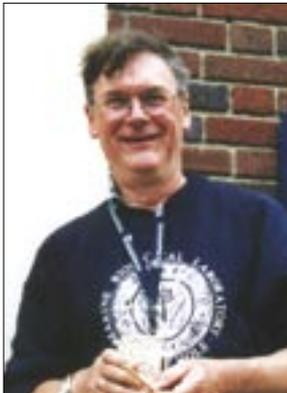


## ASCB PROFILE

# Tim Hunt

Tim Hunt only had a week this summer for MBL and Woods Hole. “Hardly long enough to fertilize a clam,” Hunt says. But official duties awaited at his Cancer Research UK lab and elsewhere; most of all, Hunt is wanted at home where he assumes his favorite title these days—dad to two young daughters.



Tim Hunt

Yet Woods Hole still exerts a powerful pull on Tim Hunt. Here on a July morning in 1982, Hunt performed an experiment that led 20 years later to the Nobel Prize in Physiology or Medicine for his part in what has been called

the cell cycle revolution. The experiment was to follow protein biosynthesis in fertilized sea urchin eggs, using radioactive methionine and sampling at various times for electrophoresis and autoradiography. That

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morning Hunt noticed a novel protein band on the gel which rose steadily in concentration from fertilization until entry into mitosis before plunging out of sight a few minutes before the eggs divided, only to reappear in the next division cycle and abruptly disappear again at cell division. The saw tooth profile of this cycling protein seemed

so precisely timed that Hunt felt it had to be integral to the cell cycle. Later he named it “cyclin.” But from the first, Hunt recalls, “The question I had to constantly ask myself was, ‘Am I missing something? Am I completely stupid?’ I’ve been completely stupid many times in my life.” That was Thursday morning.

On Friday evening, Hunt went along to the wine and cheese party following MBL’s weekly lecture and bumped into John Gerhart. Hunt had heard Gerhart’s 1979 MBL

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talk on the work that he and Marc Kirschner were doing on the mitotic spindle and its connections, if any, to the mysterious Maturation Promoting Factor, or MPF. “The day after I discovered cyclin, I ran into John,” says Hunt. “That was, by far, the most exciting scientific conversation I’ve ever had anywhere in my life, because John told me about some data that he and Marc had got [on MPF]. It was

just a shard of data, but it was so encouraging—the fact that you needed protein synthesis for MPF to come back the second time. It was right in line with what I’d seen.”

It sounds quaint today, but Hunt conveyed the news to his Cambridge University colleague Richard Jackson in a typed, airmail letter. Hunt

and Jackson had been grad students together in the Cambridge lab of Asher Korner and then lab mates as independent Research Fellows in the university’s Biochemistry Department. Jackson recalls, “Tim described what essentially was the discovery of cyclin: ‘I have very little idea of what all this means or what’s going on but I have a strong sense of being onto something quite important.’”

From the beginning, cyclin caused a stir. One journal referee rejected Hunt’s first cyclin paper as “gross speculation based on dubious logic.” Eventually the paper found friendlier reviewers and publication in 1983, but skepticism dogged Hunt’s hypothesis that cyclin’s rise and fall was driving the cell cycle and not just following in its wake.

The turning point came in 1986 with Joan Ruderman’s cloning of cyclin in clams. Ruderman and Katherine Swenson used their clone of clam Cyclin A to perform the

first functional assay of cyclin; they injected cyclin mRNA into *Xenopus* oocytes and found that this mRNA acted just like MPF—the oocytes matured.

In the meantime, it was becoming clearer

that there was more than one cyclin. In 1987, Hunt's lab cloned Cyclin B in sea urchin eggs. Jonathon Pines, a cell cycle researcher at the Wellcome Trust/Gurdon Institute of Cancer Research UK, was the graduate student who cloned Cyclin B under Hunt's watchful eye. How Pines got the assignment as a grad student is a classic tale. After a successful undergrad research project under Hunt, Pines was invited to become his graduate student in the fall of 1983. The Biochemistry lab shared by Hunt and Jackson was renowned for its protein synthesis work on hemoglobin, but fresh from another productive summer in Woods Hole, Hunt offered Pines an unexpected choice: Pines could work on reticulocyte protein synthesis or clone cyclin. Pines recalls, "Being naïve, I said, 'Oh, I think I'll clone that,' not really knowing what cyclin was or even what cloning was for that matter. That was the fateful decision."

For cell cycle science, the fateful cloning of Cyclin B in sea urchin eggs yielded cDNA sequences that could be compared to cDNAs derived from Ruderman's clam Cyclin A. Together the sequences led to the identification of a highly-conserved region called the "cyclin box," which was then matched to homologs from yeast to humans. What eluded him at the time, says Hunt, was how cyclins could regulate the complex and finely-detailed processes necessary for cell division. There turned out to be another cast of intermediaries, a vast new troupe of cellular actors called cyclin-dependent kinases or CDKs. It was Paul Nurse who elucidated the CDKs and shared in the 2001 "cell cycle" Nobel along with Hunt and Leland Hartwell, who pioneered the genetics of the cell cycle.

Says Pines, "The importance of discovering cyclin was showing that proteolysis was central to cell cycle control. That changed the emphasis in cell cycle from everything to do with phosphorylation and de-phosphorylation to the idea that what's important is that you degrade these proteins at this very specific time. That's what people were so skeptical about. How could the disappearance of this one protein be driving the cell cycle? They all thought that it was only being modified so you couldn't see it at the same place on the gel. This is Tim's real contribution, thinking of other ways in which the cell

cycle could be regulated and in particular through proteolysis." Besides, adds Pines, "Tim is just the sort of scientist you want to win these things—a very nice man who is not a *prima donna* at all, but very modest and generous with his time and his ideas."

R. Timothy Hunt was born in 1943 near Liverpool where his father Richard was an Oxford University lecturer in medieval paleography. Going through old letters after his father's death, Tim Hunt discovered that his father, who'd never said a word about "his" war, apparently worked for a branch of British intelligence. Tim Hunt's earliest memories are of post-war Oxford where his father was Keeper of the Western Manuscripts at the Bodleian Library. Academics were not well paid in those days, but his father gloried in the scholarly life. Hunt says his mother Katherine ("Kit"), who came from a solidly commercial family background, provided "a healthy antidote to the university, because while my dad was so connected to everything Oxford,

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**GEICO DIRECT**

my mother thought a lot of Oxford people were more clever than sensible. Growing up in Oxford, I learned to take the university life with a grain of salt."

Despite the influence of medievalists, young Tim had little interest and less talent in Latin or Greek, but found his own niche in biology at his prep school, the renowned Dragon School. For high school, he attended Oxford's Magdalen College School where science was given more emphasis. "I loved Chemistry in particular, largely because the teacher, Colonel Simmons, was more concerned with principles than facts. We were allowed considerable freedom, and on more than one occasion started fires by distilling volatile flammable solvents," he recalls.

For university, Hunt left Oxford for Cambridge, entering Clare College as a Natural Scientist but was quickly drawn to biochemistry under the influence of the Very Great Men of molecular biology then at Cambridge, including Sydney Brenner and Francis Crick. In his graduate work with Asher Korner, Hunt worked on mRNA protein synthesis and hemoglobin. At a 1966 hemoglobin meeting in Greece, Hunt met Irving London who was at New York's Albert Einstein College of Medicine, and Hunt spent the next summer in the Bronx, followed by a two-year post-doc at Einstein after he finished his PhD in 1968. It was London who also introduced Hunt to Woods Hole where he fell in love with the non-stop science talk, the novel marine model systems like sea urchin eggs, and the chance encounters with Very Great Biologists. In 1970, Hunt returned to Cambridge University and the post of Research Fellow in Biochemistry but continued as a summer regular at MBL, teaching Physiology and Embryology.

Hunt says that he's always avoided professorships and directorships, preferring the title of "Doctor" and the position of Principal Scientist at Cancer Research UK's Clare Hall Laboratories where he's been since 1991, continuing work into the structure, function

and destruction of CDKs. He commutes from his home near University College London, where his wife, Mary Collins, is Professor of Immunology and Chair of Infection and Immunity in the Medical School. Their oldest,

Celia Daisy Collins, is nine and her sister, Agnes Beatrix Collins, is six. Hunt anticipates the obvious question. "People ask, 'What's it like to be an older father?' I say, 'I have no idea because I never was a younger one, but I do like being a dad very much.'" Aggie has just moved on from Barbie dolls to playing shops and offices while Celia

is a champion reader, he reports. The girls are not as fond of country rambling as he would like, but he's working on them. The whole family, though, loves their weekend cottage north of London.

For old Cambridge friends, Hunt becoming a doting dad in his fifties was a minor shock compared to the news that he had finally acquired a driver's license. Richard Jackson recalls that Hunt was famous in Cambridge for championing the Moulton, an ungainly, semi-folding bicycle with tiny wheels and a tall seat, that could allegedly be hefted onto public transport. Later on, Hunt was said to have owned the first skateboard and first mountain bike in Cambridge. Hunt says that getting his driver's license fulfilled a promise he'd made to Mary on being ready for modern fatherhood.

Becoming a dad may have changed his life more than winning the Nobel Prize, but Hunt says that he has deliberately put his new Laureate clout at the service of one special cause, promoting more European cooperation in science. "We're very Balkanized and we suffer for it," Hunt says. "Much as I love America, it's not fair that you have it all. If you think of the great glory days of European molecular and cell biology—The Pasteur in the '50s or the Laboratory of Molecular Biology in the '60s—a lot of that was fueled by American post-docs coming over to work with the likes of François Jacob or Sydney Brenner. Now the traffic is almost entirely in the opposite direction. A little more two-way flow would be good for both." ■

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