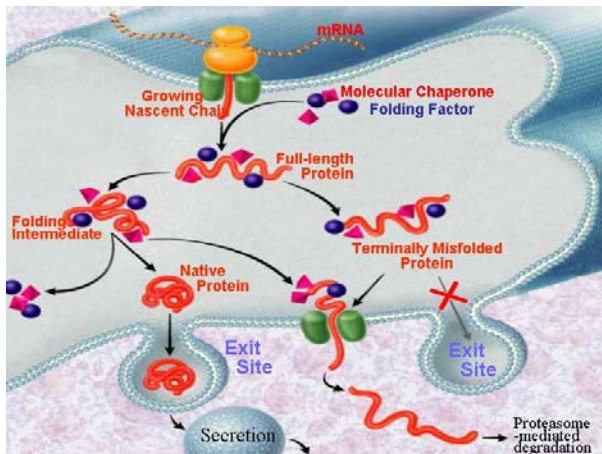


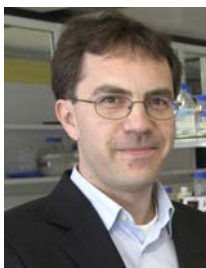
### *How misfolded proteins are degraded from the endoplasmic reticulum*

The endoplasmic reticulum (ER) is a site of protein synthesis. The ER is endowed with a quality control machinery that allows the transport of correctly folded proteins to their final destination, e.g. plasma membrane or intracellular organelles, but in the case of aberrant products triggers their destruction (see figure). Recently, a number of hereditary human *conformational* diseases such as cystic fibrosis, alpha1-antitrypsin deficiency and neurodegenerative diseases have been linked to defective functioning of the ER quality control machinery. Moreover, a number of human pathogens exploit the ER folding and quality control machinery to invade the host cell or to escape immunosurveillance.



In a study that will be published in *The Journal of Cell Biology*, the group of Maurizio Molinari at the IRB gives an important contribution for the understanding of the mechanisms that regulate the ER quality control machinery. The beta-secretase (BACE501) is an aspartic protease expressed in the human brain. The enzyme cleaves the amyloid precursor protein (APP),

thereby initiating a processing pathway which can lead to the generation of beta-amyloid peptides that are deposited in senile plaques associated with Alzheimer's disease. Maurizio Molinari and colleagues are studying an isoform of beta-secretase that is specifically expressed in the pancreas (BACE457). Characterization of BACE457 revealed that the protease does not contribute significantly to APP processing, because folding of BACE457 is inefficient and most of newly synthesized BACE457 is rapidly degraded by the ER quality control machinery. Detailed analysis revealed that upon expression in the ER, BACE457 enters the calnexin cycle, a folding machinery, in order to acquire its native conformation. However, most of BACE457 folds incorrectly and does not become transport-competent. This feature BACE457 shares with other proteins such as the cystic fibrosis channel or alpha1-antitrypsin. Their inefficient folding and subsequent degradation are linked with serious human pathologies. Using BACE457 as a "model substrate" Molinari and colleagues have characterized proteins resident in the ER (BiP, PDI and EDEM) that are involved in the degradation of aberrant products. They demonstrate that upon release from the folding machinery (the calnexin cycle), transport-incompetent products enter an unfolding machinery (EDEM-BiP-PDI network) that prepares them for degradation. Preparation for degradation consists in extensive unfolding of the polypeptide chain to allow the export of misfolded proteins through a narrow pore residing in the membrane of the ER into the cytosol where final degradation occurs.



### *Award for the IRB group leader Dr. Maurizio Molinari*

Dr. Maurizio Molinari received on May 29<sup>th</sup>, from the "Fondazione per lo studio delle malattie neurodegenerative" (Foundation for Research on Neurodegenerative Diseases) sited in Lugano an award for his achievements in research on Alzheimer's disease.

**Meetings:** On April 3<sup>rd</sup> – April 5<sup>th</sup> the IRB and Virginia Tech (USA) organized a scientific joint meeting at Riva San Vitale (Lake Lugano). During this occasion collaborative student exchange program between the two institutions was decided.