With extensive development of nanotechnology in last few years, scientists have discovered that nanoparticles (NPs) can be used as a Drug Delivery System (DOS). In able to develop better drug delivery tool, it is crucial to understand the interaction between NPs and the cell membrane. In our previous studies, cerium oxide nanoparticles (CNPs) have been reported to have therapeutic potentials, specifically against abnormalities associated with oxidative stress. Therefore, CNPs with different sizes and shapes were selected as a model NPs for this purpose. We analyzed mechanical property of cell membranes using Atomic Force Microscopy (AFM) with and without CNPs. In particular, Force-Distance spectroscopy mode was used to estimate elasticity of cells membrane. Different concentrations (50 to 250 μM) of CNPs were added to the cells (squamous cells; CCL30) and incubated for different time periods (0 to 60 minutes). Cell membrane elasticity/Young's modulus was calculated using a modified Hertz model. Changes in the cell elasticity were observed in high concentration of CNPs over 1hr of time. Significant changes in cell elasticity were observed at high concentration of CNPs for 1hr of incubation. No significant change in cell elasticity was observed over 1hr time period for 50nm of CNPs. Moreover, by using selected inhibitors to block different cells internalization pathways, we also investigated the correlation between the cellular uptake and the tracking of NPs with their size. Specifically, similar change in cell elasticity was observed after blocking the cell energy production for CNPs with smaller diameter (3-5nm). On the other hand, bigger size NPs (20-30nm) showed no change in cell elasticity after blocking the cell energy production. This results indicate that 3-5nm particles internalize cell by non-energy dependent pathway i.e. passive diffusion whereas 20-30nm particles entered in cell by energy dependent pathways i.e. endocytosis of particles. Further, we have also indentified the cellular uptake of 20-30nm particles is by enclosing those CNPs in membrane vesicles in caveolae-mediated endocytosis mechanism. In summary, these results indicate that the nanoparticles-cell interaction has pronounced influence on shape and size of the nanoparticles and cell nanoparticles interaction can be monitor real time by measuring the mechanical property of cell membrane.