Public Lecture by Dr. Immo E. Scheffler
"Is Aging Caused by a Decline in the Cell's Powerhouse (Mitochondria)?"
February 20, 2002 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Mitochondria were first described by microscopists more than a century ago. Their central role in bioenergetics (energy metabolism) was, however, not established until about fifty years ago. Their intricate structure became apparent from pioneering studies by G. Palade and colleagues using the newly developed electron microscope in the study of biological materials (cells). At the same time a technique described as "exploring cells with a centrifuge" by DeDuve and colleagues made it possible to isolate mitochondria as relatively pure subcellular organelles. This was the birth of Cell Biology and the recognition that the cytoplasm of eukaryotic cells is a highly compartmentalized space where different organelles have specialized functions.

Biochemical studies with pure mitochondria in turn provided experimental proof that respiration (the consumption of oxygen) takes place exclusively in mitochondria. The lecture will provide a brief historical overview of the evolution of ideas about respiration and bioenergetics, starting with Lavoisier's experiments and hypothesis that respiration in living organisms and combustion have a lot in common.

From a consideration of muscle and questions about the source of the energy expended for mechanical activity, ATP was discovered as the "energy currency" of the cell, that is, ATP was recognized as a "high energy" compound that could be made in mitochondria and then transported to various parts of a cell to participate in a wide variety of biological functions. These include movement in muscle, transmission of signals by the nervous system, biosynthesis of macromolecules, turnover and repair of cells and tissues, etc.

It became clear that the controlled "combustion" of carbohydrates to carbon dioxide, with the consumption of oxygen (respiration), involved in the final stages a transfer of electrons to oxygen through an electron transport chain localized in mitochondria. The energy liberated from this process must be utilized for the synthesis of ATP. One of the great triumphs of Biological Science in the 20^{th} century is the Chemiosmotic Hypothesis of P. Mitchell, which provided a mechanism for this energy inter-conversion.

Mitochondria were discovered to contain DNA. This discovery, and very convincing additional experimental findings, support a generally accepted hypothesis that mitochondria originated as bacteria that were taken up into another cell very early in the evolution of life on earth. Three to four billion years later mitochondria are no longer autonomous, and most of their original genes have been lost or transferred to the nucleus. However, seven genes on mitochondrial DNA encode proteins made inside the mitochondria and then incorporated into large protein complexes making up the electron transport chain.

Leakage of electrons from complexes of the electron transport chain to oxygen leads to the formation of reactive oxygen species (ROS). These reactive oxygen species are capable of damaging proteins, lipids and mitochondrial DNA. A special set of enzymes in mitochondria serves to scavenge these ROS, but some escape and cause damage (mutations) in mitochondrial DNA. It is hypothesized that an accumulation of this damage over a lifetime reduces the capacity of mitochondria to produce ATP for biological work. The phenomena associated with aging may be a reflection of this accumulated damage in mitochondrial DNA.

Recent discoveries have also shown that mutations in mitochondrial DNA can be inherited giving rise to a new broad class of diseases referred to as "mitochondrial diseases". Symptoms are variable in severity, often show a delayed onset with age, and generally the defects are in the nervous system (neuropathy, blindness, hearing loss), or in muscle (myopathy, cardiomyopathy). The genetic basis for these diseases will also be discussed in light of the facts that 1) we inherit all of our mitochondrial DNA from our mothers, and 2) we have of the order of a thousand mitochondrial DNAs per cell (in contrast to two copies of most of our genes).