The main aim of NEXT-3D project is to develop the next generation of multifunctional 3D materials for orthopaedic and dental implants. Multifunctional materials with drug delivery properties and antibacterial properties are desirable by clinicians. Research will be conducted following a multi- and inter-disciplinary research methodology designed to develop innovative biomedical materials using advanced processing technologies (3D laser printing and sintering) with market potential. The proposed research and innovative programme will lead to the advancement of knowledge in the field and to new materials with superior properties. In this NEXT 3D Newsletter describes the latest updated news about the project.

**Latest News**

**Development and Optimization of Hydroxyapatite and Chlorapatite powders for 3D-printing**  
Zeinab Salary, Parastoo Jamshidi, Zuzanna Trzcinska, David Grossin, Ghislaine Bertrand, Olivier Marsan, Cédric Charvillat, Imane Demnati, Moataz Attallah, and Artemis Stamboulis  
*Contact persons: Dr. Artemis Stamboulis/Dr. Sooraj Nandyala, Email: a.stamboulis@bham.ac.uk*

The improvement of 3D-printing processes (3DPP) technology in biomedical and tissue engineering has dramatically influenced the potential ability of making biomedical implants and scaffolds by applying data from clinical imaging and computer aided designs. Among different types of 3D printing techniques, Selective Laser Sintering / Melting (SLS/M) and Stereolithography (SLA) are very appropriate for the manufacturing of highly precise structures which can be used for different biomedical applications such as aids for surgery, scaffolds and body implants [1]. The aim of this work is to select and optimise appropriate hydroxyapatite (HA) or chlorapatite (ClA) powder applied in 3DPP. Different apatite powders were characterised in order to identify the effect of particle size (P.S), flowability and thermal stability for various 3DPPs. A specimen SLA 3D printed HA and ClA was shown in the images. A comparison between HA and CIA in terms of thermal properties and structure was also studied.

![SLA 3D-printed (a) HA and (b) CIA](image)

**Antimicrobial functionalization of surface of Ti6Al4V using an antimicrobial organic coating**  
Gabriela Melo Rodriguez, James Bowen, Besim Ben-Nissan and Artemis Stamboulis  
*Contact person: Dr. Artemis Stamboulis, Email: a.stamboulis@bham.ac.uk*

Currently, the majority of load bearing replacement implants are made by titanium alloys. Titanium alloys are widely used due to their biocompatibility, non-toxicity and mechanical properties, which allow the implant to integrate with the body preventing fracture and rejection of the implant. In this project, Ti6Al4V plates are coated with polydopamine and antimicrobial peptides (AMPs). AMPs are a part of the innate immunity system of all organisms and have been shown to be effective against a broad range of microbes. Polydopamine is an adhesive polymer which mimics the mussel adhesive proteins, can attach on virtually any surface, is not cytotoxic and improves cell attachment. The purpose of this work is to study different possibilities of coating Ti6Al4V surfaces with polydopamine and peptides, and test the mechanical properties of the coated surfaces.
Conventionally, polydopamine is applied on the surface by immersing the surface into a solution of 5 mg/mL dopamine in Tris buffer (pH 8.5) at room temperature (RT) overnight. In this research polydopamine was coated at two different temperatures ambient and 60°C and by three different coating techniques: simple immersion, dip coating and spin coating, followed by covalent immobilisation of AMPs on the coated polydopamine as shown in the schematic diagram.

Hydroxyapatite/PLA biocomposite thin films for slow drug delivery of antibiotics for the treatment of bone and implant-related infections

Innocent J. Mach, Besim Ben-Nissan, Jerran Santos, Sophie Cazalbou, and Bruce Milthorpe

Contact persons: Prof. Besim Ben-Nissan, Email: Besim.Ben-Nissan@uts.edu.au

Drug delivery technology presents an interesting interdisciplinary challenge for pharmaceutical, chemical engineering, biomaterials and medical communities. In general, a biomaterial that will act as a drug carrier must have the ability to incorporate a drug, to retain it in a specific site, and to deliver it progressively with time to the surrounding tissues without an adverse effect. This research is aimed at developing and testing gentamicin (due to its widely use for the treatment of bacterial infections) loaded hydroxyapatite particles (HAp) within thin film of polylactic acid (PLA) biocomposites as slow release drug delivery devices. In this work, drug delivery systems were developed from coralline hydroxyapatite (HAp) and biodegradable polylactic acid (PLA). Gentamicin (GM) was loaded to either directly PLA (PLAGM) or in HAp microspheres. Drug loaded HAp microspheres were used to make thin film composites (PLA-HApGM). Dissolution studies were carried out in a phosphate buffered saline (PBS) solution. The release profiles suggested that HAp particles improved drug stabilization and availability as well as controlled the drug release rate.

Release profile of gentamicin from PLAGM and PLAHApGM thin films as shown in the Figure. Gentamicin drug delivery device produced from PLA-coraline HAp thin film composite. (a) the SEM image of the coralline HAp surface used for drug delivery (only the struts are used as drug delivery vehicles-shown in the circled area), and (b) drug release profile of only gentamicin within PLA (PLAGM) and HAp coralline particles loaded with gentamicin and embedded within a PLA matrix (PLHApGM) showing lower amounts of drugs release as well as a longer release rate up to 8 weeks.
SEM picture of gentamicin loaded PLAGM and PLAHApGM before and after three weeks of drug release in PBS revealing degraded morphologies.

**Calcium Phosphate Formation: Conversion of marine structures to calcium phosphate materials:**

Mechanisms of conversion using two different phosphate solutions

Innocent Macha, David Grossin and Besim Ben-Nissan,

Contact person: Prof. Besim Ben-Nissan Email: Besim.Ben-Nissan@uts.edu.au

The potential applications of natural biogenic materials such as marine structures can be easily overlooked due to environmental concerns. While it is true, that a wide range of marine structures are limited and protected, similarly there are also a variety of materials that are abundantly available and are yet to be exploited for their possible use. Among marine structures, coral mineral consisting of calcium carbonate in the forms of aragonite or calcite with trace elements of strontium, magnesium and sodium, has considerable success as apatite precursor and bone graft material. Corals have porous structure with pore size ranging from 150 to 500 μm similar to cancellous bone and form a chemical bond with bone and soft tissue in vivo. This research aims to evaluate the mechanism of conversion of a natural calcium carbonate such as coral under acidic and basic conditions using mechano-chemical conversion techniques.

SEM pictures showing the morphology of coral after 0.5 and 24 hrs conversion under acidic and basic condition.
In this study, coralline materials were successfully converted to HAp under acidic and basic conditions. It was previously reported, that coral converts hydrothermally into HAp in ammonium phosphate solutions with preservation of sample form and morphology signifying topotactic ion exchange reaction mechanisms. Mechano-chemical conversion of coral to HAp follows the topotactic reaction mechanism under ammonium phosphate solution and dissolution-recrystallization using an orthophosphoric acid phosphate solution. Utilization of natural biogenic materials such as coral in the production of HAp addresses the significant cost of synthetic raw materials and the high cost of HAp. Artificially grown coralline HAp has significant potential in the medical field especially in orthopaedic and tissue engineering.

**Infection Studies - Clinical cases**

Dr. Gerard Giordano, Consultant Orthopaedic Surgeon, JDH, Toulous, France.
Contact email: ortho.giordano@gmail.com

Periprosthetic infections are frequently caused by coagulase-negative *Staphylococci* (CoNS). These bacteria are often resistant to methicillin. Bacteria culture tests remain the gold standard but they require often several days in order to obtain a result. Thus, a rapid test could be interesting in order to advice sooner the antibiotic strategy. RT-PCR (Cepheid®) has been previously validated to detect *Staphylococcus aureus* and the presence of MecA gene, which shows a methicillin resistance. The purpose of this study was to evaluate the detection of methicillin resistance of CoNS isolated from articular prosthesis by the RT-PCR technique.

Further, in the treatment of prosthetic joint infection often prosthesis replacement is required. However, the question is whether a two-stage revision would be better than a one-stage revision. This is still controversial and criteria proposed in order to choose one or another strategy, are not universally accepted. The success of the treatment depends mainly on the surgeon’s experience. Some of the clinical case studies have been reported in the following link: [http://www.boneandjoint.org.uk/search/procs/giordano](http://www.boneandjoint.org.uk/search/procs/giordano)

**Dissemination of Results**

- Gabriela Melo Rodriguez, James Bowen, Besim Ben-Nissan and Artemis Stamboulis, *Titanium oxide formation for peptide functionalization*, 10th World Biomaterials Congress (WBC), which will be held in Montreal May 17-22, 2016. (Poster Presentation).
- Innocent Macha, David Grossin and Besim Ben-Nissan, *Conversion of marine structures to calcium phosphate materials: Mechanisms of conversion using two different phosphate solution*, Bioceramics 27, the Annual Meeting of the International Society for Ceramics in Medicine to be held in Bali Island, Indonesia on October 27 to 29, 2015. (Poster Presentation).

**Publications**


**Posters**
Evaluation of a new Computer-assisted Guidance System
Gerard Giordano1, Michel Brax2, Bernard Stulberg3, Nicolas Hohl4, Sandrine Polakovic5
1Hospital Joseph Ducuing, Toulouse, France; 2Hôpital de Haguenau, Haguenau, France;
3Cleveland Clinic, Cleveland, United States;
4Exactech France, Illkirch, France; 5Blue Ortho, La Tronche, France

INTRODUCTION
Total Knee Arthroplasty (TKA) continues to be a popular treatment method with great success rates for most designs. The literature proves that the way the prostheses are implanted have a great impact on the longevity of the device1. Navigation has been a great help to the decision making process for surgeons in the OR and new systems should continue to improve to be simpler, faster and cheaper.

The goal of this study was to report the in-surgery results for a continuous series of Exactech Optetrak knee prostheses (Exactech Inc., FL, USA) implanted by three operators between July 2010 and May 2014.

MATERIALS AND METHODS:
The study analyzed 410 knee prostheses implanted at the Hôpital de Haguenau, Haguenau, France (site 1), Hôpital Joseph Ducuing, Toulouse, France (site 2) and The Cleveland Clinic, Cleveland, USA (site 3) by three senior surgeons with the help of a new computer-assisted guidance system: the Exactech GPS (Exactech, Inc., FL, USA).

The Exactech GPS features a unique “surgeon profiler” that allows the surgeon to define exactly the steps he wants the computer to help him with during surgery. The three centers did not follow the same surgical technique and therefore had different “profiles”. On site 1, the technique was a tibia first technique with balancing in flexion to determine the external rotation of the femoral component while on site 2, the technique was either the same tibia first technique or a femur first technique. On site 3, the surgeon used indifferently a variety of techniques including a tibia first technique with balancing either in flexion or in extension and flexion to determine the external rotation of the femur.

The goal was to determine the error between the planned cuts for both the tibia and the femur compared to the actual cuts digitized using the guidance system (see Figure 1). The operating time as well as the chosen external femoral rotation were also analyzed. Finally, the post-operative leg alignment was compared to the pre-operative one.

RESULTS:
The difference between the planned and digitized cuts as well as the final registered HKA angle are detailed in Table 1.

Table 1: Differences between planned and digitized cuts and HKA angle

<table>
<thead>
<tr>
<th>BONE</th>
<th>PARAMETER</th>
<th>SITE 1</th>
<th>SITE 2</th>
<th>SITE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2.26°±1.11°</td>
<td>-0.03°±0.87°</td>
<td>0.28°±0.95°</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.00°±0.99°</td>
<td>-0.48°±0.92°</td>
<td>0.24°±1.21°</td>
</tr>
<tr>
<td>Tibia</td>
<td>Varus/Vexion*</td>
<td>0.03°±0.99°</td>
<td>-0.11°±0.81°</td>
<td>0.18°±1.43°</td>
</tr>
<tr>
<td>Femur</td>
<td>Flexion/Extension*</td>
<td>-0.67°±1.36°</td>
<td>-0.41°±0.86°</td>
<td>0.03°±1.66°</td>
</tr>
<tr>
<td>Tibia &amp; Femur</td>
<td>HKA angle*</td>
<td>17° (17°-187°)</td>
<td>180° (172°-180°)</td>
<td>179° (175°-183°)</td>
</tr>
</tbody>
</table>

*Varus/Vexion: varus is signed positive, valgus is signed negative;
*Flexion/Extension: more flexion is signed positive, less flexion is signed negative;

Average operating time was 30 minutes for Site 1, 20 minutes for Site 2, and 41 minutes for Site 3. External femoral component rotation from the posterior condyles ranged from 0° to 18° with an average of 3.7° degrees for Site 1, from -3° to 8° with an average of 2.9° for Site 2 and from -3° to 10° with an average of 2.4° for Site 3. Post-operative Hip-Knee-Ankle angle (HKA) varied between 177° and 182° with an average of 179° for Site 1, 172° to 188° with an average of 180° for Site 2, and 175° to 183° with an average of 179° for Site 3; Pre-operative HKA ranged from 162° to 191° (see Figure 2).

DISCUSSION:
Despite different techniques and teams, all surgeons experienced similar results. Cuts were aligned in the frontal plane, while guidance was harder to follow in the sagittal plane, possibly due to saw blade bending during resection. Average surgical time was similar. GPS guidance added an average of 10 minutes to standard surgical times. All surgeons agreed the increased accuracy justified the additional time. Regardless the site, all average femoral rotations were close to the accepted 3° standard. Average post-operative HKA was 180°. HKA scores were within 3° of perfect alignment in all Site 3 cases and in 95% of Site 2 and Site 3 cases. According to the literature, HKA between 177° and 183° is linked with high implant survival.

Participating surgeons associated Exactech GPS with satisfactory immediate post-operative results.

References:

Figure 1: GPS Screens detailing A: the tibial cut planning, B: the tibial cut control, C: the femoral cut planning and D: the femoral cut control

Figure 2: Pre and Post-operative HKA angles
Knee joint infection after anterior cruciate ligament reconstruction: a series of 33 cases among 2822 patients
E. Bonnet1,2,3, F. Potel1, R. Limal1, D. Jones4, C. Javols5, F. Limous6, A. Bicart-See1, J. Remy7, G. Giordano8.
1 Hôpital Joseph Ducuing Toulouse, 2 Clinique Médigalone Garonne Toulouse, 3 Clinique d’Occitanie Muret, France.

Introduction and purpose
Septic arthritis of the knee is a rare complication following anterior cruciate ligament reconstruction (ACLR) and no standardized treatment is available. The aim of our study was to evaluate the prevalence, the causes, the management and the short-term outcome of patients with knee joint infection (KJ) after ACLR.

Methods
We conducted a retrospective descriptive study including all patients with a diagnosis of septic arthritis of the knee after ACLR during a 2 year-period (from November 2010 to October 2012) in 3 major orthopedic units, located in the same metropolitan area and sharing the same infectious disease specialist.

Results
From our consecutive case series of 2822 patients who underwent ACL reconstruction, we identified 33 cases of KJ (incidence rate = 1.1%).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Male/female</th>
<th>Mean age (years)</th>
<th>Antibiotic prophylaxis</th>
<th>Techniques used for ACLR</th>
<th>Mean/median time from ACLR to surgical management of infection (days)</th>
<th>Mean/median time from the date of clinical suspicion of infection to management (days)</th>
<th>Classical signs of local inflammation</th>
<th>Fever</th>
<th>Elevated Protein C Reactive</th>
<th>Elevated WBC count</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>31/2</td>
<td>30.5</td>
<td>Cefazolin or cefuroxim</td>
<td>DIET (n = 22) Kenneth Jones (n = 9) others (n = 2)</td>
<td>25/24</td>
<td>5</td>
<td>All patients (81.8%)</td>
<td>All patients (mean value = 146 mg/l)</td>
<td>9 patients (37.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Results of perioperative samples
<table>
<thead>
<tr>
<th>Bacteria (n = 36)</th>
<th>Number of aspirates</th>
<th>First-line antibiotic treatment</th>
<th>Second-line antibiotic agents</th>
<th>Mean duration of treatment (months)</th>
<th>Mean Duration of follow-up (months)</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (n = 11) (30.6%) CoNS (n = 13) (36%) S. lugdunensis (n = 1) (13.9%) Enterobacteriaceae (n = 6) (16.7%) P. acnes (n = 4) (11.1%) P. aeruginosa (n = 2) (5.6%)</td>
<td>One (n = 28) Two (n = 3) Three (n = 1)</td>
<td>Vancomycin (n = 1)</td>
<td>Gentamicin + Rifampin (n = 5)</td>
<td>6 weeks (4 to 8 weeks)</td>
<td>18</td>
<td>All patients cured (one after material removal) except one (chronic osteomyelitis)</td>
</tr>
</tbody>
</table>

Conclusions
To our knowledge this is the largest reported series of infection after ACLR. The incidence was close to 1%. The great majority of infections occurred in the month following surgery and was due to staphylococci (with an unexpected frequency of S. lugdunensis). A conservative strategy consisting in arthroscopic lavage and 6 weeks of antibiotic treatment was effective. A more prolonged follow-up period is required to determine the long term functional outcome.

Complications of vancomycin perfusion by central venous catheter
M. Saussan-Dahan, L. Gault, N. Rouge, E. Bonnet, G. Giordano, C. Chassery, A. Bicart-See
Joseph Ducuing Hospital, Toulouse, France

Background
Infections and thrombotic events related to Central Venous Catheter (CVC) are life-threatening complications which may aggravate the initial prognosis. To the best of our knowledge, the risk factor linked to vancomycin administration by CVC was not reported in the literature.

Methods
- Retrospective observational study, conducted between April and December 2012.
- Inclusion criteria: Patients who have received vancomycin by CVC placed in our institute and who presented:
  - a major complication (thrombotic or infectious);
  - a minor complication (dislodged catheter, local signs or pain or inflammation).

Results
8 PATIENTS INCLUDED

Characteristics of patients
- Average age = 61 year-old [27.80].
- Sex ratio = 0.3.
- At least one risk factor per patient: Risk factors of patients (N=8). Number of patients

Reasons for hospitalization
- 100% of septic surgery (orthopedic for n=7).
- With intraoperative insertion of double lumen polyurethane CVC: supravascular for 6 patients, subclavian for 2 patients.
- 50% of patients transferred.
- Treatment with vancomycin by CVC

Vancomycin dosage: 2 to 4.5 gram
Vancomycin concentrations: 33 to 75 mg/ml after dilution in sodium chloride 0.9%.

COMPLICATIONS
- 3 patients with a minor complication (deep vein thrombosis).
- 5 patients with a minor complication and a catheter-related infection.

Discussion
These cases underline the potential of high vancomycin dose perfused by CVC, diluted to concentrations higher than those recommended (10 mg in sodium chloride 0.9% or 40 mg in 5% glucose) in these complications.

Perspectives
Further studies with a larger population are required to determine whether a continuous infusion of high vancomycin dose by CVC facilitates the risk of septic and thrombotic complications.

PS-097 eahp
Portal explores the Horizon 2020-funded NEXT-3D project with co-ordinator Dr Artemis Stamboulis. The MSCA brings together European and Australian researchers to realise breakthroughs in 3D multifunctional materials for biomedical applications.

3D connection

Realising the global potential of the EU’s research and innovation framework programme whilst benefiting patients is encapsulated in the Horizon 2020-backed ‘Next generation of 3D multifunctional materials and coatings for biomedical applications’, or NEXT-3D, project. In September 2014, it was announced that the UK’s University of Birmingham, along with the National Polytechnic Institute of Toulouse (INPT), and the Association des Amis de la Médecine Sociale in France had been successful in their funding application.

The project is a Marie Skłodowska-Curie Action (MSCA) funded under the Research and Innovation Staff Exchange scheme. The project has financing worth €193,500 between 2015 and 2017, and a unique attribute of the venture is its links with Australia, where the project is partnering with both universities and a private firm.

As a third country partner, from Australia involved in a Horizon 2020 project must bring their own money to the table. In the University of Technology, Sydney, the University of New South Wales, and the company BresaMedical have all been successful in securing match funding for the project from the Australian Academy of Science.

To find out more about the NEXT-3D project, Portal spoke to its co-ordinator, Dr Artemis Stamboulis of the University of Birmingham, who detailed the main objectives, provided a further insight into the Australian connection, and outlined the benefits of using funding from the Marie Skłodowska-Curie Action.

What are the core aims of NEXT-3D?

Whilst writing this project proposal, we set the goal of making a commercial product which can be 3D printed and multifunctional. We began by looking at the individual difficulties that such a development would have and brought this into the project. In particular, we are looking at tackling problems with ceramics, especially regarding hydroxyapatite, and the problems associated with 3D printing, notably why 3D printing cannot currently be completed and why it is difficult. We want to make it possible to successfully 3D print ceramics like hydroxyapatite, which has multifunctional behaviour properties.

Another goal is to 3D print metallic surfaces that we are able to functionalise and have the ability to add antimicrobial properties to, as well as other behaviour attributes, for example drug release, anaesthetic and anti-inflammatory properties.

Which partners are involved in the project?

NEXT-3D is based on a secondment to industrial partners, helping to ensure knowledge transfer from industry to academia. We are going to assess the difficulties industry faces in developing these types of materials, and at the start of the project we will aim to identify the problems with the processing of these materials and the difficulties in developing the final product.

We have six partners in total; three of them are beneficiaries, whilst the others are associate members and all come from Australia. This latter group applied, and received, funding from the Australian Academy of Science. Receiving match funding is easier if we are successful at securing European funding; most of the time match funding is awarded.
Upcoming Events

10th World Biomaterials Congress - Montreal, QC Canada - 17-22 May, 2016.  
http://www.wbc2016.org/

https://bio2016.abstractcentral.com/

Useful Links

http://www.birmingham.ac.uk/research/activity/metallurgy-materials/next-3d/index.aspx

Job Opportunities

At present there are no available job opportunities. If you are interested in submitting your CV, please contact Dr. Sooraj Nandyala, Project Manager, at s.h.nandyala@bham.ac.uk for future consideration.

Contact us

Dr. Sooraj Nandyala, Project Manager, University of Birmingham, UK. Email: s.h.nandyala@bham.ac.uk