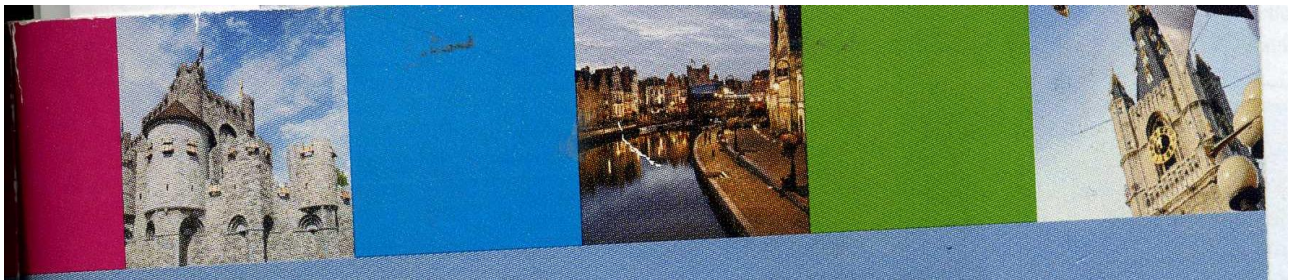

First International Symposium on the Ehlers-Danlos Syndrome

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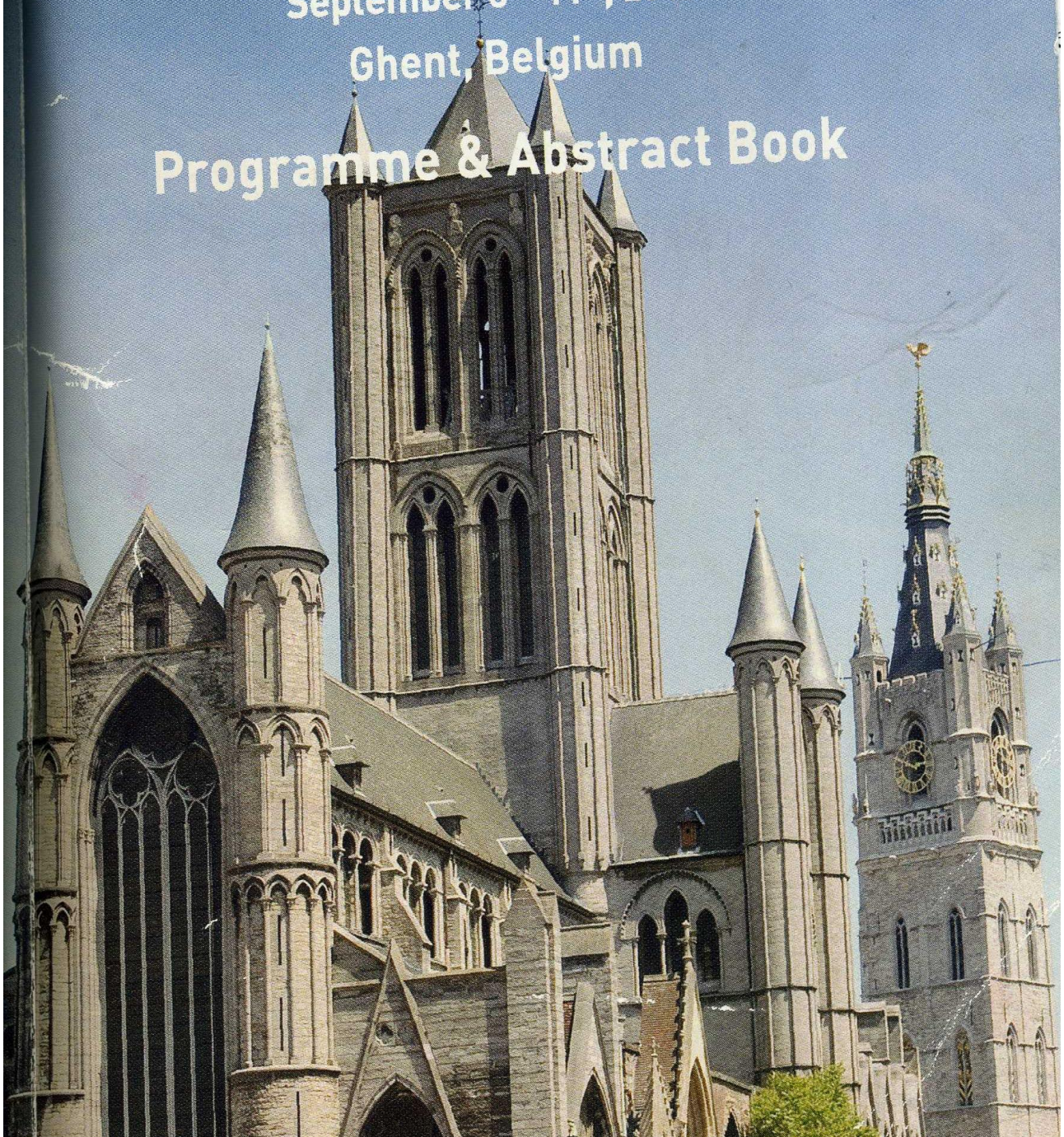
Programme & Abstract Book



P.3

Type V and type III collagen modulate the expression and assembly of fibronectin extracellar matrix in classic and vascular Ehlers-Danlos syndrome fibroblasts affecting cell survival and migration

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Extracellular matrix (ECM) regulates cell proliferation, migration, survival and gene expression, via signal transduction pathways differentially activated by ECM ligands interacting with specific integrins. In vitro cultured skin fibroblasts derived from classic and vascular Ehlers-Danlos syndrome (cEDS, vEDS) patients show a fibronectin (FN)-ECM disarray, consequent to the altered type V and III collagen (COLLV, COLLIII) expression and deposition. The COLL-FN-ECM disassembly is associated to the reduction of the COLLs alpha2beta1 integrin receptor, the FN alpha5beta1 integrin receptor substitution with alphavbeta3, rescuing from anoikis through a FAK-independent and epidermal growth factor-mediated signalling, and to the impairment of in vitro migration.

The role in the ECM-mediated survival and migration of COLLV and COLLIII, respectively mutated in cEDS and vEDS, was investigated in cultured skin fibroblasts by indirect immunofluorescence, Western blotting, Q-PCR and in vitro wounding assay.

Purified COLLV and COLLIII restore in cEDS and vEDS cells respectively, the COLL-ECM and the alpha-2beta1 integrin. This receptor transduces for the FN gene expression and splicing modulation, EDA-FN isoform synthesis and organisation, alpha5beta1-phosphorylated FAK colocalisation and EDA-FN specific alpha9beta1 integrin up-regulation. The induced COLL-FN-ECM, binding to alpha2beta1-alpha-5beta1-alpha9beta1 integrin complex, restores the FAK-mediated survival and the cell migration.
These findings show the role of COLLV- and COLLIII-ECM-mediated transduction signalling in in vitro cEDS and vEDS fibroblasts' survival and migration and give insights in the comprehension of the molecular mechanisms regulating these processes in vivo.