

EMBO Gold Medal Review 2003

Boveri revisited

Anthony A Hyman*

MPI für Molekulare Zellbiologie und Genetik, MPI-CBG, Dresden, Germany

In memoriam Laura Alice Hyman

The EMBO Journal (2005) 24, 1104–1110. doi:10.1038/sj.emboj.7600583; Published online 10 March 2005

Subject Categories: cell & tissue architecture; cell cycle

Keywords: *C. elegans*; kinetochore; microtubules; mitosis; RNA interference

When I was about 14 years old, I conceived the idea that I should become a doctor. Partially I think this was because the only other option offered by my school (William Ellis) career advisor was to join the Navy. As my school career progressed, it became increasingly clear that I did not have the academic ability necessary to become a doctor, finally culminating in such a bad set of A levels that I left school without much idea of what to do. Fortunately one of my neighbors was Peter Medawar, who suggested that I start to work at UCL in London. (Interestingly, Peter Medawar had also encouraged Freeman (2002) early in his career). For this I received the princely sum of 30 pounds sterling per week to make up the media for tissue culture. After a few months Terry Preston suggested my first ever experiment, to look at the effects of ionic strength on the rate of movement of a protozoan. I trace my decision to be a scientist back to the following incident. Every Friday evening the technicians would go out for a beer. One Friday evening I was looking down the microscope. As they departed for the pub I looked at the microscope looked at them and then stayed to finish the experiment. Clearly this must have made an impression on Terry, because he suggested that I apply as an undergraduate.

It was a great stroke of luck that I ended up at the Department of Zoology at UCL, which was at that point chaired by Ave Mitchison. This was the department of Abercrombie, and his appreciation of cell biology still infiltrated the place (Abercrombie *et al.*, 1970). My interest was captivated. Here were small machines such as the protein translocators microtubules and actin filaments, but no one knew how they worked. How did a protein get across a membrane? How did a cell move? The most important single piece of education I received was a 100-page literature review I wrote on the T-cell receptor. This was before the receptor

had been identified, and involved sorting through hundreds of papers supporting different models on antigen recognition in the context of the MHC, an idea proposed by Zinkernagel and Doherty. I was supervised in this task by Nick Crispe, a graduate student, who spent many months with me discussing the issues. Nick more than anyone else helped me to understand the excitement of science. I would wait anxiously every month for the next issue of JEM, hoping for some answers to questions that we would discuss.

My father, who had suffered from a number of idiotic managers in industry, encouraged me to think of an academic career. That summer I went to the US to work at the Roche institute at Nutley, NJ, now sadly departed, with Jim Morgan. Roche ran an undergraduate student program, which was excellent, and introduced me to bench work. At the end of my stay, Jim suggested that I should do my PhD with someone called Sulston at the LMB on *Caenorhabditis elegans*, a name and an organism and an institution I had never heard of. Luckily the first edition of molecular biology of the cell had just come out, with a section on *C. elegans*. PhD entrance in those days was a matter of a phone call, which I duly made to John. His only question to me was 'why *C. elegans*', an exam I passed by nervously answering that the lineage was invariant. When I came up to Cambridge I had to find a subject for my PhD. Little did I realize how little my cell biology undergraduate education had prepared me for the LMB. Surrounded by molecular biology, start and stop codons about which I only had a vague understanding, I ended up in John White's office. He talked to me about the cytoskeleton and polarity; finally I felt a sense of familiarity and asked to work on the project. John explained to me that polarity was interesting and that I should 'look into it'. John practiced the old English tradition of 'corridor supervision'. How is it going, he would ask when passing in the corridor? Fine I would say, to which he would reply: 'Good, carry on then', a phrase my students will recognize. After a couple of months in the lab, John called me down to his office and told me that the postdocs (Andy Fire, Jim Priess and Cynthia Kenyon) had suggested that I be thrown out. When I enquired why, he replied they thought I was too lazy. Well this came as somewhat of a surprise to me since I had been working 9–7, 5–6 days a week, which I assumed to be adequate. It was true that I was getting little done but I blamed that on my inexperience. John said he would support me but suggested I stay in the lab until the postdocs left. I assumed they had been going home at say 8.00. So the next evening, equipped with my sandwiches, I decided to stay on but as 8.00 disappeared into 9 o'clock and midnight approached there seemed to be no sign of going home. I staggered out of the lab at one in the morning, leaving Cynthia and Jim still talking about *C. elegans* development, realizing that science would be difficult.

After a few months of working on an obscure problem in a corner of the LMB, I went to the University library and

*Corresponding author. MPI für Molekulare Zellbiologie und Genetik, MPI-CBG, Pfortenhauer Strasse 108, Dresden 01307, Germany. Tel.: +49 351 210 1700; E-mail: hyman@mpi-cbg.de

Received: 15 October 2004; accepted: 21 January 2005; published online: 10 March 2005

opened EB Wilson, 'the cell in development and heredity'. It is hard to forget the excitement of finding out that the cell biology of embryonic divisions had been an excellent and active field in the 1920s. It was driven by that greatest of cell biologists, Boveri, hence the title of this review. I returned to the LMB with my head held a little higher. There was more to life than molecular biology. I was also a little chastened to find out that my work was recapitulating ideas of 80 years ago. However, Jim encouraged me by telling me that introductions to my papers could now start with 'a classic problem in cell biology is...'

C. elegans embryos were clearly a beautiful system to work on the cell biology of polarity. The 50 μm long embryo fitted perfectly when viewed with a $\times 100$ objective, and divisions were fast and stereotyped (Figure 1). *C. elegans* polarity had been little worked on at that stage (Strome and Wood, 1983), but there had been some classic work on cell division axes (Laufer *et al*, 1980). One of the interesting issues raised from this work was the fact that from the two-cell stage on the axes of division were stereotyped. The daughters of AB divided orthogonally with respect to each other, while the daughters of P1 divided successively on the same axis. What accounted for these different patterns of division? The cell division axes of any cell are determined by the position of the mitotic spindle (Rappaport and Rappaport, 1974). It was thought then, as now, that in embryonic mitotic blastomeres the two spindle poles are defined by the position of the centrosomes. Jim Priess was studying the cytoskeleton in *C. elegans* development and took me under his wing. I decided to follow the patterns of centrosome movement prior to division. Our examination of the embryos showed that each cell has stereotyped patterns of centrosome movement. In AB and its daughters each cell inherited a centrosome, which divided into two. These two centrosomes migrated apart from each other until diametrically opposed, and a mitotic spindle formed between them. Therefore the mitotic spindle of AB formed at 90° to the angle of its mother. In the P1 cell, centrosomes again migrated apart from each other, but subsequently executed a rotation of 90° , thus placing the axis of the mitotic spindle on the same axis as its mother (Hyman, 1989). About this time, John White started to develop a confocal microscope for use in biomedical research. This

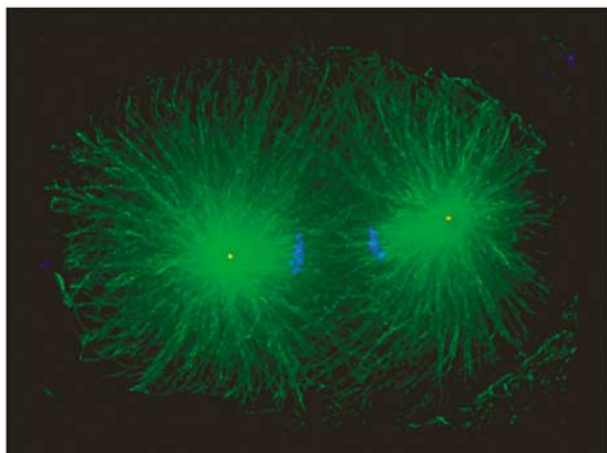


Figure 1 A *C. elegans* embryo going through the first cell division. Tubulin is in green, DNA in blue.

dramatically improved the visualization of microtubules, and we proposed models in which microtubules interacted with the cell cortex to orient the cell divisions.

From John I learned the necessity of looking for an understudied problem and developing and applying suitable technology to its solution, a perfect introduction to science. In fact, as part of the tearoom atmosphere of the LMB, much of the discussions were devoted to technology development and how to apply it to one's problem. It was a privilege to do a PhD at the LMB. There were few students and although you were nominally associated with a lab, you were completely free to do as you wanted as long as you submitted your thesis within 3 years of starting.

We were interested in understanding how the cell induced rotation of the centrosome-nuclear complex in the P blastomeres. Using laser ablation, we were able to map the sites of force generation to the interaction between the centrosome and a region of the cortex that lay next to the contact of the two blastomeres. Since the process was microtubule dependent, it seemed logical to conclude that interaction between centrosome-nucleated microtubules and the cortex somehow drove the rotation process (Hyman, 1989). Our knowledge of microtubules at that time made it difficult to understand how microtubules from only one centrosome could interact with the cortical site and how this capture could lead to rotation. They were seen as rather dull structures that grew and shrank at a leisurely pace. During my PhD, Tim Mitchison and Marc Kirschner published their classic papers on dynamic instability of microtubules (Mitchison and Kirschner, 1984). In essence, dynamic instability showed two things. Firstly, microtubules could interconvert between phases of slow growth and rapid shrinking, driven by GTP hydrolysis. As a consequence, different microtubules could grow and shrink in the same population. Secondly, the transition between growing and shrinking is stochastic. You can estimate that a given microtubule has, for instance, a 50% chance of interconverting between growing and shrinking, but never predict exactly when this event would happen. Mitchison and Kirschner went on to develop a search and capture model for how centrosomes could attach to a chromosome during mitosis (Kirschner and Mitchison, 1986). Microtubules would grow out from a centrosome. If they attached to a chromosome, they would be 'captured'. If not they would undergo catastrophe and shrink back to the centrosome. I remember what a bomb shell that was: here for the first time was a mechanism by which cells could form cytoskeletal structures. We applied these ideas to form a model of centrosome-nucleus rotation in *C. elegans* blastomeres. Microtubules would grow from each centrosome under dynamic instability conditions until a microtubule would be captured by the cortical site. If the cortical site contained a force-generating molecule, the microtubule would allow torque to be generated between the cortical site and the centrosome, rotating the centrosome-nuclear complex (Figure 2).

The next step in my career was to think of a postdoctoral position. Although I had greatly enjoyed *C. elegans* cytology, I wanted to train in aspects of biochemistry. In particular I felt that the next stage in analyzing complex *in vivo* problems was to isolate them into subproblems using *in vitro* assays. Mitchison and Kirschner had established *in vitro* assays to look at the interaction between kinetochores and microtubules. Kinetochores are those structures on mitotic chromo-

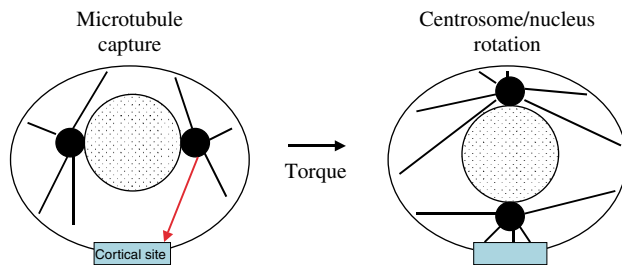


Figure 2 A potential mechanism to reorientate the centrosomes in the P1 blastomere of the *C. elegans* embryo. (A) Microtubules nucleated from both centrosomes are undergoing dynamic instability. A cortical site that can capture microtubule is built on the cortex. (B) A microtubule at random is captured by the cortical site. The interaction of the microtubule with the cortical site generates torque, either through motor proteins or through depolymerization-coupled movement. This reorientates the centrosome-nuclear complex.

some that attach them to microtubules. Changes in the dynamic properties of microtubules at kinetochores seemed essential for chromosome movement. To me, kinetochores seemed to be the canonical structures with which to understand the interaction between microtubule dynamics and structures: a kinetochore would be similar to a cortical site.

Tim Mitchison has just taken a job at Mill Hill and I applied to his lab for a postdoc. I was not unhappy to return to London where I had grown up, but Tim soon moved to UCSF and so it was off to California. Despite my attempts to work hard at my PhD, I departed Cambridge without convincing everyone that I had a career in science. Nichol Thomson, the renowned EM technician, who has cut 8000 serial sections through a *C. elegans* for John White, shook his head as I left the lab with a nice fellowship to go to California saying (with a broad Scottish accent). 'Tony, you are living proof of the phrase B.S. baffles brains'. I was lucky to arrive at UCSF just at the time that a whole set of people decided to focus on the development of *in vitro* assays using video microscopy. Lots of things were going on; for instance, Andrew Murray had perfected *Xenopus* extracts to look at spindle assembly and cell cycle control (Shamu and Murray, 1992) (and taught me how to construct a good lecture). This was certainly one of the most enjoyable periods of my life. America had such freedom! While my enthusiasm had been looked on with some suspicion in the UK, in the US it was welcomed. I encountered the American work ethic and how powerful engine it is to get things done. From Tim I learned the power of quantitative analysis, fearless experimentation in biology, the art of the buzz cut, and that at the bottom of every biological problem is chemistry. One of the most enjoyable things I did was to build a time-lapse system from scratch. My friend Richard Durbin came over from Berkeley and wrote an outline of the code in C, which I then used to write a control programme. Recently, I looked at that code, but it is like the Latin I learned at school. I cannot recognize a word of what I wrote, which is one of the interesting things about science; how quickly the technology you learn becomes obsolescent.

Tim suggested that I look at the interaction between microtubules and kinetochores. In particular, we wanted to record these interactions using the nascent field of time-lapse video microscopy. By isolating chromosomes from cells, and

adding rhodamine-labeled microtubules stabilized with taxol, we were able to watch kinetochore capture of these microtubules (Hyman and Mitchison, 1991). Addition of ATP triggered these microtubules to move along the kinetochore, demonstrating the presence of active microtubule-based motors on kinetochores. Microtubules have a structural polarity with a fast-growing plus end and a slow-growing minus end. *In vivo*, the plus ends are located at kinetochores and the minus ends are located at centrosomes. Microtubule-based motors were known to move with different polarities: some are minus-end directed while others are plus-end directed. Therefore, a minus-end-directed motor and a kinetochore would move a chromosome toward the spindle pole. We set up means of looking at microtubule polarity in our *in vitro* assays and from these methods we were able to show that microtubule-based movement on kinetochores could either be plus- or minus-end directed. This movement was determined by the phosphorylation state of the kinetochores. Thus we demonstrated that, in principle, a kinetochore contained the necessary motors to determine its own position on a mitotic spindle (Figure 3). At the same time, together with a student Lisa Belmont, we set up assays to look at microtubule dynamics, both *in vitro* and in *Xenopus* egg extracts (Belmont *et al*, 1990). From these experiments, we showed that the dynamics of microtubule ends in *Xenopus* was modulated during the transition from interphase to mitosis, providing a powerful assay with which to dissect out the proteins required for microtubule dynamics *in vivo*. Just as I was finishing in Tim's lab, I started to work on kinetochore assembly in extracts from *Saccharomyces cerevisiae*, together with John Carbon's laboratory (Hyman *et al*, 1992). The power of yeast genetics suggested that it should be possible to identify the factors responsible for kinetochore binding to microtubules and was the beginning of my re-entry into genetic analysis, which I had left with the *C. elegans* project.

If I look back at my training, I was lucky to be at LMB and UCSF. Both had superb intellectual atmospheres, but were interested in different problems. UCSF believed in quantitative cell biology in the same way LMB believed in molecular genetics. My research program has always been based on a fusion of the ideas that came from these two different viewpoints.

After 4 years at UCSF, I was going back to the UK for Christmas when Tim suggested that I go and visit Kai Simons, who ran the cell biology program at the EMBL in Heidelberg. While I was there, I met Eric Karsenti, who was doing pioneering work on mechanisms of meiotic spindle assembly (Karsenti *et al*, 1984). Kai Simons offered me a job, and at that time the NIH was going through one of its bouts of funding crisis. It seemed too good an opportunity to turn down and off I went to Heidelberg. The way in which a lab gets started depends entirely on the people who are prepared to put their trust in a young untried investigator of (in my case) 29 years. I was fortunate to have a great starting lab: my postdocs, Michael Glotzer from San Francisco, Rita Taba from Vienna, Fedor Severin from Moscow, my technician Tony Ashford from London, and my two French students, Regis Tournebize and Ingrid Sasoon. In addition, I was joined by Peter Sorger while he set up his own lab at MIT. Peter and I had been students at the LMB and postdocs at UCSF together, and had decided to attack the problem of kinetochore assembly in *S. cerevisiae* together. That year the weather was

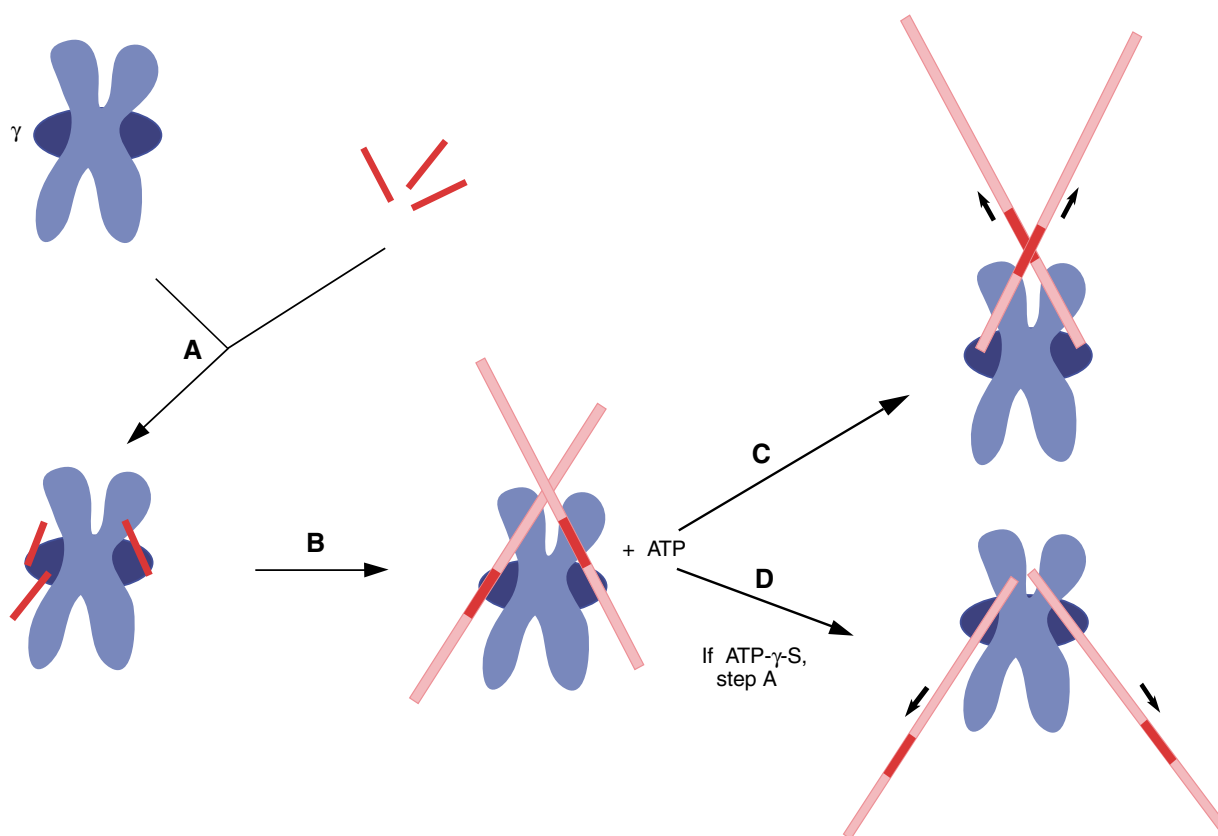


Figure 3 Movement of microtubules on kinetochores of isolated chromosomes (Hyman and Mitchison, 1991). Microtubules added to isolated CHO chromosomes will bind and move along kinetochores in the presence of ATP. The direction depends on phosphorylation.

perfect. I used to walk from the lab to Eric Karsenti's house, where he and his partner Catherine made me very welcome for supper: we would discuss spindle assembly and play the saxophone late into the night. He also taught me how to make foie gras. The key issue is the rate at which the water boils.

While he was in Marc Kirschner's lab, Eric and John Newport had shown that in meiotic oocytes, spindles could apparently assemble around naked DNA that had been injected into the egg (Karsenti *et al*, 1984). This suggested that meiotic spindles did not require centrosomes in order to be bipolar. This was at odds with the prevailing view that the bipolarity of a spindle could only be determined by its two centrosomes. We thought that this would be a good starting point to pursue issues of cytoskeletal organization.

In a classic piece of EMBL collaboration, Rebecca Heald showed that chromatin beads, developed in Peter Becker's lab, when added to *Xenopus* extracts made beautiful bipolar spindles, in the absence of centrosomes (Heald *et al*, 1996). This suggested that a driving force for spindle assembly in meiosis was the self-organization of the cytoskeleton by microtubule-based motors (see Figure 4) Karsenti and Vernos, 2001). Therefore there seem to be two possible mechanisms for spindle bipolarity. One mechanism does without centrosomes, as seen in meiotic spindles and plants. The other mechanism uses both centrosomes. In the future, it will be interesting to determine the extent to which these two assembly pathways are used in different systems (Heald *et al*, 1997). Soon after arriving at EMBL, I started to work on

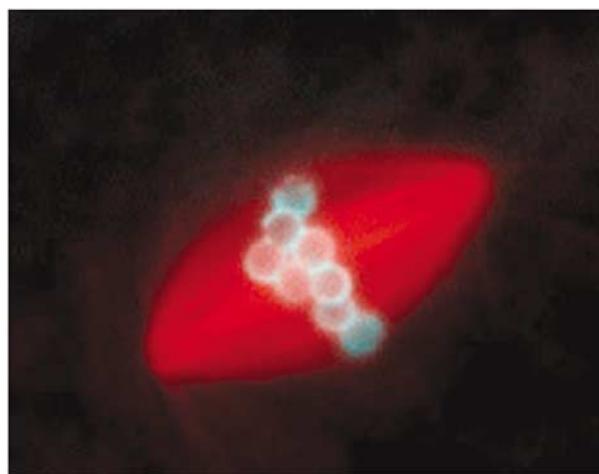


Figure 4 Assembly of meiotic-like spindles around DNA beads (Heald *et al*, 1996). Meiotic spindles will assemble around beads coated with DNA (figure courtesy of Rebecca Heald).

control of microtubule dynamics, a problem that has occupied my laboratory since then. Using *Xenopus* extracts to study microtubule dynamics, Regis Tournebize showed that microtubule stability depends on the opposed interaction of stabilizing and destabilizing factors (Figure 5). The stabilizing factors are part of a conserved family of proteins of which the first member was XMAP-215. We were able to take this to the next stage and reconstitute the dynamic behavior of

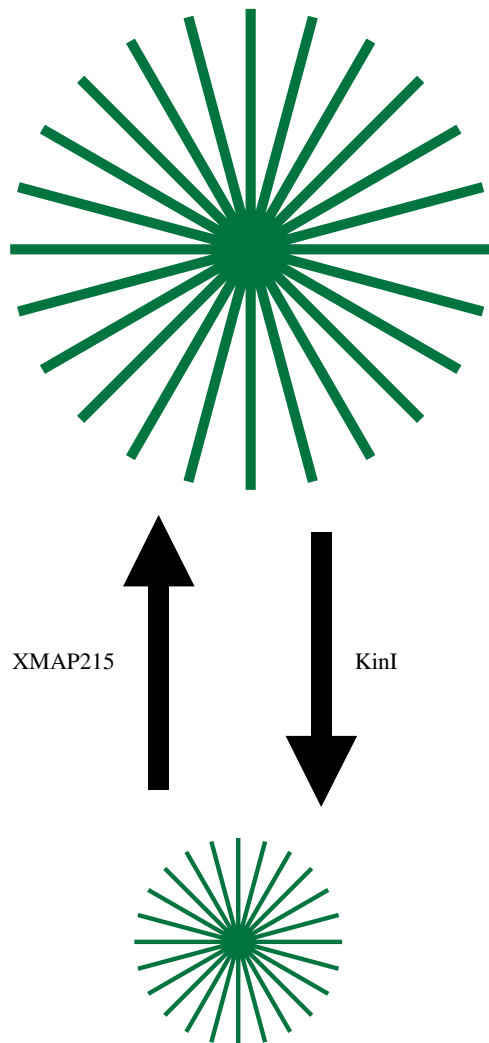


Figure 5 Stability of microtubules in *Xenopus* egg extracts is determined by the opposition between the stabilizing factor XMAP215, a microtubule-associated protein, and the destabilizing factor XKCM1, a member of the KinI kinesin family (Tournebize *et al.*, 2000).

microtubules *in vitro* using proteins expressed in baculovirus (Kinoshita *et al.*, 2001). We also investigated how GTP hydrolysis destabilizes microtubules. Working together with Dick Wade from Grenoble, and Thomas Mueller-Reichert, Denis Chretien and Isabelle Arnal in Heidelberg, we showed that GTP hydrolysis increases the curvature of the protofilaments, thus destabilizing the microtubule lattice (Hyman *et al.*, 1995; Muller-Reichert *et al.*, 1998).

If you had asked anyone what the major problem in cell division was even 5 years ago, most people would have told you it was identification of the molecules required for building the cell division machinery. This had posed innumerable difficulties. Biochemistry was hampered by the fact that most cell division organelles are small in number (1–2 centrosomes per cell, for instance) and their structure was cell cycle dependent. In contrast, a ribosome is extremely abundant, and invariant in its structure throughout the cell cycle. Genetics was hampered by the fact that most mutants in cell division proteins are cell lethal. Thus, although we had many beautiful assays for mitosis, both *in vivo* and *in vitro*, we were

having a hard time in the field reducing this to molecular understanding.

Just as I had left UCSF, Peter Sorger and I had developed assays to study yeast kinetochore assembly using the yeast *S. cerevisiae*. Kim Nasmyth was just round the corner in Vienna, and over the years taught me the basics of analysis of cell physiology using genetics. Our work with Fedor Severin on spindle assembly in yeast (Severin *et al.*, 2001) suggested to me that similar methods could be brought to attack the problem of cell division in *C. elegans*. At that point, Pierre Gönczy joined my lab, and was keen on setting up *C. elegans* as a system to study spindle positioning and microtubule dynamics. I had not worked on *C. elegans* for 7 years and my initial enthusiasm paled as Pierre looked over my shoulder as I tried to remember how to move worms around and showed a complete blank when discussing this and that cross. So in order to get started, we called up Heinke and Ralph Schnabel, with whom I had been together at the LMB, and asked them about getting hold of some wild-type worms, and help with culture conditions. To my surprise, they offered us a complete mutant collection on chromosome III, beautifully mapped and characterized. Pierre then proceeded to screen all of these mutants and showed that when analyzed in large numbers, it was possible to define certain phenotypic classes of mutants in different cell division processes. He was able to define particular mutants that affected spindle position (Gönczy *et al.*, 1999, #14).

We also came back to the work of my PhD to study the biophysics of spindle positioning, working at the one-cell stage. How does a spindle move eccentrically within the cell prior to division? This eccentric movement sets up an asymmetrically placed cleavage furrow, thus defining an unequal cleavage in the cell. At this point, Stephan Grill joined the lab as a joint student with Ernst Stelzer's lab. By applying techniques for laser ablation developed by Aist and Berns in the 1980s (Aist and Berns, 1981), we demonstrated that the force is greater on the posterior than the anterior spindle pole and that the PAR proteins determine this asymmetry (Figure 4). By collaboration with Joe Howard, we used biophysical methods to demonstrate more precisely that this was due to a two-fold increase in the number of force generation elements on the posterior of the cortex (Grill *et al.*, 2003) (Figure 6).

However, the difficulty of cloning the genes meant that very few new molecules were coming on line. At this time, two

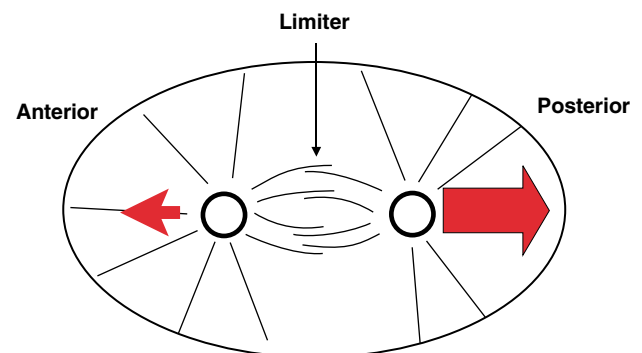


Figure 6 Force generation during asymmetric movement of the first cleavage spindle in *C. elegans*. There is greater force on the posterior than the anterior pole, the central spindle of which acts as a governor (Grill *et al.*, 2001).

things changed in my scientific life. First, Kai Simons proposed that together with Wieland Huttner and Marino Zerial, we should build a new Max Planck institute for molecular cell biology in Dresden, part of the old DDR. Joe Howard from Seattle and our scientific administrator Ivan Baines, from NIH, later joined us and were crucial for this endeavor (Huttner, 2001). Moving to Dresden was a hard decision, since I was very happy at EMBL. However, I was intrigued by the challenge of building something new. Furthermore, I thought it would be interesting to build, in one institute, facilities that would allow all the tools of modern molecular cell biology to bear on the problems of cell division. In fact building the new institute, which opened in the beginning of 2001, has been a great experience and I especially enjoyed being part of a team focused on a common goal. The second thing that changed in my scientific life was the discovery of RNA interference (RNAi) by Andy Fire (one of the postdocs who had despaired of me in Cambridge) and Craig Mello (Fire *et al.*, 1998). It became immediately clear that one could use RNAi for genome-wide screening for genes required for cell division. *C. elegans* had a number of advantages for such a screen. Firstly the first cell division can easily be followed by simple transmitted light. Secondly, the structure of the gonad meant that one could ameliorate the problem of protein stability (see Figure 7). Thirdly, at that time, it was one of the few organisms with a sequenced genome.

Taking account of these advantages, Pierre Gönczy and Chris Echeverri initiated a genome-wide screen for cell division

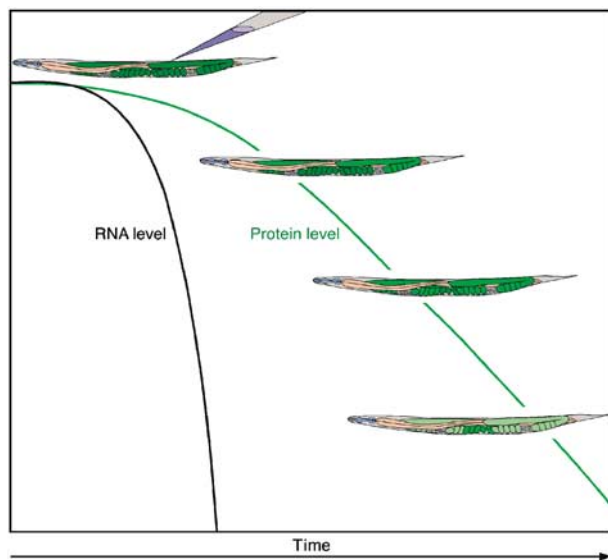


Figure 7 RNAi quickly catalyzes the destruction of the mRNA, but the protein then slowly degrades as a function of its half-life; thus, any phenotype in a tissue culture cell is the result of a slow run down. The structure of the *C. elegans* gonad provides a unique advantage for RNAi by allowing silencing of the maternal message before cell division. The *C. elegans* gonad is a syncytium in which nuclei cellularize prior to fertilization. Continuous formation of oocytes means that the maternal cytoplasm is flushed out and new protein must be constantly synthesized. To perform an RNAi experiment, the dsRNA is injected into the gonad. Then, one has to wait around 24 h while the maternal protein of interest is flushed out as oocytes are produced. Because the mRNA has been degraded, no new protein of interest is synthesized. Thus after about 24 h, the newly formed embryos have very little of that specific maternal protein, and the meiotic and mitotic divisions take place in the presence of very low protein of interest (figure courtesy of Martin Srayko).

proteins (Gönczy *et al.*, 2000). Karen Oegema, Arshad Desai and my technicians Sonja Rybina and Matthew Kirkham, together with my student Eva Hannak, developed a set of assays that have allowed for the first time a genome-wide analysis of the assembly of key mitotic organelles such as centrosomes and kinetochores (Desai *et al.*, 2003; Kirkham *et al.*, 2003). What have we learned from genome-wide screening? One of the key issues of course is that we have bypassed the laborious step of cloning all the genes. However, I think one obtains one extra level of understanding by looking at a genome-wide data set. In conventional genetics, you clone a mutant, giving you one piece of a puzzle. But how big is the puzzle? If it is 10 pieces, you are well along the way. If it is 100 pieces, you have a long way to go. Genome-wide screens describe the rough size of the puzzle. This allows one to design experiments based on the complexity of the problem. There is indeed a big change in biology taking place using high-throughput screens, because it allows genetics to take place on a scale that was previously not possible. This I call 'the industrial revolution of genetics'. Similar to the way that the movement of production from a cottage industry to the factory in the 18th century standardized the production of goods in the industrial age, the industrial revolution of genetics allows the standardization of mutagenesis, screening and phenotype interpretation, with all its associated advantages.

When should these large-scale operations take place? My take on it is that it is worth doing them when the technique can as easily be performed in large scale as in individual labs. Small research labs should get on with solving problems in biological mechanism. Whether this should be carried out commercially or in large-scale academic operations is a different issue. While chromosome III was screened in my lab, the whole genome was screened in a biotech company Cenix Bioscience, founded by Chris Echeverri, Pierre Gönczy and myself, with Chris taking the lead personally as CEO, which has ascertained the role of each gene in the first cell division in *C. elegans*. This monumental task involved taking 43 000 movies (Soenichsen *et al.*, *Nature*, in press). There were two reasons we decided to do this commercially. The first thing is that a large-scale screening operation and individual experiments are not compatible in the same lab. The scientists trying to eke out results from mechanism-directed experiments feel depressed by the amount of data coming out from the screens. The scientists running the screens feel depressed that they are not doing hypothesis-driven research. The second reason was the amount of money that the private sector can bring into a problem. However, one thing is clear: genomics has not changed the basic way science is done, rather it has removed one of the bottlenecks. Individual scientists still have to work on individual problems, just as they have always done.

Acknowledgements

I thank my father RA Hyman for his encouragement, Suzanne Eaton for her constant support and the more recent help of Luke and Max. That is what makes it all worthwhile. I would also like to thank my colleagues in Cambridge, San Francisco, Heidelberg and Dresden for the stimulating environment they have created. In particular I would like to thank for their encouragement, Richard Corfield at the secondary school and Sean Munroe as a PhD student.

References

- Abercrombie M, Heaysman JE, Pegrum SM (1970) The locomotion of fibroblasts in culture. I. Movements of the leading edge. *Exp Cell Res* **59**: 393–398
- Aist JR, Berns MW (1981) Mechanics of chromosome separation during mitosis in *Fusarium* (Fungi imperfecti): new evidence from ultrastructural and laser microbeam experiments. *J Cell Biol* **91** (Part 2): 446–458
- Belmont LD, Hyman AA, Sawin KE, Mitchison TJ (1990) Real-time visualization of cell cycle-dependent changes in microtubule dynamics in cytoplasmic extracts. *Cell* **62**: 579–589
- Desai A, Rybina S, Muller-Reichert T, Shevchenko A, Hyman A, Oegema K (2003) KNL-1 directs assembly of the microtubule-binding interface of the kinetochore in *C. elegans*. *Genes Dev* **17**: 2421–2435
- Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**: 806–811
- Freeman M (2002) A fly's eye view of EGF receptor signaling. *EMBO J* **21**: 6635–6642
- Gönczy P, Echeverri C, Oegema K, Coulson A, Jones SJ, Copley RR, Duperon J, Oegema J, Brehm M, Cassin E, Hannak E, Kirkham M, Pichler S, Flohrs K, Goessen A, Leidel S, Alleaume AM, Martin C, Ozlu N, Bork P, Hyman AA (2000) Functional genomic analysis of cell division in *C. elegans* using RNAi of genes on chromosome III. *Nature* **408**: 331–336
- Gönczy P, Schnabel H, Kaletta T, Amores AD, Hyman T, Schnabel R (1999) Dissection of cell division processes in the one cell stage *Caenorhabditis elegans* embryo by mutational analysis. *J Cell Biol* **144**: 927–946
- Grill SW, Gönczy P, Stelzer EH, Hyman AA (2001) Polarity controls forces governing asymmetric spindle positioning in the *Caenorhabditis elegans* embryo. *Nature* **409**: 630–633
- Grill SW, Howard J, Schaffer E, Stelzer EH, Hyman AA (2003) The distribution of active force generators controls mitotic spindle position. *Science* **301**: 518–521
- Heald R, Tournebize R, Blank T, Sandaltzopoulos R, Becker P, Hyman A, Karsenti E (1996) Self-organization of microtubules into bipolar spindles around artificial chromosomes in *Xenopus* egg extracts. *Nature* **382**: 420–425
- Heald R, Tournebize R, Habermann A, Karsenti E, Hyman A (1997) Spindle assembly in *Xenopus* egg extracts: respective roles of centrosomes and microtubule self-organization. *J Cell Biol* **138**: 615–628
- Huttner WB (2001) Birth of a new institute—Biopolis Dresden. *Nat Rev Mol Cell Biol* **2**: 699–703
- Hyman AA (1989) Centrosome movement in the early divisions of *Caenorhabditis elegans*: a cortical site determining centrosome position. *J Cell Biol* **109**: 1185–1193
- Hyman AA, Chretien D, Arnal I, Wade RH (1995) Structural changes accompanying GTP hydrolysis in microtubules: information from a slowly hydrolyzable analogue guanylyl-(alpha,beta)-methylene-diphosphonate. *J Cell Biol* **128**: 117–125
- Hyman AA, Middleton K, Centola M, Mitchison TJ, Carbon J (1992) Microtubule-motor activity of a yeast centromere-binding protein complex. *Nature* **359**: 533–536
- Hyman AA, Mitchison TJ (1991) Two different microtubule-based motor activities with opposite polarities in kinetochores. *Nature* **351**: 206–211
- Karsenti E, Newport J, Kirschner M (1984) Respective roles of centrosomes and chromatin in the conversion of microtubule arrays from interphase to metaphase. *J Cell Biol* **99** (1 Part 2): 47s–54s
- Karsenti E, Vernos I (2001) The mitotic spindle: a self-made machine. *Science* **294**: 543–547
- Kinoshita K, Arnal I, Desai A, Drechsel DN, Hyman AA (2001) Reconstitution of physiological microtubule dynamics using purified components. *Science* **294**: 1340–1343
- Kirkham M, Muller-Reichert T, Oegema K, Grill S, Hyman AA (2003) SAS-4 is a *C. elegans* centriolar protein that controls centrosome size. *Cell* **112**: 575–587
- Kirschner M, Mitchison T (1986) Beyond self-assembly: from microtubules to morphogenesis. *Cell* **45**: 329–342
- Laufer JS, Bazzicalupo P, Wood WB (1980) Segregation of developmental potential in early embryos of *Caenorhabditis elegans*. *Cell* **19**: 569–577
- Mitchison T, Kirschner M (1984) Dynamic instability of microtubule growth. *Nature* **312**: 237–242
- Muller-Reichert T, Chretien D, Severin F, Hyman AA (1998) Structural changes at microtubule ends accompanying GTP hydrolysis: information from a slowly hydrolyzable analogue of GTP, guanylyl (alpha,beta)methylenediphosphonate. *Proc Natl Acad Sci USA* **95**: 3661–3666
- Rappaport R, Rappaport BN (1974) Establishment of cleavage furrows by the mitotic spindle. *J Exp Zool* **189**: 189–196
- Severin F, Habermann B, Huffaker T, Hyman T (2001) Stu2 promotes mitotic spindle elongation in anaphase. *J Cell Biol* **153**: 435–442
- Shamu CE, Murray AW (1992) Sister chromatid separation in frog egg extracts requires DNA topoisomerase II activity during anaphase. *J Cell Biol* **117**: 921–934
- Strome S, Wood WB (1983) Generation of asymmetry and segregation of germ-line granules in early *C. elegans* embryos. *Cell* **35**: 15–25
- Tournebize R, Popov A, Kinoshita K, Ashford AJ, Rybina S, Pozniakovskiy A, Mayer TU, Walczak CE, Karsenti E, Hyman AA (2000) Control of microtubule dynamics by the antagonistic activities of XMAP215 and XKCM1 in *Xenopus* egg extracts. *Nat Cell Biol* **2**: 13–19



Anthony A Hyman