Basel, October 19th 2012

# Charles Betz, Misrock Fellow

# Final Progress Report, 2008-2012

The Target of Rapamycin or TOR pathway is a cellular signaling cascade conserved in all organisms other than bacteria. It relays and integrates signals coming both from external and internal sources, informing the cell of the availability of nutrients and thereby instructing the cell to invest energy in growth. Initially discovered in the early 1990's at the Biozentrum in the laboratory of Michael Hall, this diverse and highly complex pathway has elicited much interest because of its involvement in numerous disorders including cancer, diabetes, aging and obesity. TOR in mammalian cells functions in two distinct multi-protein complexes termed mTORC1 and mTORC2.

Charles Betz started both his PhD studies and his Misrock Fellowship in the Hall laboratory in August 2008. The initial focus of his project was to investigate the TOR pathway specifically in the liver, using the mouse as an experimental system.The approach to inhibit TOR signaling in the liver by genetically deleting raptor, a component of mTORC1, was stopped after 12 months of investigation, in August 2009. Charles Betz found that it was impossible to completely stop TOR signaling using this approach and that the approach was thus not worth pursuing further.

Following the high-impact study "Activation of mTORC2 by Association with the Ribosome" published by Zinzalla et al. from the Hall group, Charles Betz started a deeper characterization of the observations made in this publication. Zinzalla and colleagues showed for the first time that ribosomes, the cell's "building factory", activate mTORC2 and that this process is important in certain cancer cells. Charles Betz analyzed whether mTORC2 is associated with only a specific subset of ribosomes and where in the cell this association takes place. The results from these studies showed that mTORC2 localizes to a subdomain of the endoplasmic reticulum termed MAM (mitochondria associated ER membrane). This subdomain forms a "bridge" between the ER, where proteins are synthesized, and the mitochondria, where energy is produced inside the cell. This novel finding has important implications since it helps explain how mTORC2 regulates cell growth, survival and metabolism. Since these three processes are deregulated in cancer and obesity, the discoveries made by Charles Betz may help in the development of treatments for these diseases.

The work realized by Charles Betz is being prepared for submission to a scientific journal and should be finalized by the end of 2012. Furthermore, Charles Betz contributed to the publication by his colleague Asami Hagiwara titled "Hepatic mTORC2 Activates Glycolysis and Lipogenesis through Akt, Glucokinase, and SREBP1c" (cf attachment).

Charles Betz successfully completed his PhD studies on October 2nd, 2012 and his work was awarded the distinction "Magna Cum Laude" by the Faculty of Natural Sciences of the University of Basel. His work contributes to a better understanding of the fundamental process of cell growth in healthy and diseased cells.

With deepest gratitude to the Misrock Foundation for its generous support during the past years,

Prof. Michael Hall

Biozentrum, University of Basel