Phase I/II CANON study: Oncolytic immunotherapy for the treatment of Non-Muscle Invasive Bladder Cancer using intravesical CAVATAK (Coxsackievirus A21)

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Introduction

The treatment of non-muscle invasive bladder cancer (NMIBC) has not changed significantly in 25 years. Treatment with intravesical BCG (Bacille Calmette Guerin) and chemotherapy after transurethral resection of tumor (TURBT) does not alter the natural history of the disease and has significant toxicity for patients. CAVATAK (Coxsackievirus A21, CVA21) is a novel intercellular adhesion molecule-1 (ICAM-1)-targeted immunotherapeutic virus. Surface ICAM-1 is up-regulated on a number of cancers including melanoma, non-small cell lung, prostate and in particular, bladder cancer. CVA21 displays potent oncolytic activity against *in vitro* primary cultures of NIMBC cancer cells and *ex-vivo* human bladder tumor material (***Figure 1***). Combining CVA21 with either radiotherapy or chemotherapy (mitocycin C) synergistically enhances cytotoxicity *in vitro* in bladder cancer cell lines. Low (non-cytotoxic) doses of mitocycin C enhances CVA21 viral replication and oncolysis by increasing expression levels of ICAM-1 on bladder cancer cells (***Figure 2***). In this two stage Phase I study, patients with NMIBC will receive neo-adjuvant CVA21 or low dose mitomycin C plus CVA21 prior to routine surgical removal (TURBT). We present preliminary data from the Phase I/II CANON (***CA***VATAK in ***NON***-Muscle invasive bladder cancer: NCT02316171**)** study which is investigating the tolerance of multiple escalating intravesicular doses of CVA21 in approximately 30 first-line NMIBC cancer patients.

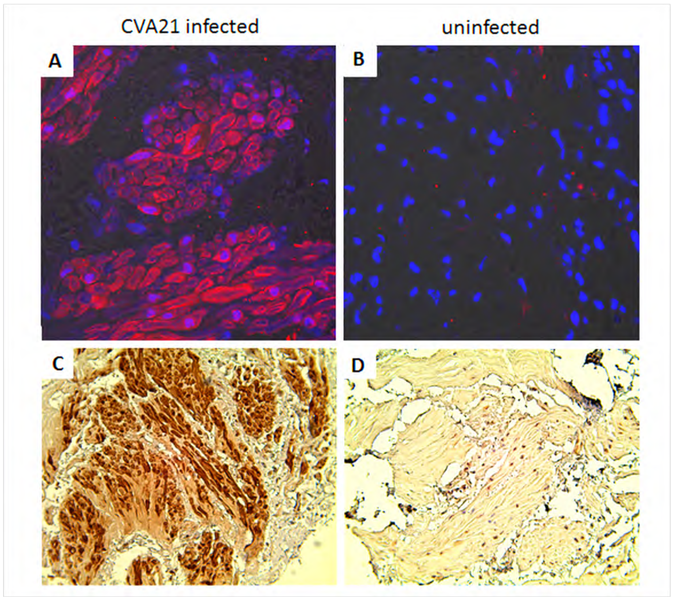


Figure 1. Ex-vivo human bladder tumor tissue is highly infectable by CVA21. Tissue pieces originating from the same human bladder tumor were either infected with CVA21 or left uninfected. Immunofluorescence and enzymatic staining for CVA21 viral protein was performed 48hrs post infection. Viral infections are visualized by the red staining in A (the blue colour shows the DAPI stained nuclei of the cells) and by the brown 3,3'-Diaminobenzidine (DAB) staining in C. No positive viral staining was observed in the uninfected bladder tumor tissues (B and D).

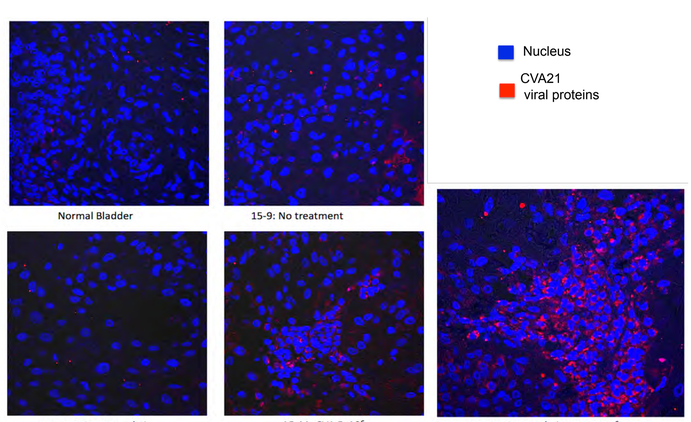
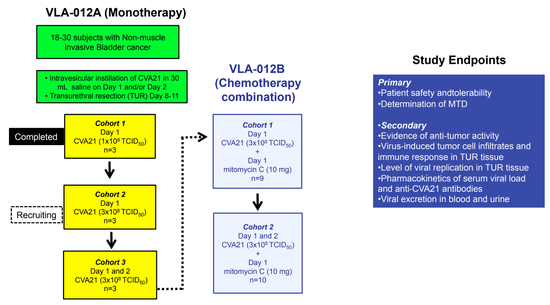


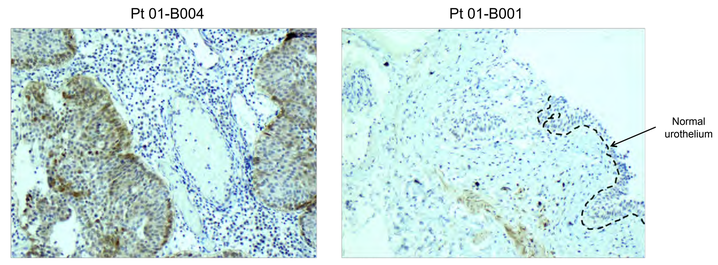
Figure 2. Enhanced CVA21 replication in combination with mitomycin C in *ex-vivo* human bladder tumor. Tissue tumor sections from a patient with NMIBC cut with a vibrating microtome were challenged with CVA21 (5 x 10^6 $TCID_{50}$) in the presence or absence of mitocycin C (5μg/ml). Immunofluorescence staining for CVA21 viral protein was performed 48hrs post infection. Viral infections are visualized by the bright red staining with the blue colour indicating DAPI stained nuclei of the cells

Preliminary Data

VLA-012 (CANON study): Phase I intravesicular ***CA***VATAK in subjects ***NON***-muscle invasive Bladder cancer



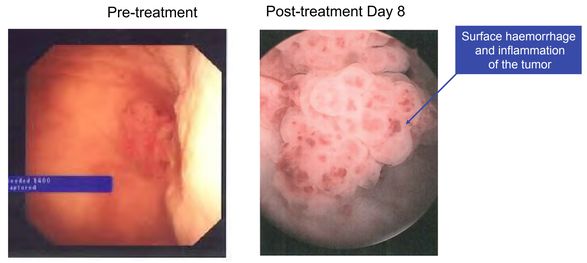
VLA-012 (CANON study) Phase I trial: Tumor specific CVA21 replication in Transuretheral resection tissue; Cohort 1: 1.0 x 10^8 $TCID_{50}$



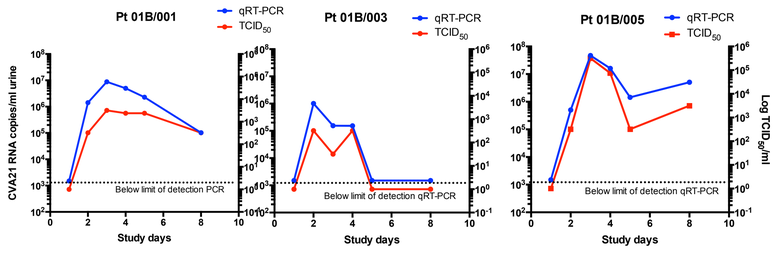
Anti-enterovirus staining (brown) only present on tumor cells and not on stromal cells and lymphocytic infiltrate

Absence of anti-enterovirus staining on normal urothelium (delineated by broken line)

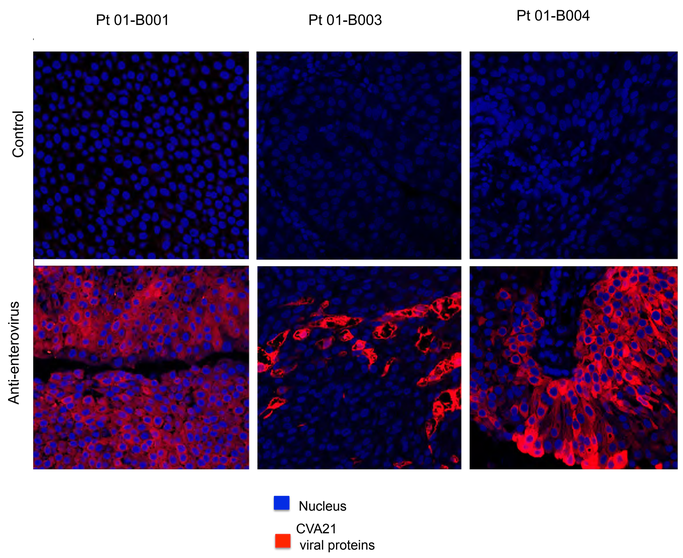
CANON Phase I trial: Pt 01B-001: Pre and post treatment cystoscopy



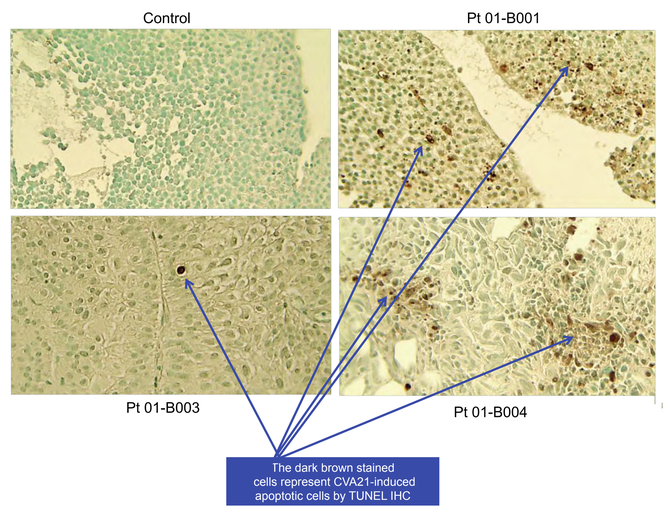
CANON Phase I trial: Levels of CVA21 in Urine Cohort 1: 1.0 x 10^8 $TCID_{50}$



VLA-012 (CANON study) Phase I trial: Intralesional CVA21 viral protein in Transuretheral resection tissue; Cohort 1: 1.0 x 10^8 $TCID_{50}$



VLA-012 (CANON study) Phase I trial: Intralesional CVA21 induced apoptosis in Transuretheral resection tissue; Cohort 1: 1.0 x 10^8 $TCID_{50}$



Conclusions

- CANON Phase I trial: Proof of concept tumor specific viral targeting, replication and tumor cell death following a single intravesicular administration of CVA21 was achieved in patients from Cohort 1 (1.0 x 10^8 $TCID_{50}$)
- To date intravesicular administration of CVA21 has been generally well tolerated with no Grade 2,3 or 4 product-related AE's
- Recruitment of Cohort 2 (3.0 x 10^8 $TCID_{50}$) is underway
- Overall observed tumor targeting and viral replication is likely to provide a strong signal in generating both a strong local and systemic anti-tumor immune response

Future Directions

- Phase II neo-adjuvant study with patients administered CVA21 via the intravesicular route prior to TURBT against patients with TURBT alone, Recurrence-free survival as primary endpoint.
- Phase Ib/II study with patients administered CVA21 in combination with immune checkpoint blockade.

OVC 2015, June 13-16, Boston, USA. *Corresponding author, Hardev Pandha: h.pandha@surrey.ac.uk*