NEWSLETTER

Issue No:1 December 2015

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.

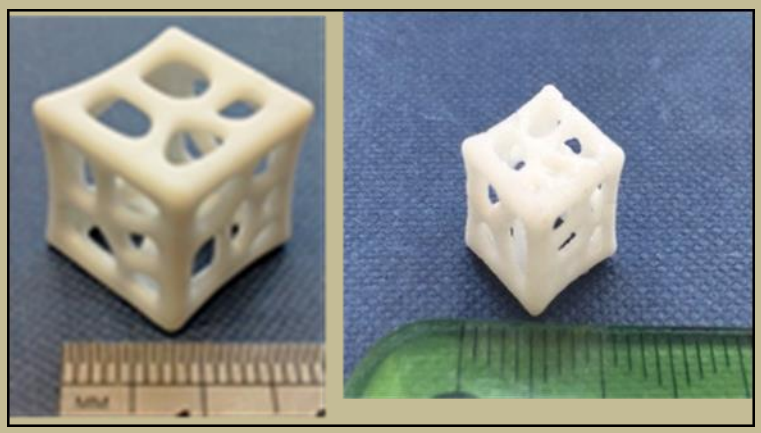
Latest News

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 ClA in terms of thermal properties and structure was also studied.



SLA 3D-printed (a) HA and (b) ClA

Antimicrobial functionalization of surface of Ti6Al4V using an antimicrobial organic coating

Gabriela Melo Rodriguez, James Bowen, Besim Ben-Nissan and Artemis Stamboulis

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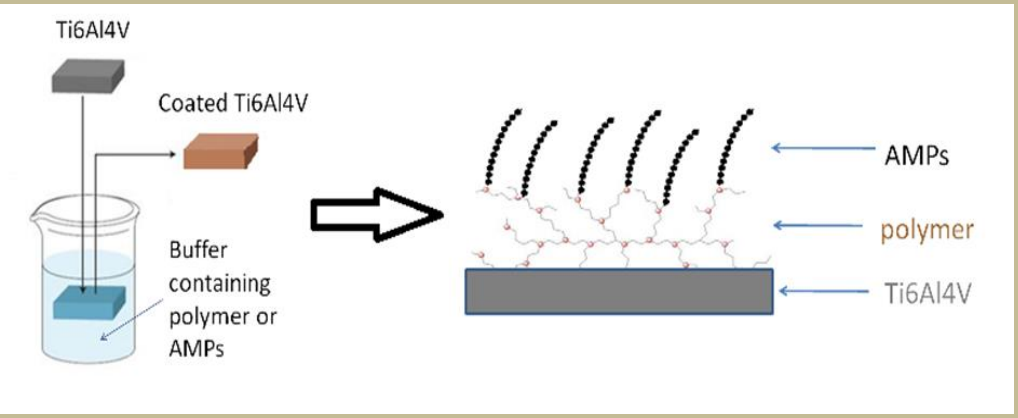
Currently, the majority of load bearing replacement implants are made by titanium alloys. Titanium alloys are widely used due to their biocompatibility, non-toxicity and mechanical properties, which allow the implant to integrate with the body preventing fracture and rejection of the implant. In this 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.



A schematic diagram of coating preparation technique

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

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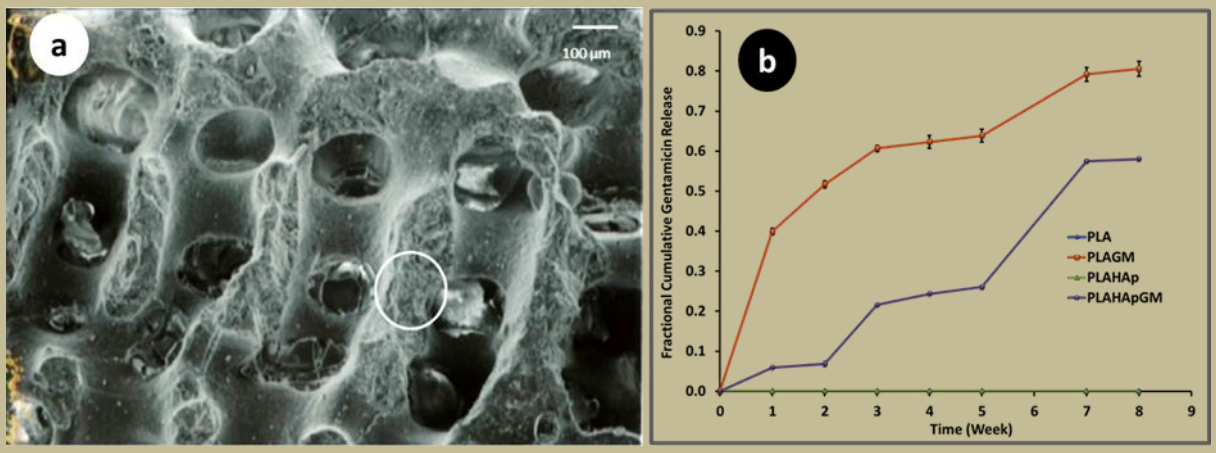
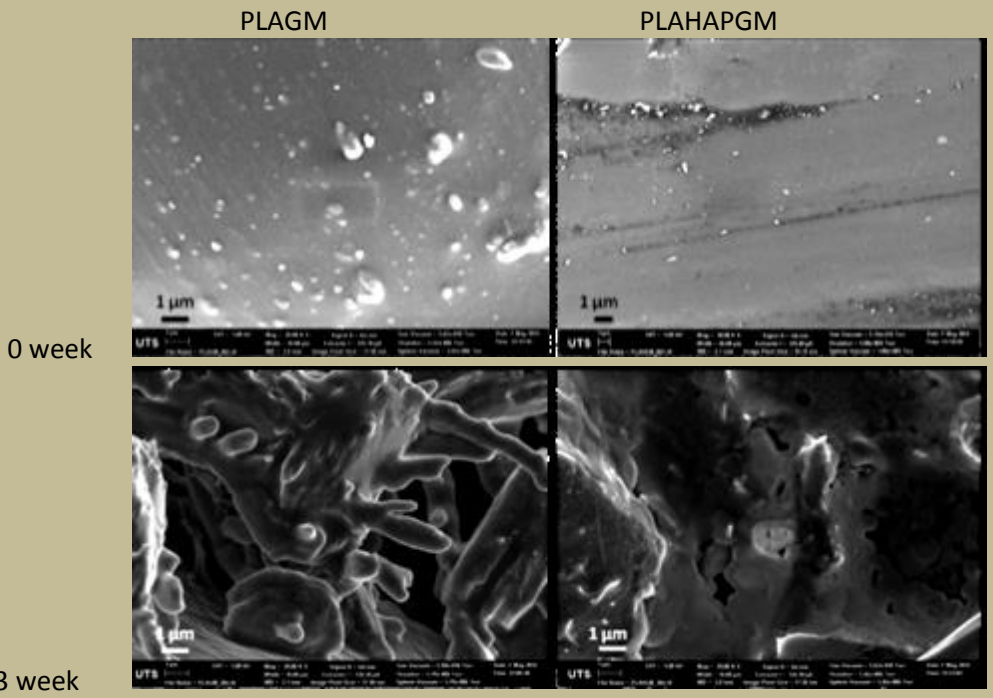
Drug delivery technology presents an interesting interdisciplinary challenge for pharmaceutical, chemical engineering, biomaterials and medical communities. In general, a biomaterial that will act as a drug carrier must have the ability to incorporate a drug, to retain it in a specific site, and to deliver 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-HAp-GM). 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-coralline 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.



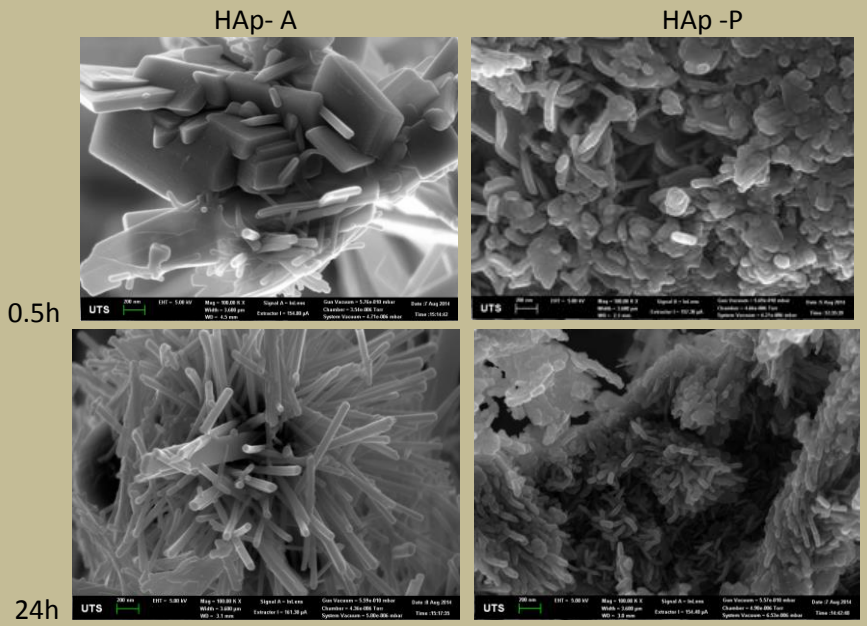
SEM picture of gentamicin loaded PLAGM and PLAHApGM before and after three weeks of drug release in PBS revealing degraded morphologies.

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.
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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 methicilline 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**

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).
- Zeinab Salary, Cédric Charvillat , Parastoo Jamshidi, Artemis Stamboulis, Moataz Atallah, David Grossin, Besim Ben-Nissan, Olivier Marsan, ***Additive manufacturing of Bio-ceramics for bone repair***, 10th World Biomaterials Congress (WBC), which will be held in Montreal May 17-22, 2016. (Poster Presentation).
- Innocent J. Macha, Besim Ben-Nissan, Jerran Santos, Sophie Cazalbou, Bruce Milthorpe, ***Hydroxyapatite/PLA biocomposite thin films for slow drug delivery of antibiotics for the treatment of bone and implant-related infections***, 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. (Oral 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

- J. Macha, Besim Ben-Nissan, Jerran Santos, Sophie Cazalbou, Bruce Milthorpe, ***Hydroxyapatite/PLA biocomposite thin films for slow drug delivery of antibiotics for the treatment of bone and implant-related infections***, Bioceramics 27, (2016) (In press).
- Innocent Macha, David Grossin and Besim Ben-Nissan, ***Conversion of marine structures to calcium phosphate materials: Mechanisms of conversion using two different phosphate solutions***, Bioceramics 27,(2016) (In press).

Posters

Evaluation of a new Computer-assisted Guidance System

Gerard Giordano[1], Michel Brax[2], Bernard Stulberg[3], Nicolas Hohl[4], Sandrine Polakovic[5]

[1]Hopital Joseph Ducuing, Toulouse, France; [2]Hopital de Haguenau, Haguenau, France;
[3]Cleveland Clinic, Cleveland, United States;
[4]Exactech France, Illkirch, France; [5]Blue 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 devices[1]. 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.

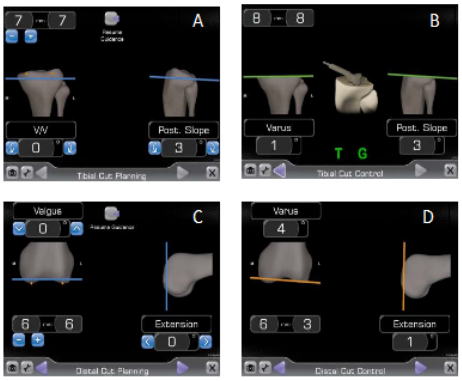


Figure 1: GPS Screens detailing A the tibial cut planning, B the tibial cut control, C the femoral distal cut planning and D the femoral distal cut control

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

BONE	PARAMETER	SITE 1	SITE 2	SITE 3
Tibia	Varus/Valgus*	-0.26° ± 1.11°	-0.01° ± 0.87°	0.28°± 0.95°
	Slope*	0.06° ± 0.99°	-0.48° ± 0.92°	0.24°± 1.21°
Femur**	Varus/Valgus*	0.03°± 0.99°	0.11°± 0.81°	0.18°± 1.43°
	Flexion/Extension*	-0.67°± 1.36°	-0.41°± 0.86°	0.03°± 1.56°
Tibia & Femur	HKA angle*	179° [177-182°]	180° [172-186°]	179° [175-183°]

*Varus/Valgus: varus is signed positive, valgus is signed negative;
Slope: more posterior slope is signed positive, less slope is signed negative;
Flexion/Extension: more flexion is signed positve, less flexion is signed negative;
HKA angle: less than 180° is varus, more is valgus.

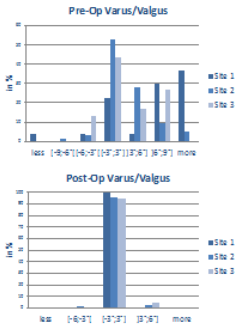


Figure 2: Pre and Post-operative HKA angles

Average operating time was 39 minutes for Site 1, 29 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 186° 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 1 cases and in 95% of Site 2 and Site 3 cases. According to the literature1, HKA between 177° and 183° is linked with high implant survival.

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

References:
1. Ritter et al. Postoperative alignment of total knee replacement: its effect on survival. CORR 1994; 299:153-56

EFORT 2014
poster 14-875

Knee joint infection after anterior cruciate ligament reconstruction: a series of 33 cases among 2822 patients

E. Bonnet[*1,2,3], *J.-F. Potel*[2], *R. Limozin*[2], *D. Jones*[2], *C. Javois*[2], *F. Limousy*[3], *A. Bicart See*[1], *J. Remy*[1], *G. Giordano*[1].

1 Hôpital Joseph Ducuing Toulouse, *2* Clinique Médipôle 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 (KJI) 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.

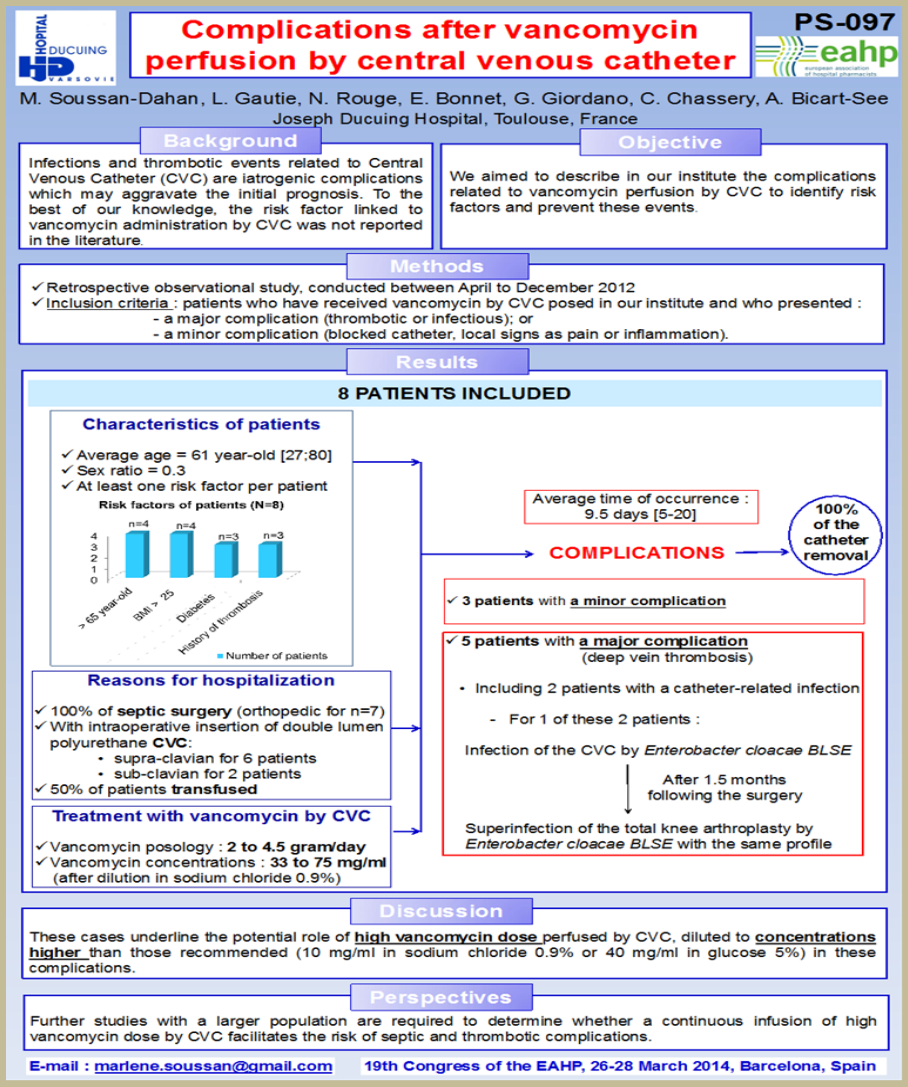
Results

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

Number of patients	Male/ female	Mean age (years)	Antibiotic prophylaxis	Techniques used for ACLR	Mean/median time from ACL to surgical management of infection (days)	Mean time from the date of clinical suspicion of infection to management (days)	Classical signs of local inflammation	Fever	Elevated Protein C-Reactive	Elevated WBC count
33	31/2	30.5	Cefazolin or cefuroxim	DIDT (n = 22) Kenneth Jones (n = 9) Others (n = 2)	26/14	5	All patients	27 patients (81.8%)	All patients (mean value = 146 mg/l)	9 patients (37.5%)

Results of perioperative samples	Bacteria (n = 36)	Number of arthoscopic lavage	First-line antibiotic treatment	Second line antimicrobial agents	Mean duration of treatment	Mean Duration of follow-up (months)	Evolution
Sterile (n = 3) Monomicrobial (n = 26) Polymicrobial (n = 4)	*S. aureus* (n = 11) (30.6%) CoNS (n = 13) (36%) *S. lugdunensis* (n = 5) (13.9%) *Enterobateriaceae* (n = 6) (16.7%) *P. acnes* (n = 4) (11.1%) *P. aeruginosa* (n = 2) (5.6%)	One (n = 28) Two (n = 3) Three (n = 1)	Vancomycin (n = 11) Antistaphylococcal penicillin (n = 10)	Levofloxacin + Rifampin (n = 13)	6 weeks (4 to 8 weeks)	18	All patients cured (one after material removal) except one (chronic osteomyelitis)

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.



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

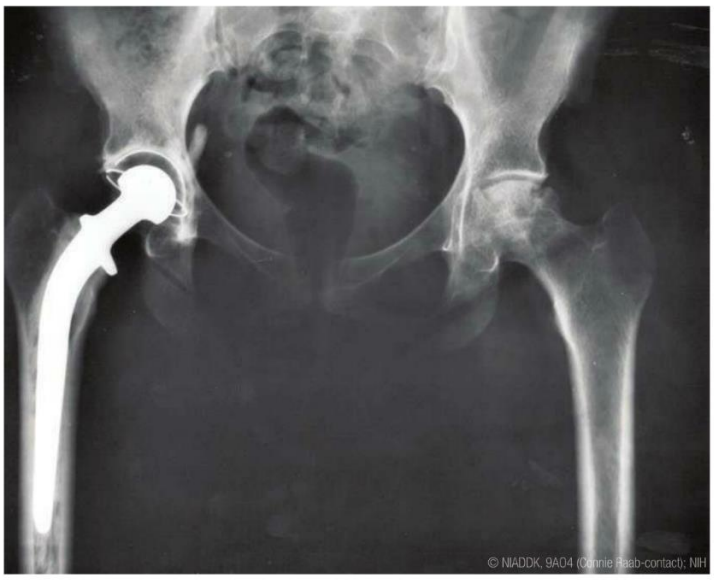
3D connection

Realising the global potential of the EU's research and innovation framework programme whilst benefitting 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, partners from Australia involved in a Horizon 2020 project must bring their own money to the table. The University of Technology, Sydney, the University of New South Wales, and the company BresMedical 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.



X-ray of a hip replacement: the project hopes to 3D print commercially orthopaedic implants

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, analgesic 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.

The NEXT-3D project has a number of partners in Australia, including the University of New South Wales, Sydney

In addition to working with universities in Sydney, we are also working with a company called BresMedical based in Ingleburn, New South Wales. This relatively new firm specialises in 3D printed and personalised implants and is interested in developing its own products.

Also involved in the project is L'hôpital Joseph Ducuing in Toulouse, France, where we are in contact with a clinician who identifies and advises on the current clinical problems in this area, as well as the current demands, available materials, and what role they are unable to fulfil.

Why are you focusing on 3D materials for orthopaedic and dental implants?

The clinical applications in orthopaedics are quite advanced; there are very serious problems associated with bacterial infections, especially in open operations on the hip and the knee. It is the use of materials that might trigger this kind of infection, so multifunctionality is therefore necessary, as well as a good design and the rapid treatment of problematic areas. A core focus is how the industry can process materials and provide them to the patient.

The orthopaedic and dental fields are closely related as they both deal with bone. Applications of biomaterials in orthopaedic and dentistry have progressed in the last ten years, and it is important that we have suitable materials being used as this will lead to further research developments. Orthopaedics and dentistry are costly to the UK NHS, so everything that can be done to make this job easier is important.

Why did you choose the MSCAs?

We can use both early stage as well as experienced researchers, and the funding can be used in a flexible way. The scheme supports the mobility of researchers and therefore the transfer of knowledge and experience between different places, which is important.

Before even applying for funding, we had chosen our partners; we wanted to work with Australia. We were also advised of the possibility of securing match funding from third countries, and it was this flexibility that attracted us.

Yet this action has a problem as I believe the funding is not enough to cover local expenses for the seconded researchers, especially when the secondments take place in Australia, where the cost of living is much higher than in Europe.

Why did you choose to work with Australian partners?

The two universities are extremely well equipped in the area of the commercialisation of materials; for example, the University of New South Wales has extremely good infrastructure regarding the characterisation of materials similar to the ones that we want to develop.

Another motive is the people –for example, in the University of Technology Sydney, there is strong expertise in the development of biomimetic calcium phosphates that could be used in the project. Furthermore, there is also a lot of experience of how to take such materials from the lab to the market. They have some successful schemes and strategies for how to achieve this which would be very useful to have in Europe.

What are the next steps in undertaking the project?

At the University of Birmingham, we have plans to generate further funding from Europe that will complement this project, including further applications to Horizon 2020 as we aim to advance the project beyond 2017.

Throughout July, August and September, we will have our first secondments to Australia. Within these three months we hope to gather enough data in order to complete deliverables that we have promised to finish in the next six months of the project.

After arriving back in the UK, we will have Australians visit us for a project update. Academics from the two Australian universities will also mentor students from the University of Birmingham and INPT, which is important.

We hope that this project will create a basis to better structure this area of research at the University of Birmingham, and seek further funding in order to develop materials for other applications, in tissue engineering and drug release.

HORIZON 2020

Dr Artemis Stamboulis
University of Birmingham

BROWSE www.birmingham.ac.uk

Upcoming Events

10th World Biomaterials Congress - Montreal, QC Canada - 17-22 May, 2016.
http://www.wbc2016.org/
Innovations in Biomedical Materials 2016 - Chicago - 28-31 July 2016.
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