

# PKC zeta inhibitors to modulate drug permeation in epithelia and tumors



## Prof Gerrit Borchard

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**Biography:** Gerrit Borchard is a licensed pharmacist and obtained his Ph.D. in pharmaceutical technology from the University of Frankfurt (Germany) for his thesis on the interaction of colloidal drug carrier systems with the immune system. After holding several academic posts, including a lecturer position at Saarland University (Germany) and Assistant and Associate Professorships at Leiden University (The Netherlands), he joined Enzon Pharmaceuticals, Inc. (USA) as Vice President Research. In 2005, he was appointed Full Professor of Biopharmaceutics at the University of Geneva (Switzerland), and Scientific Director of the Centre Pharmapeptides in Archamps (France), an international center for biopharmaceutical research and training.

In the past, Prof. Borchard has served as Scientific Advisor for the *Controlled Release Society* (CRS), as Scientific Secretary of the *European Association of Pharmaceutical Biotechnology* (EAPB), and has headed the Academic Section of the *International Association for Pharmaceutical Technology* (APV). In 2012 Prof. Borchard joined the *Non Biological Complex Drugs* (NBCD) working group hosted at *Top Institute Pharma* (TIP, Leiden, The Netherlands) and was nominated Chair of the NBCD working party at the *European Directorate for the Quality of Medicines & Health Care* (EDQM) by Swissmedic.

Prof. Borchard was nominated Fellow of the *Swiss Society of Pharmaceutical Sciences* (SSPhS) in 2010, and elected President of the *Swiss Academy of Pharmaceutical Sciences* in 2014. Since 2013, he is also Vice President of the *European Federation of Pharmaceutical Sciences* (EUFEPS).

**Abstract:** Tight junctions (TJ) regulate the paracellular pathway and induce differentiation in epithelial and endothelial tissues. Regulation of mucosal TJ is considered to be essential in inflammatory mucosal diseases (Crohn's disease, asthma), to protect against infection and restrict drug diffusion (e.g., blood-brain barrier). In intestinal epithelial cells (IEC) [1] and in bronchial epithelial cells [2] a link between the ligation of Toll-like receptor 2 (TLR2), a receptor of the innate immune system, has been shown. We were able to unravel the mechanism implied, showing that the expression of claudin-1 and ZO-1 tight junction proteins was significantly enhanced through the activity of the atypical protein kinase C Zeta. This phenomenon of strengthening the barrier defense has also been shown in primary human bronchial cells obtained from normal and asthmatic individuals.

The elucidation of the pathway for tight junction regulation in these epithelial cell layers has led to the identification of potential targets that may be addressed for strengthening compromised TJ associated barrier function.

In addition, we have investigated the effect of PKC Zeta inhibition on epithelial permeability in terms of reduction of tight junction protein expression. Through molecular modeling we have developed short cell-permeable peptidic PKC Zeta inhibitors [3] able to reversibly enhance paracellular permeability in epithelial cell layers, allowing paracellular passage of molecules up to 150 kDa molecular weight. Studies to evaluate these peptides as potential enhancers for macromolecular drug and vaccine delivery at mucosal surfaces have been performed.

Using a bronchial epithelial cell/tumor nodule co-culture, we also investigated the possibility to enhance tumor drug penetration of a cytotoxic drug (gefitinib) by modulating TJ present within the tumor and counteracting the enhanced penetration and retention (EPR) effect. We could show that a combination of peptidic inhibitor in combination with gefitinib was significantly more effective to reduce tumor volume than the cytotoxic drug alone.

### References:

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