July 20, 2009

To Whom It May Concern:

I am pleased to write this letter enthusiastically endorsing the continued existence and funding of the Center of Physiopathology of Cell Differentiation at the Vita-Salute San Raffaele University. I am aware not only of the excellent work carried out in the Center but consider the research conducted there of tremendous relevance and of great impact at the international level and on the national level.

I offer, on the attached sheet, a summary of the achievements of the Center and my admiration and respect for the brilliant scientists and their research performed there.

Sincerely yours,

Günter Blobel, M.D., Ph.D.
John D. Rockefeller, Jr. Professor of Cell Biology
Investigator, The Howard Hughes Medical Institute
Nobel Laureate, 1999

GB: lrq

Short summary of Achievements Reached in the Center of Excellence on the Pathophysiology of Cell Differentiation

Vita-Salute San Raffaele University, Milan, Italy.

Many of the results obtained in the Center during its life have been widely appreciated. Here we will make reference to only a few of them.

Marco Bianchi's group has focused on the unexpected discovery that the nuclear protein HMG1, investigated for its role in chromatin structure and function, is released by many cells to the extracellular space. The released protein, after binding to the receptor RAGE, plays a key role in inflammation and immunology. This line of research has attracted numerous external collaborations and is having a great impact in the field.

Blasi's team, through the combination of cell biology and transcription studies, revealed the unique properties of the urokinase receptor. This unique strategy enabled his group to contribute substantially to the rapid increase of the knowledge about the role of this receptor in cell growth and in cancer thereby opening new perspectives for diagnosis and therapy.

Marchisio and Biffo and their co-workers identified new mechanisms that control protein synthesis, demonstrating the importance of initiation factors and of their interactions with the ribosome subunits. These mechanisms, regulated via surface signaling, were also shown to play a role in cell growth and tumor transformation.

Meldolesi's team, working on wild type and defective pheochromocytoma PC12 cells, obtained two series of results: 1) the identification of a new class of regulated exocytic vesicles which they named enlargeosomes, are

characterized by unique structural and functional properties; and 2) and the identification of the transcription repressor REST as the factor that orchestrates the expression of neurosecretion.

Pardi's group continued its work on the adhesion and migration of cells, in particular, macrophages and neutrophils, revealing new roles of integrins and identifying their interactions with recently identified surface proteins. These results provided an explanation of the processes and mechanisms which play important roles in inflammation and immunology.

Roberto Sitia's team continued its work on the ER lumen and the structure/function of its proteins leading to the identification of Ero1. His group further demonstrated the cooperation of this protein with other segregated proteins; revealed the key role of Ero 1 in the control of the oxidative environment. His team likewise introduced the concept of quality control in the ER protein factory.

Flavia Valtorta's group continued the work on the structure and function of presynaptic terminals, focusing in particular on the mechanisms that underlay the critical role of synapsin 1; on the kinetics of synaptic vesicle traffic; and on the cycling of specific membranes taking place in the growing cone. The latter process has been shown to make possible the presynaptic surface expansion and, ultimately, the generation of synapses.

In addition to the scientific work, the Center has also been active at the translational level, with the development of ten new patents and one small spin-off company.