

Barros A.¹, Browne S.², Oliveira C.³, Reis R.L.¹, Duarte A.¹, Healy K.⁴, Lima E.E.³

¹3b's Research Group, Dept. of Polymer Engineering, Gmr, Portugal, ²Centre for Research in Medical Devices (CÚRAM), National University of Ireland Galway, Galway, Ireland, ³Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal, ⁴University of California, Dept. of Bioengineering, Berkeley, United States of America

INTRODUCTION & OBJECTIVES: Urothelial tumors of upper urinary tract are ranked among the most common types of cancers worldwide. The current standard therapy to prevent recurrence is intravesical Bacillus Calmette–Guerin (BCG) immunotherapy, but it presents several disadvantages such as BCG failure and intolerance. Another way is to use chemotherapy, which is generally better tolerated than BCG. In this case, drugs such as epirubicin, doxorubicin, paclitaxel and gemcitabine are used. Nevertheless, intravesical chemotherapy only prevents recurrence in the short-term. These failings can be partially attributed to the short residence time and low bioavailability of the drug within the upper urinary tract and the cancer cells, resulting in a need for frequent drug instillation. To avoid these problems, biodegradable ureteral stents impregnated by supercritical fluid CO₂ (SCF) with each of the four anti-cancer drugs were produced.

MATERIAL & METHODS: Four formulations with different concentrations of gelatin and alginate and crosslink agent were tested and bismuth was added to confer radiopaque properties to the stent. The preliminary *in vivo* validation studies in female domestic pigs was conducted at the University of Minho, Braga, after formal approval by the institution's review board and in accordance with its internal ethical protocol for animal experiments.

Paclitaxel, epirubicin, doxorubicin and gemcitabine were impregnated in the stents and the release kinetics was measured in artificial urine solution (AUS) for 9 days by UV spectroscopy in a microplate reader. The anti-tumoral effect of the developed stents in transitional cell carcinoma (TCC) and HUVEC primary cells, used as control, was evaluated.

RESULTS: The *in vivo* validation of this second-generation of ureteral stents performed was herein demonstrated. Biodegradable ureteral stents were placed in the ureters of a female pigs, following the normal surgical procedure. The animals remained asymptomatic, with normal urine flow. The *in vitro* release study in AUS of the stent impregnated showed a higher release in the first 72h for the four anti-cancer drugs impregnated after this time the plateau was achieved and the stent degraded after 9 days.

The direct and indirect contact of the anti-cancer biodegradable stents with the TCC and HUVEC cell lines confirm the anti-tumor effect of the stents impregnated with the four anti-cancer drugs, reducing around 75% of the viability of the TCC cell line after 72h and no killing effect in the HUVEC cells.

CONCLUSIONS: The use of biodegradable ureteral stent in urology clinical practice not only reduce the stent-related symptoms but also open new treatment therapy's, like in urothelial tumors of upper urinary tract.

Furthermore, we have demonstrated the clinical validation *in vivo* pig model. This study has thus shown the killing efficacy of the anti-cancer drug eluting biodegradable stents *in vitro* for the TCC cell line, with no toxicity observed in the control, non-cancerous cells. The direct and indirect contact of the anti-cancer biodegradable stents with the TCC and HUVEC cell lines confirm the anti-tumor effect of the stents impregnated with the four anti-cancer drugs, reducing around 75% of the viability of the TCC cell line after 72h and no killing effect in the

HUVEC cells. This study has thus shown the killing efficacy of the anti-cancer drug eluting biodegradable stents in vitro for the TCC cell line, with no toxicity observed in the control, non-cancerous cells.