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The scanning ion conductance microscope is more than a microscope

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The quest for microscopes that can surmount light diffraction limits has resulted in Scanning probe microscopes. However many of these are not ideal for living biology. The scanning ion conductance microscope (SICM) bridges the gap between the resolutions of (a) the Atomic Force Microscope (AFM) or the scanning electron microscope, and (b) the functional capabilities of conventional light microscopy. The SICM is a high-resolution (submicron) microscope similar in principle to the AFM. But while morphologically defining membrane near nanostructure, unlike the AFM, which taps the cell, the SICM is no-touch. A nanopipette, on a three-axis piezo-actuator scans the nanopipette over living preparations in physiological solutions. Ion current is measured between the pipette tip and the sample. (The sample stage can also move - with pipette stationary.) Feedback control maintains a given ion current and thus maintains distance between the sample and the pipette (no touch). Recorded XYZ pipette movement generate 3D topographical images of live biological samples. The hollow nanopipette probe provides added modalities, enabling functional studies. The same pipette and feedback control, precisely targets, and patches, discrete regions of the cell for ion channel recording. The SICM can include fluorescence (pipette stationary, sample moves) facilitating structure-function correlations. Also, as a "mechanical" instrument it can precisely measure local membrane compliance (Young's Modulus). Moreover, applied pressure through the pipette, targeting selected areas indents the membrane, liberating intracellular calcium by mechanosensitive processes. All this is on living tissue. The SICM as a high resolution multifunctional instrument has significant future potential.

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Integrative and translational mechanotransduction in myocardium

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Max Lab was fortunate in having been a major contributor to the establishment of Mechanoelectric Transduction or coupling (MEC)-Mechanosensitivity (stretch) in heart. MEC is essentially a reverse of the unidirectional excitation-contraction coupling (ECC) and is now a physiological entity. MEC is also gaining widespread clinical application in cardiac electrophysiology and is a novel, unexpected, mechanism of sudden heart-related death with potential profound therapeutic implications. (Mechanosensitivity in general is achieving a global presence initiating a plethora of downstream signals in biology influencing neonatal development, organ systems and disease.) Max Lab's integrative work started on isolated papillary muscle extending "up" to the intact ventricle in anaesthetized animals and to man as well as "down" to cellular studies. In collaboration he is currently integrating a nano-research path exploiting the Scanning Ion Conductance Microscope (SICM). The SICM is a high-resolution (submicron) imaging and research tool similar in principle to the Atomic Force Microscope but with the advantages of a no-touch nanopipette as a probe instead of a rigid tapping cantilever, no required staining or fixing of dead tissue and the use of living preparations in physiological solutions. Dedicated soft and hardware scans the probe over the membrane surface without touching it, morphologically defining its near nanostructure and with appropriate hybridization enabling functional studies such as ion transport and receptor regulation and cell signaling. This can be exceedingly difficult to do in living cells with other high-resolution systems. Current study includes mechanosensitivity by mechanically probing nano-precise areas of a cell. Applying hydrostatic pressure through the nanopipette mechanically indents discrete areas of the surface membrane to study regional mechanosensitivity and Mechanoelectric Coupling. Indenting liberates intracellular calcium by mechanisms still under investigation.

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