An integrated urine biomarker / cytology based assay for monitoring and diagnosis of bladder cancer

Introduction
A plethora of biomarkers for malignant disease have been published. Most lack the required sensitivity and specificity. MCM-2 detection has been demonstrated to offer high sensitivity and specificity coupled to data capture that can be flexed for use in surveillance or primary diagnostic use in multiple clinical contexts. The whole-cell approach also offers the prospect of including further diagnostic and prognostic markers in a single multiplexed-package.

The MCM complex:
The monoclonal antibody used in this assay is specific for minichromosome maintenance protein-2 (MCM2). MCM2 is a member of a family of six proteins (MCM 2-7), initially identified in S. cerevisiae, but now known to be ubiquitous in eukaryotes. The six members of the family form a complex around chromosomal DNA at specific loci and mediate several functions including interactions with histone proteins in chromatin, and helicase activity – relaxing the tightly coiled DNA molecule and permitting the replication fork to progress. The activity of the MCM family of proteins is itself regulated by cell cycle dependent kinases. The MCM complex serves the role of licensing DNA replication, permitting it to occur only once during each cell cycle.

MCM positive nuclei present in urine:
Fully differentiated, quiescent cells would not be anticipated to demonstrate MCM positive nuclei. However, urine samples contain a diverse range of cell types, originating from both within the genitourinary tract and the immune system. Several of these populations would be anticipated to be engaged in the cell cycle. Skilled cytopathologists routinely use the morphological and staining characteristics to identify such cells. By not relying purely on a molecular approach, the additional parameters captured in collaboration with clinical cytopathologists from whole cells are currently being applied to eliminate such potential false positives from consideration in the assay.

The Future:
Based on the results outlined in the poster plus feedback from urologists and pathologists we have improved the MCM assay by i) optimising analyte quality via a single use device which captures and preserves bladder cells at point of urine collection, ii) immunofluorescence labelled MCM plus two additional markers, and iii) digitizing slides for subsequent interrogation of whole urothelial cells using software developed with experienced cytopathologists. Training sets shows improvement of sensitivity and specificity to the mid to high 90’s.

Further information:
This is now the subject of a multi-center clinical trial in the USA and EU, Q1 2018. For further information or to express interest in trial participation please contact: Dr Nigel McLean; nigel.mclean@cytosystems.com