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My interest in research is addressed at investigating the structure-function relation in muscle. This is the result of the combination of my studies for the Physics degree at the University of Turin (Italy) on imaging techniques (2002), and my PhD studies at the Laboratory of Physiology of the University of Florence (2003-2005). During my PhD I integrated the sarcomere-level mechanics in single cells from frog muscle, mastered by the staff of the Florence Laboratory, with time-resolved X-ray diffraction at the European Sychrotron Radiation Facility, (ESRF, Grenoble, France) and the Advanced Photon Source (APS, Argonne, USA). A breakthrough in these studies was the application of the effect of the X-ray interference between the two arrays of myosin motors in each sarcomere, that made possible to directly measure, with subnanometer precision, the motion of myosin motors in an intact muscle cell. This method brought substantial advance in muscle research as demonstrated by the publications in high impact factor journals (*Proc. Natl Acad. Sci. USA, Cell, FASEB Journal and Journal of Physiology*).

We investigated the molecular basis of the braking action of muscle in eccentric contractions, showing that a stretch of active muscle elicits rapid attachment to the actin filament of the second motor domain of myosin molecules with the first motor domain already attached (Brunello *et al.* 2007, *Proc. Natl Acad. Sci.* 104:20114).

In a subsequent series of experiments we defined the molecular determinants of muscle performance and efficiency (Piazzesi *et al.* 2007, *Cell* 131: 784), finding that, for shortening against high and intermediate loads, the number of myosin motors decreases in proportion with the decrease in load, so that the motors maintain a constant force of 6 pN while undergoing a 6 nm stroke. We made progress also on some still controversial points that are related to the mechanical and structural changes occurring in the myosin motors and myofilaments during the transition from the resting state to the plateau of an isometric contraction and during the relaxation that follows the end of stimulation. We showed that during the development of isometric contraction the number of myosin motors increases in proportion to the isometric force and that only the M3 reflection, originated from the axial periodicity of myosin heads, can be related to the force generating myosin motors. (Brunello *et al.* 2006, *J. Physiol.* 577:971). We found that during the slow “isometric” phase of relaxation, even if the calcium concentration attains rapidly a low value, the myosin filament retains its “ON” state, due to the presence of the myosin motors attached to actin and that

the final fast phase of relaxation is induced by the increase in the average motor strain (Brunello *et al.* 2009, *J. Physiol.* 587:4509).

During the last two year I also applied fast mechanics to demembranated muscle fibres, a preparation that allows to control the biochemical milieu bathing the myofilaments. Demembranated fibres from mammalian muscle are also a powerful tool for investigating the molecular basis of pathologies. In experiments where we compared the mechanical and kinetic properties of psoas fibres from wild type mice and mice knockout for nebulin, we could reveal a direct role of nebulin in promoting the strong actomyosin interaction (Bang *et al.* 2009, *FASEB J.* 23:4117). My next step is to combine demembranated fibre mechanics with time-resolved structural studies, using either X-ray diffraction (Florence Laboratory) or fluorescent probes (King's College London), to directly define the coupling between mechanical, structural and biochemical states of the molecular motor of muscle in situ. A four year project under my responsibility, that combines the X-ray interference method with synchrotron light and skinned fibre mechanochemistry, has been funded in these days by the Italian Ministery of University and Research under the program "Futuro in Ricerca".