

## ASCB PROFILE

# Inke Näthke



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While still a post-doc at Stanford, Inke Näthke came up with an original but controversial hypothesis to explain why a mutated form of the APC protein (adenomatous polyposis coli) was found in 85% of all human colorectal cancers. Näthke believed that defective APC protein was linked through the cytoskeleton to defective cell migration in epithelial gut cells. “It was brave and original research to discover new functions for this protein, especially when a strong consensus had emerged of its role as a regulator of catenins (proteins that control growth factor production),” says Sir David Lane, who helped to recruit Näthke in 1998 to the School of Life Sciences at the University of Dundee in Scotland. “She has established beyond doubt that the protein has other key roles in the control of mitosis and genetic stability.”

Näthke’s former PI at Stanford, James Nelson says, “She developed an original hypothesis in a crowded, dogmatic field, and she deserves a great deal of credit for testing the hypothesis and obtaining results that support it. The roles of APC in regulating microtubule dynamics, cell-cell interactions and migration that originated in her work are now widely accepted in the field.”

Inke (pronounced “Inca”) Näthke joined the Nelson lab in 1992 after finishing her doctorate on clathrin structure with Frances Brodsky at the University of California, San Francisco. Working with graduate student Lindsay Hinck, Näthke was developing antibodies for  $\beta$ -catenin, a signaling and adhesion protein, when Paul Polarkis, who was working at a Bay Area biotech company, called, looking for a sample. His interest was APC because of its notorious and mysterious connection to colorectal cancer. APC was known to bind to a variety of molecules that he suspected included  $\beta$ -catenin so Näthke’s

new antibodies might be useful. In exchange, Polarkis offered an APC antibody. That led Näthke to thinking about APC and to the experiments that eventually led to her theory that endogenous APC was cytoskeletally associated, that it was microtubule dependent and that it correlated with cell migration.

It would explain why trouble with APC would be so significant a marker for colorectal cancer. Says Näthke, “If you look at the gut epithelium where the loss of APC manifests itself most severely, it is uniquely dependent on a balance of proliferation, migration, adhesion and differentiation—it all has to happen. In the gut, active migration is a big component and I think that’s what distinguishes it from any other tissue in the adult body.”

The mucosal lining of the human colon and rectum takes a constant beating. Rubbed

and scratched by the passing contents, the mucosal layer has to be constantly replenished by epithelial cells that are produced by stem cells in the “crypts of Lieberkühn” and then crawl towards the gut lumen. If APC-deficient cells were poor crawlers, they would stay in the gut

longer. This would leave them exposed to the chemical and mechanical stresses of this environment longer than normal, allowing things to go wrong. Linking endogenous APC to the cytoskeleton and to cell migration was Näthke’s gamble.

It paid off for Näthke because of her precise and exhaustive molecular cell biology and immunohistology, says Bill Dove at the University of Wisconsin. Her experiments accounted for APC’s many cross-reactions with other molecules while making the central association of the endogenous APC with the cytoskeleton clear. “It was Inke’s rigorous testing and experimental design,” says Dove, “that made her case so compelling.”

Lindsay Hinck, now at UC Santa Cruz, agrees. “Clarity is what makes her such an

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exceptional experimentalist," says Hinck. She continues, "It's still hard to be a woman in science today. Women are timed out when they have kids. But Inke is incredibly clear minded about even that. I think it's part of the reason she went to Scotland. She knew she needed a supportive environment where she could have her family and her science."

Inke Näthke was born in 1961, in the small Schleswig-Holstein town of Itzhoe, north of Hamburg. She always felt slightly out of place in the rigid German educational system where science and art seemed mutually exclusive. After high school, with her parents' support, she took a year off and went to work for a family in San Jose. She felt instantly at home in California.

Auditing classes at San Jose State, Näthke also found an ideal education alternative. She could study both arts and sciences. She could actually speak with professors. At the end of the year, her parents flew to California for a conference about Inke's future with her American family which had, more or less, adopted her by then. The families agreed: Inke would return to Germany, enrolling in medical school while she applied for a US student visa and admission to San Jose State. A semester at medical school in Hamburg reminded Näthke of everything she didn't like about German education and about medicine as a profession. She returned to San Jose in 1982 and raced through her requirements for an Honors degree in Chemistry with a minor in Biochemistry in three years. She also hugely enjoyed her literature and music classes.

For graduate school, she chose UCSF and eventually the lab of Frances Brodsky. "When I started in her lab, I was clueless," Näthke recalls. "I hadn't done much cell biology but I learned a tremendous amount working with Frances. UCSF was just a fabulous place for cell biology at the time. Cell biology was just coming into its own and all the other disciplines were using its tools. UCSF was so crowded that you couldn't help but know what the people around you were doing. I think that it was being exposed to that variety and everybody being so keen on what they did that made it such an exciting

time." In 1992, Näthke moved to Stanford and the Nelson lab for her first post-doc and her rendezvous with the APC molecule.

Although Näthke says America is her adopted home, she decided after a short post-doc in Tim Mitchison's Harvard lab to accept a faculty offer from the University of Dundee. Dundee has been gathering steam as a research center since the early 1990s with increasing support from Cancer Research UK, the Medical Research Council and the Wellcome Trust. It was Birgit Lane, Director of Dundee's Cell Structure Research Group, who first told Näthke at a Gordon Conference about the prospects there. In 1998, Näthke arrived in Dundee just as the new £13.5 million Wellcome Trust Biocentre was nearing completion.

"Going to Dundee was an adventure," Näthke admits. "But it was an opportunity

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to be part of something that was just beginning. Besides, "Dundee is a beautiful place and the quality of life here is amazing. I am five minutes from my work. It takes me one hour a week to do my shopping. My son takes the bus home from school and he can walk almost anywhere in Dundee without my worrying about someone pulling a gun in his face, which happened to

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me in San Francisco."

Näthke's son, Jan, 11, was born in California; her daughter Lena, 7, was born in Boston. Both speak English in school, some German at home, and the local Scots dialect, Dundonian, on the street. Näthke admits that Dundonian is often beyond her. "When I'm talking to a real Dundonian, I'm lucky to understand 80%. But both my kids

are good with languages so they can translate."

Scotland has an unfortunate relevance for an APC researcher—it has one of the highest colorectal cancer rates in the world. Näthke collaborates with a local hospital which runs an extensive colorectal screening program. The screening team provides Näthke with important tissue samples.

"Most of what they are seeing are early stage polyps and 80% percent are nothing to worry about. So the question becomes, how do we identify the 20% that we do need to worry about?" Defective APC is not the entire answer, says Näthke. In her view, defective APC destabilizes many cell func-

tions in the epithelium but some other factor tips them onto a malignant pathway. "How can we distinguish them? What else has to have gone wrong? The prognostic markers or flags are still too vague."

Working directly with the clinic's gastroenterologists, surgeons and oncologists has changed her perceptions of her own research. "I'm learning a lot from them. After having seen the clinic, I come away thinking about other issues with this disease. What do we need to do to improve the lives of these patients and the outcomes in the end?"

For her research accomplishments, Inke Näthke will receive the prestigious ASCB Women in Cell Biology Junior Award next month. Näthke feels that winning the award is particularly meaningful because it comes from women scientists who share the common experience of growing up different. "We all had to learn early on that if we were going to do the things that really interested us, we couldn't worry about what other people thought. So this [award] feels really good because it's saying, 'You've done the right thing'." ■

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Observing tissue collection in the clinic and working directly with gastroenterologists and oncologists has changed Näthke's perceptions of her own research.

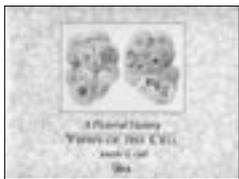
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