

## **DIGITAL LIBRARY FOR DENTAL BIOMATERIALS**

### **ABSTRACT**

*There is an urgent need in Dentistry biomaterial science to channel the knowledge gained from diverse disciplines toward the applications in maxillo-facial, oral and dental therapeutics, including regenerative medicine, and growing number of non-therapeutic medical uses such as surrogates for animal models in drug discovery, biomaterials toxicology screening and so on. Demonstrating the feasibility of designing an engineered tissue is not enough. Realizing the full benefits of tissue-biomaterial engineering science requires increased reproducibility, robustness, and user-friendliness that will enable the broad distribution of products. Therefore, in this article we will demonstrate and describe project to develop a unique Database with multilingual information and knowledge resource for biomedical dental materials and their properties. The Database will be populated with high-quality, peer-reviewed information, equipped with an original search engine which would include all necessary information to (1) do standardization of therapeutics treatments (2) understand (to be controlled), the tissue response to biomaterials; (3) identify biomaterials and tissue matrix environment, to allow deeper understanding of the underlying relationship which allow more effective device design and engineering; (4) develop enabling tools by improvements in high-throughput assay and instrumentation, imaging, modalities, fabrication technologies, computational modelling and bioinformatics; (5) promote scale up, translation and commercialisation.*

*A top of the biomaterial's digital library, several online search algorithms will be developed and made accessible through the Web site: (i) Classic search engine for the database, which would enable simple, flexible and high-performance search, (ii) Google search engine, for fast, unstructured search and (iii) Special algorithms based on artificial intelligence and fuzzy search that would resolve many issues, such as:*

*(a) Cross-referencing of biomaterials. When there is no official recommendation by standards or manufacturers, the algorithm would be able to propose equivalents and »close matches«. Recommendations that take biocompatibility into account are very rare if not nonexistent, and the newly developed algorithm would use biocompatibility as a criterion as well.*

*(b) • Translating research for human Oral health to increase Europe's biomaterial knowledge, and promote their use in Maxillo-facial and Oral applications,*

*(c) • Optimising the delivery of healthcare to European citizens to cover a multidisciplinary area of research and to integrate this knowledge in future applications, to create an intelligent learning biomaterials ie., devices.*

*(d) To benefit The Health Industry in dental sector. The Small and Medium firms are the main economic drivers of healthcare, biotechnology and medical technologies. Strong biomedical research will enhance competitiveness of the European pharmaceutical and healthcare industries. It is therefore imperative that the EU creates an environment conducive to innovation in the public and private sectors, and our project with its digital library will help significantly.*

*Our digital library will be readily available as an online service for medical devices manufacturers, medical and dentistry practitioners, material professionals, regulatory bodies, scientific community, and other interested parties through single- and multi-user licensing. If it provides useful and requested by the market, CD editions would be derived from the main digital library. Special opportunities will be offered to universities and scientific community. They can enter into collaboration by contributing to the Dental Digital Library knowledge base. In return, access would be granted for educational and research purposes, thus stimulating knowledge and information exchange. In the future, similar benefits may be mutually exchanged with regulatory bodies and Standards Development Organizations (SDOs).*

### **INTRODUCTION**

The digital revolution affects our lives daily. The introduction of computer technology has greatly affected the way the restorative dentist practices, and the evolution of cyber technologies in dentistry are no longer a fantasy. Adhesive dentistry has replaced the manner in which we prepare, restore, and bond restorations to teeth. The entire field of ceramics and methods of fabricating

aesthetic restorations are entering a new era. The exceptional prognosis of various implant systems has changed the way we think about maintaining hopeless teeth. Through tissue engineering (TE), the 21st century may be revolutionary in the way we replace missing teeth and lost tooth structure. Further on, in today's globalized world, scientific discoveries are introduced and swiftly absorbed into clinical practice. In dentistry, new products are launched daily, most of which are used in dental surgery. When these products or biomaterials, are used, they come into direct contact with living tissues, such as dentin, pulp, the alveolar bone and periodontal tissue, and sometimes stay in contact for prolonged periods.

Biomaterial is defined, in the broader sense, as any pharmacologically inert material that is capable of interacting with a living organism without causing adverse reactions either at the site of the implant or across the whole organism (Agrawal, 1998). The treatment with dental biomaterials of gum, mucosal and hard tissues, represents a therapeutic risk that can only be contained if the dental professional has knowledge of the qualities, strengths and properties of the products. The use of biomaterials without any recognized criteria for bio-safety not only causes clinical problems such as therapeutic failure, but also gives rise to ethically conflicting situations. This is because the patient may undergo treatment without knowing about the subsequent risks, either to himself or to the dental professional.

Because of that we need to open up new ways to use masses of data resulting from experiments and observations in the scientific process and to extract meaning from this data stored in repositories in combination with other scientific information resources. We need more effective technologies for **intelligent content creation and management** (Ref. 11), and for supporting the capture of knowledge and its sharing and reuse. Examples of few digital libraries are shown in Tab.1.

In order to gather together huge knowledge from this interdisciplinary field, we will try to help in this work, organizing **digital library for dental biomaterials**, its long-term preservation, accessibility and usability. Consequently, our tem plan to create new Digital library which will be designed to cover the following aims, as presented in Road map at Fig.1

- Allowing content and knowledge to be produced, stored, managed, personalized, transmitted, preserved and used reliably, efficiently and at low cost;
- Allowing making the management and production tools for digital resources easier and more cost-effective, to create and reuse;
- Allowing more creative approaches to content and knowledge, enabling creators to design more participative and communicative media and increase the productivity of publishers;
- Enabling the mass-individualization of learning experiences, through systems allowing faster acquisition of competences and skills, increased knowledge worker productivity, and more efficient organizational future learning processes.

## **STATE OF THE ART OF THE DIGITAL RESEARCH AREA**

Everything started and came from the projects **DELOS** and **ERPANET**. DELOS, a thematic network on digital libraries, co-organized a joint workshop with the National Science Foundation in 2003, which gave rise to the report "Invest to Save". This report identified the main problems faced by libraries in particular and organizations in general with the transition from the analogue to the digital world in terms of long-term archiving and preservation. The associated research agenda identified a number of priorities later reflected in calls for proposals under FP6-IST of Euporean Commision (EU) and in the activities of the **NDIIPP (National Digital Information Infrastructure and Preservation Program)** in the United States. The ERPANET project was an accompanying measure whose main objective was to raise awareness of digital preservation among the organizations concerned: memory institutions (museums, libraries and archives), the ICT and software industry, research institutions, government bodies, entertainment and creative industries, and commercial sectors (including for example pharmaceuticals, petro-chemicals and finance). This included the creation of a knowledge base on state-of-the-art developments in digital preservation

and the transfer of that expertise among individuals and institutions. ERPANET organized, between 2003 and 2004, more than 20 workshops bringing together several hundred experts and practitioners in digital preservation across Europe (Ref.27,28). The project **PLANETS** brings together the national libraries and archives of several European countries (UK, NL, DK, CH, DE, AT) and focuses on the preservation of the assets held by these institutions. The goal is to develop a coherent methodological approach and a set of technological tools that can be adopted by similar organisations across Europe. The project **CASPAR95** involves major research organisations in Europe (CCLRC (UK), CNRS (FR), CNR (IT), European Space Agency) and broadens the scope of work to also cover the preservation of scientific data, audiovisual content and digitised cultural heritage. The research agenda of these projects includes the discussion and development of relevant technical standards, their adoption by standards bodies and their promotion among the industry and users. Both projects adopt the OAIS model as the main architectural reference for their implementation of digital preservation systems. These developments are expected to offer a solution to the immediate problems faced by organisations having to deal with the long-term preservation of their digital resources. Despite the high expectations placed in PLANETS and CASPAR, the magnitude of the problem faced requires further research work. In order to prepare more extensively for future work in this area, the Commission is also funding the coordination action **DPE (Digital Preservation Europe)** (Ref. 19-24) whose remit includes updating the research agenda of DELOS, reflecting the new challenges resulting from the evolution of the internet and web-publishing technologies and the wide adoption of ICT by the research community. The work being carried out by DPE is already visible in the preparation of FP7-IST. The work programme 2007-2008 in challenge 4 – “Digital Libraries and Content” establishes digital preservation as a priority and calls for research on “radically new approaches to digital preservation”, capable of addressing critical issues of high volume, dynamic and volatile web content, the evolving meaning and usage context of digital content and the need to safeguard integrity, authenticity and accessibility over time. Other relevant projects are **DILIGENT, DRIVER** and **EURO-VO-DCA** launched in FP6 EU funding projects. The DILIGENT project aims to build a knowledge layer on top of the existing **GEANT** and middleware layers. DILIGENT deals with many issues relevant for digital repositories (i.e. data management, common approach to standards, protocols and interfaces, interaction between national and international repositories, handling complex objects). One of the main objectives for the achievement of the **Lisbon Agenda** is the investment of three percent of GDP in research and development by EU Member States by 2010 (Ref.26). In connection with the fact that all research builds on earlier work, and depends on scientists’ possibilities to share and access scientific publications and research data, the efficiency of the system for dissemination of and access to research results and data significantly contributes to overall technological advance, and is essential for innovation and economic performance. The environment in which research is conducted and disseminated is undergoing profound change, with new technologies offering new opportunities and changing research practices demanding new capabilities. New opportunities and new models could enhance the dissemination of research findings and maximize the returns on investment in R&D. The potential benefits of better and quicker access to scientific information for the efficiency of research include:

- 1.acceleration of the research and discovery process, leading to increased returns on R&D investment;*
- 2.avoidance of duplicative research efforts, leading to savings in R&D expenditure;*
- 3.enhanced opportunities for multi-disciplinary research, as well as inter-institutional and inter-sectional collaborations.*

Another important benefits of digital library is **data mining** (Ref.3). New information services could emerging that build on the results of individual research projects, gathering scientific literature and data, and using data mining techniques. More and more examples of the use of text mining technology in the academic field and in the commercial sector demonstrate the value of this

technology for such diverse applications as content production for bio-databases, mining of electronic health records and mining the abstracts of journal articles. Peer-reviewed journals play a critical role in the selection of relevant raw material and are frequently the starting point for the development of new information resources. An interesting example is the **Cochrane Library**. The Cochrane Library is a growing source of reliable evidence about the effects of health care.

Evidence-based results from among the major bibliographic databases are collected and evidence is put together for and against the effectiveness and appropriateness of treatments (medications, surgery, education, etc.) in specific circumstances.

Patents are also an important scientific and technical information resource with great potential. Given their public domain nature, facilitating its digitization and online access will also contribute to enhancing access to and preservation of scientific information. Some initiatives have been taken to this end by both institutional and private entities. The European Patent Office – a major player in the digital patent databases and related services – has set up **espace@net**.

More recently, **Google** has launched a service that aims at enabling the wider public to access patent information in a structured and user-friendly way.

In the domain of Biomaterials Engineering, the **Materials for Medical Devices Database®**, **ASM International** is **the first and only comprehensive database** created specifically to support medical device design (Tab.1, ex.2); fully relational and modular, featuring both materials properties and biological response data for medical device designers. The **Materials for Medical Devices Database** provides designers of medical devices with a comprehensive and authoritative source of mechanical, physical, biological response and drug compatibility properties for the materials and coatings used in cardiovascular devices. Researchers and designers of medical devices get access to authoritative information and knowledge from thousands of citations to published literature, **FDA device approval information**, and manufacturers’ datasheets and websites (Ref. 8) (Tab. 3). It is useful for the identification, screening and selection of material grades, manufacturing processes and suppliers appropriate for orthopedic and cardiovascular applications. In-house installations can be extended to include someone’s own proprietary data to provide organization a complete materials information management solution. The main imperfection of the **Materials for Medical Devices Database®**, **ASM International** is in absence of relevant legal and regulatory information within the EU related to biomaterial manufacturers, final products and medical devices (Ref.25,26).

## **AIM**

Our project aims to develop a unique, multilingual information and knowledge resource for dental materials and their properties, populated with high-quality, peer-reviewed information, equipped with an original search engine which will include biocompatibility criteria, and readily available as a Web service. Detailed schematic presentation in Fig.1. Since this is one of the first project or research in this domain, our starting point in research and development will be the key results available in the literature.

Objectives of this proposal are as follows:

- *Development of new techniques for biomaterials data collection and clasification*
- *Development of a new design methodology for overlapping decentralized algorithms*
- *Design of the knowledge-based expert system for data classification (Defining system architecture and developing heuristics and methodology for data classification)*
- *Software development - Design of computer architecture for implementation and integration*
- *Implementation of the digital library, databases, search engines and software modules*
- *Setting up a strategy for transfer of the developed project onto the users level*
- *Specific training activities for End-user Partners.*

The work will strengthen the link between content, knowledge and permanent learning processes. The work carried out under this project will contribute to the implementation of the **"i2010: Digital Libraries"** initiative (Ref.29).

Our project objectives are also in accordance with *the European Council Conclusions on scientific information in the digital age: access, dissemination and preservation 2832nd COMPETITIVENESS (Internal market, Industry and Research) Council meeting Brussels, 22 and 23 November 2007 (Ref.22,23):*

- 1.access to and dissemination of scientific information – publications and data – are crucial for the development of the European Research Area, and can help accelerate innovation;*
- 2.the Internet has created unprecedented possibilities to disseminate, share and build on the outcome of research efforts;*
- 3.Information and Communication Technologies revolutionize the way scientists communicate, perform research and produce knowledge;*
- 4.in an era of high speed connectivity and high performance computing, data emerges as key for modern science;*
- 5.the systems by which scientific information is published are pivotal for its dissemination and quality control, in particular through peer review, and thus have a major impact on research funding policies and on the excellence of European research;*
- 6.universities, libraries, research performing and research funding organizations, scientific publishers and other stakeholders have in recent years made considerable investments in information technologies for online accessibility;*
- 7.effective and long-lasting digital preservation of scientific information is fundamental for the current and future development of European research.*

## **DIGITAL COLLECTION STRATEGIC PLAN**

One of the main problems faced by scientists today is that they are overwhelmed with data. As scientific problems become more complicated, the models and instruments they use to study them become more complex, so the amount of data is increasing rapidly. This explosion in scientific data creates new challenges in how the data is stored, retrieved, analyzed and manipulated.

This is not just a problem for the scientists. Given the importance of research in science and engineering for innovation, our ability to find answers to these questions will directly affect Europe's competitiveness. Europe has the opportunity to be in the front line of international developments in this field. The digital libraries initiative aims at making European information resources easier and more interesting to use in an online environment. Technological progress can greatly contribute to the accessibility and use of scientific information. For example, better search tools can help researchers find information and progress in new areas and collaborative tools can enhance the way in which researchers share information.

High-speed communication networks, distributed storage, and sharing of computational resources and data processing allow scientists to tackle the full scientific process in an innovative and more effective way. What is missing, however, is effective ways of sharing and transferring knowledge. The scope of our project is to include information on biomaterials (including ethical questions) for application in various Specialties of Dentistry, such as: Dental Public Health , Endontics, Oral and Maxillofacial Radiology, Oral and Maxillofacial Surgery, Orthodontics, Pedodontics, Periodontics, Prosthodontics, as well as for legislative and regulatory authorities (Fig.1).

- Several online search algorithms will be developed and made accessible through the Web site:
- Classic search engine for the database, which will enable simple, flexible and high-performance search.
- Google search engine, for fast, unstructured search.

- Special algorithms based on artificial intelligence and fuzzy search that will resolve *two issues*:
  - Cross-referencing of biomaterials, with the opportunity to propose equivalents and »close matches« when there are no official recommendations by standards and manufacturers. Normally, recommendations that consider biocompatibility are very rare if not nonexistent, and the newly developed algorithm will use biocompatibility as a criterion as well.
  - Identification of biomaterials, based on their chemical composition. Similarity of biomaterials will be calculated by considering biocompatibility.

Development of marketing strategy will be based on extensive analyses of international marketing environments, researching foreign markets, especially views about the dimensions, from creators of each market environment separately, analyses and comparisons of the competitive marketing strategies. Market opportunities, weaknesses, risk, priorities for the proposed Biomaterials digital library on each specific market, separately (for EU and other world markets) will be determined, as well as optimal marketing communication according to the needs of the end-users of digital library (with the well-known methods). Our multidisciplinary research aim will:

- Set up a strategy for transfer of the developed digital library for dental materials onto the users level;
- Provide distribution of such digital library;
- Transfer knowledge of marketing strategy for the emergence of our digital library onto a specific market for industrial products;
- Provide development of own international marketing programme for use in the future;
- Provide marketing communication between the manufacturer and end-user in the field of dental biomaterials;
- Develop a marketing model as an efficient response to digital library end-users
- Provide an international recognition of the proposed digital library in the targeted markets.

The result of this project will be translation of the multidisciplinary research on biomedical materials and devices data and processes to wide range of biomedical materials digital library users, optimizing the delivery of information to healthcare professionals, biotechnology engineers, graduate and postgraduate students, biomedical materials manufacturers, medical device manufactures, etc. Strong EU-based biomedical research will enhance competitiveness of the European pharmaceutical and healthcare industries. It is therefore imperative that the EU creates an environment conducive to innovation in the public and private sectors.

Additionally **innovative aspects** of the project:

- Highly configurable and customizable collaboration environment supporting the creation of close virtual communities, providing services like Members Management, Email/Sms, Calendar with Chat and Whiteboard functionalities, Forum, Workflow, Web Content Management, Advanced Search, etc (Ref.28);
- Powerful workflow engine able to simulate and orchestrate the execution of any collaboration process;
- Knowledge Management module for annotating the material stored in the Digital Library based on a pre-defined ontology for later semantic information and knowledge extraction;
- Semantically enhanced search engine, able to retrieve information based on knowledge base entities patterns search;
- Semantic annotation, discovery and invocation of web services based on the WSMO initiative;
- Advanced security methods for authentication, authorization, access control and non-repudiation (Certificates, Smart cards, Time Stamping, Biometric Authentication, RBAC)

Estimated global market size of electronic data libraries for biomaterials on mid- to long-term (5 to 7 years) is 20 million Euros. Even at that point, market will be far from being mature. Our project will provide reliable digital library, technology-enhanced learning concept and appropriate algorithms to be used in different fields of biomaterials research and processing. These results will support the work programme's goal „**Digital libraries and technology-enhanced learning**“. Developed algorithms will, with minor modifications, be suitable to monitor and identify the faults and range of irregularities in vehicles, increasing their safety, with significant socio-economic implications for the society. Furthermore, the growing use of life sciences and biotechnology, for the development of drugs, vaccines and innovative therapies, as well as the applications of "nanomedicine" and “nanobiomaterials”, represent huge potential for innovation and growth. The health sector must take advantage of innovation and technology where this will lead to greater efficiency and health improvements.

**Table 4. Dental materials**

<p><b>Restorative Materials</b> DENTAL AMALGAM</p> <p>ZINC PHOSPHATE CEMENT POLYCARBOXYLATE CEMENT GLASS IONOMER CEMENT ZINC OXIDE AND EUGENOL</p> <p><b>Dental Resins, Dental Materials, and Dental Gold/Alloys</b></p> <p><b>DENTAL RESINS FOR RESTORATIVE DENTISTRY</b></p> <p>ACRYLIC RESINS COMPOSITE RESINS ACID ETCH TECHNIQUE PIT AND FISSURE SEALANTS INTERMEDIATE RESTORATIVE MATERIAL</p> <p><b>MISCELLANEOUS DENTAL MATERIALS</b></p> <p>CALCIUM HIDROXIDE ROOT CANAL FILLING MATERIALS GUTTA-PERCHA POINTS SILVER ROOT CANAL POINTS CAVITY LINING VARNISH DENTAL PORCELAIN POLISHING MATERIALS</p> <p><b>DENTAL GOLD AND GOLD ALLOYS</b></p> <p>GOLD FOIL CASTING GOLD ALLOY GOLD ALLOY SOLDER WROUGHT GOLD GOLD PLATE NON PRECIOUS ALLOYS</p>	<p><b>Gypsum Products, Dental Waxes, and Impression Materials</b></p> <p><b>GYPSUM PRODUCTS</b></p> <p>GENERAL – GYPSUM PLASTER OF PARIS ARTIFICIAL STONE</p> <p><b>DENTAL WAXES</b></p> <p>GENERAL – WAXES INLAY WAX BASEPLATE WAX STICKY WAX UTILITY WAX DISCLOSING WAX BOXING WAX LOW-FUSING IMPRESSION WAX</p> <p><b>IMPRESSION MATERIALS</b></p> <p>AGAR-TYPE HYDROCCOLOID ALGINATE-TYPE HYDROCCOLOID SYNTHETIC RUBBER BASE IMPRESSION MATERIALS</p>
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***Defining digital library architecture and developing heuristics and methodology for data classification***

Firstly, characterization methodologies, process modeling, functional tests and specifications of biomedical constructs and devices will be defined. Based on the review of resources, distribution and limitations, we will select the best way to classify biomaterials associated to the medical

devices, TE and regenerative medicine. After analyzing, compiling and peer reviewing of the information sources and industrial needs, details of the system architecture of the digital library will be defined. The basic building blocks of the architecture will be: (1) central database, (2) data input databases and workflow, (3) content management system, and (4) online search engines.

Our **Dental biomaterials digital library**, after analyzing, compiling and peer reviewing of the information sources and industrial needs, details of the system architecture of the digital library will be defined. The basic building blocks of the architecture will be: (1) central database, (2) data input databases and workflow, (3) content management system, and (4) online search engines

A large relational database as a unique, consistent data infrastructure for including all the compiled information will be in the core of the system. This central database will synthesize and include comprehensive biomaterial information, such as biomaterials classification and composition, physical and mechanical properties, special properties, biological behavior and biocompatibility, application guidelines, cross-referencing etc. Fig.1 and Tables 4,5,6,7,8,9,10,11,12,13. The central database will be structured to provide flexibility, extensibility and high search performance, and will consequently have data warehouse architecture. In order to populate central database, production databases for data entry will be defined. The data entry process needs to follow clear editorial and quality assurance guidelines, which will be defined using a workflow, which will then be implemented in data input applications. In order to provide access to all the information to as broad audience as possible, the system will be intrinsically multilingual. Starting with major European languages like English, German, and Italian, the system will be extensible to other European languages.. To manage large amounts of multilingual system and content, a dedicated content management system (CMS) will be designed. Beside managing content and editorial workflow, the CMS will include the complete humane-machine interface of the system, thus making it easily expandable to new languages.

A hybrid Web-based search engine will be defined atop of the central database in this step, with the objective to achieve robustness, superior search performance, and multiplicity of search modes. Classic search strategies will be combined with Google search engine and special algorithms based on artificial intelligence and fuzzy search for material identification and cross-referencing.

### ***Implementation of the digital library, databases, search engines and software modules***

The system will be implemented as a versatile, easy-to-use and multilingual online service, readily available for medical devices manufacturers, medical and dentistry practitioners, material professionals, regulatory bodies, scientific community, and other interested parties (Tab.2).

Implementation includes central database creation, implementation and deployment of production databases, data entry workflow, content management system and Web-based programs for peer-to-peer knowledge exchange, and entering compiled data information into the production databases. In parallel, Web site interface and search engines will be implemented. (Tab. 2).

After relevant amount of information and content is added, it will be propagated to the central database and functional prototype will be launched to the Web for testing by selected groups of users from industry and academia.

### ***System deployment***

The goal of this activity is to form a large network of participants for information and knowledge exchange and leverage. Special opportunities will be offered to universities and scientific community: they can enter into collaboration by contributing to the digital library and in return access will be granted for educational and research purposes, thus stimulating knowledge and information exchange. In the future, similar benefits may be mutually exchanged with regulatory bodies and **Standards Development Organizations (SDOs)**.

Together with special courses and training workshops that will be organized predominantly for academic users, beta testing and refinement of the system will be organized.

Our work plan directly covers most of the objectives, including the following advances:

### ***Standards, Metadata, Interoperability and Preservation***

Standards are a part of every day life whether we realize it or not. Metadata is used to facilitate the understanding, characteristics, and management usage of data (Tab 2). The metadata required for effective data management varies with the type of data and context of use (Ref.19,20). In a library, where the data is the content of the titles stocked, metadata about a title would typically include a description of the content. Standards particularly relevant to the development of digital asset management in Further Education are: METS Metadata Encoding and Transmission Standards. METS is a developing standard for the sharing of assets and related metadata and it can reasonably be expected to establish a 'market' presence as an exchange standard. The potential of METS to digital asset management systems is that it is capable of storing and exchanging metadata from a number of standards at once. It can also bundle this data with the object. This will allow the developed system to exchange the wider range of metadata formats that it has created in a single transaction. Standards are essential for interoperability between systems.

Interoperability refers to the ability of a system to interact and exchange data with one or more other systems. This can be in the form of direct data exchange or the exporting, transformation and importing of records. Interoperability is not just about being able to get multiple services to present their data coherently in the same place - it is also about the data making sense in that other context. When data moves between systems the differences between the internal requirements of the systems creates an "interoperability boundary" that has to be crossed. The changes to the metadata that are required to cross this interoperability boundary may be structural, semantic, or syntactical. Another reason for supporting the use of a standards in a system is the potential to migrate to future systems. Further, standards are essential to support preservation FOREVER (Tab.2).

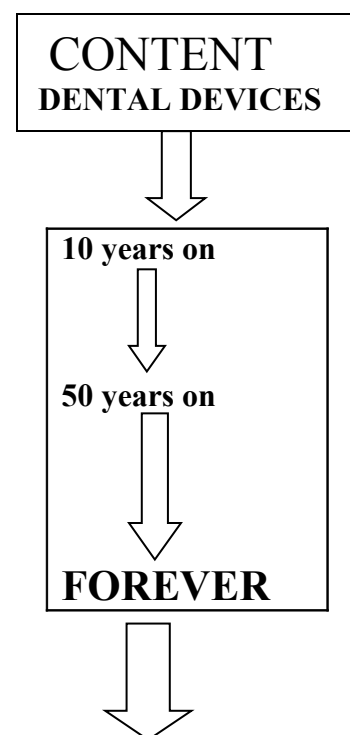
**Table 2. Basics Standards for creating Digital Libraries:**  
Implementing Standards, Metadata, Interoperability and Preservation

**How do these standards work together for digital libraries?**

- A container format such as METS allows for packaging together forms of metadata with objects or pointers to object
- METS records the (possibly hierarchical) structure of digital objects, the names and locations of the files that comprise those objects, and the associated metadata
- A container for metadata and file pointers
- A METS document may be a unit of storage or a transmission format
- METS is extensible and modular, using “wrappers” or “sockets” where elements from other schemas can be plugged in
- METS uses the XML Schema facility for combining vocabularies from different Namespaces
- Using METS, MODS, PREMIS and MIX: <http://www.loc.gov/premis/louis.xml>
  
- **PREMIS** is a data dictionary for metadata to support the long-term preservation of digital objects
- A piece of the necessary infrastructure for implementing reliable, sustainable preservation programs
- A supporting set of XML schema for implementation in a variety of contexts
- A maintenance activity hosted at LC including an Implementers’ Group and Editorial Committee

**A quality Website must:**

- be transparent, clearly stating the identity and purpose of the Website, as well as the organization responsible for its management;
- select, digitize, author, present and validate content to create an effective Website for users;
- implement quality of service policy guidelines to ensure that the Website is maintained and updated at an appropriate level;
- be accessible to all users, irrespective of the technology they use or their disabilities, including navigation, content, and interactive elements;
- be user-centered, taking into account the needs of users, ensuring relevance and ease of use through responding to evaluation and feedback;
- be responsive, enabling users to contact the site and receive an appropriate reply. Where appropriate, encourage questions, information sharing and discussions with and between users
- be aware of the importance of multi-linguality by providing a minimum level of access in more than one language;
- be committed to being interoperable within cultural networks to enable users to easily locate the content and services that meet their needs;
- be managed to respect legal issues such as **IPR** and privacy and clearly state the terms and conditions on which the Website and its contents may be used;
- adopt strategies and standards to ensure that the Website and its content can be preserved for the long time.



Long-term preservation of assets is an important aspect of digital asset management within the wider information environment. It is particularly important in ensuring that future users have access to original information, so that knowledge may be built upon. In traditional knowledge repositories this has been recognized since the earliest libraries; in modern society this has tended to be catered for by national and university libraries maintaining copies of works. Preservation in the academic world is particularly important for historical, cultural, and scientific research; it should be noted however, that the usefulness of an information asset in the future cannot be completely predicted in the present.

In many ways, preservation of paper-based assets is a simple matter assuming that storage and curation costs can be borne. Digital assets offer opportunities of much lower cost storage but also raise new problems relating to the formats in which assets are stored and ability to retrieve them in the context of new technologies. In considering the development of a strategy for digital asset management it might be useful to consider the OAIS model of preservation (Ref.5).

*Intellectual property rights IPR to be implemented in our project are:*

- Defining architecture of the digital library, databases, search engines and software modules (COPYRIGHT)
- Developing methodology for classifying biomaterials properties and the structure of the central database (COPYRIGHT)
- Defining production databases, data entry workflow, editorial process and content management (COPYRIGHT)
- Developing search engine and artificial intelligence based algorithms for biomaterials search, comparison and cross-referencing (COPYRIGHT and possibly PATENT)
- Implementation of operational and production databases (COPYRIGHT)
- Implementation of developed algorithms, their interdependences and integration (COPYRIGHT)
- Design and implementation of online, multilingual HMI (Human Machine Interface) in user-friendly programme environment adapted for application in biomaterials industry (COPYRIGHT)
- Systems, algorithms and programmes which will be subject of intellectual property protection are related to:
  - New biomaterial classification methods
  - New AI-based search algorithms
  - System design and implementation

## **DENTAL BIOMATERIALS - DIVERSITY AND COMPLEXITY**

### *Research from concept to clinic*

The subject of **biomaterials** resides at a multidimensional interface between chemistry, chemical engineering, materials science, mechanics, surface science, bioengineering, biology, and medicine, with considerable input from ethicists, government-regulated standards organizations, and entrepreneurs. The field has seen consistent growth since its inception and a steady introduction of new ideas and productive branches. Some examples of these outgrowths from biomaterials that have evolved into identifiable fields of their own include controlled release, diagnostic arrays, and tissue engineering TE.

Although medical implant materials have been used for at least 2000 years (some historians trace sutures back 32,000 years), most early medical implants were doomed to failure because important concepts relating to infection, materials, and the biological reaction to materials were not yet established.

A Little History on Biomaterials indicates the **socio-cultural importance** of digital library developments as shown in frame:

**The Romans, Chinese, and Aztecs used gold in dentistry over 2000 years ago □ Ivory & wood teeth □ Aseptic surgery 1860 (Lister) □ Bone plates 1900, joints 1930 □ Turn of the century, synthetic plastics came into use - WWII, shards of PMMA unintentionally got lodged into eyes of aviators - Parachute cloth used for vascular prosthesis □1960 - Polyethylene and stainless steel being used for hip implants.**

On the other hand, the history of implants development confirms the permanent evolution of biomaterials:

**The first generation of biomaterials:** (1) "ad hoc" implants, (2) specified by physicians using common and borrowed materials, (3) most successes were accidental rather than by design (Galletti,1988).

Examples of first generation implants: (i) gold fillings, wooden teeth, PMMA dental prosthesis, (ii) steel, gold, ivory, etc., bone plates, (iii) glass eyes and other body parts (iv) dacron and parachute cloth vascular implants.

**The second generation of biomaterials:** (1) engineered implants using common and borrowed materials (2) developed through collaborations of physicians and engineers, (3) built on first generation experiences, (4) used advances in materials science.

Examples of second generation implants: (i) titanium alloy dental and orthopedic implants, (ii) cobalt-chromium-molybdenum orthopedic implants, (iii) UHMW polyethylene bearing surfaces for total joint replacements and (iv) heart valves and pacemakers

**The third generation of biomaterials:** (1) bioengineered implants using bioengineered materials, (2) few examples on the market, (3) some modified and new polymeric devices and (4) many under development.

Examples of third generation implants: (i) tissue engineered implants designed to regrow rather than replace tissues (Letic et al.,2005), (ii) Integra Life Sciences artificial skin.

Biomaterials (Tab. 3, 4 and 6) are used in the oral cavity either to restore function, comfort, or aesthetics caused by developmental disorders, disease, or trauma. More elective procedures are being requested and performed purely for aesthetic purposes as the incidence of caries has dropped in certain population groups and as patients have become more aware of various restorative or cosmetic options. However, the replacement of diseased tooth structure or missing teeth accounts for the bulk of work in restorative dentistry. The instruments and materials used in the surgical aspects of oral, maxillofacial and periodontal surgery have much in common with medicine (Tab.5).

Laboratory-based biomaterials (Tab. 4) research is essential to the genesis and development of new and improved biomaterials for dentistry and orthopaedics. The number and complexity of questions requiring resolution far exceeds the worldwide resources available for Randomized Clinical Trials. Hence, careful and appropriate laboratory modeling is also needed to replicate key features of the oral environment, including its biomechanical, thermal, optical, chemical, biochemical and cellular aspects. Our digital library will address all of these dimensions of research, and contribute to an enhanced mechanistic understanding of biomaterial behavior in vivo. Our research interest involves the whole field of dental and orthopaedic biomaterials, but especially in metals, ceramics, polymer systems, composites/adhesives, smart and nanomaterials (Tab. 3,4,6,11,12). Biomaterials for dental operative use entail special 'boundary conditions' on account especially of: 1) micro-engineered small quantities; 2) constrained cavity-filling placement; 3) alveolar bone grafting within GTR (guided tissue regeneration) and GBR (guided bone regeneration); 4) in situ composites solidification. The following specific topics are illustrative of diversity and complexity of biomaterials used in dental daily practice. The digital library could greatly facilitate understanding of their use: The stability of interfaces between host tissues and restorative biomaterials is crucial (Tab.7) Substantial advances have been made in understanding the interface of hard substrates such as dentine and bone, but these hybrid bonding zones are challenged clinically by the rapid development of intra-coronal stress arising from molecular setting processes. Are to be studied polymerization-shrinkage phenomena, especially in the dynamics of photo-polymerization. Photo-activation methods, based on LED light sources, have now been deployed and these are being carefully evaluated, along with composite biomaterials based around novel chemistry and systematically-varied formulations. Metal-free biomaterials - required to withstand functional stresses - are usually designed around composite structures and/or high performance ceramics. These cannot be dissolved so as to apply classical analytical methods. Investigation of their behavior and internal microstructures, down to the molecular and nano-scales requires development of appropriate spectroscopic, viscoelastic and image-analysis techniques. There are much more experimental methods, including Photo-DSC, FTIR, Rheology, X-Ray 3-D micro-tomography and Fracture-Mechanics, for this purpose. Natural bio-composites utilize fibers as well as particulate ceramics for reinforcement. Are to be develop user-friendly, economical and strong fiber-reinforced biomaterials for applications in endodontics, temporary restoratives and fixed and removable prosthodontics. Clinical placement of biomaterials is greatly affected by their perceived ease of handling and manipulation in vivo. However, these clinical impressions are frequently highly subjective and non-transferable. Aesthetic dentistry relates to the optical properties of biomaterials, and this also depends on their surface morphology as well as their internal microstructure.

**Table 8. Biomaterials Properties** (Ref. 3) [http://www.lib.umich.edu/dentlib/Dental\\_tables/toc.html](http://www.lib.umich.edu/dentlib/Dental_tables/toc.html)

1. Bond Strength Between Restorative Materials and Tooth Structures
2. Brinell Hardness Number
3. Coefficient of Friction
4. Coefficient of Thermal Expansion (Linear)
5. Color Range of Natural Teeth
6. Colors of Dental Shade Guides
7. Contact Angle
8. Creep of Amalgam
9. Critical Surface Tension
10. Density
11. Dynamic Modulus
12. Elastic Modulus
13. Flow
14. Heat of Fusion
15. Heat of Reaction
16. Impact Strength, IZOD
17. Index of Refraction
18. Knoop Hardness Number
19. Melting Temperatures and Ranges
20. Mohs' Hardness
21. Penetration Coefficient
22. Percent Elongation
23. Permanent Deformation
24. Poisson's Ratio
25. Proportional Limit
26. Shear Strength
27. Shore A Hardness
28. Solubility and Disintegration in Water
29. Specific Heat
30. Strain in Compression
31. Surface Free Energy
32. Surface Tension
33. Tear Energy
34. Tear Strength
35. Thermal Conductivity
36. Thermal Diffusivity
37. Transverse Strength
38. Ultimate Compressive strength
39. Ultimate Tensile Strength
40. Vapor Pressure
41. Vickers Hardness
42. Viscosity
43. Water Sorption
44. Yield Strength
45. Zeta Potential

The success of biomaterials is seen in the importance to modern medical therapies, in the **economic potential** of the market, and the steady growth of the field over more than 50 years. The next several years will be critical for the maturation of biomaterials for TE science and its role in clinical medicine. Elucidation of the fundamental structure-function relationships in normal and

diseased or damaged tissue through sound basic research will continue to be a prerequisite. In addition, consideration of the different elements in the product development continuum from inspiration, product design and bench studies, to the clinic are vital. Because of the limited availability of organs and the increasing demand of such, new research has been initiated some years ago to develop biological, *in vitro* engineered transplants. Although great progress has been made in field, still remains some serious problems in biomaterials and TE science, such as: defining, researching and/or selecting the appropriate biomaterial's physical/chemical and other weakness in relation to host (Tab.7) and the problems and challenges in the field of biocompatibility. These problems need to be understood and specifically address the general lack of knowledge relating to:

- the rapid development of **regulations and standards** over recent years in the biomedical field;
- the principles behind the correct interpretation and use of such regulations and standards, the best methods necessary as part of the evaluation of **safety of biomedical materials and devices**;
- the importance of issues relating to **standardization and quality of testing**;
- the forthcoming role that **risk analysis** will play in evaluating biological safety;
- the structure of standardisation and the function of the standards within the framework of the European and US legislation and the moves towards **global harmonisation**.

In order to approach resolutions of aforementioned problems, our digital library project will be focused on (Road map schematised in Fig.1):

1. Selecting and collecting data from literature, experimental results (*in vitro*, *in vivo*, etc.), standards, manufacturing specifications, scientific papers and other equivalent data sources related to biomedical materials from all over the world.
2. Analyzing, compiling and peer reviewing all these data and information sources prior to Web publication.
3. Structuring large relational database as a unique, consistent data infrastructure for including all the compiled information. Besides that, the database will be structured to provide flexibility, extensibility and high search performance.
4. Entering the compiled information into the database. As a part of this process, data structures and Web-based programs for the database updating will be created, as well as Web-based program for peer-to-peer knowledge exchange.
5. Publishing the content via the specialized Web site to professionals worldwide, with a flexible multi-layer access system, thus providing a quick, easy online access via a single portal to consistent and relevant materials information.
6. Developing Web-based search engine that will combine robustness, superior search performance, and multiplicity of search modes, and will be combined with additional special software modules for material cross-referencing and identification.
7. Deploying multilingual system and content, in order to provide access to all the information to as broad audience as possible. Starting with major European languages like English, German, French, Spanish, and Italian, the system will be extensible to other European languages, as well as to Chinese, Japanese, Arabic, etc.

Having all this in mind our project will provide comprehensive **Digital library** which will synthesizes and include the following data and information (Fig. 1):

1. Biomaterials classification and composition with Relevant references (Tab. 4,6);
2. Standards and best practices for determining properties and biocompatibility; Physical properties, such as density, conductivity, melting ranges, solubility in water, surface tension,

- viscosity, biomaterials performances for application in biomedical environments, resorbability, etc. surface characterization (Tab. 7,8,9,10,11)
3. Mechanical properties, such as tensile stress, compressive stress, hardness, impact strength etc (Tab.7 and 8).
  4. Special properties, applicable for some groups of materials, such as colours of dental shade guides, creep of amalgam, etc.
  5. Biological behaviour in the human body (Tab. 7).
  6. Biocompatibility, such as corrosion properties, toxicity (systemic and local), allergic potential, mutagenicity and carcinogenicity, biocompatibility test methods and test results (when available and applicable), affinity and strength among inorganic and organic phases as interface phenomena (Tab. 7)
  7. Guidelines for the biomaterials applications (Tab.6);
  8. Cross-reference tables of equivalent materials;
  9. Technologies of application and processing Biomaterial manufacturers; (Tab. 3,4,10).
  10. Relevant legal and regulatory information both from within and outside of the EU
  11. Biomaterial manufacturers;
  12. Final products and medical devices (Tab 3).

**Table 5. Various metal and non metal materials are used to fabricate Instruments for dental use and in the high level dental technologies**

<b><u>TYPICAL INSTRUMENTS SETUPS</u></b>	<b><u>DENTAL TECHNOLOGIES</u></b>
Basic Examination Setup Anesthetic Setup Rubber Dam Instrument Setup Restorative Setups Surgical Setups Routine tooth Extraction Setup Endodontic Instrument Setups	Air-Abrasion, Bone Replacement, CAD/CAM, Caries Detection Solution, CAT Scans, Composite Materials, Diagnodent, Dental Implants, Desensitizers, Digital X-rays, Electric Hand Pieces, Internet, Intra-Oral Camera, Lasers, Optical Scanners, Microscope, NTI Splint, Periodontal Antibiotics, VELscope, ViziLite, Periometer, The Wand, Pedodontics, Periodontics, Prosthodontics,
<b><u>LIST OF INSTRUMENTS USED IN RESTORATIVE PROCEDURES</u></b>  Removing Decay Finishing The Cavity Preparation Preparing and Placing the Base Material Confining the Restorative material in Cavity Preparation Preparing and Placing of the Restorative Material Finishing the Restorative Material	

## CLASSES OF DENTAL BIOMATERIALS

**Dental materials for restorative dentistry include** (Tab. 4 and 6) (Ref.4): Metals, such as Amalgam alloys for direct fillings; Noble metals and alloys for direct fillings, crowns and bridges, and porcelain fused to metal restorations (Letic et al., 2000).

Base metals and alloys for partial-denture framework, porcelain-metal restorations, crowns and bridges, orthodontic wires and brackets, and implants; Ceramics for implants, porcelain-metal restorations, crowns, inlays, and veneers, cements, and denture teeth; Composites for replacing missing tooth structure and modifying tooth colour and contour; Polymers for denture bases, plastic teeth, cements, and other applications. These materials must withstand forces during either fabrication or mastication, retain their strength and toughness, and be resistant to corrosion, friction, and wear. Similar to implantable devices for non dental applications, they must also be biocompatible (Craig et al.,2002).

**Table 9. Types of titanium and titanium alloys used for dental devices and implants**  
 (Letic-Gavrilovic et al.,2000)

**A. Pure titanium** (cpTi, grade 1-4)

**B. Titanium alloys**

Ti90-6AL-4V (Ti6Al4V)

NiTi (Ni90Ti10; Ti50Ni50; Ti70Ni30)

Ti-6AL-7Nb

TiNbZr

Titanium beta 3 (Ti77.5/Mo12/Zr6/Sn4.5)

**C. Technological improvements of Titanium surface**

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**Physical manipulations:**

a) mechanical working (machining, polishing)

- grooved surface (V shaped)
- smooth polished
- surface blasted

b) plastic forming

- hydrothermal method for coating HA
- sol-gel prepared sintered titanium
- shape memory

c) plasma treatment

- argon plasma cleaning and etching treatment

d) ion implantation (N, C, B )

**Chemical manipulations:**

a. ACID-ETCHED - pretreated with: hydrofluoric/ nitric acid (HF/HNO<sub>3</sub>)

HF/HNO<sub>3</sub> and machined

HF/HNO<sub>3</sub> and sand-blasted and HCl/H<sub>2</sub>SO<sub>4</sub> acids

HF/HNO<sub>3</sub> and electropolished

HF/HNO<sub>3</sub> and Ti plasma-sprayed

b. chemically treated with Ca-P

c. alkali- and heat- treated [43, 60]

d. covalent immobilization of bioactive organic molecules

e. ethylene plasma polymeric film coating

f. electropolished

g. biomimetic method

---

**D. Relationship of various biomaterials with host tissue**

- |   |  |                                 |
|---|--|---------------------------------|
| 1. BIOTOLERANT (Co, Cr, Mo, Au, Polymers)                         | connective tissue capsulae                     | - distant contact with tissue   |
| 2. BIOINERT (Ti, Al, Ta, ceramic)                                 | direct contact between the bone and implant    | - direct contact                |
| 3. BIOACTIVE (Ca-HA, CaP materials, bioceramics, Bioglass, Coral) | chemical bonds between bone and implant        | - bonding osteogenesis          |
| 4. BIOINERT - OSTEOINDUCTIVE (Titanium alloys; with coatings)     | physico-chemical bond between bone and implant | -connective tissue osteogenesis |
-

**Table 6. Example of dental and medical materials and their applications**

<i>Materials</i>	<i>Principal applications</i>
<b>Metals and alloys</b>	
316L stainless steel	Fracture fixation, stents, surgical instruments
CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti 13Nb-13Zr, Ti-Mo-Zr-Fe	Bone and joint replacement, fracture fixation, dental implants, pacemaker Encapsulation
Co-Cr-Mo, Cr-Ni-Cr-Mo	Bone and joint replacement, Dental implants, dental
Ni-Ti	Bone plates, stents, orthodontic wires
Gold Alloys	Dental restorations
Silver products	Antibacterial agents
Platinum and Pt-Ir	Electrodes
Hg-Ag-Sn amalgam	Dental restorations
<b>Ceramics and glasses</b>	
Alumina	Joint replacement, dental Dental Implants
Zirconia	various parts of dental replacement
Calcium phosphates	Bone repair and augmentation, Surface coatings on metals
Bioactive glasses	Bone replacement
Porcelain	Dental restorations
Carbons	Heart valves, percutaneous Devices, dental implants
<b>Polymers</b>	
Polyethylene	Joint replacement
Polypropylene	Sutures
PET	Sutures, vascular prosthesis
Polyamides	Sutures
PTFE	Soft-tissue augmentation, vascular prostheses
Polyesters	Vascular prostheses, Drug-delivery system
PVC	Tubing
PMMA	Dental restorations, Intraocular lenses, joint replacement (bone cements)
Silicones	Soft-tissue replacement,
Hydrogels	Drug-delivery system
<b>Composites</b>	
BIS-GMA-quartz/silica filler	Dental restorations
PMMA-glass fillers	Dental restorations (dental cements)
PLLA/beta-TCP	bone replacement

## **METALS - data collection and selection**

Metals are probably the oldest form of materials used for dental implants and the most common type of materials used so far.

Metals are widely used as biomaterials due to their properties, such as strength and toughness (Tab. 8). For instance, some of the most common orthopaedic surgeries involve the implantation of metallic implants. In addition to orthopaedics, metallic implants are used in maxillofacial and oral surgery. Although many metals and alloys are used for medical device applications, the most commonly employed are stainless steels, commercially pure titanium and titanium alloys, and cobalt-base alloys.

**Shape Memory Alloys**, patented as Nitinol (nickel-titanium alloy), have very wide use because of their exceptional elasticity, their shape memory, their good resistance to fatigue and wear, and their relatively good biocompatibility.

Shape memory alloys are characterized by their ability to return to their original shape after heating to their transformation temperature after having been deformed. This is known as the shape memory effect and is caused by a change in the crystalline structure during the transition from the martensitic phase to the austenitic phase. It gives these materials attractive actuation capabilities.

Shape memory alloys have a high power to weight ratio (up to ten times that of conventional actuation systems) and in the martensitic phase they can withstand large amounts of recoverable strain (up to 8%). When heated to above their transition temperature they can exert high recovery stresses of up to 700MPa which can be used to perform work. On the downside, they are relatively inefficient (less than 10%), having a slow response speed (predominantly dictated by the need for cooling) and are relatively complex to control due to inherent non-linearities and hysteresis in the shape memory effect. The most common shape memory alloy is Nitinol and alloy of nickel and titanium.

**Amalgam** remains the hardest and strongest material available today for direct placement restorations. It is easy to use, helps maintain a seal against leakage by developing corrosion at the amalgam-tooth interface (although modern amalgams do this much less effectively), and has withstood the test of time. Use of amalgam in humans has become controversial due to concerns regarding its mercury content and resultant potential health hazard. As in many controversies, opposing views vary widely and are argued passionately by their proponents. A poor aesthetic result is another reason for a decline in amalgam use since it does not match natural tooth structure and darkens over time.

**Gold-based alloys** were the first alloys to be used for implants, probably because these alloys were available in dentistry, but they promoted the fibrous interface with a bone, i. e. a distant osteogenesis with a short lifespan. **Cobalt-chromium** alloys were also developed and used as endosseous implants and in prosthodontics. However, the fundamental problem with these metals and alloys was the fibrous response which they promoted with the bone. By today's standards, none of these materials are biocompatible, probably because of their corrosion effected by the living tissue and the release of elements into the tissue. Today, these metals have largely been replaced by titanium and titanium alloys (Tab. 6,9d,10).

### ***Titanium, titanium alloys and modifications of implant devices***

Titanium is used in stomatology, particularly in implantology because its chemical, physical and biological properties provide good biocompatibility. As titanium has a unique combination of properties (light weight, high strength to weight ratio, low modulus of elasticity, and excellent corrosion resistance), titanium and some of its alloys are important materials in medicine.

Superior fracture and fatigue resistance caused them to become the materials of choice in traditional load-bearing applications. Friction and wear are important properties of materials (Tab. 8) and represent the response of a material pair in a certain environment to imposed forces, the characteristics of the relative motion, the contact pressure between the surfaces, the temperature, the stiffness and vibration properties of the supporting structures, and lubrication (the presence of a lubricating film, such as saliva, separates surfaces during relative motion and reduces frictional forces and wear). Nowadays, titanium and its alloys, with additional advantages (excellent biocompatibility, good local spot wettability, and easy shaping, weldability and finishing via a number of mechanical and electrochemical processes) have become important material in dentistry. Although more research is needed in such areas as development of optimum casting investments, device design and control of biological responses, the future holds bright prospects of use of titanium as biomaterial.

Cp Ti (Tab. 9A) and titanium alloys, such as Ti-6Al-4V or as NiTi or TiNbZr, Ti-6Al-7Nb and others (Tab. 9B), have been used for manufacturing implants for the last 25 years. However, in spite of their excellent mechanical and physical properties, the worldwide medical use was hindered by their alleged toxicity, carcinogenicity or genotoxicity, hard metal disease by TiN and TiC fibroblast-mediated osteolysis or merely by their highly questionable longevity in vivo. An extensive and excellent metanalytic review on biological factors contributing to failures of osseointegrated oral implants of Branemark type was published by Esposito, 1998. Comparative investigation found that Ti implant system, apposes more bone than ceramic systems, although alternatives concerning the type of Ti alloy and bioactive surface layer engineering, generate extremely diverse results in osseointegration (Letic-Gavrilovic, 2000).

From the biocompatibility point of view, the two critical success factors for inductive osteogenesis i.e. osteoinduction that we expect from titanium or other implants, are: i) chemical composition and reactivity of bioactive surface layer; and ii) topography i.e. roughness of the surface in contact with the bone.

Ti implant surface has been the focus of multi technical approaches and manipulations (both mechanical and physico-chemical), which were targeted to enhance the responsiveness of the host tissue to the implant, to promote in situ osteoinduction and thus to prolong the longevity of the implant (Tab. 7,9). Pure titanium (cpTi) is available in four grades: 1-4. Ti contains dissolved oxygen, N, H, C and Fe in various amounts and forms a strong and tightly-bound oxide over the surface (TiO<sub>2</sub>). This oxide forms instantaneously and spontaneously at all temperature. Its thickness is 5-10 nm, with tendency to grow up to 200 nm. This layer, described as passive, is capable of withstanding a saline, physiological environment without disintegrating, and is believed to give Ti its biocompatibility. This oxide layer (TiO<sub>2</sub>) makes Ti casting difficult, largely is responsible for the outstanding corrosion resistance of cpTi and Ti alloys of any known implant material.

Recently, many biotechnological improvements were made to the surface layer of Ti (Tab. 7 and 9). The question which arises is whether the efforts that scientist have undertaken thus far, for upgrading both the quality of the composition of the implant and the quality of its bioactive surface layer, are sufficient to achieve a desirable control of tissue response, i.e. to have a better osteogenesis. Combination of chemical and mechanical manipulations were reported to improve the surface layer. For instance: polished cpTi was acid-etched in two ways: i) the natural oxide was dissolved with hydrofluoric acid and a new oxide layer was grown by oxidation in nitric acid (HF/HNO<sub>3</sub>); or ii) Ti was pre-treated with HF/HNO<sub>3</sub> and then machined, HF/HNO<sub>3</sub> etched, fine or coarse sand-blasted and then HCl/H<sub>2</sub>SO<sub>4</sub> etched, HF/HNO<sub>3</sub> etched and electropolished and HF/HNO<sub>3</sub> etched and Ti plasma-sprayed. The different chemical treatments resulted in distinct differences in surface roughness when examined by light microscopy, i.e., roughness was changed from the smoothest to the roughest. Subsequently, the effects of surface roughness on the function of osteoblast-like cells were measured. Acid-etching pre-treatment were used for covalent attachment of selected biological molecules as alkaline phosphatase and

albumin. These developments generated different kinds of interfaces between Ti and bone tissue, as described later. Subsequent chemical procedures on Ti were: deposition of thin polymeric film from ethylene plasma, alkali- and heat-treated Ti, biomimetic method for apatite nucleation for bone-like apatite-formed Ti or electrochemical apatite deposition. These chemical manipulations have two key results in common: changes on TiO<sub>2</sub> layer reactivity and surface fine topography.

The implant surface roughness is essential for interfacial interaction with local tissue around implant, particularly for osteoblast. Osteoblasts, osteoblast-like osteosarcoma cells, macrophages, fibroblasts, bone marrow cells, nicely grow on polished Ti surfaces. However, they need not only excellent chemical conditions, but also particular topographic conditions of the surface layer to create an environment conducive to optimum cell morphology and activity. Optimum roughness of Ti implants (e.g. 4000-4500 nm, or 600 grit, or 300 Å) was shown to significantly affect osteoblast cell response. For instance, it can decrease the cell number, but increase the expression of more mature cellular phenotype such as: alkaline phosphatase (ALP), osteocalcin (OC), transforming growth factor  $\beta$  and prostaglandin E<sub>2</sub> and the response of MG63 osteoblast-like cells to 1,25-(OH)<sub>2</sub>D<sub>3</sub>. An example of such a coating material is the commercially available composite materials, such as "Bonelike" which is a synthetic bone material, hydroxyapatite reinforced with tiny glass particles. This material can be used to provide a layer on the surface of pure titanium that its developers hoped will lead to better incorporation of any implant.

Surface roughness modulates the local production of growth factors and cytokines such as prostaglandin (PGE<sub>2</sub>) and transforming growth factor  $\beta$  1 (TGF- $\beta$  1) by osteoblast-like MG-63 cells. Significant high levels of cellular attachment were observed when using rough, sand-blasted surfaces with irregular morphologies.

### ***Coatings on implant devices***

Bone formation on the bioactive surface layer of the implant may be directly influenced by effects of the quality of the surface layer on osteogenic cells behaviour (Tab.8 and 10). From the character and amount of bone formation around different implants, it can be concluded whether the used materials are biocompatible. This is why we should fully understand the process of bone growth around implants, as well as the reaction of the bone to trauma or to various properties of the implant surface layer

The classical protocol of osseointegration was based on the success of the uncoated cpTi, treaded root-form implant. Long-term clinical data support the use of this material as an ideal dental implant. Basically, Ti is osteoinductive and it may create physico-chemical bonds with the bone. However, current data substantiate the use of a variety of implant surface biomodifications, coatings, as well as geometries to attain osseointegration.

Therefore, the next step in the upgrading of the quality of implant surfaces was the addition of coatings onto the implant in the following ways (Tab.10) : a) metal to metal; b) ceramic to metal; and c) biological active molecules on metal on ceramics or diverse functional carriers. Ti has been used to date as a biological substrate of many osteoconductive and osteoinductive, inorganic or organic coatings, such as ceramics of different kind, glass, adhesion proteins, extracellular bone matrix proteins, growth factors and cytokines. The primary goal of coated implants was to combine the benefit of a bioactive surface layer with the properties of the substrate i.e. the strength of the underlining metal. The application of different types of ceramics onto titanium surface, was aimed at gaining two advantages: bonding osteogenesis and connective tissue osteogenesis. Ceramic coatings on titanium-based implants combine osteoconductivity and osteoinductivity, and additionally improve the strength of chemical bonds of the implant-bone interface.

Various Ti implant coating methods were developed: plasma spraying, chemical vapour deposition process (CVD) and physical vapour deposition process (PVD), slip casting/sintering,

electrophoretic deposition/sintering, electrochemical deposition, and sputter coating, but plasma spraying is most commonly used one. Chemical vapour deposition (CVD) process with high temperature (500-1000°C) of the substrate is not very suitable for dental alloys. In dentistry, the more recent physical vapour deposition (PVD) process may be used. For example, under vacuum conditions, evaporated Ti is applied on thoroughly-cleaned metal surfaces, while feeding nitric or carbon gas in order to produce TiN or TiC.

Coatings have a paramount clinical importance in the following cases: a) big defects and poorly supportive bone; b) when a very small or very big implant should be applied; c) repeated surgical procedure or re-implantation; d) type III and IV bone; and e) in fresh extraction site. In each of these cases, given the adverse local conditions, the use of an implant with a coating or a sol-coated biomaterial, as a carrier of biologically active molecules, is recommended.

## **CERAMICS - data collection and selection**

Traditionally, ceramics have seen wide scale use as restorative materials in dentistry. (Tab. 3,4,6,10) These include materials for crowns, cements, and dentures. Some ceramic materials are used for bone repair and augmentation.

Ceramics are stiff, hard and chemically stable and are often used when wear resistance is vital. Of the large number of ceramics known, only a few are suitably biocompatible. The main problem with ceramic components is that they are brittle and relatively difficult to process.

Bioceramics can have structural functions as tissue replacements, can be used as coatings to improve the biocompatibility of metal implants, and can function as resorbable lattices, which provide temporary structures and a framework that is dissolved, replaced as the body rebuilds tissue. The thermal and chemical stability of ceramics, their high strength, wear resistance and durability all contribute to making ceramics good candidate materials for surgical implants. Some ceramics even feature drug-delivery capability. Smart Ceramics (Cercon) was invented in 1995 as "all ceramic teeth bridge" enabling the direct machining without stainless steel or other metals. The overall product is metal-free, biocompatible and crack resisting formation.

## ***Gadgets for Dental Applications***

Ceramics play a vital role in the manufacture and function of various gadgets used in dental science (Tab.5). Various recently introduced diagnostic and working tools of which ceramics play an integral part include: Radio Visio Graphy (RVG), Pulp tester Apex locators 1st generation - resistance based, 2<sup>nd</sup> generation - impedance based, 3rd generation - frequency based.

## ***Piezo Ceramics***

Piezoelectricity can be defined as pressure electricity which is a property of certain classes of crystalline materials including natural crystals of Quartz, Rochelle salt and Tourmaline plus manufactured ceramics such as Barium Titanate

and Lead Zirconate Titanates (PZT). When mechanical pressure is applied to one of these materials, the crystalline structure produces a voltage proportional to the pressure. Conversely, when an electric field is applied, the structure

changes shape producing dimensional changes in the material.

The piezoelectric materials use polycrystalline ceramics instead of natural piezoelectric crystals. They are more versatile with physical, chemical and piezoelectric characteristics able to be tailored to specific applications. The hard, dense ceramics can be manufactured in almost any given shape or size, which are chemically inert and immune to moisture and other atmospheric conditions.

**Table 10. Application of different coatings on Implantable dental device in order to improve biological response** (Letic-Gavrilovic et al.,2000)

1. metal on metal
2. ceramic on metal
3. biologically active molecules on metal/ceramic

***Methods for coatings on metal:***

- a) arc plasma spraying
- b) CVD - chemical vapor deposition process  
The CVD process is defined as the deposition of a thin solid film from a chemical reaction involving gas species at a heated substrate (Nanocrystalline Diamond - NCD),
- c) PVD - physical vapor deposition process - ion planting  
The surface to be coated is in contact with a plasma  
- high vacuum thermal evaporation  
- RF magnetron sputtered

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**Ceramic coatings (osteoconductive)**

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nonapatite calcium phosphat,  
apatite CaP (principally HA)  
glass ceramic, bioactive glass  
titanium nitride (TiN)  
titanium carbide (TiC)  
diamond-like carbon (DLC)  
silicon carbide (SiC) AlCaP  
HA ceramic  
bioactive glass membrane  
TCP beta  
bone ceramic (TBC)  
coraline  
Titanium  
3-dimensional carbon/carbon composite (3D C/C)

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**Functional carriers for different growth factors**

***Natural and synthetic biomaterials***

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1. allogeneic demineralized bone matrix (DBM)
  2. collagen - fibrous collagen membrane, type I collagen, type IV collagen
  5. bovine matrix non-collagen protein
  6. cartilage strips
  7. resorbable and nonresorbable membranes for Guided Bone Regeneration
    - a) basement membrane matrix (Matrigel)
    - b) expanded polytetrafluoroethylene (ePTFE) membrane
  8. fibrin
  9. biodegradable synthetic polymers of polylactic acid (PLA),(PLA-PEG; PLGA)
-

## **Therapeutic Ceramics**

### *Silicate cement*

Silicates constitute the first dental cement to use glass as its component. The cement powder is a glass consisting silica, alumina and fluoride compounds. The liquid, on the other hand, is an aqueous solution of phosphoric acid with buffer salts. The cement powder and liquid are mixed together resulting in an acid-base reaction. Fluoride ions are leached out from the set cement, which is responsible for the anti-cariogenic property exhibited.

### *Glass Ionomer Cement (GIC)*

Glass ionomer cement represents a logical step in the evolution of therapeutic cements. GIC's are composed of glass powder and a polycarboxylic acid. They constitute an improved version of the silicate cement, in which the liquid is replaced by carboxylic acids with glass remaining as the powder. It is the most popular dental cement that is used in various aspects. The highlight of this material is demonstrated by its superior biocompatibility and anti-cariogenic property. Modifications of glass ionomer cement include the high density Glass ionomers, packable ionomers for use in Atraumatic Restorative Treatment (ART). Resin modified GIC incorporate resins in their powder component for better strength. When mixed wet, protons from the polymeric acid exchange with calcium and aluminium cations in the surface of the glass particles. The cations then form electrostatic bonds with carboxylate groups in the polymer chains, effectively cross-linking them to form a gel that sets the cement.

## **Bioceramics**

Bioceramics are a group of ceramics, which are biologically active materials rich in calcium and phosphate. Hydroxyapatite and tricalcium phosphate are similar in composition to bone and teeth and can be used for augmentation of alveolar ridges and filling bony defects. They are manufactured and are available in block, granular and injectable forms. These bioactive materials are packed in the required site providing a scaffold for new bone growth and are osseointegrative in nature. The various forms of bioceramics are Single crystals (Sapphire), Polycrystalline (Hydroxyapatite) Glass (Bioactive glass) Glass ceramics (Ceravital) Composites (Stainless steel reinforced Bioglass). There are about four types of bioceramics:

- INERT: Attached by compact morphological fixation. e.g, Alumina, Carbon
- POROUS: Attached by vascularization through pores. e.g, Porous Alumina.
- SURFACE ACTIVE: Directly attach by chemical bonding with bone.e.g, Bioglass, Hydroxyapatite
- RESORBABLE Designed to be slowly replaced by bone.e.g, Tricalcium Phosphate (TCP).

Ceramic coatings on dental implants, such as **Calcium phosphates (hydroxyapatite- HA)** appear to have better biological response than cpTi or Ti alloy alone, even if their clinical predictability remains controversial. Coatings seem to promote faster bone adaptation, higher bone implant strength, better osteoblast precursor activity, bone growth around dental implants and thus bonding

of the bone to the implants, i.e. osseointegration. HA coatings were highly considered because they enhance osseointegration, and they lead to the formation of more mineralised extracellular matrix (ECM) and to faster bone formation with respect to Ti substrates alone. The philosophy was that HA has an advantage over smooth Ti surfaces having: 1) bioactive surface versus an inert Ti surface; 2) higher bond strength of the bone to the implant; and 3) increased bone-to-implant contact. In spite of reports about overstressing, rapid, bone-resorption adjacent to HA-coated implants, short-term survival rates (from 6 months to 6 years), or other causes of failures, there are still evidence of positive effects of HA coatings on osseointegration.

Recently, other ceramic coatings, such as **titanium nitride (TiN)** and **titanium carbide (TiC)**, have been proposed for implantology (Tab.9 and 10). In general, biocompatibility of TiN in cell culture and animal tests was evaluated positively. Aesthetic appearance (gold-coloured layer) is questionable and probably culture dependent. However, longitudinal clinical studies have been scarce so far. In total joint arthroplasty, a diamond-like carbon (DLC) coating was applied onto Ti. TiC coatings were developed to fit straight stems and cementless acetabular implants. Subsequent studies questioned the biocompatibility of TiC on grounds of toxicity or hard metal disease. Also vitreous carbon, pyrolytic carbon, pyrolytic graphite/silicon-carbide were occasionally used as Ti coating on implants.

**Table 11. Synthetic Polymers – Selected Examples**

<i>Non - Degradable</i>		<i>Biodegradable</i>	
Polyamides	sutures	Polylactic/glycolic acid	suture
Polycarbonates	device housings	Polyorthoesters	bone plates
Polyesters	vascular grafts	Polyorthoesters	bone plates
PVC	tubing, blood bags	Cyanoacrylates	wound closure
Polyurethanes	tubing, coatings	Polylactic acid	alveolar bone
Silicones	tubing, soft tissue		tendon repair
UHMWPE	hip & knee		
bearings			

## **BIOCOMPOSITES** - data collection and selection

The most successful composite biomaterials (biocomposites) are used in the field of dentistry as restorative materials or dental cements (Tab. 6). Although carbon-carbon and carbon reinforced polymer composites are of great interest for bone repair and joint replacement because of their low elastic modulus levels, these materials have not displayed a combination of mechanical and biological properties appropriate to these applications. Composite materials are, however, used extensively for prosthetic limbs, where their combination of low density/weight and high strength make them ideal materials for such applications. Smart composites containing ACP (amorphous calcium phosphate) is one of the most soluble of the biologically important calcium phosphates, exhibiting the most rapid conversion to crystalline hydroxyapatite (HAP) (Letic et al.,2004). ACP, when incorporated in specially designed and formulated resins to make a composite material, will have an

extended time-release nature to act as a source for calcium and phosphate, useful for preventing caries. Biodegradable bone cements are highly desirable because they can provide for immediate structural support and, as they degrade from the site of application, they allow the ingrowth of new bone for complete healing of the bone fracture.

Although improvement has occurred in the field of dental adhesives and composites, problems with composite restorations still exist. The most serious problem is polymerization shrinkage, which causes gap formation and cusp deflection. Both of these problems show clinically as postoperative sensitivity and pain. Based on the review of available articles, it appears that the use of liners is still desirable because liners may help overcome these problems. Both flowable resin composites and resin-modified glass ionomers (RMGIs) have a lower modulus of elasticity than restorative composites, which may counteract some of the polymerization shrinkage of the restorative composites. Because of the low viscosity of RMGIs and flowable resin composites, they can wet the tooth better than restorative composites and decrease the chances of gaps. RMGI liners appear to perform better than flowable resin composites because of their physical properties. Additionally, placing the self-adhesive RMGI liner on the areas of deep dentin can protect this sensitive dentin from the strong conditioners needed for the subsequent bonding procedure. From the clinician's standpoint, overcoming these problems translates into less postoperative sensitivity.

## **BIOPOLYMERS - data collection and selection**

A wide variety of polymers are used in medicine as biomaterials. Their applications range from facial prostheses to tracheal tubes, from kidney and liver parts to heart components, and from dentures to hip and knee joints (Tab. 6 and 11). Polymeric materials are also used for medical adhesives and sealants and for coatings that serve a variety of functions. They are widely used as implant materials as they have physical properties that are most similar to the natural tissues. Use of polymers includes wound dressings, tendon replacements, intraocular lens replacement and joint linings. The polymers that are widely used include polyethylene, PET, PTFE and polyurethane and themselves are well tolerated in the human body. However, additives and molecules released from polymer breakdown can lead to allergic and inflammatory responses.

The use of polymers as biomaterials started over 2500 years ago with collagen (found in animal tissue) used as a surgeons thread. In the 1970's the polymer polyglycolic acid (PGA) was developed as synthetic degradable sutures.

PGA was further developed over the next few decades and was used in implants that would slowly release desired chemicals into the body and scaffolding on which replacement organs could be grown, for TE (Letic-Gavrilovic et al.,2004; 2005). Over 25 different types of cells have been grown on the polymer scaffolds, and skin grown on these scaffolds has been successfully transplanted to heal diabetic skin ulcers. It is hoped that in the future these scaffolds will be used to grow nerve cells for use in spinal cord repairs, bone or cartilage cells for joint repairs, pancreatic cells to make insulin for diabetics, and liver cells to make livers for transplantation Advances in the design of stimuli-responsive polymers have created opportunities for novel biomedical applications. Changes in shape, surface characteristics, solubility, formation of an intricate molecular self-assembly and a sol-gel transition enabled several novel applications in the delivery of therapeutics, tissue engineering, cell culture, bio separations, bio mimetic actuators, immobilized bio catalysts, drug delivery and thermo responsive surfaces. One area of intense research activity has been the use of biocompatible polymers for controlled drug delivery. It has evolved from the need for prolonged and better control of drug administration. The goal of the controlled release devices is to maintain the drug in the desired therapeutic range with just a single dose.

The list of new polymers developed specifically for medical applications is far too long to describe here. We have chosen to focus on two types of synthetic biomaterials: (a) hydrogels and hybrid polymer systems, which are attractive owing to their high water content and tissue-like properties, and (b) smart materials, which can rapidly respond to changes in the in vivo environment.

**Hydrogels** are crosslinked polymer networks that are insoluble but swellable in aqueous medium. These materials offer an environment that resembles the highly hydrated state of natural tissues, making them excellent candidates for tissue engineering and drug delivery. Hydrogels and bone cements, can, for instance, be used as an interface between bone and an implant with the aim of providing a mechanism for fixing a prosthesis in the intramedullary cavity. The bone cements would, in principle, dilate in a controlled manner by absorption of body fluids and achieve fixation by an expansion mechanism. The physical properties of hydrogels make them also very useful for controlled-release applications, such as the delivery of contraceptives, ophthalmic, antiarrhythmics, hormones, enzymes, anticancer agents, anticoagulants, antibodies. Biodegradable polymers like poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers, have recently found numerous applications in a variety of drug-delivery systems. A potential alternative, for the currently used materials, is starch-based polymer which are well-known biodegradable materials.

Hydrogels are three-dimensional polymeric networks held together by cross-linked covalent bonds and weak cohesive forces in the form of either hydrogen bonds or ionic bonds. These mechanisms include ionic (e.g., alginate), physical (e.g., pluronics and peptide self-assembling gels), and chemical bonds (e.g., fibrin glue and multivinyl methacrylate and acrylate derivatives). Hydrogels are, by definition, a broad class of hydrophilic polymeric materials which have the inherent ability to swell in water and other suitable solvents, capable of imbibing and retaining more than 10% of their weight in water within the gel structure. Attributes such as permeability to small molecules (such as tissue metabolites), a soft consistency, and a low interfacial tension between the gel and an aqueous solution are some of the important properties which have helped to generate interest in hydrogels as useful biomaterials. Additionally, the facility of purification, a high equilibrium water content (advantageous for the permeability and biocompatibility of these materials), along with their sterilizability makes them extremely versatile. The utility of hydrogels as biomaterials lies also in the similarity of their physical properties with those of living tissues.

There has been great interest in implantable biomaterials that are injectable as well as biodegradable. The development of **hybrid polymer systems** (copolymers, complexes, hydrogels, blends, etc.) based on natural and synthetic macromolecules and their open wide spectrum of applications in the biomaterials science has received tremendous attention.

Natural and synthetic biodegradable polymers hold great promise for use as scaffolds in TE. Main advantage of polymers are their properties which can be engineered for a wide range of medical applications (Letic et al., 2002;2002a). Of particular interest to oral-maxillofacial applications are injectable, in situ polymerizable, biodegradable polymer scaffolds for filling irregularly shaped bone defects with minimal surgical intervention. A biodegradable support material would be ideal, as it would eliminate the need for a second surgery to remove the fixation device. Furtheron, in order to avoid the inconvenient surgical insertion of large implants, injectable biodegradable and biocompatible polymeric particles (microspheres, microcapsules, nanocapsules, nanospheres) could be employed. Since the range of potential TE applications is broad, there is a continuous ongoing search for materials which either possess particularly desirable tissue-specific properties, or which may have broad applicability and can be tailored to several tissue systems.

Naturally **derived materials** biodegradable polymers show great promise, for TE applications. Natural biopolymers are composed of extracellular matrix (ECM) glycoproteins that are conserved among different species and that can serve as intrinsic templates for cell attachment and growth. Contrary to the synthetic, natural polymers are more easy for processing, degradability, biocompatibility, exhibition of bone-analogous properties, bone bonding, and ability to be surface engineered to produce desired mechanical and biological behaviours. In addition, and not less important, polisaccharide-based natural polymers are significantly less

expensive than most commercial synthetics. Bio-polymers could be used as filling elements of irregular defects for orthopaedic and maxillo-facial surgery, as bone cements, and drug delivery carriers. Other proposed natural polymers could be used for preparation of biodegradable and resorbable (Tab. 11) bio-membranes for epidermis protection, with special relevance in the field of burning, separation membranes to avoid adherences between different tissues in postoperative process, dental filling composites, membranes and supports for jaw regeneration, etc.

From the practical point of view, we expect that this new biomaterials will promote biological response of the treated tissue giving the following results:

- Plastic, multy-functional device, which dramatically help surgeons to fill irregularly shaped defects with **minimal intervention**;
- To enormously faster osseointegration (not less than **50% reduction of ossification** time);
- To **eliminate second surgery step**, and therefore prolongs life of implanted prosthesis and reduce number of post-surgery complications;
- Drug delivery device for long controlled drug release will enormously help chronic patients **eliminating multy interventions** and **reducing more than 50% costs** of their treatments.

### ***Resorbable and non resorbable membranes for TGR and BGR***

Guided Tissue Regeneration (GTR) is a procedure that enables bone and tissue to re-grow around an endangered tooth or if the tooth is lost to increase the amount of bone for implant placement. Guided tissue regeneration (GTR) is a surgical procedure that specifically aims to regenerate the periodontal tissues when the disease is advanced and could overcome some of the limitations of conventional therapy.

Guided bone regeneration (GBR) is a current treatment for periodontal bone defects. In the GBR technique, a barrier membrane (Tab.11) is placed over the periodontal defect to prevent the in-growth of cells from the gingival connective tissue, epithelium, and the periodontal ligament. GBR membrane materials must maintain their barrier function long enough to allow osteoblasts to migrate into the wound. The distance to be spanned determines the time the membrane must function properly. Resorbable and non-resorbable membranes have been used as a GBR barrier. However, non-resorbable membranes must be surgically removed after the healing period. A resorbable membrane that can transmit tissue fluid, but excludes undesired cells from the clot, would have the advantage of not requiring surgical removal. Recent studies have reported the successful use of resorbable membranes in GBR (Letic et al.,2002;2002a;2005)

1) Osteopromotive membranes of expanded polytetrafluoroethylene (ePTFE; GORE-TEX) facilitate guided bone regeneration, are **not resorbable** and require a second procedure to be removed. The combination of membrane placement with rhBMP-2 may be of value in the clinical applications for bone regeneration purposes. This finding is also valuable for choosing carrier materials for delivery of other growth-stimulatory substances, in combination with membranes. ePTFE membrane plus BMP can be combined with Ti implants, demineralized freeze-dried bone (DFDB), and with the growth factors PDGF-BB, PDGF/IGF-I or rhBMP (Tab. 10). Clinical results, demonstrated that ePTFE membranes plus PDGF/IGF-I, had the -highest bone density compared with controls receiving membranes alone and they also allow the bone to grow directly around the implant.

2) Basically there are two types of biologically **resorbable** biomaterials: a) synthetic polymers of lactide-/glycolide- and polylactic acid; and b) collagen. Collagen plays an important role in wound healing since it is present in connective tissue capsules which lie around implanted

materials. The influence of collagens, including collagen I, III and IV on *in vitro* cell proliferation greatly depends on the cell cultures. Collagen membranes are used in clinical applications because their compact layer protects against soft tissue invasion and their porous texture enables the integration of newly formed bone tissue. The amount of collagen type I and III during soft tissue capsule formation varies, depending on the type of metal implants. The properties of collagen favour cell attachment. Collagen I was reported to inhibit cell proliferation, whereas collagen IV had no effect. It can be used independently or in association with various biomaterials, such as polystyrene, low and high crystallinity HA and rough Ti.

### ***Osteopromotive growth factors on implant devices***

Polypeptide growth factors are a class of natural biological bone mediators regulating the critical cellular events which are involved in wound healing: cell proliferation, chemotaxis, differentiation, and matrix synthesis. Growth factors elicit their effects by binding to specific cell surface receptors, which transduce signals to the nucleus via complex signal transduction pathways. Examples of growth factors found in bone, cementum and healing tissues include platelet-derived growth factor (PDGF), transforming growth factor  $\beta$  (TGF- $\beta$ ), acidic and basic fibroblast growth factors (a- and b-FGF), insulin-like growth factors (IGF-I and II), cementum-derived growth factor (CGF) and the bone morphogenetic proteins (BMPs). The *in situ* factors which induce osseointegration of the implant material are not fully understood, but most researchers agree that the contact between the bioactive surface layer of the implant and the bone is not static but dynamic (Letic et al., 2001; 2003).

### **SMART BIOMATERIALS - data collection and selection**

The use of biocompatible smart materials has revolutionized many areas in regenerative medicine (Gautam, 2008). The term "smart materials" refers to a class of materials that are highly responsive and have the inherent capability to sense and react according to changes in the environment. Biomedical applications of smart materials involve their use in tissue engineering, cell culture, bioseparations, biomimetic actuators, immobilized biocatalysts, drug delivery and thermoresponsive surfaces. Applications of stimuli-responsive, or "smart", polymers in areas like dentistry, biomedical engineering, delivering of therapeutics, tissue engineering, bio separations are an indicator of the potential and rapid progress in this area.

Smart Biomaterials can sense and react according to changes in the environment. For that reason they are often also called "responsive materials". Early smart material applications started with magnetostrictive technologies. These involved the use of nickel as a sonar source during WWI. Smart materials can be classified as: 1) **passive smart materials** that respond to external change without external control; 2) **active smart materials** that utilize a feedback loop to enable them to function like a cognitive response through an actuator circuit; 3) **very smart materials** that sense a change in the environment and respond (e.g., by altering one or more of their property coefficients, tuning their sensing or actuation capabilities); and 4) **intelligent materials** that integrate the sensing and actuation functions with a control system. When smart biomaterials respond *in vivo*, it can be exploited to control parameters such as drug release, cell adhesiveness, mechanical properties, or permeability. Several approaches have been examined for stimulants such as pH, temperature, and light.

The body employs changes in pH to facilitate a range of different processes.

For example, drug delivery by oral administration is attractive to many patients who require routine, periodic delivery of drugs. However, for the drug to remain effective, it must survive the acidic pH of the stomach.

## **BIOLOGICALLY INSPIRED MATERIALS**

In an effort to design materials that will perform their intended functions in the presence of cells and/or in vivo, we as engineers and scientists can look to biology and take advantage of biological processes that have evolved over thousands of years.

### *Self-assembled biomaterials*

One of the many fascinating aspects of biology is the self-organization of molecules into hierarchical structures that perform a specific task. This self-organization or self-assembly is based on the formation of weak noncovalent bonds, typically hydrogen, ionic, or van der Waals bonds or hydrophobic interactions. For example, amphiphilic molecules have hydrophobic and hydrophilic segments that self-assemble into distinct structures, such as micelles, vesicles, and tubules that are nanometers in length. When dispersed in an aqueous solvent, the hydrophobic segments in the amphiphilic molecules agglomerate, driving out water and, as a result, producing a well-ordered structure that can be useful in a number of different biomedical applications. A naturally occurring amphiphilic molecule is a **phospholipid**, which largely composes the cell membrane. Alternatively, a polymer (or oligomer) of amino acids can be synthesized to contain a number of different regions (hydrophobic, hydrophilic, charged, etc.) that under certain conditions will self-assemble into a macroscopic hydrogel. In general, the final three dimensional structure of the self-assembled material is dependent on the molecule's length and composition. Thus, by systematically synthesizing a molecule, a desired 3-D structure can be produced. These self-assembled biomaterials are promising new materials that can be engineered for applications in nanotechnology and in tissue engineering for drug and cell carriers. These materials may be particularly beneficial because the engineered peptides will take on a 3-D shape that may be recognized by the in vivo environment, more so than a conventionally synthesized material, and furthermore will breakdown into amino acids that the body is well equipped to deal with.

### *Biomimetic biomaterials*

Direct mimicry of biological processes represents an important strategy in modern biomaterials. Hydroxyapatite is the natural mineral in bone. There is now a huge amount of literature describing the use of hydroxyapatite and other forms of calcium phosphate coupled with synthetic and other natural biomaterials to induce bone formation. Nacre, the aragonite-rich lining of many seashells, also induces rapid bone formation. Nacre contains about 5% protein that serves as a “mortar” to bind together a brick-like mineral structure. A biomimetic approach to creating synthetic nacre-like structures has been published. Normal tissues have a complex 3-D architecture important for the mechanics and functionality of the biological organism. Biomimetically, we might emulate such structures with synthetic biomaterials. Synthetic materials offer the ability to generate many different kinds of 3-D structures with precise control over the

final macroscopic properties and degradation profiles by varying the chemistry and processing techniques. However, synthetic materials provide little control over cell behavior and tissue response in vivo. Thus, to generate a biomaterial for a specific cell type and/or tissue, efforts have focused on adding biological cues to synthetic materials in an attempt to mimic the native tissue while simultaneously maintaining control over the material properties.

### ***Biomimetic nano-scaffolds***

Repair of tooth-supporting structures destroyed by the chronic inflammatory disease-periodontitis is a major goal of oral reconstructive therapy. It was proposed developing a novel scaffolding system that can also deliver regenerative agents to periodontal defects. This system consists of a nano-fibrous polymer scaffold modified with bone mineral- mimicking apatite that contains microspheres for delivery of bioactive molecules such as bone morphogenetic protein- 7 (BMP- 7), to periodontal defects. It is expected that this scaffolding/factor delivery system will promote periodontal regeneration at the defect site by providing an environment for enhancing adhesion and migration of putative cells such as osteoblasts, cementoblasts, and periodontal ligament (PDL) fibroblasts as well as promoting differentiation of their progenitor cells. Moreover, this scaffolding delivery system will allow for permeation of nutrients, metabolites, and signaling molecules required for cell proliferation, differentiation and 3D tissue formation.

### ***Periodontal engineering using biomimetic nano-scaffolds***

Periodontal diseases result in loss of supporting tissues including bone, cementum, and periodontal ligament (PDL), ultimately leading to tooth loss if left untreated. Unfortunately, dental tissue loss has the second largest patient population next to blood transfusion. The restorative results of the current therapies are often disappointing and unpredictable. It was proposed a novel biomimetic/tissue engineering approach. In this approach an unique nano-fibrous polymer scaffolding (mimicking collagen architecture), modified with apatite (mimicking bone mineral), and containing microspheres for delivery of bioactive factors (mimicking development and reparative signaling cascades) will be used in periodontal osseous defects to: promote activities of cells at the healing site, e.g., osteoblasts, cementoblasts, and PDL fibroblasts (and their progenitor cells), allow for nutrients, metabolites, and signal molecules to permeate, and guide cell proliferation, differentiation and tissue neogenesis in 3D.

The specific aim of this project would be:

- To test whether polymer scaffolds with nano-fibrous pore walls are superior to scaffolds with "solid" pore walls, and whether bone mineral-mimic apatite promotes calcified tissue formation, in vitro.
- To develop a combined nano-fibrous scaffold/biodegradable microsphere delivery system that allows for controlled release and improve bioavailability of putative periodontal regenerative factors and to evaluate their regenerative function, in vitro.
- To confirm that the microsphere/scaffold systems selected based on the results from studies under aims 1 and 2, provide a superior environment for regeneration of periodontal tissues, in vivo. By accomplishing these specific aims, results will be significantly advanced, in new and improved periodontal regenerative therapies. Furthermore, the ability to manipulate the scaffolding structure and control the rate and types of factors delivered, this system can be utilized to answer many fundamental questions in regenerative biology, including other tissue engineering applications.

## **NANOBIOMATERIALS**

### ***Nano-features and nano-particles in restorative dentistry***

The word "nano" in Greek actually means "extremely small" or one billionth. The actual size of the calcium deposits on the NanoTite Implant (3i) are as small as 20 nanometers and can best be seen

at 20,000X magnification. Nanotechnology is technology done on a nanometer scale. In the physical world we have

all been familiar with the three states of matter, solid, liquid and gas. There is one more, the interfacial or surface state. The physical world becomes very different at the surface of materials, and some very interesting physical properties come with materials in this "surface" state. When materials are at the nanometer scale, they are in many ways in the surface state of matter. We can also manipulate down to individual molecules or groups of atoms to make useful materials and devices (Tab.12). Nanomaterials, sometimes called nanopowders when not compressed, have grain sizes in the order of 1-100 nm in at least one coordinate and normally in three. Patient applications and benefits of the NanoTite Implant include use to replace single or multiple missing teeth due to cavities, decay, trauma or disease. The NanoTite Implant (3i), like all dental implants, is designed to help preserve bone structure and natural facial contours. Additionally, the NanoTite Implant may help patients increase overall confidence due to a brand new smile! "I think It's One Nano Step For Man, One Giant Leap For Implant Dentistry!" adds Dr. Meltzer.

**Hybrid Plastics Inc.** (USA) received a \$750,000 grant from the National Institutes of Health to develop nanocomposite-based dental materials. This grant will allow the company to develop a prototype adhesive and restorative system for bonding, shrinkage control and corrosion resistance. The materials will be based on Hybrid's "POSS Nanostructured" building blocks. **Hybrid** is working on the project with Ohio State University's College of Dentistry (USA) and dental supply firm Pentron Corp. Another company **Hybrid and Pentron** developed Nano-Bond, dental bonding agents commercially launched 2003 year.

Two technologies are currently under investigation, nano-fibre coatings to encourage linear cellular growth and mineral nano-particles in a colloidal suspension to interact with the damaged tooth.

**Table 12. The applications in surface coating and medicine of selected nanomaterials**

<b>NANOMATERIALS</b>	<b>APLICATIONS</b>
Metal oxides such as Ceria, Zinc oxide, Aluymina, Zirconia	Coating on dental implants, Car catalysts, fuel cells, transparent UV, absorbers, antibacterial functions, structural ceramics, Sunscreens.
Carbon	Electrical and thermal conductors Coating on dental implants
Aluminosilicate (imogolite)	Catalyst support, ceramics filter, and humidity controlling building materials
Calcium phosphates (hydroxyapatite)	Bone grafts in periodontology, Coatings on dental Implants

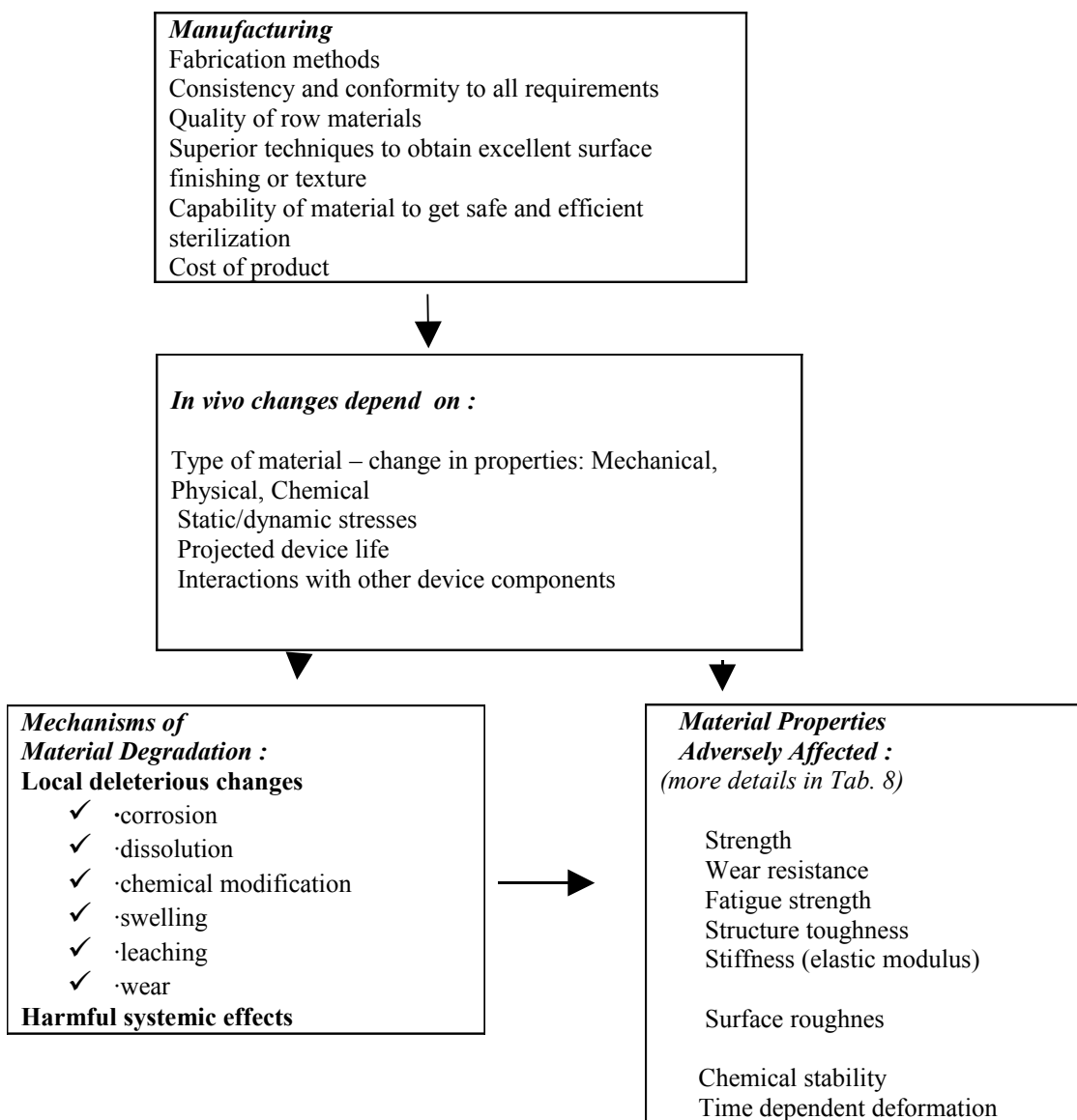
***Nano-fibre coatings***

The investigation of the biological effect of nano-fibre coatings on the trans-mucosal element of the endosseous dental implants. Human gingival fibroblast cells have demonstrated the ability to align, proliferate and secrete collagen in the direction of the nano fibres in preference to other topographies. It was hypothesised that if this topography is applied in a circumferential direction around the implant abutment, gingival fibroblasts will align to this surface nanotopography, leading to the secretion of collagen fibres circumferentially around the implant, forming a tight fibrous collar This fibrous soft tissue attachment will protect the underlying osseous attachment from bacterial attack and breakdown.

***Mineral nano-particles***

The investigation of the ability of colloidal nano-particles (Hydroxy-apatite, silica, an analogue of silica or a calcium compound) to infiltrate demineralised (cariou) dentine and act as a "seed" for further remineralisation. It is hypothesis that the application of an appropriate formulation of colloidal nano-particle to a cariou lesion may prevent further demineralisation and given the right environment it may encourage remineralisation.

**Table 7. The effect of the physiological environment on materials/devices**  
 (Adapted from Ref 10.- Gautam P., Valiathan,,2008)



## SAFETY OF DENTAL DEVICES AND BIOMATERIALS

### *Biological Response to Dental Device Materials*

All materials intended for application in humans as biomaterials, medical devices, or prostheses undergo tissue responses when implanted into living tissue (Anderson, 2001). Alloys must demonstrate biocompatibility by conducting toxicity testing according to ANSI/ADA (USA) document, which describes recommended standard practices for biological evaluation of dental materials. This testing requirements include cytotoxicity testing that evaluates cell death in L929 or HeLa cell cultures exposed to the alloy, hemolysis testing in rabbit blood and mutagenicity testing conducted according to the Ames test. Corrosion testing must be completed for new alloys by comparing their performance to alloys that have been in use successfully for at least five years. In order to avoid undesirable problems with Biomaterials and/or Devices, we suggest to follow the materials safety procedures as shown in Tab.13. Any material implanted into the body evokes a biological response which could be dangerous. Some responses are simply fibrous capsule formation protecting both the implant and the host. However some responses develop into chronic inflammatory responses with macrophage accumulation and development of giant cells. The in vitro studies are being developed, and so far there is much data accumulated on PMMA (polymethylmethacrylate: bone cement), HA (hydroxyapatite, a calcium phosphate ceramic used to coat dental and orthopedic implants), and the oxides of titanium and cadmium which would be the surface of implants made of these metals. The production of biologically active substances such as nitric oxide and tumour necrosis factor TNF alpha (which are important substances in inflammatory responses and the production of cytokines such as Il-6, Il-4, and Il-10) involved in the immune responses are being assessed. Lipopolysaccharide (LPS), which is a component of the cell wall of Gram negative bacteria and a known stimulant of cells, is added to macrophage cultures in the presence and absence of the particles. It is evident to date that there is strong production of the biologically active substances by the LPS alone. The addition of HA or PMMA, with the LPS to the macrophage cultures, markedly potentiates the production of these substances. Whether it is additive or synergistic is still being assessed. On the other hand, the presence of the metallic oxides depresses the response to LPS.

The in vivo data have indicated the formation of a capsule composed of fibroblasts and macrophages when the material is placed into the peritoneal cavity for several days. These cells can then be grown in culture and their activity assessed. The production of the biologically active substances by these peritoneal cells in the absence of LPS is very low. The addition of LPS stimulates the active response. The in vitro data and the in vivo data seem to be in agreement and giving correlative studies.

These findings on the different responses to the different particles and materials will help delineate the differences in biological reaction. Natural latex in medical devices can cause life-threatening Type 1 allergic reactions in individuals sensitized to latex proteins. HSB latex research project was initiated to solve the problem of severe allergic reactions. It included efforts to provide basic data on the nature of allergens and to develop methodology for evaluating the allergenic potential of latex products. The studies are focused on the identification of allergenic proteins in latex in order to reduce or eliminate them from finished latex products.

***Risk associated with metals in dental prostheses***

Development of tumours near medical implants raises concerns regarding the safety of certain implant materials. Metal prostheses consist mainly of iron in **titanium and cobalt alloys**. **Copper** is the main component of dental casting alloys and amalgams. All implanted metallic materials corrode and release ions or particulate matter into the surrounding tissue. It has been suggested that long-term use of medical implants, made from either metallic or synthetic materials, may cause mutations or be carcinogenic. Better understanding of the processes and interactions between materials and the biological environment is needed for assessing the risk of a variety of metal-containing dental devices.

Studies are being conducted in order to evaluate the effects of **mercury** vapour on gene expression in rat brain. Mercury constitutes 50% of dental amalgam, and amalgam restorations release small amounts of mercury vapour (elemental mercury). This vapour is absorbed and distributed throughout the body, localizing in the kidney and brain. Dental practitioners who use mercury have elevated urinary mercury levels, and in persons who have amalgam restorations, the number of amalgams is directly proportional to the urinary mercury concentration. Since mercury is a known neurotoxicant, exposure to mercury vapour during pregnancy may interfere with brain development. In contrast to animal studies, reports of human reproductive and developmental effects due to occupational vapour exposure have been inconclusive.

**Table 13. Dental Devices Safety Data Sheet**

Product and Company Identification  
Composition and Information of Ingredients  
Hazards Identification  
First aid Measures  
Fire Fighting  
Accidental Release Measures  
Handling and Storage  
Exposure Controls/Personal Protection  
Physical/Chemical Characteristics  
Stability and Reactivity  
Toxicological Information  
Ecological Information  
Disposal Consideration  
Transport Information  
Regulatory Information

**CONCLUSION**

The Dental Biomaterials Digital Library will be structured as a unique, consistent data infrastructure including all the compiled information, and it will provide flexibility, extensibility and high search performance. The compiled information will be entered into the database, data structures and Web-based programs for the database. Updating will be created, as well as Web-based program for peer-to-peer knowledge exchange.

The content will be published via the specialized Web site to professionals worldwide, with a flexible multi-layer access system, to provide a quick, easy online access via a single portal to

consistent and relevant materials information. Web-based search engine with superior search performance, and multiplicity of search modes will be developed, combined with additional special software modules for material cross-referencing and identification. Multilingual system and content will be deployed, in order to provide access to all the information to as broad audience as possible.

### ***Expected benefits of digital library***

The expected results are to:

1. Research, structure, review and harmonize various data and information sources for Dental Biomaterials worldwide.
2. Develop and deploy digital library for dental biomaterials, as the world's most comprehensive information resource for biomaterial properties, applied in dentistry, and other fields.
3. Develop innovative ways and search mechanisms for finding information from the database.
4. Create necessary know-how, human and equipment infrastructure to continue with permanently updating and upgrading the database and the complete system.
5. Form a large network of participants for information and knowledge exchange and leverage.
6. Market segments will include:
  - Dental device manufacturers
  - Dentistry practitioners
  - Material specialists
  - Regulatory bodies (Institutes on Standards and Technology, Institutes of health, etc.)
  - Research and scientific community (Universities, Research institutes and centres, University hospitals, Pharmaceutical companies, Biomedical engineering students, etc.).

The obtained results will gain a broader understanding of the work being performed globally by identifying, visiting and assessing work being done at key research centres for Dental Biomaterials. Examining new cross-disciplinary strategies will help to identify “knowledge gaps” in critical areas of material and clinical science and engineering that need to be filled in order for the potential of biomaterials engineering to be realized by end users of Dental Biomaterials Digital Library.

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**Key words:**

Dental biomaterials digital library; Computer technology; Databases, Search engines and Software, Material properties, Titanium, Biocompatible materials, Dental implants, Calcium phosphates (hydroxyapatite- HA), Periodontal, Bone defects, Safety, Dental devices

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