Management Committee Meeting of COST Action CA16217 “European network of multidisciplinary research to improve the urinary stents” Report

Istanbul, Turkey
3th-4th march, 2022

SCIENCE COMMUNICATION MANAGER. UPDATE.
The website mainly for two purposes, firstly to inform about the objectives of our network and secondly to disseminate the activities of the network. Both those that we are going to carry out and the reports of those that we have carried out. Anyway, whenever we update something on the website, AC usually send members an email to advertise it. Any member can send information about their projects, scientific papers, or disseminate their activities. The twitter is used directly to announce ENIUS events, to disseminate the events in real time, and to support the activities that the different groups that make up ENIUS are carrying out. AC encourage members to follow it on the ENIUS twitter. Despite the end of our Action, both the website and Twitter account will remain operative to provide a meeting point for researchers interested in urinary stents.
It was also noted that the video repository of our Workshops (including the one to be held on 4 March 2022) is open to everyone. On the subject of the "Urinary stents. Info Meeting Point", A. Barros (WG4 leader) will speak when he has an update on WG4-5.

IMPLEMENTION OF COST POLICES ON: PROMOTION OF GENDER BALANCE.
Gender Balance Coordinator. Valentina Cauda. ENIUS promote gender balance in all of our activities. ENIUS has 36% women among its MC members, and among all ENIUS members the ratio is very equal, with 49% women and 51% men. On the other hand, there is a big deviation if we evaluate the leadership positions in our Action, we only have a 20% representation of women. This percentage has decreased compared to other GPs, due to the fact that some female members have resigned during the lifetime of ENIUS. And their replacement has not been matched, despite proposals from the MC. We can congratulate ourselves on having done a good job in choosing the speakers and trainers for our training activities with a good gender balance (46% versus 54%).

ECI (YOUNG RESEARCHERS).
AC showed a summary table of all ENIUS lifetime. Young researchers have performed 77.7% of our STSMs, hold 46.6% of leadership positions, and have been invited as speakers in 47% of our network's training activities. They make up 79.6% of the attendees at our training activities. This gives an idea of the great involvement that our network has had with young researchers and the important impact it has had on their training.

INCLUSIVENESS.
The percentage related to activities carried out in these countries have been 66%. Mainly, MC Meetings, TS and Workshops (Porto, Sofia, Belgrade, Lublin, La Valleta, Istanbul). The leaderships roles from ITC countries have been 45% in ENIUS.

FOLLOW-UP OF MOU OBJECTIVES
: MoU Achievements.
.**CIG proposal.** Our proposal is called “Urinary stents and catheters from bench to bedside software”. Acronym “UriSoftware”.

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Our CIG proposal describes the assessment and validation protocols with the whole test methodology in the main test methods: in silico, in vitro and in vivo. Developing a series of algorithms that connect these tests and allow decision making related to the results in each of the tests.

The result of this project will be a software tool to be commercialised, UriSoftware, which will allow researchers, companies involved in the manufacture of stents and catheters, entrepreneurs, and Academia to evaluate and validate their prototypes in a fast, integrated, safe and controlled way. This will reduce the assessment and validation process due to the availability of a unique and innovative tool, carried out by experts, which will shorten development times, reduce costs and increase the efficiency of this industrial design process.

ENIUS DISSEMINATION ACTIVITIES

ENIUS MC MEETINGS & CORE GROUP MEETINGS. AC shows a slide with the information: We have had a series of 7 meetings. From the kick off in Brussels in September 2017 to the current one, Istanbul 2022, with a total of 163 MC members involved.

ENIUS WORKSHOPS/CONFERENCES/TS. Since the Kick off, we have carried out 17 activities to disseminate our network, including TS, Workshops and conferences. Five of them were online, and in spite of their online presentation format, the results were very positive, both for the possibility to see each other online and for the very interesting lectures. We reached an audience that often cannot travel to our face-to-face activities. That is the reason because our last ENIUS Workshop (tomorrow), we have held the in a hybrid format (face to face and online). Venues: Porto Workshop; Oxford TS; Cáceres TS; Sofia Workshop.; La Valleta Workshop; Bern TS, Lublin TS; Belgrade Workshop; I Virtual Workshop-WG4-5; Virtual Conference-WG1; Virtual Conference-WG2; Virtual Conference-WG4-5; II Virtual Workshop-WG6; Istanbul Hybrid-Workshop.

We reached up to 594 participants in our Workshops-TS. AC comments: Honestly, this is a great audience for our objectives and quite surprising.

DISSEMINATION MEETINGS. An important focus of our activity as a network has been dissemination activities to raise knowledge about our multidisciplinary group and the aims of ENIUS.

We have carried out 7 dissemination activities during the duration of our network. It is necessary to highlight the National Congress of the Spanish Association of Urology, the Hands-on of the European Association of Urology. The Symposium on Research & Innovations in Urology in Lisbon, thanks to the invitation of Dr. Barros and Prof. Lima.

And Prof. Kallidonis, during a lecture at the World Endourology Congress in Paris (2018), also made an interesting diffusion of ENIUS.

Another Dissemination Meetings attended by Prof. Missirlis was the 4th international symposium on Nanoengineering for Mechanobiology (N4M) in Genova (Italy) March in 2019. Another request for a dissemination meeting was submitted by Prof. Sarah Waters and Dr. Dario Carugo, both from the UK. Attending to the: *Incontinence: The Engineering Challenge XII. Institution of Mechanical Engineers. London (UK) November, 2019.*

The last ENIUS Dissemination Meeting was held in Porto at the *31 Conference of the European Society for Biomaterials. Porto (Portugal). 5th-9th september, 2021.* Dr. Federico Soria.

The initial idea was to organise an ENIUS Symposium within this Congress, but finally due to the pandemic, the congress was on line and we could only give one presentation. Urinary stents. Side effects in patients. Why do we need to improve them? Biofilm, Coatings and new stent designs. ENIUS.

DELIVERABLES: One of the most important deliverables of ENIUS is the scientific or dissemination manuscripts. Fortunately, we have reached up to 18 scientific papers, mainly as a result of collaborations between groups within STSMs, or as part of the tasks of the different working groups.

The excellent work of V. Cauda, T. Vladkova and A. Barros should be highlighted, as their research groups has been one of most important groups in ENIUS.

Scientific paper. WG5. Laurenti M, Grochowicz M, Cauda V. Porous ZnO_2-hydroxyethyl Metacrylate eluting coatings for ureteral stent applications. Coatings 2018, 8(11):376.

-Scientific paper. WG6. Bayir E, Sendemir A, Missirlis YF. Mechanobiology of cells and cell systems, such as organoids. Biophys Rev. 2019 Oct;11(5):721-728.

-Scientific paper. WG5. Venkatesh C, Laurenti M, Bandeira M, Lanzagorta E, Lucherini L, Cauda V, Devine D. Biodegradation and antimicrobial properties of Zinc oxide-polymer composite materials for urinary stent applications. Coatings 2020;10 (10);1002.

-Scientific paper. ENIUS. European Network of multidisciplinary research to Improve the Urinary Stents. COSTS Actions. CA16217. European Cooperation in Science & Technology. Urolithiasis. 2020 Dec;48(6):553-559.

-Scientific paper. WG4-5. A Staneva, M Albu-Kaya, B Martinov, et al. Preparation and antimicrobial activity of collagen/(rgo/zno/tio2 /sio2) composites. Journal of Chemical Technology and Metallurgy, 55, 5, 2020, 1078-1086.

-Scientific paper-STSM. Laurenti M, Grochowicz M, Dragoni E, Carofiglio M, Limongi T, Cauda V. Biodegradable and Drug-Eluting Inorganic Composites Based on Mesoporous Zinc Oxide for Urinary Stent Applications. Materials (Basel). 2020 Aug 29;13(17):3821.

- Scientific paper-STSM. Alves P, et al. Analysing the initial bacterial adhesion to evaluate the performance of antifouling surfaces. Antibiotics, 2020.

- Scientific paper-WG4. Gomes M, et al. PDMS in urinary tract devices: Applications, problems and potential solutions. Polydimethylsiloxane: Structure and Applications, 1 st ed; Carlsen, PN, 2020.

- Scientific paper-STSM. Alves P, et al. The potential advantages of using a poly (HPMA) brush in urinary catheters: Effects on biofilm cells and architecture. Colloids and Surfaces B: Biointerfaces, 2020.

-Scientific paper-WG4. Gospodinova D, Ivanova I, Todorka D. Fabrication and Characterization of Antimicrobial Magnetron Computtered TiO_2/Ag/Cu Composite Coatings. Coatings, 2021.

-Scientific paper-WG4-5. Zmejkoski DZ, Markovic ZM, et al. Bactericidal and antioxidant bacterial cellulose hydrogels doped with chitosan as potential urinary tract infection biomedical agent. RSC Adv., 2021,11, 8559-8568.

-Scientific paper-WG6. Gizem Ors Kumoglu, Aylin Sendemir, M. Bahattin Tanyolac, Birdal Bilir, Omer Kucuk, Yannis Missirlis. Epigenetic mechanisms in cancer. Longhua Chin Med 2022.

-Scientific paper WG2. Zeng S, Carugo D, Mosayyebi A, Turney B, Burkhard F, Lange D, Obrist D, Waters S, Clavica F. Fluid mechanical modelling of the upper urinary tract. WIREs Mech Dis 2021;e01523

-Scientific paper WG6. Abou-Hassan A, Barros A, Buchholz N, Carugo D, Clavica F, de Graaf P, de La Cruz J, Kram W, Mergulhao F, Reis RL, Skovorodkin I, Soria F, Vainio S, Zheng S. Potential strategies to prevent encrustations on urinary stents and catheters - thinking outside the box: a European network of multidisciplinary research to improve urinary stents (ENIUS) initiative. Expert Rev Med Devices. 2021;18(7):697-705.

-Scientific paper WG4-5. M Kovacova, Z Spitalsky, Z Markovic. From antibacterial polymer nanocomposites to bioimaging. the use of carbon quantum dots. European Polymer Federation. P-Congress Workshop 28 June 2021 Programme and Abstracts

-Scientific paper WG4-5. Domingues B, Pacheco M, de la Cruz JE, Carmagnola I, et al. Future Directions for Ureteral Stent Technology: From Bench to the Market. Advanced Therapeutics, 2022.

-Scientific paper WG3-6. Buchholz N, Budia A, de la Cruz J, Kram W, Humphreys O, Reches M, Soria F, Valero R. Urinary stent development and evaluation models: in-vitro, ex-vivo and in-vivo. A European Network of Multidisciplinary Research to Improve Urinary Stents (ENIUS) Initiative. Polymers, 2022.

-Scientific paper WG2. Zheng Shaokai, Amado Pedro, Kiss Bernhard, Stangl Fabian, Haeberlin Andreas, Sidler Daniel, Obrist Dominik, Burkhard Fiona, Clavica Francesco. Quantitative Evaluation of Encrustations in Double-J Ureteral Stents With Micro-Computed Tomography and Semantic Segmentation. Frontiers in Urology, 2022.

-*Springer Book. WG1. Urinary stents. Current state and future perspectives.2022. Soria F, Rako D, Degraaf P editors.*

WORKING GROUPS ACHIEVEMENTS:

WG1. D. Rako (Leader WG1). Dr. Rako commented on the achievements of this WG1. The tasks related to this WG are summarised in three scientific manuscripts, mainly Systematic Reviews (one on metallic ureteral stents, one focused on polymeric stents and a last manuscript related to ureteral stents). As well as the edition of a book summarising all the current knowledge on urinary stents and showing the current and future lines of research in this area of knowledge. This WG has also held in GP4 a virtual conference for the dissemination of the work done. The three manuscripts have been included in the book managed by this WG1. Although one of them, the one on metallic ureteral stents, is going to be submitted to a Scientific Journal in the near future. The book, which has been accepted for publication by Springer-Nature, is already in its last phase of production, the invoice has been paid. We are only waiting for the first proof of the book to be sent to us for review. *The tasks related to this WG have therefore been achieved.*

WG2. S. Waters. (Leader WG2). Prof. Waters commented on the achievements of this WG2. The tasks related to this WG are summarised in two scientific manuscripts and one Whitepaper. “Fluid mechanical modelling of the upper urinary tract. Zheng S, et al. Wires, 2021”, among the top download WIREs articles in 2021. “Quantitative evaluation of encrustations in double-J ureteral stents with micro-computed tomography and semantic segmentation. Zheng S, et al. Frontiers in Urology, 2022”. Also this WG2 have contributed with one chapter in the Springer Book “ Flow dynamics in stented ureter”. Upcoming review article , providing critical recommendations and guidelines on how modelling methods could help addressing key clinical challenges related to the stented ureter. They were also present by means of an Dissemination meeting in “Incontinence: the engineering challenge, London, November, 2019”. Oral presentations in “European Society of Biomechanics. Milan-Italy, 2021”, and 9th World Congress of Biomechanics 2022 Taipei, 2022. Research funding: “Developemnt and validation of a biologically inspired in-vitro platform for a long-term assessment of commercially and innovative stent design” Swiss National Science Foundation, 2019-2021. “Investigating the interplay between urine flow, encrustation and bacteria to improve the performance of a ureteral stents” Swiss National Science Foundation, 2021-2025. *The tasks related to this WG have therefore been achieved.*

WG3. S. Stavridis. (Leader WG3). In the absence of the group leader, the presentation is made by the AC (F. Soria). Deliverables.The production of a Comprehensive Validation protocol on new stents designs and a *Whitepaper: Comprehensive Validation protocol on new stents designs.*

This WG has contributed two chapters to the book managed by WG1. Chapter 15: Methodology for the development and validation of new stent designs: *in vitro* and *in vivo* models. Chapter 16: Methodology on clinical evaluation of urinary stents.

As well as, with a scientific manuscript corresponding to the whitepaper: Buchholz N, Budia A, de la Cruz J, Kram W, Humphreys O, Reches M, Soria F, Valero R. Urinary stent development and evaluation models: in-vitro, ex-vivo and in-vivo. A European Network of Multidisciplinary Research to Improve Urinary Stents (ENIUS) Initiative. Polymers, 2022.

Therefore, this WG has achieved all the proposed objectives and allows us to present to the scientific community an expert-validated protocol for the evaluation and validation of new urinary stents.

WG4&WG5. A. Barros (Leader WG4), a joint presentation of WG4 and 5 was made. Milestones: Database of materials used in Ustents and of those that could potencially be used in stents. Done.

Creation of guidelines concerning the requirements for biomaterials and coatings exposed to the urinary environment. It´s a Review paper, *Domingues B, Pacheco M, de la Cruz JE, Carmagnola I, et al. Future Directions for Ureteral Stent Technology: From Bench to the Market. Advanced Therapeutics, 2022.*

http://enius.org/urinary-stents-info-meeting-point

Database of materials used in UStents and those that could potencially be used in stents. In “Urinary stents Info Meeting Point”, ENIUS Website, open.

Chapters Springer-Book: Chapter 20-Biomaterials in urinary stents. Chapter 22. Coatings in Urinary stents. Chapter 23. Bacterial adhesion and biofilm formation and hydrodynamics effect. Chapter 24. Antibiotic-free solutions for the development of biofilm prevention coatings.

WG5. Tasks: to create a database of all the drugs assessed for DESs. This task is shared with WG4.

Task 2. Creation of a detailed and critic of the characteristics required for these drugs to reduce the stents morbidity. A chapter in the ENIUS Book (Springer-Nature) has been included.

Task 3. Suggestion of a new research lines for future studies. This information is included in the collaborative scientific manuscript between WG4-5- 6. *Abou-Hassan A, Barros A, Buchholz N, Carugo D, Clavica F, de Graaf P, de La Cruz J, Kram W, Mergulhao F, Reis RL, Skovorodkin I, Soria F, Vainio S, Zheng S. Potential strategies to prevent encrustations on urinary stents and catheters - thinking outside the box: a European network of multidisciplinary research to improve urinary stents (ENIUS) initiative. Expert Rev Med Devices. 2021;18(7):697-705.*

Contributions: Chapter: “Techniques to create drug eluting stents”; 6 abstracts and presentation in International Congresses.

-Laurenti M, Grochowicz M, Cauda V. Porous ZnO_2-hydroxyethyl Metacrylate eluting coatings for ureteral stent applications. Coatings 2018, 8(11):376.

- Laurenti M, Grochowicz M, Dragoni E, Carofiglio M, Limongi T, Cauda V. Biodegradable and Drug-Eluting Inorganic Composites Based on Mesoporous Zinc Oxide for Urinary Stent Applications. Materials (Basel). 2020 Aug 29;13(17):3821.

-Budimir M, et al. Gamma ray assisted modification of carbón quantum dot/polyurethane nanocomposites: structural, mechanical and photocatalytic study. RSC advances, 2019.

-Venkatesh C, Laurenti M, Bandeira M, Lanzagorta E, Lucherini L, Cauda V, Devine D. Biodegradation and antimicrobial properties of Zinc oxide-polymer composite materials for urinary stent applications. Coatings 2020;10 (10);1002.

-Alves P, et al. Analysing the initial bacterial adhesion to evaluate the performance of antifouling surfaces. Antibiotics, 2020.

-Alves P, et al. The potential advantages of using a poly (HPMA) brush in urinary catheters: Effects on biofilm cells and architecture. Colloids and Surfaces B: Biointerfaces, 2020.

- Gospodinova D, Ivanova I, Todorka D. Fabrication and Characterization of Antimicrobial Magnetron Computtered TiO_2/Ag/Cu Composite Coatings. Coatings, 2021.

-Gomes M, et al. PDMS in urinary tract devices: Applications, problems and potential solutions. Polydimethylsiloxane: Structure and Applications, 1 st ed; Carlsen, PN, 2020.

-Domingues B, Pacheco M, de la Cruz JE, Carmagnola I, et al. Future Directions for Ureteral Stent Technology: From Bench to the Market. Advanced Therapeutics, 2022.

The tasks related to both WGs have therefore been achieved.

WG6. In the absence of the group leader, the presentation is made by the AC (F. Soria). Deliverables. ***Paper:*** *Systematic Review of the different technologic tools suitable for Ustent development. Future in Urinary Stents.* In addition to two chapters in the Springer book, they have organised two Workshops and also published two scientific papers, which together with the manuscripts contributed by Prof. Missirlis make 5 manuscripts in this WG6.

They have also been able to combine researchers from different disciplines and give a vision of the future on the development of new stents.

-Abou-Hassan A, Barros A, Buchholz N, Carugo D, Clavica F, de Graaf P, de La Cruz J, Kram W, Mergulhao F, Reis RL, Skovorodkin I, Soria F, Vainio S, Zheng S. Potential strategies to prevent encrustations on urinary stents and catheters - thinking outside the box: a European network of multidisciplinary research to improve urinary stents (ENIUS) initiative. Expert Rev Med Devices. 2021;18(7):697-705.

-Bayir E, Sendemir A, Missirlis YF. Mechanobiology of cells and cell systems, such as organoids. Biophys Rev. 2019 Oct;11(5):721-728.

-Buchholz N, Budia A, de la Cruz J, Kram W, Humphreys O, Reches M, Soria F, Valero R. Urinary stent development and evaluation models: in-vitro, ex-vivo and in-vivo. A European Network of - Multidisciplinary Research to Improve Urinary Stents (ENIUS) Initiative. Polymers, 2022.

-Chapter 34. Abou-Hassan A, Barros A, Buchholz N, Carugo D, Clavica F, Mergulhao F, Zheng S: Preventing biofilm formation and encrustation on urinary implants: (bio)molecular and physical research approaches.

-Chapter 33. Buchholz N, de Graaf P, De la Cruz, Kram W, Skovorodkin I, Soria F, Vainio S. Preventing biofilm formation and encrustation on urinary implants: (bio)coatings and tissue engineering.

Short Term Scientific Missions (STSM): D. Carugo (STMS coordinator). The estimation for this 5GP is 2 STSM. With a total budget of 2,000 €. To the current date, we have financed 2 STSMs. STSM applicant. Yannis F. Missirlis (Patras University-Greece). Microfluidic devices for dynamic cell culture assays. Sabanci University (Istanbul, Turkey). STSM applicant. Fabio Carvalho (University of Porto, Portugal). Evaluation of biofilm development by urinary pathogens using a microfluidic-based model. Host-University College London, UK. Dr. D. Carugo.
The assessment of ENIUS' lifetime in this area can be summarised as follows: In our MoU we had a forecast of 16 STSMs and finally up to 28 STSMs have been carried out, which is a great pleasure for this network. This has been one of the activities most in demand due to the large number of centres that make up ENIUS and the importance of establishing relations between the different research groups. The participation of a very high percentage of young researchers has led to our expectations being exceeded. 72% of the applicants have been women and the expenses generated by the STSMs have reached €50,000.
VMGrant. We have also developed two Virtual mobility Grant. These grants are to help build capacity and improve virtual collaborations, in ways that help us deliver the overall objectives of the Action (these are described in full in the Action Memorandum of Understanding). Fluid mechanical modelling of stented ureters. Applicant: Ricardo Constante Amores. University of Oxford. UK. Recent developments in Layer-by-Layer (LbL) coatings against Urinary Tract Infection (UTI): Review Part1. Applicant: Maryam Mosayebi. University of Southampton, UK.

MoU objectives Assessment.

The first step to conclude our COST Actions is to assess the achievement of our objectives. These are the objectives of ENIUS, as described in the MOU that was approved by the CSO.

Research Coordination Objectives

Objective 1. To determine the causes of failure and side effects of urinary stents from the clinical point of view and industrial design. *This objective has been achieved and is included in three chapters of the book coordinated by WG1.*

Objective 2. Develop multidisciplinary guidelines for the evaluation and validation new stent designs at computational, experimental and preclinical level. *This objective has been achieved and is included in two chapters of the Springer book (Urinary stents) coordinated by WG1. The scientific manuscript published in this year 2022 with first author N. Buchholz is the one that justifies the Whitepaper related to this objective.*

Objective 3. Assess opportunities for improved stents related to the assessment of new biomaterials, new coatings, drugs eluting stents. *This aim has been achieved, due to the great work of WG4 and 5 we have a database, as well as papers and chapters in the book.*

Objective 4. To develop a realistic computational environment to assess the Computational simulation and modelling and computational fluid dynamics to evaluate new urinary stents designs. *This is an overly ambitious goal that we modified and changed according to the advice of WG2 leaders. It was changed by a database, and scientific papers.*

Objective 5. Stimulate innovative scientific ideas and propose new lines of research and technological innovation in the field of urinary stents. *This objective has been achieved, there are several proposals underway and thanks to the STSMs several proposals have emerged among the ENIUS groups.*

Capacity-building objectives

Objective 6. To consolidate a multidisciplinary network actively involved in urinary stents research to facilitate scientific knowledge exchange through, workshops, TS, scientific papers, and guidelines. AC comments: *I think this is one of the aims that has been best achieved. It is a real satisfaction for me, as it was one of the most important goals at the beginning of the design this network. And it is the work of each and every member of ENIUS.*

Objective 7. To create a cohort of skilled bioengineer/researchers with experience in stents by providing TS and supporting Exchange visits between Research Centres. AC comments: *As in the previous aim, this one has also been achieved in a great way. As we have mentioned throughout this Meeting, we have had 28 researchers who have attended an STSM, and our training activities have had more than 500 participants.*

Objective 8. This COST Action will play a seminal role in facilitating links within researchers and industrial communities. A transfer of technological knowledge to the industry will foster industrial competitiveness of Europe. *We have successfully established interactions with up to 10 companies over the past four and a half years.*

AC comments: I believe that despite the major drawbacks of not being able to meet face-to-face for two years, we have achieved the objectives to a high degree. I can only thank all the members of our network for their involvement and hard work to achieve all the objectives.

ENIUS FUTURE DECISIONS.

A discussion is opened on which could be the future of this multidisciplinary network. The AC comments that it would be a shame to lose all the work that has been done to build this network and that the network is strong because of the participants that make it up, and this strength is our union. The opportunities mentioned by the Science Officer have been taken up and are discussed below. The main route could be the CIG that has been presented, and we will have news of whether it has passed the cut-off at the beginning of May, and at the end of May would be the Hearings. The most widely accepted proposal is to wait for the CIG evaluation until May. If there is no funding for this Innovative Grant proposal, in May there would be a call via Teams for all those interested in keeping ENIUS going and looking for new European initiatives to maintain this working group.

There are different European project proposals and this ensures that some groups will continue to work in the following years, due to the synergies that have been achieved during these years. So, everything is on stand-by pending the decision of the CIG until May or June if they pass the first threshold.

SHORT TERM SCIENTIFIC MISSION (STSM) SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA16217 - European network of multidisciplinary research to improve the urinary stents

STSM title: Biomaterials and stent coatings

STSM start and end date: 19/07/2021 to 13/08/2021

Grantee name: Raquel Valero Boix

PURPOSE OF THE STSM:

My STSM proposal aims to collaborate with ENIUS and the associated company Hydrumedical on the latest advances in urinary stents by working on the characterisation of new materials and the analysis of the surfaces of the stents coated with the different peptides.

The motivation of this STSM is to gain a better understanding of the processes involved in the development of urinary stents. These medical devices are currently used in clinical practice and their usage presents, in most cases, both intraoperative and postoperative problems. Consequently, during this STMS, research will be carried out at Hydrumedical to accompany the development of the proprietary biodegradable ureteral stent – Hydrustent. This device aims to improve patients'quality of life and significantly reduce the costs associated to a second intervention, which is currently required to remove the currently used non-degrdable stents.

Therefore, this STSM aims to stimulate innovative scientific ideas and propose new lines of research and technological innovation in the field of urinary stents, towards new ureteral stents to reduce complications and morbidity.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

My scientific mission at Hydrumedical was motivated by the development of a new biodegradable urinary device, Hydrustent. For this purpose, different tasks were performed during the stay:

During the first week of the STSM, all the literature related to the manufacturing process of the stent, which is currently in the optimization stage, was reviewed, including previous studies already published and the work done so far with the new materials. These include, but are not limited to, radiopacity, permeability and degradation.
For the development of the functional prototypes, a new injection molding system was specifically designed and assembled for the first time during this week.

In the second week, the stent manufacturing process was optimized. Different parameters including injection pressure, injection speed, amount of required solutions to obtain a samples, as well as the cleaning process at the end of the fabrication step and the identification of possible process bottlenecks and pitfalls.

Once the injection parameters had been optimised, the manufacturing process began during the third week. First, a small-scale study of the process was carried out. The cleaning process had to be optimised during the manufacturing since, from time to time, there were parts of material affecting the homogeneity of the stent.

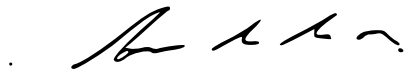
Finally, during the fourth week, the processing of the injected samples was finalized. First, the concentricity and homogeneity of the stents' cross-setions was evaluated. After this validation, the processing of the stents was fully validated.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

- The injection process for the fabrication of the stents was optimized
- The iterative process for the injection optimization was performed by analyzing the samples after each batch production
- Samples were evaluated in terms of concentricity and homogeinity of the cross-sections

FUTURE COLLABORATIONS (if applicable)

Dr. Alexandre (Hydrumedical's CEO) requested me to consider an extension of my stay for two more weeks to follow the full process of development of the Hydrustent device.
During the extension, the processing parameters to tune the final diameter of the stents will be optimized in a well-established in house manual mold, thus a new technique. In this new experimental phase, the aim is to determine the ideal initial outer diameter of the stents to obtain specific dimensions (Fr scale) after full processing. This will allow to identify which modifications will have to be performed in the automatic injection systems.



Report on the outcomes of a Short-Term Scientific Mission[1]

Action number: CA16217 - European network of multidisciplinary research to improve the urinary stents

Grantee name: Fábio Rafael Moreira Carvalho

Details of the STSM

Title: Evaluation of incrustation in ureteric stents using a microfluidic-based model

Start and end date: 14/02/2022 to 14/03/2022

Description of the work carried out during the STSM

Description of the activities carried out during the STSM. Any deviations from the initial working plan shall also be described in this section.

(max. 500 words)

The initial plan of this STSM comprised the use of a stent-on-chip (SoC) microfluidic model as a platform to test the efficacy of antimicrobial/antifouling surfaces against different bacterial biofilms. However, due to technical constraints, the original plan was adapted to more feasible objectives. Therefore, the new goals of this project consisted in assessing the influence of the side-hole size of ureteral stents on the accumulation of encrusting crystals and inferring how the presence of different degrees of ureter obstruction affects flow distribution in stent side-holes. For this purpose, SoC models with different configurations of occluded and unoccluded ureters were designed to replicate key hydrodynamic regions of the stented ureters by Computationally Assisted Design (CAD) using Autodesk Inventor (Figure 1).

[1] This report is submitted by the grantee to the Action MC for approval and for claiming payment of the awarded grant. The Grant Awarding Coordinator coordinates the evaluation of this report on behalf of the Action MC and instructs the GH for payment of the Grant.

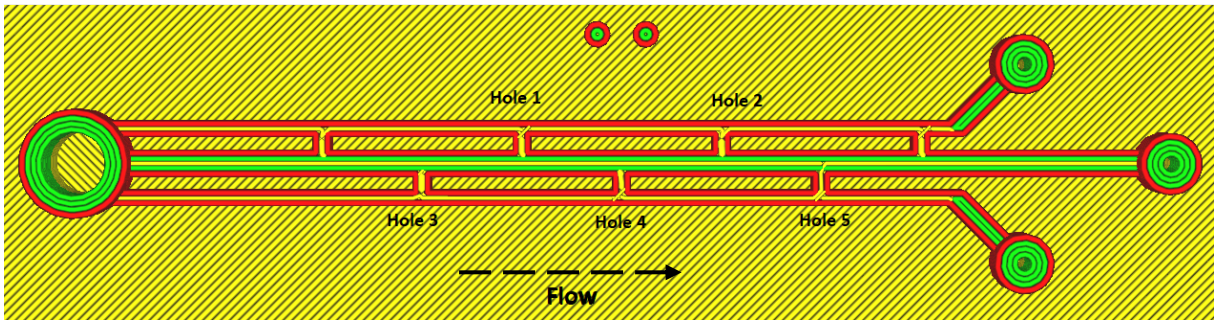


Figure 1. Top view of the model with no obstructions

The model's architecture included three flow channels, two mimicking the extra-luminal (0.9 mm wide) and one the intra-luminal (1.5 mm wide) compartments of a ureteral stent, separated by a 0.7 mm septum modelling the stent's wall [1]. The septum contained drainage holes connecting intra- and extra-luminal parts, modelling the side-holes of a ureteric stent. To evaluate the effect of side-holes size on crystal deposition, two different diameters of side holes (0.5 [2] and 1 mm [3]) were compared. Additionally, different degrees of external obstruction were evaluated for each hole size to replicate occlusion of the ureter lumen caused by ureteral stenosis [4], characterized by a narrowing of the extraluminal channels to a diameter that corresponds to a specific stenosis percentage: (i) no occlusion, mimicking an ideal scenario with no obstructions (Figure 1); (ii) 52% of occlusion, replicating a partial ureter obstruction [3]; (iii) complete ureter occlusion. The obstructions were positioned in the extension between holes 1 and 2, on both sides, to replicate the proximal and distal areas of the obstruction, enabling to obtain flow domains with different characteristics, such as "active" and "inactive" side-holes. The SoC models were manufactured by moulding as follows: (i) a negative mould was fabricated by 3-D printing using polylactic acid (PLA) as printing material; (ii) liquid poly(dimethylsiloxane) (PDMS, produced at a curing agent monomer ratio of 1:10 (w/w)) was poured over the positive mould, degassed using a vacuum chamber, and cured overnight at 37 ºC; (iii) the cured PDMS was removed from the mould and bonded to a glass slide by plasma treatment. The experiments were carried out for 90 minutes, which was sufficient to detect the initial stages of crystals' deposition, using a peristaltic pump at a constant inlet flow rate of 1 mL/min (within the range of flow rates typically found in physiological conditions [2]). To promote crystal deposition, a supersaturated artificial urine (AU) solution was recirculated through the microfluidic device. The device was placed horizontally on the stage of an optical microscope and the encrustation was monitored over time by capturing images of selected locations (holes 1-5, at 4x magnification) every 30 minutes, using a CCD camera. All experiments included at least three independent replicates.

References: [1] Mosayyebi, A. et al., Reducing deposition of encrustation in ureteric stents by changing the stent architecture: A microfluidic-based investigation, 2019; [2] Waters, S. L. et al., Ureteric stents: investigating flow and encrustation, 2008; [3] Hyoung-Ho, K. et al., Numerical Analysis of Urine Flow with Multiple Sizes of Double-J Stents, 2020; [4] Keys, T. and Mirzazadeh, M., Urological Complications of the Renal Graft, 2017.

Description of the STSM main achievements and planned follow-up activities

Description and assessment of whether the STSM achieved its planned goals and expected outcomes, including specific contribution to Action objective and deliverables, or publications resulting from the STSM. Agreed plans for future follow-up collaborations shall also be described in this section.

(max. 500 words)

The proposed goals of this STMS were achieved since the grantee received specific training on a new technique that may be of interest for Dr. Filipe Mergulhão's group after the course of the STSM, while

enabling a research collaboration with Dr. Dario Carugo from the ENIUS network. The work developed contributed to the Action objectives through the investigation of the correlation between some fluid dynamic processes, deposition of encrusting particles, and some geometric parameters of ureteral stents, with the aim of improving the stent's architecture to reduce stent encrustation.

Although image analysis was not performed yet, from the visual analysis of the captured images, it can be seen that regarding partial and complete occlusion of the external compartment, holes 1 and 2 presented less amount of deposited crystals compared to the model with no obstructions, resulting most likely from an increased wall shear stress (WSS) at this holes (an inverse correlation between WSS and deposition of encrusting particles was reported in previous studies [1, 5]). Thus, it can be proposed that these holes actively contributed to urine drainage, forcing the urine to flow into the intra-luminal part. On the other side, regions more susceptible to encrustation, and presumably with low WSS, were identified, including ''inactive'' side holes with increased fluid stagnation. Additionally, particle accumulation in ureteric stents seemed to be independent of the side-hole size.

The follow-up activities will include image processing by using the software ImageJ to quantify the percentage area covered by encrusting deposits over the regions of interest and determine the time evolution of encrustation. Also, computational fluid dynamic (CFD) simulations of the multiple SoC architectures may be performed to determine the spatial distribution of WSS. Thus, in addition to the grant report, these results will be gathered in a collaborative publication resulting from this STSM, establishing a continuous collaboration with Dr. Dario Carugo's group.

References: [5] Mosayyebi, A. et al., Particle Accumulation in Ureteral Stents Is Governed by Fluid Dynamics: *In vitro* Study Using a "Stent-on-Chip" Model, 2018.

Report on the outcomes of a Short-Term Scientific Mission[1]

Action number: CA16217

Grantee name: Yannis Missirlis

Details of the STSM

Title: Microfluidic devices for dynamic cell culture assays

Start and end date: 05/02/2022 – 15/02/2022

Description of the work carried out during the STSM

Description of the activities carried out during the STSM. Any deviations from the initial working plan shall also be described in this section.

(max. 500 words).

During my visit at Sabanci University , SUNUM center, I had the chance to have a real tour of all the facilities of the Center, had intensive discussions with several investigators, and gave a hybrid lecture on the Complexity of Information transfer within Cells and Among Cells.

In particular I discussed about the Center's projects with its Director, Professor Fazilet Vardar, and I was offered to be an external Research Collaborator of the Center, aiming among other things, at submitting proposals to EU programs. Had also discussions and saw the facilities of Prof. Ismet Deliloglu Gurhan, and observed the preparation of antibodies, cloning and other methods of cell manipulations. A very interesting project was shown to me by a young researcher, Dr. Morteza Ghorbani, had to do with the use of Cavitation studies in microfluidics Devices he gets from EPFL (Switzerland), with the aim to clear thrombi or biofilms from small vessels or other tubular structures using this simpler technique instead of Ultrasounds.

My discussions with Dr. Sibel Cetinel were very interesting as well, related to many common interests in Nanomedicine, Tissue Engineering, but it was left unfinished due to a case of Covid in her lab.

A very promising collaborative effort seems to be highly probable with Prof. Meltem Elitas, a collaborator of SUNUM, head of the Biomechatronics group of Sabanci University. The projects on

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cancer-immune system interactions (using microfluidic devices) and the development of biosensors for specific applications are well designed and executed. She was very interested in our Bioreactor sytems, and we planned to continue exploring possible projects together.

Description of the STSM main achievements and planned follow-up activities

Description and assessment of whether the STSM achieved its planned goals and expected outcomes, including specific contribution to Action objective and deliverables, or publications resulting from the STSM. Agreed plans for future follow-up collaborations shall also be described in this section.

(max. 500 words) .

Overall it was a very successful mission, that set the ground of important collaboration. The use of cavitation techniques in “clearing” deposits from urinary stents, for example, or observing detailed fluid flows in microfluidic devices incorporaring mechanical signals to appropriate cells will be further explored.

SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA16217 - European network of multidisciplinary research to improve the urinary stents

STSM title: Hydrustent, process and characterization

STSM start and end date: 16/08/2021 to 31/08/2021

Grantee name: Raquel Valero Boix

PURPOSE OF THE STSM:

My STSM proposal aims to collaborate with ENIUS and the associated company Hydrumedical on the latest advances in urinary stents by working on the characterisation of new materials and the analysis of the surfaces of the stents coated with the different peptides.

The motivation of this STSM is to gain a better understanding of the processes involved in the development of urinary stents. These medical devices are currently used in clinical practice and their usage presents, in most cases, both intraoperative and postoperative problems. Consequently, during this STMS, research will be carried out at Hydrumedical to accompany the development of the proprietary biodegradable ureteral stent – Hydrustent. This device aims to improve patients'quality of life and significantly reduce the costs associated to a second intervention, which is currently required to remove the currently used non-degradable stents.

Therefore, this STSM aims to stimulate innovative scientific ideas and propose new lines of research and technological innovation in the field of urinary stents, towards new ureteral stents to reduce complications and morbidity.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

My scientific mission at Hydrumedical was motivated by the development of a new biodegradable urinary device, Hydrustent. For this purpose, different tasks were performed during the stay:

During the first week of the STSM, the processing parameters to tune the final diameter of the stents was performed in a well-established in house manual mold, thus a new technique. In this new experimental phase, the aim is to determine the ideal initial outer diameter of the stents to obtain specific dimensions (Fr scale) after full processing. Three different diameter sizes were studied and all injected samples were further processed.
This will allow to identify which modifications will have to be performed in mold of the automatic injection system.

During the second week, I have performed the automatic injection process using raw materials from a different supplier. This allows to validate that the properties of the stents obtained with different reagents yield the same results. This is highly important at the industrial scale if the supplier is not able to deliver/provide the usually used reagents and reagents from a different supplier must be used as “plan B”.

The process was well documented to allow a different operator to proceed with with the Hydrustent fabrication process.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

- The samples obtained using the manual injection were obtained and characterized.
- The variation of the initial outer diameter has an impact on the final diameter.
- The new reagents in the same quantities previously used resulted in a very viscous solution. Samples were obtained and the injection was successful, but they were more difficult to process. The cross-sections analysis revealed that these were less homogeneous than the previous ones.
- In addition, when using these reagents and since the solutions are more viscous, the cleaning process of the machine took longer.

FUTURE COLLABORATIONS (if applicable)

SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA16217 – European Network of multidisciplinary research to improve the urinary stents
STSM title: Animal model validation of ureteral Drug eluting stents
STSM start and end date: 29/05/2021 to 13/06/2021
Grantee name: Beatriz Domingues

PURPOSE OF THE STSM:

This collaboration aims to bring together the expertise of two groups involved in the development and assessment in vitro and in vivo of ureteral stents focused on the improvement of drug-eluting stents and biodegradable devices. This STSM will consist in participating in a project focused in the development of a biodegradable ureteral stent for the controlled release of drugs, with the aim to acquire knowledge in the experimental assessment in the porcine model.

On the one hand, the Host Institution has plenty of experience in translational research on endourology and ureteral stents in the porcine species, which is of great value to provide an overview to the applicant of the possibilities of in vivo testing of medical devices in large animals. Some of the laboratory trials included in this project will take place during this stay and will also enhance the exchange of knowledge between the applicant and the Host institution, and count on her collaboration in these tasks.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

The research project involved the validation of the BraidStent®-MMC took place during the STSM time and the applicant was able to participate in some of the stages of the *in vivo* and *in vitro* assessments.

The work plan was structured as follows:

The animals underwent radical nephrectomy for the induction of single-kidney models.

After a minimum of three weeks, the models were subjected to a baseline assessment and the placement of the BraidStent®-MMC. Urine samples were taken every 6 hours during the following 48 hours. Urine was analyzed and prepared for the study via HPLC-DAD of the release of Mitomycin-C.

Afterwards, weekly follow-ups are performed for a total of 6-8 weeks. These follow-ups included laboratory analysis of blood and urine. The upper urinary tract and the effect of the stents in animal model were assessed by ultrasonography, fluoroscopy and endoscopy techniques.

Attendance and participation in the laboratory activity were also performed with the approval and supervision of the Head of the Stem Cell Laboratory. The T24 cell line, which is used to evaluate cytotoxicity of drugs *in vitro*, was

cultured, using Dulbecco's Modified Eagle Medium.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

Through the support and assistance in the operating room (OR) during the endourological placement of the ureteral stents and during the follow-ups of the stented animal models, it was possible to follow the validation process of the BraidStent®-MMC. The entire process was explained and clarified, taking into account established regulations and ethical standards.
Additionally, collaboration in JUMISC's Stem Cell Therapy Laboratory, on the days with no experimental surgeries, T24 cell line was thawed and cultured with Dulbecco's Modified Eagle Medium, at 37°C, with 5% CO_2.

SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA 16217
STSM title:
Effect of mechanical strains on cells in tubular bioreactors

STSM start and end date: 21/04/2021 to 28/04/2021
Grantee name: Yannis Missirlis

PURPOSE OF THE STSM:

(max.200 words)
The purpose of this STSM was to visit the specific laboratory of my long-time collaborator , Professor Aylin Sendemir , of the Department of Bioengineering at Ege University, and review, on site, the progress of several projects that we collaborate, and new ones that I could be advising. Especially those that are continuing , based on previous ones, designed to include bioreactors with flow characteristics, and how appropriate cells are functionally affected by flow. At the same time to give a lecture , open to all the Department members, on a subject of general interest.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

(max.500 words)
After more than one year I gave my first lecture “live”. The title was “Information Highways in Cells and Tissues” with appropriate acknowledgement to ENIUS. I considered it succesfull as it generated a lot of discussion with colleagues and students participating.
Next day we had a hybrid meeting with Prof. Sendemir’s team. Seven presentations live and nine online. Each one presented their project followed by questions and suggestions.
I had, in addition, more in depth discussion and work with two graduate students:

1. with Gizem Ors Kumoglu, whose Ph.D. thesis is on the effects of changing microRNA profiles in the inflammatory microenvironment on **Prostate Cancer** development. It was an opportune time, that came after I had talks with another member of our Action, Dr. Noor Buchholz, preparing a special issue for a Journal. Therefore we spent considerable time in drafting the outline of a paper on “Epigenetic factors in drug resistance in cancers” to be coauthored by Kumoglu-Sendemir-Missirlis.
2. Discussed and advised with Dilara Lal on her ongoing project in creating , with the use of Tissue Engineering principles, of Esophageal long Segments for repairs of specific pertinent defects. Part of the project deals with the design of a tubular flow reactor in a way that will facilitate the investigation of flow conditions on esophageal endothelial cells.

In all discussions Prof. Sendemir was present. Furthermore me and Sendemir reviewed the progress (or lack of it) on previous attempts to improve on bioreactors to be used either for small diameter vascular constructs, or for more realistic blood-brain-barrier simulations.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

1. Draft paper on epigenetics and prostate cancer
2. Design parameters for esophageal cell performance in tubular bioreactor

FUTURE COLLABORATIONS (if applicable)

Our collaboration with the specific laboratory will be going on on similar research lines.

SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA16217
STSM title: 3D printing of different biodegradable metallic ureteral stents designs
STSM start and end date: 06/09/2021 to 15/10/2021
Grantee name: Margarida Pacheco

PURPOSE OF THE STSM:

(max.200 words)

This STSM was integrated on a PhD work where the main aim is to develop a biodegradable metallic ureteral stent. With that end, one of the milestones is to develop different ureteral stents designs with the biodegradable metals selected previously, and study their behaviour in the *in vitro* urinary tract environment. In this phase it is intended to access the corrosion and propensity for encrustation of the different ureteral stent's prototypes generated and study the influence of the design on corrosion and encrustation behavior. To that aim, the objective of this STSM was to develop the different ureteral stents designs through 3D printing, and exploiting the wide variety of possible designs that ca be made using this technique for ureteral stenting.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

(max.500 words)

With this work it was intended to produce the different ureteral stents prototypes through laser powder bed fusion (LPBF), using Mg1Y (%wt) powder. However, due to delays on the production of the powder and delivering from the company from where we ordere from, we have decided to proceed to the introduction to the 3D printer (ACONITY 3D) by starting to understand and relate the influence of different parameters on the structure of the constructs, thus stablishing process parameters. In this phase, it was used 420 stainless steel alloy, one of the metals that was on use and was already familiar for the group.
For every printing, the supplier was filled with the 420 stainless steel powder and after the adjustment of the slider and the building plate, the printing started. For this optimization part, the constructs were in the form of cilinders and 9 cilinders were builded in each print, each of them with a different parameters. The objective was then to analyse the structure of the construct and narrow the range where the best structures could be obtained. The parameters changed were the laser power and the speed and different combinations were made along the various prints. After each one, the samples were removed from the building plate and the density of the ocnstructs was asccessed. The samples were then grinded with sequential sanding papers and polished using adequate diamond suspensions (protocols already stablished) and the porosity was accessed through scanning electrom microscope (SEM) images.

DESCRIPTION OF THE MAIN RESULTS OBTAINED

- Different constructs with different porosities were obtained;
- Increasing the speed and diminuishing the power leads to lowest porosity;
- Constructs with a high density and lower rates of porosity were obtained.

FUTURE COLLABORATIONS (if applicable)

Future works will be done using Mg1Y, involving the two groups of the present collaborative work. The present work was important to understand how the printer works and how we can tune the parameters in order to obtain the desired structural characteristics. In the future, an intense process parameter development with Mg1Y will be done and different stents designs will also be produced.

SHORT TERM SCIENTIFIC MISSION (STSM)
SCIENTIFIC REPORT

This report is submitted for approval by the STSM applicant to the STSM coordinator

Action number: CA16217
STSM title: Optimization and characterization of ureteral stents prototypes produced by 3D printing
STSM start and end date: 16/10/2021 to 26/10/2021
Grantee name: Margarida Pacheco

PURPOSE OF THE STSM:

(max.200 words)

This work consisted on a continuation of the previous STSM where the initial objectives were not fulfilled. With the present STSM it was pretended to produce different ureteral stents designs and consructs with the same design but different processing parameters for future comparison in terms of performance on ureteral stent's environment.

DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS

(max.500 words)

This work was intended to be done with Mg1Y (%wt), which was the metal selected in previous works as the best one in terms of corrosion under urinary tract environment. Unfortunately, the Mg1Y powder needed for this work did not arrive due to problems on the producing company. In order to contour this situation the best way, another Mg alloy, also widely used for biomedical applications was used, WE43. Indeed this metals is widely described in the literature and used for cardiac stents applications, therefore can be seen as a potential candidate for this work, even though was not on the initial plans. This time the prints were performed on the EOS M 100, a 3D printer that works by laser powder bed fusion (L-PBS).
Metallic wires (tubes) were produced, with 1 mm diameter and 3 cm high, in order to be possible to compare with the previously used materials that were wires as well but produced by extrusion. Besides, contructs in tubular shape were produced, with an internal diameter of 1.70 cm and external diameter of 2.33 cm. A process parameter development work was made both for the wires and for the tubes, resulting on the production of constructs with different scan hatch space (0.4, 0.5 and 0.6 nm) and laser power (80 and 90 W). the metals were then grinded using some process parameters already stablished, and evaluated by scanning electron microscopy (SEM).

DESCRIPTION OF THE MAIN RESULTS OBTAINED

- It was possible to produce wires with the same dimensions as the ones previously used, produced by extrusion, which will be used to understand the influence of the two techniques on the metal behaviour under urinary tract environment;
- Tubes with the same values, in terms of thickness, as the commercial ureteral stents were produced;

FUTURE COLLABORATIONS (if applicable)

It is pretended that this work can be continued through this collaboration (University of Minho and Uppsala University), with the objective to do a comprehensive study on ureteral stents designs, using Mg1Y powder and eventually other Mg alloys used for biomedical applications.