Shoichiro Tsukita

1953–2005

We all know examples of prominent artists, notably poets and musicians that have had a short, high-intensity, creative life, suddenly interrupted by an all too early death. An artist of molecular cell biology, Shoichiro Tsukita left us on December 11 2005, at only 52 years of age, after more than a year's fight against pancreatic carcinoma. The international community of fellow cell biologists shares the grief of his wife and long-time coworker, Sachiko, and of the research team at the Department of Cell Biology in Kyoto University. However, great discoverers like Shoichiro leave us their findings and published thoughts, and so our grief at his death is accompanied by a global applause for what he has achieved.

Shoichiro Tsukita was born in Kobe on July 7 1953, received his M.D. in 1977 and a Ph.D. in 1981 from the University of Tokyo. At the young age of 32 he became director of the Department of Ultrastructural Research in the Tokyo Metropolitan Institute of Medical Science. After a very fruitful period of research at the National Institute for Physiological Sciences in Okazaki he was made full professor and head of the Department of Cell Biology in Kyoto in 1996, where he attracted and formed one of the most active research teams in contemporary cell biology research.

Originally trained as an electron microscopist, Shoichiro was deeply interested in the architecture of cells and the underlying molecular and functional principles. He became fascinated by the highly organized interplay of special types, or special domains, of plasma membranes and their specific 'undercoats', which served as plaques for the anchorage of specific cytoskeletal filament bundles. The 1980 article by Sachiko and Shoichiro Tsukita, published together with their mentor, Harunori Ishikawa, on a "cytoskeletal network underlying the human erythrocyte membrane" may be considered to have set the general theme of study for the rest of his life. The vast majority of Shoichiro's 220 publications deal with membrane domains and their cytoplasmic plaques anchoring cytoskeletal filaments. His analysis of the diverse kinds of cell–cell junctions resulted in major contributions to the elucidation of the molecular compositions of desmosomes, adherens junctions and the tight junctions forming the *zonula occludens*. However, his pioneering studies on other classic plasma membrane domains, such as the cortices and cleavage furrows of amphibian and sea urchin eggs and the special 'undercoat' of squid axon plasma membranes, must also be mentioned, as must his important reports on microtubular and peri-centriolar proteins.

Since the 1980s a substantial part of his work was devoted to studies of the molecular composition of the actin filament anchoring plaques of the cell–cell adhering junctions, specifically of polar epithelia, culminating in the discovery of radixin and the general regulatory roles of members of the so-called ezrin–radixin–moesin (ERM) family of proteins in cadherin-based junctional plaques. Reports from the Tsukita laboratory on adhering junction proteins, on their functions and their regulations, and on their importance in certain diseased states, provided a constant flow of information that fertilized the field of cell–cell interaction research.

Surely, what will keep Shoichiro's name *in omnem memoriam* is that he found the long sought-after 'holy grail' of membrane biology and

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polar tissue formation — the molecules and principles that determine the orientation of 'outside, inside and within' for epithelia, endothelia and other cell layer systems. All his epochal discoveries were made by risk and labour, by good old reductionism and careful description — words often used as pejoratives by the biologists of today.

In 1989, the Tsukitas reported the isolation and purification of a fraction of bile canalicular junctions from liver tissue that was enriched in both adherens and tight junctions and this provided the basis for the identification of all known four-spanning transmembrane proteins of tight junctions. The structure forming ability of these proteins was elegantly demonstrated by freeze-fracture intramembrane immunoelectron microscopy and by cDNA transfections of cultured cells lacking these junctions. The discoveries of occludin (1993), the family of 24 cell type-specific claudins (1998) and tricellulin (2005, his last paper), their amino-acid sequence determinations, immunolocalizations and the biochemical demonstrations of their interactions with other proteins, represent landmarks in the history of the elucidation of the molecular architecture of tight junctions.

Shoichiro always asked questions of functional *raison d'être*, as well as of possible medical application, resulting, for example, in the findings of mechanisms that may lead to disruptions of *zonula occludens* barrier functions in unicellular polar epithelia (diarrhoea), stratified epithelia (water loss and shrinkage) and endothelia (oedema). The work of Shoichiro, his students and collaborators also opened a new avenue of medical research as it allowed the design of molecular methods to interfere with tight-junction function. The enormous impact that the discovery of the cell type-specific claudin ensembles has had on our understanding of the importance of tight junctions in diverse functions in our bodies is already visible, only seven years after its first publication: the water retention by claudin-1 in the epidermis; the selective blood-brain barrier control by claudin-5; tissue-specific claudin effects in functions of the kidney and the ear. And many further insights into claudin functions lie ahead.

Shoichiro's contributions to cell biology, however, were not only his publications and lectures. We all owe him respect and thanks for his tireless service to the community of cell researchers, as director of the Japanese Biochemical Society, as a review author and reviewer of manuscripts and grant proposals, a meetings' organizer and editorial board member.

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