

# **Department of General and Visceral Surgery**

# Regulation and Functions of Members of the Casein Kinase 1 (CK1) Family and Especially of CK1 $\delta$

## Head: Doris Henne-Bruns

Research in the Department of General and Visceral Surgery is concentrated on malignant diseases and obesity-related research. Cancer research is focused on basic and translational research projects, including the characterization of alterations in signal transduction pathways, and the identification of new target molecules and prognostic factors, especially for pancreatic, colorectal and gastrointestinal stroma tumors.

Our group is interested in the validation of CK1 isoforms to gain detailed information regarding their functions and regulation. Members of the highly conserved CK1 family are ubiquitously expressed in all eukaryotes. Mammalian CK1 isoforms ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\varepsilon$ ) and their splice variants are involved in

The Team:

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### Localization of CK1δ expression in RGCs

Immunofluorescence staining (A) and phase contrast image (B) of the neurite growth cone of a retinal ganglion cell (RGC) using the CK1&specific monoclonal antibody 128A (red) and the ßIII-tubulin-specific monoclonal antibody RB-9249-Po (green). Epifluorescence microscopy of RGCs revealed that CK1& is located in granular particles aligned at microtubules all over the growth cone.

diverse cellular processes, including membrane trafficking, circadian rhythms, cell cycle progression, chromosome segregation, apoptosis, differentiation and regeneration processes. Mutations and deregulation of CK1 expression and activity have been linked to various diseases, including neurodegenerative disorders, as in Alzheimer's and Parkinson's diseases, sleeping disorders, and proliferative diseases such as cancer. Consequently, recent interest in its role in carcinogenesis and degenerative diseases, and in developing CK1-specific inhibitors, has enormously increased.

Within the last two years, Joachim Bischof has concentrated on: (i) the identification of cellular kinases which influence CK1 $\delta$  activity by phoshorylating CK1 $\delta$  within its C-terminal regulatory domain; (ii) the role of CK1 $\delta$  in the regeneration of retinal ganglion cells after optic nerve injury; and (iii) the identification of new CK1 isoform-specific small inhibitors. At the same time, Julia Richter has focused on the characterization of the role of CK1 $\delta$  in tumorigenesis and the progression of colorectal cancer.

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### Selected Publications:

- Kornfeld JW, Baitzel C, Könner A, Nicholls H, Vogt M, Hermanns K, Scheja L, Haumaitre C, Wolf AM, Knippschild U, Seibler J, Cereghini S, Heeren J, Stoffel M, and Brüning JC (2013): Obesity-Induced Overexpression of miR-802 Impairs Glucose Metabolism Via Posttranscriptional Silencing of Tcf2/Hnf1ß. Nature 494:111-5. doi: 10.1038/nature11793.
- Hirner H, Gunes C, Bischof J, Wolff S, Grothey A, Kuhl M, Oswald F, Wegwitz F, Bosl MR, Trauzold A, Henne-Bruns D, Peifer C, Leithauser F, Deppert W, and Knippschild U (2012): Impaired CK1 delta activity attenuates SV40induced cellular transformation in vitro and mouse mammary carcinogenesis in vivo. PLoS One 7, e29709.
- Bischof J, Leban J, Zaja M, Grothey A, Radunsky B, Othersen O, Strobl S, Vitt D, and Knippschild U (2012): 2-Benzamido-N-(1H-benzo[d]imidazol-2-yl)thiazole-4-carboxamide derivatives as potent inhibitors of CK1delta/epsilon. Amino Acids 43, 577-591. Epub 2012.
- Bischof J, Muller A, Fander M, Knippschild U and Fischer D (2011): Neurite Outgrowth of Mature Retinal Ganglion Cells and PC12 Cells Requires Activity of CK1delta and CK1epsilon. PLoS One 6, e20857.
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- Brockschmidt C, Hirner H, Huber N, Eismann T, Hillenbrand A, Giamas G, Radunsky B, Ammerpohl O, Bohm B, Henne-Bruns D, Kalthoff H, Leithauser F, Trauzold A and Knippschild U (2008): Anti-apoptotic and growthstimulatory functions of CK1 delta and epsilon in ductal adenocarcinoma of the pancreas are inhibited by IC261 in vitro and in vivo. Gut. 57, 799-806.