person·month (6 employees: 1 MSC in Chemistry – 13 person·month, and 5 technical engineers - 48 person·month). Total costs 286,000 Euro.

Partner RD: Allocated human resources for RD tasks are 30 person·month (4 employees: 2 senior researchers grade II - 16 person·month, 1 engineer of technological development grade III - 10 person·month, and 1 laboratory technician - 4 person·month). Total costs 66,000 Euro.

Partner Teh: Allocated human resources for Teh tasks are 12 person·month (5 employees: 2 senior researchers grade II - 7 person·month, 1 engineer grade III - 3 person·month, 2 technicians – 2 person·month) Total cost 30,600 Euro.

Partner UB: Allocated human resources for UB-DBMB tasks are 12 persons·month. UB-DBMB team involves: 1 senior researchers grade II (4 person/month), 1 senior researchers grade III (3 person·month), 1 research assistant (2 person·month), 1 PhD-student (2 person·month) and *1* person·month to *support personnel* (*project financial responsible*). Total costs will be 30,000 Euro.

5.2 Material and supply

Partner MUG (Coordinator): Total cost 48,000 Euro for: chemical reagents (salts, acids, bases) for the electrolyte, degreasers (40,000 Euro); tooling for samples fixture (8,000 Euro).

[2] Contact your regional / national agency to know about the eligibility of costs and maximum project duration in your region/country before filling the table.

Partner RD: Total cost 25,300 Euro for: raw materials acquisitions (13,000 Euro), spare parts for cold crucible melting furnace (vacuum sensor – 1,500 Euro, gaskets sets 1,400 Euro, capacitors 2,500 Euro), consumables materials (1,000 Euro for abrasive and diamond cutting disks; 600 Euro for lathe knives; 500 Euro for lubricants; 700 Euro for embedding resin and abrasive paper with different granulations) and auxiliary materials for equipment operation and maintenance (3,900 Euro for argon, oil for primary vacuum pump, oil for diffusion pump, hydraulic press oil) and office supplies (about 200 Euro for toner, paper etc).

Partner Teh: Total cost 11,700 Euro for: lathes and milling machine spare parts (8,950 Euro); tools and tool holders for lathes and milling machine (1,850 Euro); lubricants and cooler agents (650 Euro); office supplies (250 Euro).

Partner UB: Total cost 8,500 Euro for: cell culture media, sera & supplements (650 Euro); kits for the evaluation of cell viability and alkaline phosphatase activity (1,500 Euro); chemicals (1,200 Euro); antibodies & supplies (1,500 Euro); ELISA kits (2,000 Euro); cell culture plastics (1,650 Euro).

5.3 Equipment

Partner Teh: Total cost 15,250 Euro for dynamic testing machine specialized for dental implants.

5.4. Subcontracting

Partner MUG (Coordinator): Total cost 95,400 Euro for the subcontracting of IK4-TEKNIKER research centre. TEK will develop the new electrolyte and set-up the PEO process parameters at lab scale. As well, TEK will characterize all the developed treatments achieve at lab scale and experimental installations.

5.5 Travel and Subsistence (for one project meeting in the Basque Country and one in Romania)

Partner MUG (Coordinator): 2,000 Euro for two people participation at one Project Meeting in Romania: 850 Euro for the transport, 800 Euro for accommodation, 350 Euro for daily-allowance).

Partner RD: 1,500 Euro for one person participation at one Project Meeting in Spain: (600 Euro for the transport, 725 Euro for accommodation, 175 Euro for daily-allowance).

Partner Teh: 1,500 Euro for one person participation at one Project Meeting in Spain: (600 Euro for the transport, 725 Euro for accommodation, 175 Euro for daily-allowance).

Partner UB: 1,500 Euro for one person participation at one Project Meeting in Spain: (600 Euro for the transport, 725 Euro for accommodation, 175 Euro for daily-allowance).

5.6 Overheads

Partner MUG (Coordinator): 42,900 Euro, representing 15% from direct costs (personnel costs).

Partner RD: 23,200 Euro, representing 25 % from direct costs (personnel costs + travel, accommodation, allowances + consumables). The overheads consist in rents, equipment depreciation, energy, water, phone, Internet, post mail (for samples supply), expenses with administrative personnel etc.

Partner Teh: 10,950 Euro, representing 25 % from direct costs.

Partner UB: 10,000 Euro, representing 20 % from direct costs.

5.7 Other costs

Partner MUG (Coordinator): 2,000 Euro for audit cost.

6. RESULTS AND EXPLOITATION

6.1 Identify the exploitable results of the project for each partner and the related business plans for each partner/country/region

The project exploitable outcomes will be the new products and their manufacturing technologies to be transferred in production, patent applications, new knowledge that will be disseminated to scientific community, but can be used in new research and development projects.

● The *new products* are: - the new advanced Ti implants with bioactive and antibacterial coatings for improved osteointegration and infection prevention developed by RD, Teh and MUG; - the new superelastic Ti bioalloy with high biological and mechanical compatibility developed by RD.

● The *new technology chain* for dental implants obtaining: - synthesis of new bulk superelastic Ti bioalloy (developed by RD), Ti bioalloy thermo-mechanical processing (developed by RD), implants manufacturing (developed by Teh), bioactive and antibacterial surface coating (developed by MUG).

The Consortium Agreement will detail projects outcomes exploitation by partners and IPRs allocation.

In the project final stage will be carried out the project exploitation plan and the technical and economic evaluations of project outcomes implementation in participating countries, the Basque Country and Romania.

The world and European market of dental implants are continuously growing due to increased care for oral health and demand for improved products able to work in a more reliable manner. This is a big challenge for the producers in the field to answer to these needs, supplying new advanced dental implants with improved characteristics. BioTiDent proposal will enable the participating companies to widen their competences and acquire the necessary experience in order to design and produce in an effective and economical way novel innovative and competitive products. Actually the dental metallic implants market is mostly covered by those from CpTi and Ti6Al4V. Recently were introduced TiZr alloy Roxolid with better mechanical and corrosion resistance, suitable also for small diameter implants and Zirconia implants, preferred by the patients from esthetical reasons, but with limited applicability, especially in the anterior maxilla, due to the lower tensile strength. In this market, where the range of titanium dental implants is very wide, with strong companies in this sector and with a continuous line of research in their design and properties, the development of new implants from safer superelastic bioalloys with innovative multifunctional (bioactive and antibacterial) surface treatments, such as those developed in this project, would provide clear advantages.

Benefits for partners

The transnational cooperation and implementation of project expected outcomes will bring benefits for all project partners. The main benefit of the industrial partners is the development of their companies by the enlargement of production profile with the new dental implants and coatings with good chances in the market. Participating in the project with co-financing, they will benefit of free rights to implement the developed technologies (based on IPRs allocation stated in Consortium Agreement). The improved technical performances and market competitiveness will increase their turn-over for medium and long term and their employees' number. The research units will benefit of the developed knowledge through the transfer to industry, the potential use in other projects, increased visibility in the scientific community through dissemination.

Economic benefits

In Romania **Teh** will integrate the developed technologies in company's dental implants production, having appropriate specialized machining endowment. It is expected that by the implementation of project results Teh will become more competitive implants producer, with an increased turnover of more than 20 % three years after the project end (considering the time necessary for in vivo and clinical tests, followed by new implants certification for the market). For the enlarged production of the new implants and increased labour productivity are necessary additional 3 employees. The technical–economic analysis will assess the applicability of the developed technology for the advanced implants production from the new Ti bioalloy, including a new shop for implants surface coating. *The availability of the new Ti bioalloy would be a differentiating value that would provide an important argument for sale, which would help to scale positions towards their competition. As well, the new surface treatment would bring a plus to the sales, offering a higher quality product and with profits in the short, medium and long term.*

RD will increase its competence in the field of Ti based biomaterials for implants by improving personnel scientific and technical expertise in this specific domain. The potential project success will impact RD bringing increased revenue through knowledge transfer (technology for synthesis and thermo-mechanical processing of the new Ti bioalloy) to the Romanian company, ZIROM - Giurgiu, one of the experienced Ti and Ti alloys producers in Europe, interested in diversifying its production profile with new high added value products, for domestic and foreign clients (including from the Basque Country). Another possibility is to receive from ZIROM royalty on new Ti bioalloy sold production.

UB will develop the knowledge in the biological characterization of Ti based bioalloys and advanced coatings

which will increase its turn over by providing advanced services to medical sector and other interested clients.

In the Basque Country **MUG** is now immersed in a process of sectors diversification, which aim is to bring it towards high technological level. For the medical sector, the turning out is more difficult as a result of high barriers to entry which MUG face up to, which are mainly technological. Hence the company needs the cooperation of research partners in order to expand their technological level in this field. This project could mean for MUG the incursion into a high-tech sector as the medical segment is, which may have a high economic impact by becoming a pioneering company in innovative surface treatments for the biomedical sector at national and European level. MUG, specialized in PEO deposition on metallic materials, will enlarge its profile with the new bioactive and antibacterial coatings developed in the project. The possibility to extent the PEO process by application for Ti alloys, will give an opportunity to further exploit it in their new installation at industrial scale. Thanks to this project, MUG could be totally well established in the medical sector. The company will commercialize the PEO coatings for Ti implants. This coating technique could be extended to a number of other medical devices as instruments for greater chemical resistance and durability. The project results implementation will increase MUG turn-over with 17% providing the new coatings for interested clients.

TEK, the Basque Country SME's subcontractor, will support MUG in the different steps of further development, scale-up and characterization of the new products. Accordingly, they will provide means for facilitating the commercialization of these new surface modifications coatings that will be applied on dental implants. Thus, TEK will increase its turn-over by supplying consulting and technical assistance to MUG during the project results implementation and further up to the industrial scale.

Scientific benefit. The project scientific benefit will increase all partners' competitiveness in advanced medical devices and biomaterials field and their international visibility through publications and scientific communications. Due to their novelty and complexity, the project scientific outcomes will have an important impact on the involved partners, and also on the European and international scientific community. Project long term scientific impact on the partners is their possibility to continue the transnational cooperation by participation in new research projects for scientific and technological knowledge development. The new developed knowledge will be used by UB and TEK for high educational training (master and PhD degrees).

Social impact. The social impact refers to job consolidation for the existent personnel of all project partners and creation of 4 new jobs with high qualification degree in the SMEs project partners (Teh 3, MUG 1). The industrial implementation of project outcomes will have an extended social impact on the patients' community needing dental implants, increasing their life quality, by the use of the new advanced implants. The medical community will benefit from reliable dental implants with reduced infection risk and higher success of the implantation rate.

Environmental impact. All the manufacturing technologies for the new Ti alloy, implants and surface coating are environmental friendly for the working personnel and for the neighbouring area and community, being with low energy consumption, efficient use of the raw materials and without dangerous effluents and scraps.

Exploitation plan and market accessibility

The exploitation plan which will be prepared in the project will include a detailed allocation of the IPR rights (patents, licences for the developed technologies etc.) and implementation opportunities. *The technical economic analyses will study the production and commercialization alternatives for the involved industrial companies, will roughly establish the business expenses and benefit for each partner/country, the time period required for new medical products certification for the market, the manufacturing and commercialization program. The production level and the selling prices will be proposed based on the survey of the dental implants market at that time.* For industrial application of the technologies developed in the project and for business activity of new implants production and commercialization in the Basque Country and Romania, there are necessary the following three main steps which will be provided in the exploitation plan and strategy for product bringing to the market:

i) Development of the new product manufacturing implies: -scale up of the developed technologies; -feasibility study for establishing the production capacity tailored to market accessibility at that time, investment cost and efficiency, financing possibilities; -design of manufacturing facilities and investments achievement; -commissioning and production start up. The new products market penetration and success will be assured by their special properties and by the manufacturing in accordance with all European and national regulations for medical devices, including performance integrated management system (quality, health, environment).

ii) Certification of the new product according to medical devices regulations requires the following steps: -in vivo pre-clinical tests (1 year), performed by specialized clinics (universities or research units) from Romania and/or the Basque Country; -clinical tests, performed by specialized medical clinics (completed in 1.5-2.5 years after the project end) according to the European Standard EN 14155:2009; -validation of standards and end product certification according to the regulations in Romania and the Basque Country.

iii) Market entry strategy will refer to: -study of the market niches, including the selection of the target segments and main clients; -setting the products promotion ways; -establishing the sale policy as price, volume and modalities

6.2 Explain the added value of the transnational partnership.

The proposed project will be an opportunity for the SMEs proposers to establish a transnational interdisciplinary and complementary cooperation among them and the European RTD subcontractors, guaranteeing an effective approach for solving their market competitiveness issues, having therefore a greater success chance and impact than in case of participating in national projects. Sharing in this way the resources and expertise, are minimized the technical and commercial risk and uncertainty, thereby producing important multiplication of benefits and reduction of companies development cost.

The added value provided by the transnational cooperation at consortium level will be achieved through the added value brought by each partner contribution in its specialization field. The consortium is complementary in terms of partners' expertise, capabilities and the different areas of science and/or manufacturing technologies that they are able to cover. The project complexity requires for its success the presence of this transnational cooperation because the partners have unique specific complementary qualification and expertise, allowing the whole development of new high added value products and afferent manufacturing technologies for health materials industry. Project partners joined together all needed knowledge, their competence, their past experiences and expertise, adding value in their research and/or production domain related to the project topic: biomaterials (RD) and surface science (MUG/MUG by TEK), physical chemistry (MUG by TEK), metallic materials processing (RD), biology (UB, MUG by TEK). Each partner will participate in a complementary and synergistic way to reach the common project goal, the development of new modern, top products as are advanced dental implants, for a rapid grow of European market for biomaterials and medical devices.

-*The added value at scientific level* will be the *improved technical-scientific expertise, competences and experimental methods* of all involved partners in the specific field, *increasing their prestige and opening opportunities for future* participation in new projects, individually or in the same *partnership consolidated in this project*. The original results will be published in peer reviewed journals and communicated at international scientific meetings, increasing the transnational research team visibility.

-*The added value for knowledge transfer in view of future industrial application* will be the original technical innovations included in *patent application and know-how,* concerning the new Ti superelastic bioalloy obtaining and its processing (RD), implant surface bioactive and antibacterial nanocoatings (MUG and MUG by TEK). The SMEs partners have free access to apply the knowledge developed in the project, as will be provided in Consortium Agreement, for industrial implementation, but for other users, the knowledge transfer could be made as license selling or royalty.

-*The added value from the industrial application point of view,* will be the developed new integrated fabrication chain for coated dental implants: obtaining of the new Ti bioalloy and implants (Romania/RD and Teh) → implants surface bioactive and antibacterial coating (Basque Country/MUG), the validation of the new Ti bioalloy and coatings through tribological, corrosion, tribocorrosion and in vitro biological and microbiological testing (Basque Country/MUG, Romania/UB). The participating countries have as project partners SMEs interested to develop and transfer to industry the generated knowledge and technological innovations in the specific field of production, accordingly to their expertise and allocated IPRs. Based on this transnational cooperation, Teh (Romania), well established dental implant producer in the national market, will benefit of the new implant manufacturing technology by new Ti alloy machining, developed by itself, and of the advanced multifunctional coating technology developed by MUG (Basque Country), increasing its market competitiveness. In the same time, MUG (Basque Country), experienced surface coatings supplier for different applications, will benefit of the new PEO coating technology for dental implants, developed in the project, in view to consolidate its position in the dental market, where it is willing to become a competitive player. The technologies for the new Ti superelastic alloy synthesis and processing, developed by RD (Romania) could be transferred to the Romanian Ti alloys producer ZIROM, which will become supplier for implants manufacturing companies, both from Romania and Europe, including from the Basque Country.

-*The added value for the market* is given by the improved biocompatibility, bioactivity, antibacterial ability and mechanical characteristics of the new dental implants, compared with the current commercial ones. After the project achievement, *the fruitful transnational cooperation may continue in production and commercialization of the new advanced implants*, a future business network being made available. In the context of market increased demand for implant reliability, the implementation of a well-established manufacturing base for the new implants will bring some contributions not only at national, but at European level.