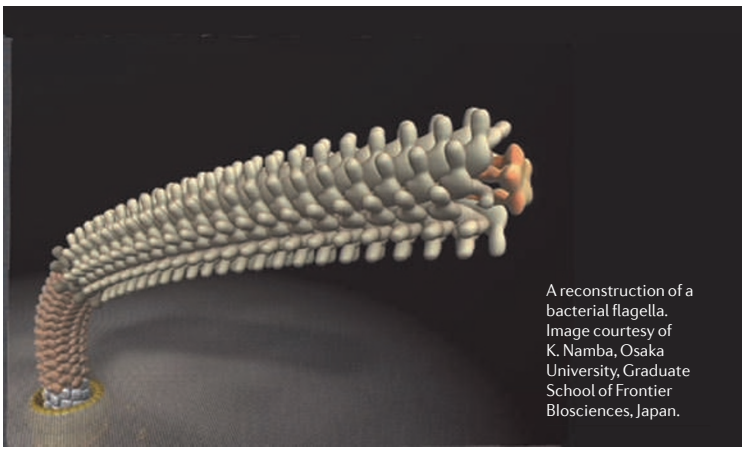

A reconstruction of a bacterial flagella. Image courtesy of K. Namba, Osaka University, Graduate School of Frontier Blosciences, Japan.

MILESTONE 22

Flagella and cilia come of age

> “…cilia and structurally identical flagella are important components of the cytoskeleton, with crucial roles in development, physiology and disease.”

For the first half of the twentieth century, the sensory cilium, which is a non-motile projection that most mammalian cells possess, was thought to be a functionless vestigial structure. A series of groundbreaking studies revealed, however, that cilia and structurally identical flagella have crucial roles in development, physiology and disease.

In 1976, Afzelius described a human disease syndrome that was caused by ciliary motility defects. He identified four patients who suffered from chronic bronchitis and sinusitis, and produced live but immotile spermatozoa. Notably, cilia from the cells of these patients lacked the motor protein dynein arms, which facilitate flagellar beating (see Milestone 4). Moreover, three out of four patients had *situs inversus totalis*, in which the left–right symmetry of the major organs of the body is reversed. Although a link between *situs inversus*, chronic bronchitis and sinusitis had already been established, as Kartagener syndrome, Afzelius proposed that the symptoms of these patients were manifestations of defective cilia. So, motile cilia are crucial for establishing embryonic polarity (which later determines the left–right symmetry of the body), for clearing particles from the lungs and for spermatozoa motility.

For nearly two decades, it was assumed that defects in motile cilia, but not in non-motile cilia, could cause human disease. In 1993, Rosenbaum and colleagues made a finding that paved the way for the discovery that non-motile, sensory cilia are also crucial for normal physiology. At that time, all cilia movement was thought to be dependent on dynein. Rosenbaum and colleagues observed a novel form of flagellar motility, dubbed intraflagellar transport (IFT), using electron microscopy. IFT occurred independently of flagella beating and dynein activity. IFT allowed both cilia and flagella, whether motile or immotile, to shuttle macromolecules bidirectionally along their lengths. IFT proteins later linked sensory cilia to various disorders, including polycystic kidney disease.

Other key studies in the second half of the twentieth century expanded our understanding of cilia and flagella. In 1984, for instance, Luck combined the findings of several groups and produced a rough, preliminary description of the genetics and biochemistry of the axoneme, which is the basic cytoskeletal structure that makes up cilia and flagella. Despite these advances, many aspects of flagellar and cilial biology remain unclear. For example, although Rosenbaum and Child reported, in 1967, that amputated flagella can regrow, and that a strict biological mechanism mediates the rate of regrowth and the length of flagella, the details of this remarkable mechanism remain unresolved.

Asher Mullard, Assistant Editor,
Nature Reviews Molecular Cell Biology
and Nature Reviews Microbiology

ORIGINAL RESEARCH PAPERS Rosenbaum, J. L. & Child, F. M. Flagellar regeneration in protozoan flagellates. *J. Cell Biol.* **34**, 345–364 (1967) | Afzelius, B. A. A human syndrome caused by immotile cilia. *Science* **193**, 317–319 (1976) | Luck, D. J. Genetic and biochemical dissection of the eukaryotic flagellum. *J. Cell Biol.* **98**, 789–794 (1984) | Kozminski K. G. *et al.* A motility in the eukaryotic flagellum unrelated to flagellar beating. *Proc. Natl Acad. Sci. USA* **90**, 5519–5523 (1993)
FURTHER READING Pazour, G. J. *et al.* *Chlamydomonas* IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. *J. Cell Biol.* **151**, 709–718 (2000)

© 2008 Macmillan Publishers Limited. All rights reserved