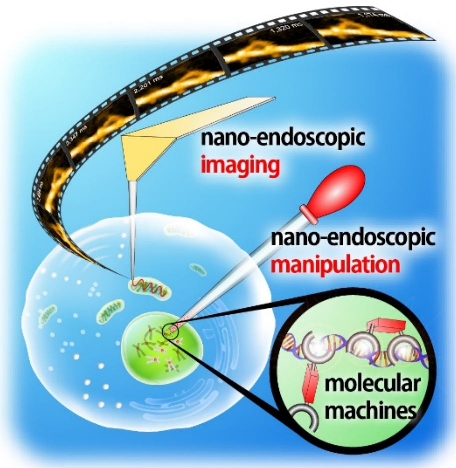
Director’s Vision

Continuous advances in science and technology have enabled humans to explore diverse realms. We have traveled across the Earth’s surface, atmosphere, and neighboring regions of space and amassed knowledge of various phenomena, gaining insights that paved the way for today’s prosperity. Yet, there still are many worlds that we have only begun to explore—the deep sea, the Earth’s interior, the vast reaches of outer space, and, at the other end of the spectrum, the microscopic universe. Optical microscopy, electron microscopy, scanning probe microscopy (SPM), and other tools have allowed us to peer into domains invisible to unaided human eye. Our observations of microorganisms, cells, molecules, and atoms have revealed various phenomena and elucidated their origins and physical properties. Today, we are even able to characterize phenomena based on knowledge of configurations and interactions among the smallest units of matter—atoms and molecules. Nevertheless, many corners of the nano world remain uncharted; science and technology are currently unable to provide an accurate portrait of nanoscale structures and dynamics. This limitation represents a significant barrier to the further advancement of science and technology.

In the life sciences, determining the behavior of proteins, nucleic acids, and other cellular components—basic building blocks of the human body—is a key step toward fundamentally understanding and controlling the mechanisms of complex biological phenomena, such as development, disease and aging. However, we lack a detailed grasp of these dynamics. For example, fluorescence microscopy allows us to visualize specific molecules tagged with fluorescent labels, but we are unable to determine the position or structural changes of the many unlabeled molecules. Electron microscopy can be used to examine the static ultrastructure of cells and molecules in a vacuum, but not to observe nanoscale behavior in physiological solutions. At present, SPM is the only available technology for the direct imaging of the position and structural changes of protein molecules in solution, and thus is promising for approaching challenges in the life sciences. However, SPM does not yet enable the direct observation of the intracellular protein behavior. Accordingly, many nanoscale properties of intra/extracellular space have yet to be mapped out, limiting our ability to fundamentally understand biological phenomena, such as disease and aging.

Our institute (NanoLSI: Nano Life Science Institute) will explore these uncharted realms with the aim of elucidating the mechanisms of biological phenomena at the atomic and molecular levels (≈ nanoscale). To advance this mission, we will create innovative technologies for direct imaging, analysis, and manipulation of intracellular and cell-surface nanodynamics. First, we will develop a tool for “nanoendoscopic imaging” that, similar to endoscopic imaging of the stomach cavity, will enable direct video imaging of intracellular nanodynamics. This tool will visualize on the nanoscale not only the dynamics of proteins, nucleic acids, and other molecules, but also the distribution of chemical properties, such as the pH and oxygen concentration, using highly environmentally responsive molecular sensors. We will seek to achieve on the cellular level something akin to therapeutic endoscopy, which includes endoscopic sampling/analysis of foreign matter in the body and drug injection. Our “nanoendoscopic manipulation” technology will make it possible to



sample/analyze specific nanoscale substances in cells and to control the function of receptors and other biomolecules via molecular machines with high-level control functions.

Bringing such innovative technologies to reality will be a major challenge, but is not unrealistic. SPM is promising for the development of nanoendoscopic technologies. SPM visualizes, at the nanoscale, surface topography and the distribution of physical properties by scanning with a fine-tipped probe. In addition, the probe can be used to apply stimuli and for structural manipulations with nanoscale precision. Kanazawa University's achievements in this field make it a world leader in technological development and applied research in bio-SPM operable in solutions. I developed the first method for in-solution nanoscale imaging of the water density and surface potential distributions, and Ando was the first in the world to create an SPM technology for the direct nanoscale visualization of protein dynamics. These technologies form the foundation for nanoendoscopic observations of the behaviors of proteins, nucleic acids, water molecules, and ions. Moreover, one of NanoLSI's members, Korchev, established the basis for scanning ion-conductance microscopy, which makes it possible to inject or sample substances in specific nanoscale regions inside or outside of cells using a nanoscale pipette. Combined, our technologies provide a platform for realizing nanoendoscopic manipulation. By leveraging these world-leading bio-SPM technologies and collaborations among the outstanding researchers who pioneered them, NanoLSI will strive to develop nanoendoscopic imaging/manipulation technologies.

Capitalizing on our innovative technologies for nanoscale imaging, analysis, and manipulation, NanoLSI will seek to establish a fundamental understanding of the mechanisms of basic cellular functions and their cancer-specific abnormalities. This focus on cancer has clear significance, as overcoming intractable diseases is a major goal in society, and has considerable research implications. Cancer involves many different types of molecular dynamics, including stemness (i.e., the ability of cells to proliferate by self-renewal and to differentiate), intra/extracellular signaling, and genome dynamics, and the elucidation of these dynamics on the nanoscale will provide a fundamental basis for understanding a wide range of biological phenomena. Furthermore, cancer research proceeds from a model defining normal and abnormal cells; this comparison can be used to determine the relationship between cellular-level abnormalities and abnormalities in the underlying molecular dynamics. Since cancer has a long research history, a relatively deep understanding of the determinants of the onset of cancer has been established. Nevertheless, cancer has yet to be conquered and accounts for one in three Japanese deaths. This suggests that current technologies are insufficient for fully understanding the underlying molecules and processes. Our proposed nanoendoscopic technology could provide insight into these elusive factors, and in so doing could lead to significant breakthroughs in the fight against cancer.

This goal cannot be achieved solely by nanometrological researchers. Naturally, medical/pharmaceutical scientists specializing in oncology, supramolecular chemists with expertise in molecular sensor-based nanoanalyses and nanomanipulation, and mathematical/computational scientists who can perform multiscale simulations are needed. NanoLSI will strive to achieve the aforementioned goals through collaborations among researchers with world-class track records in various fields. Kanazawa University, endowed with the Bio-AFM Frontier Research Center and the Cancer Research Institute, is known worldwide as a leading institute of nanobio research and cancer research. We will further build upon and expand this foundation to pioneer unexplored nanoscale realms and thus evolve into a one-of-a-kind research institute, without parallel anywhere else in the world.