# O2 Proteome-based classification of non-muscle invasive bladder cancer

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**Introduction & Objectives:** DNA/RNA-based classification of Bladder Cancer (BC) supports the existence of multiple molecular sub-types, while investigations at the protein level are scarce. Here, we aimed to investigate if Non-Muscle Invasive Bladder Cancer (NMIBC) can be stratified to biologically meaningful groups based on the proteome.

**Materials & Methods:** Tissue specimens from 117 patients at primary diagnosis (98 with NMIBC and 19 with MIBC), were processed for high resolution LC-MS/MS analysis. The proteomics output was subjected to unsupervised consensus clustering, principal component analysis (PCA), and investigation of subtype-specific features, pathways, and genesets.

**Results:** NMIBC patients were optimally stratified to 3 NMIBC Proteomic Subtypes (NPS), differing at size, clinico-pathological and molecular backgrounds: NPS1 (mostly high stage/grade/risk samples) was the smallest in size (17/98) and expressed an immune/inflammatory phenotype, along with features involved in cell proliferation, unfolded protein response and DNA damage response, whereas NPS2 (mixed stage/grade/risk composition) presented with an infiltrated/mesenchymal profile. NPS3 was rich in luminal/differentiation markers, in line with its pathological composition (mostly low stage/grade/risk samples). PCA revealed a close proximity of NPS1 and conversely, remoteness of NPS3 to the proteome of MIBC. Proteins distinguishing these two extreme subtypes were also found to consistently differ at the mRNA levels between high and low risk subtypes of the UROMOL and LUND cohorts.

**Conclusions:** Collectively, this study identifies three proteomic NMIBC sub-types and following a cross-omics validation in two independent cohorts, shortlists molecular features meriting further investigation for their biomarker or potentially therapeutic value.