# Abstracts

## Lectures by winners of the Gaetano Conte Prizes

### H-1
### Collagen VI myopathies: pathogenic mechanisms and novel therapeutic perspectives

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Mutations in any of the three genes coding for the extracellular matrix protein collagen VI cause different types of muscle diseases, including Bethlem Myopathy (BM), Ullrich Congenital Muscular Dystrophy (UCMD) and Congenital Myosclerosis (1). Collagen VI null (Col6a1–/–) mice display a myopathic phenotype with organelle defects, mitochondrial dysfunction and spontaneous apoptosis of muscle fibers (2). Based on the findings obtained in the murine model, similar defects could be revealed in muscle biopsies and cultures of UCMD/BM patients (3). Our previous studies demonstrated that one major pathogenic event is the PTP-dependent latent mitochondrial dysfunction (4), however the cause for the accumulation of dysfunctional organelles remained unsolved.

The presence of swollen mitochondria and dilated sarcoplasmic reticulum prompted to check whether the machinery for organelle removal, the autophagic system, is affected. We found that persistence of abnormal organelles and apoptosis are caused by defective autophagy in collagen VI deficient muscles. Autophagy is a process of cytosolic 'renovation', which is essential for the maintenance of cell homeostasis by clearing misfolded proteins and dysfunctional organelles. Skeletal muscles of Col6a1–/– mice display impaired autophagic flux, which matches the lower induction of Beclin 1 and Bnip3 and the lack of autophagosomes after starvation. Furthermore, muscle biopsies from patients affected by UCMD or BM show reduced levels of Beclin 1 and Bnip3. Notably, forced reactivation of autophagy by either genetic (overexpression of Beclin-1), nutritional (low protein diet) or pharmacological (cyclosporin A) approaches restores myofiber survival and leads to a marked amelioration of the structural and functional defects of Col6a1–/– muscles, with normalization of the dystrophic phenotype (5, 6)

These findings indicate that defective activation of the autophagic machinery has a key pathogenic role in congenital muscular dystrophies linked to collagen VI deficiency. Altogether, our data are the first demonstration that impaired autophagy plays a pivotal role in the pathogenesis of some muscular dystrophies, thus providing new insights into the pathogenesis of muscle degeneration and opening new perspectives for treatment.

References

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### H-2
### The benefits of a specialised myositis clinic

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A multidisciplinary referral clinic for the diagnosis and management of adult patients with inflammatory myopathy has been in operation at the ANRI in Perth since 1990. Patients are seen jointly by a neurologist, a clinical immunologist and physiotherapist and by a speech pathologist if they have swallowing problems. The diagnosis of myositis is confirmed by muscle biopsy in all cases and screening for muscle-associated and muscle-specific autoantibodies is also performed. Over 250 patients have been seen in the clinic, falling into the following categories: inclusion body myositis (32%), dermatomyositis (32%), overlap syndromes (23%), isolated polymyositis (11%), miscellaneous (2%). Muscle function is monitored by manual muscle testing (MMT) and, in selected cases myometry and isokinetic dynamometry is performed. Patients undergo regular reviews to monitor the response to treatment. This has also allowed observations to be made on the frequency of relapses in patients with dermatomyositis and polymyositis (1), and the variability in the clinical phenotype and rate of progression of muscle weakness and influence of HLA alleles in inclusion body myositis (2). Two new clinical entities have been identified: statin-associated necrotising myopathy with upregulation of MHC-I (3), and a restricted scapulospinal form of myopathy