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# **New concepts in fission yeast morphogenesis**

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# **New concepts in fission yeast morphogenesis**<br> **New concepts in fission yeast morphogenesis**

## **Damian Brunner and Paul Nurse**\*

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The ability to generate spatial form is a fundamental characteristic of all living organisms, which has The ability to generate spatial form is a fundamental characteristic of all living organisms, which has<br>been much studied by successive generations of developmental biologists. In recent years increasing<br>numbers of cell bi The ability to generate spatial form is a fundamental characteristic of all living organisms, which has<br>been much studied by successive generations of developmental biologists. In recent years increasing<br>numbers of cell bi been much studied by successive generations of developmental biologists. In recent years increasing<br>numbers of cell biologists have turned their attention to the mechanisms by which cells generate their<br>spatial form. These numbers of cell biologists have turned their attention to the mechanisms by which cells generate their spatial form. These include the mechanisms that position components in different places within the cell, that specify t spatial form. These include the mechanisms that position components in different places within the cell, that specify the position of these components, and that generate the overall shape of these components. These problem that specify the position of these components, and that generate the overall shape of these components.<br>These problems are entirely analogous to those studied by developmental biologists, although usually at<br>the level of t These problems are entirely analogous to those studied by developmental biologists, although usually at<br>the level of the whole organism, organ or tissue. Because the organization of all cells is basically similar, it<br>is po the level of the whole organism, organ or tissue. Because the organization of all cells is basically similar, it<br>is possible that the concepts and the underlying molecular mechanisms of cell morphogenesis may be highly conserved. In this article we consider the generation of spatial form within the fission yeast cell, focusing on emerging new concepts, which may be applicable to the morphogenesis of other cells.<br>**Keywords:** fissio focusing on emerging new concepts, which may be applicable to the morphogenesis of other cells.

### **1. FISSION YEAST CELL MORPHOGENESIS**

The fission yeast is a simple single-celled eukaryote. It is The fission yeast is a simple single-celled eukaryote. It is<br>cylindrical in form,  $3-4 \mu m$  in diameter, and  $8-15 \mu m$  in<br>length depending on how far the cell has proceeded The fission yeast is a simple single-celled eukaryote. It is<br>cylindrical in form,  $3-4 \mu m$  in diameter, and  $8-15 \mu m$  in<br>length, depending on how far the cell has proceeded<br>through the cell cycle. Cell diameter remains ap cylindrical in form,  $3-4 \mu m$  in diameter, and  $8-15 \mu m$  in length, depending on how far the cell has proceeded through the cell cycle. Cell diameter remains approxi-<br>mately constant during the cell cycle and so most grow length, depending on how far the cell has proceeded<br>through the cell cycle. Cell diameter remains approxi-<br>mately constant during the cell cycle and so most growth<br>occurs as a consequence of cell elongation, with newly through the cell cycle. Cell diameter remains approximately constant during the cell cycle and so most growth<br>occurs as a consequence of cell elongation, with newly<br>born cells being the shortest and cells just about to div mately constant during the cell cycle and so most growth<br>occurs as a consequence of cell elongation, with newly<br>born cells being the shortest and cells just about to divide occurs as a consequence of cell elongation, with newly tion of septation, the actin relocates from the septum to<br>born cells being the shortest and cells just about to divide the old ends and cell elongation recommences. Th born cells being the shortest and cells just about to divide<br>being the longest. The two cell ends or tips grow apart in<br>a precisely opposed manner such that cell elongation of<br>the cylinder occurs in a straight line. A newl being the longest. The two cell ends or tips grow apart in<br>a precisely opposed manner such that cell elongation of<br>the cylinder occurs in a straight line. A newly born cell<br>begins growth at only one of its ends, the end th a precisely opposed manner such that cell elongation of<br>the cylinder occurs in a straight line. A newly born cell<br>begins growth at only one of its ends, the end that<br>already existed in the mother cell before its division the cylinder occurs in a straight line. A newly born cell<br>begins growth at only one of its ends, the end that<br>already existed in the mother cell before its division.<br>Because this is the end that pre-existed in the mother c begins growth at only one of its ends, the end that already existed in the mother cell before its division.<br>Because this is the end that pre-existed in the mother cell<br>it is termed the old end. Some way into the cell cycle already existed in the mother cell before its division.<br>Because this is the end that pre-existed in the mother cell<br>it is termed the old end. Some way into the cell cycle the Because this is the end that pre-existed in the mother cell to nuclear separation. As mitosis is completed, the it is termed the old end. Some way into the cell cycle the intranuclear spindle disappears and new cytoplasmic it is termed the old end. Some way into the cell cycle the cell shifts from being monopolar to bipolar in growth<br>mode by activating growth at the new end. This tran-<br>sition termed new-end take-off (NETO) occurs around cell shifts from being monopolar to bipolar in growth<br>mode by activating growth at the new end. This tran-<br>sition, termed new-end take-off (NETO), occurs around<br>the time of S-phase when the cell attains a certain mode by activating growth at the new end. This transition, termed new-end take-off (NETO), occurs around<br>the time of S-phase when the cell attains a certain<br>minimal cell length. During mitosis and cytokinesis cell sition, termed new-end take-off (NETO), occurs around<br>the time of S-phase when the cell attains a certain<br>minimal cell length. During mitosis and cytokinesis cell<br>elongation ceases, and a sentum is formed in the middle the time of S-phase when the cell attains a certain<br>minimal cell length. During mitosis and cytokinesis cell<br>elongation ceases, and a septum is formed in the middle<br>of the cell Splitting of the septum forms two new cells elongation ceases, and a septum is formed in the middle of the cell. Splitting of the septum forms two new cells elongation ceases, and a septum is formed in the middle<br>of the cell. Splitting of the septum forms two new cells<br>each with an old end derived from the mother cell and a<br>new end formed from the septum. It is these basic gro of the cell. Splitting of the septum forms two new cells<br>each with an old end derived from the mother cell and a<br>new end formed from the septum. It is these basic growth<br>characteristics, that account for the overall form o each with an old end derived from the mother cell and a<br>new end formed from the septum. It is these basic growth<br>characteristics that account for the overall form of the<br>fission veast cell (Mata & Nurse 1998) new end formed from the septum. It is these basic growth<br>characteristics that account for the overall form of the<br>fission yeast cell (Mata & Nurse 1998).

Coincident with these morphogenetic changes during fission yeast cell (Mata & Nurse 1998).<br>Coincident with these morphogenetic changes during<br>the cell cycle are changes in the organization of both the<br>actin and microtubular cytoskeletons (figure 1) Actin dots Coincident with these morphogenetic changes during<br>the cell cycle are changes in the organization of both the<br>actin and microtubular cytoskeletons (figure 1). Actin dots<br>are found concentrated in the region of growing cell the cell cycle are changes in the organization of both the actin and microtubular cytoskeletons (figure 1). Actin dots are found concentrated in the region of growing cell ends.<br>During unipolar growth, these dots are found actin and microtubular cytoskeletons (figure 1). Actin dots<br>are found concentrated in the region of growing cell ends.<br>During unipolar growth, these dots are found mostly at<br>the sole growing end, and during binolar growth are found concentrated in the region of growing cell ends.<br>During unipolar growth, these dots are found mostly at<br>the sole growing end, and during bipolar growth they are<br>found at both cell ends (Marks & Hyams 1985) During During unipolar growth, these dots are found mostly at the sole growing end, and during bipolar growth they are found at both cell ends (Marks & Hyams 1985). During the sole growing end, and during bipolar growth they are<br>found at both cell ends (Marks & Hyams 1985). During<br>both unipolar and bipolar growth, a cytoplasmic micro-<br>tubular cytoskeleton extends throughout the length of the found at both cell ends (Marks & Hyams 1985). During<br>both unipolar and bipolar growth, a cytoplasmic micro-<br>tubular cytoskeleton extends throughout the length of the tubular cytoskeleton extends throughout the length of the<br>\*Author for correspondence (nurse@icrf.icnet.uk).

cell forming a cage around the nucleus. The microtubules cell forming a cage around the nucleus. The microtubules<br>appear to be initiated from the region of the nuclear<br>surface with their tips often terminating at the cellular appear to be initiated from the region of the nuclear<br>surface with their tips often terminating at the cellular appear to be initiated from the region of the nuclear<br>surface with their tips often terminating at the cellular<br>ends. At mitosis and cytokinesis, both the actin and<br>microtubular cytoskeletons undergo major changes. Most surface with their tips often terminating at the cellular<br>ends. At mitosis and cytokinesis, both the actin and<br>microtubular cytoskeletons undergo major changes. Most<br>of the actin relocates from the cell ends to the middle ends. At mitosis and cytokinesis, both the actin and<br>microtubular cytoskeletons undergo major changes. Most<br>of the actin relocates from the cell ends to the middle of<br>the cell where the sentum is to be formed. At the compl microtubular cytoskeletons undergo major changes. Most<br>of the actin relocates from the cell ends to the middle of<br>the cell where the septum is to be formed. At the comple-<br>tion of septation, the actin relocates from the se of the actin relocates from the cell ends to the middle of<br>the cell where the septum is to be formed. At the comple-<br>tion of septation, the actin relocates from the septum to<br>the old ends and cell elongation recommences. T the cell where the septum is to be formed. At the completion of septation, the actin relocates from the septum to the old ends and cell elongation recommences. The cyto-plasmic microtubular cage disappears at mitosis and a plasmic mictrotubular cage disappears at mitosis and an the old ends and cell elongation recommences. The cyto-<br>plasmic mictrotubular cage disappears at mitosis and an<br>intranuclear spindle is formed. The spindle elongates, the<br>nucleus divides and the two daughter nuclei move ap plasmic mictrotubular cage disappears at mitosis and an intranuclear spindle is formed. The spindle elongates, the nucleus divides, and the two daughter nuclei move apart.<br>At this stage cytoplasmic microtubules emanating f intranuclear spindle is formed. The spindle elongates, the<br>nucleus divides, and the two daughter nuclei move apart.<br>At this stage cytoplasmic microtubules emanating from<br>the spindle pole body appear and these could contrib nucleus divides, and the two daughter nuclei move apart.<br>At this stage cytoplasmic microtubules emanating from At this stage cytoplasmic microtubules emanating from<br>the spindle pole body appear and these could contribute<br>to nuclear separation. As mitosis is completed, the<br>intranuclear spindle disappears and new cytoplasmic the spindle pole body appear and these could contribute<br>to nuclear separation. As mitosis is completed, the<br>intranuclear spindle disappears and new cytoplasmic<br>microtubules form (Hagan 1998) microtubules form (Hagan 1998).

## **2. LONG-RANGE SPATIAL ORGANIZATION** IE SPATIAL ORG.<br>IN THE CELL **IN THE CELL**<br>The ability of the fission yeast cell to grow in a straight

line with the two growing ends precisely opposed to each other must reflect some sort of long-range spatial organline with the two growing ends precisely opposed to each<br>other must reflect some sort of long-range spatial organization<br>extending throughout the cell. To study this<br>problem, mutations or drug treatments producing cells other must reflect some sort of long-range spatial organization extending throughout the cell. To study this problem, mutations or drug treatments producing cells that are no longer able to maintain growth in a straight ization extending throughout the cell. To study this<br>problem, mutations or drug treatments producing cells<br>that are no longer able to maintain growth in a straight<br>line but which can still form a properly organized problem, mutations or drug treatments producing cells<br>that are no longer able to maintain growth in a straight<br>line, but which can still form a properly organized<br>growth zone, should be revealing. Such cells would be that are no longer able to maintain growth in a straight<br>line, but which can still form a properly organized<br>growth zone, should be revealing. Such cells would be<br>expected to position the growth site in the wrong place in line, but which can still form a properly organized<br>growth zone, should be revealing. Such cells would be<br>expected to position the growth site in the wrong place in<br>the cell and as a consequence to grow bent or even growth zone, should be revealing. Such cells would be expected to position the growth site in the wrong place in the cell and as a consequence to grow bent or even branched branched. e cell and as a consequence to grow bent or even<br>anched.<br>Cold-sensitive tubulin mutants (Toda *et al.* 1983) and<br>e addition of the microtubule inhibitor thiabendazole

Cold-sensitive tubulin mutants (Toda  $et$  al. 1983) and the addition of the microtubule inhibitor thiabendazole (TBZ) (Walker 1982) produce bent and branched cells at the addition of the microtubule inhibitor thiabendazole (TBZ) (Walker 1982) produce bent and branched cells at a low frequency, implicating microtubules in long-range spatial organization. A more systematic study was made (TBZ) (Walker 1982) produce bent and branched cells at<br>a low frequency, implicating microtubules in long-range<br>spatial organization. A more systematic study was made<br>possible when it was discovered that the release of a a low frequency, implicating microtubules in long-range<br>spatial organization. A more systematic study was made<br>possible when it was discovered that the release of a



Figure 1. A schematic drawing of stages of the cell cycle shown in a clockwise orientation. Multiple changes in the organization<br>of both the actin and microtubular cytoskeletons occur during the cell cycle. During interpha Figure 1. A schematic drawing of stages of the cell cycle shown in a clockwise orientation. Multiple changes in the organization<br>of both the actin and microtubular cytoskeletons occur during the cell cycle. During interpha Figure 1. A schematic drawing of stages of the cell cycle shown in a clockwise orientation. Multiple changes in the organization<br>of both the actin and microtubular cytoskeletons occur during the cell cycle. During interpha of both the actin and microtubular cytoskeletons occur during the cell cycle. During interphase, actin dots accumulate at the<br>growing ends (arrows). In cells before NETO this is at the old end, which existed in the previou growing ends (arrows). In cells before NETO this is at the old end, which existed in the previous cell cycle, and in post-NETO<br>cells it is at both the old and the new ends. At the onset of mitosis, actin relocates to the c cells it is at both the old and the new ends. At the onset of mitosis, actin relocates to the cell centre where it forms a contractile<br>ring before septum formation. During ring contraction actin dots accumulate on both sid existed before division. Interphase microtubules originate from multiple locations in the nuclear periphery and grow into both cell walls are synthesized. After the completion of cytokinesis, actin dots in both daughter cells relocate to the old ends that<br>existed before division. Interphase microtubules originate from multiple locations in the nuc existed before division. Interphase microtubules originate from multiple locations in the nuclear periphery and grow into both<br>ends of the cell. These microtubules disappear at the beginning of mitosis whilst an intranucle ends of the cell. These microtubules disappear at the beginning of mitosis whilst an intranuclear spindle forms, originating from<br>the two spindle pole bodies. While the spindle elongates, new cytoplasmic microtubules origi the two spindle pole bodies. While tl<br>When the nuclei have reached the c<br>and from the two daughter nuclei.

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and from the two daughter nuclei.<br>cdc10ts cell-cycle mutant from its G1 block in the presence<br>of TBZ generated high levels of branched cells (Sawin & of TBZ generated high levels of block in the presence<br>of TBZ generated high levels of branched cells (Sawin & fo<br>Nurse 1998) These bigh levels of branching are the conseof TBZ generated high levels of branched cells (Sawin & Nurse 1998). These high levels of branching are the conseof TBZ generated high levels of branched cells (Sawin & Nurse 1998). These high levels of branching are the consequence of cells undergoing NETO in the absence of microtubules. Instead of activating growth at the new end Nurse 1998). These high levels of branching are the consequence of cells undergoing NETO in the absence of microtubules. Instead of activating growth at the new end opposed to the old end it is activated off-axis or in the quence of cells undergoing NETO in the absence of<br>microtubules. Instead of activating growth at the new end<br>opposed to the old end, it is activated off-axis or in the<br>middle of the cell to generate bent or branched cells microtubules. Instead of activating growth at the new end<br>opposed to the old end, it is activated off-axis or in the<br>middle of the cell to generate bent or branched cells,<br>respectively. In the latter case actin dots now ac opposed to the old end, it is activated off-axis or in the middle of the cell to generate bent or branched cells, respectively. In the latter case actin dots now accumulate as a patch in the middle region of the cell where respectively. In the latter case actin dots now accumulate<br>as a patch in the middle region of the cell where the new<br>growing tip will be formed. Therefore, an intact cyto-<br>plasmic microtubular cytoskeleton is required to p as a patch in the middle region of the cell where the new<br>growing tip will be formed. Therefore, an intact cyto-<br>plasmic microtubular cytoskeleton is required to properly<br>place a new growing end exactly opposed to the old growing tip will be formed. Therefore, an intact cyto-<br>plasmic microtubular cytoskeleton is required to properly<br>place a new growing end exactly opposed to the old end.<br>Further insight into the role of microtubules in long A asmic microtubular cytoskeleton is required to properly<br>ace a new growing end exactly opposed to the old end.<br>Further insight into the role of microtubules in long-<br>page spatial order has come from analysis of a *teal* 

place a new growing end exactly opposed to the old end.<br>Further insight into the role of microtubules in long-<br>range spatial order has come from analysis of a *teal*<br>mutant which generates hent and branched cells Further insight into the role of microtubules in long-<br>range spatial order has come from analysis of a *teal*<br>mutant, which generates bent and branched cells<br>(figure 2) (Mata & Nurse 1997) Tealp is found at both range spatial order has come from analysis of a *teal* cellular long axis. Tealp is transported along the micromutant, which generates bent and branched cells tubules and accumulates in the cell tips where most (figure 2) mutant, which generates bent and branched cells<br>(figure 2) (Mata & Nurse 1997). Tealp is found at both<br>cell tips whether the cells have undergone NETO or not<br>and so appears to be a marker of cell geometry rather (figure 2) (Mata & Nurse 1997). Tealp is found at both<br>cell tips whether the cells have undergone NETO or not<br>and so appears to be a marker of cell geometry rather<br>than of cell growth (figure 2). This makes tealp a potencell tips whether the cells have undergone NETO or not<br>and so appears to be a marker of cell geometry rather<br>than of cell growth (figure 2). This makes tealp a poten-<br>tial marker for cellular ends Within minutes of disrupt and so appears to be a marker of cell geometry rather<br>than of cell growth (figure 2). This makes tealp a poten-<br>tial marker for cellular ends. Within minutes of disrupting<br>the microtubular cytoskeleton with TBZ, tealp disa than of cell growth (figure 2). This makes tealp a potential marker for cellular ends. Within minutes of disrupting<br>the microtubular cytoskeleton with TBZ, tealp disappears<br>from the cell tips and is instead found distribut throughout the cytoplasm.When TBZ is removed, tea1p is from the cell tips and is instead found distributed<br>throughout the cytoplasm. When TBZ is removed, tealp is<br>found at the distal ends of the microtubules, which are<br>growing back towards the cell tips Tealp is observed to throughout the cytoplasm. When TBZ is removed, tealp is<br>found at the distal ends of the microtubules, which are<br>growing back towards the cell tips. Tealp is observed to<br>accumulate once again at the cell ends as soon as mic found at the distal ends of the microtubules, which are<br>growing back towards the cell tips. Tealp is observed to<br>accumulate once again at the cell ends as soon as micro-*Phil. Trans. R. Soc. Lond.* B (2000)

tubules have reached them. In the absence of tealp, newly<br>forming growth zones are located incorrectly even in the tubules have reached them. In the absence of tealp, newly<br>forming growth zones are located incorrectly even in the<br>presence of microtubules tubules have reached them.<br>forming growth zones are<br>presence of microtubules.<br>These results suggest a forming growth zones are located incorrectly even in the<br>presence of microtubules.<br>These results suggest a model whereby the microtu-

middle of the cell to generate bent or branched cells, precisely opposes cell ends. Tealp is involved in properly respectively. In the latter case actin dots now accumulate placing locally organized growth zones at the opp tial marker for cellular ends. Within minutes of disrupting a transient stabilization of those microtubules that<br>the microtubular cytoskeleton with TBZ, tealp disappears happen to reach the cell ends. This would consequent bule-dependent transport of the cell end marker tea1p underlies the long-range spatial organization that bule-dependent transport of the cell end marker tealp<br>underlies the long-range spatial organization that<br>precisely opposes cell ends. Tealp is involved in properly<br>placing locally organized growth zones at the opposite or underlies the long-range spatial organization that<br>precisely opposes cell ends. Tealp is involved in properly<br>placing locally organized growth zones at the opposite or<br>antipodal ends of the cell Importantly growth zones ca precisely opposes cell ends. Tealp is involved in properly<br>placing locally organized growth zones at the opposite or<br>antipodal ends of the cell. Importantly, growth zones can<br>still be formed in the absence of tealp, but th placing locally organized growth zones at the opposite or<br>antipodal ends of the cell. Importantly, growth zones can<br>still be formed in the absence of tealp, but they are incor-<br>rectly placed with respect to the overall spa antipodal ends of the cell. Importantly, growth zones can<br>still be formed in the absence of tealp, but they are incor-<br>rectly placed with respect to the overall spatial geometry<br>of the cell. Microtubules extending through rectly placed with respect to the overall spatial geometry<br>of the cell. Microtubules extending through the length of rectly placed with respect to the overall spatial geometry<br>of the cell. Microtubules extending through the length of<br>the cell identify the antipodes at the extremes of the<br>cellular long axis. Tealn is transported along the of the cell. Microtubules extending through the length of<br>the cell identify the antipodes at the extremes of the<br>cellular long axis. Tealp is transported along the micro-<br>tubules and accumulates in the cell tips where most the cell identify the antipodes at the extremes of the cellular long axis. Tealp is transported along the micro-<br>tubules and accumulates in the cell tips where most<br>microtubules terminate. The major difficulty with this cellular long axis. Tealp is transported along the micromodel is understanding how microtubules accurately microtubules terminate. The major difficulty with this<br>model is understanding how microtubules accurately<br>identify the antipodes at the extremes of the cellular axis.<br>One possibility is that a mechanism exists which leads model is understanding how microtubules accurately<br>identify the antipodes at the extremes of the cellular axis.<br>One possibility is that a mechanism exists which leads to<br>a transient stabilization of those microtubules that identify the antipodes at the extremes of the cellular axis.<br>One possibility is that a mechanism exists which leads to<br>a transient stabilization of those microtubules that<br>hannen to reach the cell ends. This would conseque One possibility is that a mechanism exists which leads to a transient stabilization of those microtubules that happen to reach the cell ends. This would consequently<br>lead to a majority of microtubules extending the length of<br>the cell between the antipodes. An alternative possibility<br>is that microtubules have a tendency to extend al lead to a majority of microtubules extending the length of<br>the cell between the antipodes. An alternative possibility<br>is that microtubules have a tendency to extend along the<br>long axis as a consequence of them becoming def the cell between the antipodes. An alternative possibility<br>is that microtubules have a tendency to extend along the<br>long axis as a consequence of them becoming deflected<br>when they grow in middle regions of the cell cortex is that microtubules have a tendency to extend along the long axis as a consequence of them becoming deflected when they grow in middle regions of the cell cortex.



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Figure 2. (*a*, *b*) Photographs of cells stained with the fluorescent dve calcofluor and the schematic drawings Figure 2.  $(a, b)$  Photographs of cells stained with the fluorescent dye calcofluor and the schematic drawings illustrate the distribution of teal  $n$  and microtubules in Figure 2.  $(a, b)$  Photographs of cells stained with the<br>fluorescent dye calcofluor and the schematic drawings<br>illustrate the distribution of tea1p and microtubules in<br> $(a)$  wild-type and  $(b)$  Ateal cells  $(a)$  Cytoplasmic fluorescent dye calcofluor and the schematic drawing<br>illustrate the distribution of tea1p and microtubules<br>(*a*) wild-type and (*b*)  $\Delta teal$  cells. (*a*) Cytoplasmic<br>microtubules grow into the longitudinal axis of the c illustrate the distribution of teal p and microtubules in<br>
(a) wild-type and (b)  $\Delta teal$  cells. (a) Cytoplasmic<br>
microtubules grow into the longitudinal axis of the cylindrical<br>
cells and terminate in the cell tips. Teal p (a) wild-type and (b)  $\Delta teal$  cells. (a) Cytoplasmic<br>microtubules grow into the longitudinal axis of the cylindrical<br>cells and terminate in the cell tips. Tea1p accumulates at the<br>cell ends but is also found on the distal microtubules grow into the longitudinal axis of the cylindrica<br>cells and terminate in the cell tips. Teal p accumulates at the<br>cell ends but is also found on the distal tips of microtubules<br>and in dots along the microtubu cells and terminate in the cell tips. Teal p accumulates at the cell ends but is also found on the distal tips of microtubules and in dots along the microtubules. ( $b$ ) Cells deleted for *teal* cell ends but is also found on the distal tips of microtubules<br>and in dots along the microtubules. (b) Cells deleted for *teal*<br>are unable to correctly position their growth site and therefore<br>are bent or branched. In the and in dots along the microtubules.  $(b)$  Cells deleted for *tea*.<br>are unable to correctly position their growth site and theref<br>are bent or branched. In the absence of tea1p, the microtu-<br>bules do not always terminate gro are unable to correctly position their growth site and therefore are bent or branched. In the absence of tealp, the microtubules do not always terminate growth when they reach the cell tips and instead can curl around the are bent or branched. In the absence of teal  $p$ , the microtubules do not always terminate growth when they reach the cell tips and instead can curl around the end.

cen ups and instead can curi around the end.<br>Because most microtubules are initiated from the region<br>of the nucleus in the cell centre, they will be deflected Because most microtubules are initiated from the region<br>of the nucleus in the cell centre, they will be deflected<br>towards the cell ends if their growth occurs at an oblique Because most microtubules are initiated from the region<br>of the nucleus in the cell centre, they will be deflected<br>towards the cell ends if their growth occurs at an oblique<br>angle. The subsequent arrest of microtubule growt of the nucleus in the cell centre, they will be deflected<br>towards the cell ends if their growth occurs at an oblique<br>angle. The subsequent arrest of microtubule growth in the<br>cell tips could be simply due to further growth towards the cell ends if their growth occurs at an oblique<br>angle. The subsequent arrest of microtubule growth in the<br>cell tips could be simply due to further growth becoming<br>impossible when the microtubule tip is fully sur angle. The subsequent arrest of microtubule growth in the cell tips could be simply due to further growth becoming<br>impossible when the microtubule tip is fully surrounded<br>by cortex or if the microtubule is too stiff to ben cell tips could be simply due to further growth becoming<br>impossible when the microtubule tip is fully surrounded<br>by cortex or, if the microtubule is too stiff to bend away<br>when it approaches the cortex almost at right angl impossible when the microtubule tip is fully surrounded<br>by cortex or, if the microtubule is too stiff to bend away<br>when it approaches the cortex almost at right angles, as<br>will be the case at the cell tips. There is, howev by cortex or, if the microtubule is too stiff to bend away when it approaches the cortex almost at right angles, as<br>will be the case at the cell tips. There is, however, some<br>evidence that tealp itself might influence the behaviour of<br>the microtubules in the cell tips. When teal i will be the case at the cell tips. There is, however, some evidence that tealp itself might influence the behaviour of the microtubules in the cell tips. When *teal* is deleted, at a certain frequency microtubules do not s evidence that tealp itself might influence the behaviour of<br>the microtubules in the cell tips. When *teal* is deleted, at a<br>certain frequency, microtubules do not stop at the cell<br>ends but continue to grow to form U-shaned the microtubules in the cell tips. When *teal* is deleted, at a certain frequency, microtubules do not stop at the cell ends but continue to grow to form U-shaped structures extending back into the body of the cell This ob certain frequency, microtubules do not stop at the cell<br>ends but continue to grow to form U-shaped structures<br>extending back into the body of the cell. This observation<br>suggests that if tealn is not present in the cell end ends but continue to grow to form U-shaped structures<br>extending back into the body of the cell. This observation<br>suggests that if tealp is not present in the cell ends, micro-<br>tubules can continue to grow beyond these regi J extending back into the body of the cell. This observation<br>suggests that if tealp is not present in the cell ends, micro-<br>tubules can continue to grow beyond these regions. The suggests that if tealp is not present in the cell ends, micro-<br>tubules can continue to grow beyond these regions. The<br>molecular mechanisms underlying this are not clear but<br>their significance is that the location of tealp  $\mathbf S$ tubules can continue to grow beyond these regions. The<br>molecular mechanisms underlying this are not clear but<br>their significance is that the location of tealp influencing<br>the direction of its own transport provides a posit molecular mechanisms underlying this are not clear but<br>their significance is that the location of tealp influencing<br>the direction of its own transport provides a positive feed-<br>hack system. In other words, if the presence their significance is that the location of tealp influencing provide such an integration mechanism because tealp will<br>the direction of its own transport provides a positive feed-<br>back system. In other words, if the presenc the direction of its own transport provides a positive feed-<br>back system. In other words, if the presence of tealp<br>attracts microtubule ends, which in turn deliver more<br>tealp then more microtubule ends will become attracte back system. In other words, if the presence of tealp<br>attracts microtubule ends, which in turn deliver more<br>tealp, then more microtubule ends will become attracted.<br>Microtubular instability might have additional p racts microtubule ends, which in turn deliver more<br>alp, then more microtubule ends will become attracted.<br>Microtubular instability might have additional<br>plications for long-range spatial order in the cell

tealp, then more microtubule ends will become attracted.<br>
Microtubular instability might have additional<br>
implications for long-range spatial order in the cell.<br>
Recause microtubules are birbly dynamic turning over Microtubular instability might have additional<br>implications for long-range spatial order in the cell.<br>Because microtubules are highly dynamic, turning over<br>every  $1-2 \text{ min}$  the mechanism that results in microimplications for long-range spatial order in the cell.<br>Because microtubules are highly dynamic, turning over<br>every 1-2 min, the mechanism that results in micro-*Phil. Trans. R. Soc. Lond.* B (2000)











Figure 3. Schematic drawing showing cells at different stages<br>of mitosis  $(a, b)$  At the onset of mitosis, mid In exits from the Figure 3. Schematic drawing showing cells at different stages<br>of mitosis. (*a*, *b*) At the onset of mitosis, mid1p exits from the<br>nucleus and accumulates in a band at the cell cortex. This of mitosis.  $(a, b)$  At the onset of mitosis, midlp exits from the nucleus and accumulates in a band at the cell cortex. This of mitosis.  $(a, b)$  At the onset of mitosis, midlp exits from the<br>nucleus and accumulates in a band at the cell cortex. This<br>outlines an area within which actin filaments organize into a<br>central ring  $(c, d)$  During sentum f nucleus and accumulates in a band at the cell cortex. This<br>outlines an area within which actin filaments organize into a<br>central ring.  $(c, d)$  During septum formation, the actin ring<br>contracts and mid ln disappears from th outlines an area within which actin filaments organize<br>central ring.  $(c, d)$  During septum formation, the actin<br>contracts and mid1p disappears from the ring whilst<br>accumulating again in the nucleus central ring.  $(c, d)$  During septum for<br>contracts and mid1p disappears from<br>accumulating again in the nucleus.

tubules extending along the length of the cell could be tubules extending along the length of the cell could be<br>quite crude if some sort of integrating mechanism was<br>operative What is meant by this is that each individual tubules extending along the length of the cell could be<br>quite crude if some sort of integrating mechanism was<br>operative. What is meant by this is that each individual<br>microtubule only imprecisely locates the cell antipodes quite crude if some sort of integrating mechanism was<br>operative. What is meant by this is that each individual<br>microtubule only imprecisely locates the cell antipodes,<br>but the attemnt to do so by 100 microtubules will prod operative. What is meant by this is that each individual microtubule only imprecisely locates the cell antipodes, but the attempt to do so by 100 microtubules will produce microtubule only imprecisely locates the cell antipodes,<br>but the attempt to do so by 100 microtubules will produce<br>over time a distribution of microtubular tip locations<br>spread across the end of the cell. The mean of this but the attempt to do so by 100 microtubules will produce<br>over time a distribution of microtubular tip locations<br>spread across the end of the cell. The mean of this<br>distribution will define the precise antipodes of the cel over time a distribution of microtubular tip locations<br>spread across the end of the cell. The mean of this<br>distribution will define the precise antipodes of the cell.<br>Delivery of tealp along microtubules could obviously spread across the end of the cell. The mean of this<br>distribution will define the precise antipodes of the cell.<br>Delivery of tealp along microtubules could obviously<br>provide such an integration mechanism because tealp will distribution will define the precise antipodes of the cell.<br>Delivery of tealp along microtubules could obviously<br>provide such an integration mechanism because tealp will<br>be deposited at the region of the cell cortex adjace Delivery of tealp along microtubules could obviously<br>provide such an integration mechanism because tealp will<br>be deposited at the region of the cell cortex adjacent to<br>the microtubular tips providing a bistorical record of provide such an integration mechanism because tealp will<br>be deposited at the region of the cell cortex adjacent to<br>the microtubular tips, providing a historical record of<br>microtubular tip locations be deposited at the region of<br>the microtubular tips, provenincrotubular tip locations.<br>What concents of cell m the microtubular tips, providing a historical record of microtubular tip locations.<br>What concepts of cell morphogenesis have emerged

from this work? One concept to emerge is the potential What concepts of cell morphogenesis have emerged<br>from this work? One concept to emerge is the potential<br>for microtubules to establish long-range spatial order<br>within cells. This provides an alternative to the from this work? One concept to emerge is the potential<br>for microtubules to establish long-range spatial order<br>within cells. This provides an alternative to the<br>mechanism that was found to operate in budding yeast for microtubules to establish long-range spatial order<br>within cells. This provides an alternative to the<br>mechanism that was found to operate in budding yeast,

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where microtubules are not involved in the positioning<br>of the growth zone (Chant 1996). Linear polarized<br>polymers, like microtubules, can extend over long where microtubules are not involved in the positioning<br>of the growth zone (Chant 1996). Linear polarized<br>polymers like microtubules can extend over long<br>distances and can transport molecules in a controlled of the growth zone (Chant 1996). Linear polarized<br>polymers like microtubules can extend over long<br>distances and can transport molecules in a controlled<br>way allowing communication between different regions polymers like microtubules can extend over long distances and can transport molecules in a controlled way allowing communication between different regions distances and can transport molecules in a controlled<br>way allowing communication between different regions<br>of the cell. Their relative straightness is particularly<br>appropriate to define a linear axis a characteristic that way allowing communication between different regions<br>of the cell. Their relative straightness is particularly<br>appropriate to define a linear axis, a characteristic that<br>is obvious in a cylindrical fission yeast cell but wh of the cell. Their relative straightness is particularly<br>appropriate to define a linear axis, a characteristic that<br>is obvious in a cylindrical fission yeast cell but which<br>may be a general characteristic of many polarized appropriate to define a linear axis, a characteristic that<br>is obvious in a cylindrical fission yeast cell but which<br>may be a general characteristic of many polarized cells. The dynamic behaviour of microtubules combined with may be a general characteristic of many polarized cells.<br>The dynamic behaviour of microtubules combined with<br>the transport of a morphogenetic marker like tealp<br>allows an imprecise positioning mechanism to be The dynamic behaviour of microtubules combined with<br>the transport of a morphogenetic marker like tealp<br>allows an imprecise positioning mechanism to be<br>constantly reneated and then averaged resulting in a allows an imprecise positioning mechanism to be constantly repeated and then averaged resulting in a allows an imprecise positioning mechanism to be constantly repeated and then averaged resulting in a more precise process. This may well be an important general concept of spatial organization whereby reiteraconstantly repeated and then averaged resulting in a<br>more precise process. This may well be an important<br>general concept of spatial organization whereby reitera-<br>tion of an inaccurate process generates a much more tion of an inaccurate process generates a much more general concept of spatial organization whereby reiteration of an inaccurate process generates a much more accurate one. If this is combined with a positive feedback loop such as may operate in the case of microtubules tion of an inaccurate process generates a much more<br>accurate one. If this is combined with a positive feedback<br>loop, such as may operate in the case of microtubules<br>and tealn, then this will result in the emergence of a accurate one. If this is combined with a positive feedback<br>loop, such as may operate in the case of microtubules<br>and tealp, then this will result in the emergence of a<br>mechanism of considerable precision. Such a mechanism O loop, such as may operate in the case of microtubules septum is made suggesting that the ability to make a and tealp, then this will result in the emergence of a correctly organized septum is intact in these mutants, mec and tealp, then this will result in the emergence of a<br>mechanism of considerable precision. Such a mechanism<br>could in principle also allow a linear axis to be<br>established de none by a stochastic build up of tealp mechanism of considerable precision. Such a mechanism<br>could in principle also allow a linear axis to be<br>established *de novo*, by a stochastic build up of tealp<br>somewhere on the cell cortex. Such self-organization established  $de novo$ , by a stochastic build up of tealp somewhere on the cell cortex. Such self-organization established *de novo*, by a stochastic build up of tealp<br>somewhere on the cell cortex. Such self-organization<br>may occur in apolar cells like germinating spores or<br>regenerating protoplasts somewhere on the cell of<br>may occur in apolar cel<br>regenerating protoplasts.<br>Another important feat ay occur in apolar cells like germinating spores or<br>generating protoplasts.<br>Another important feature of the microtubule–tealp<br>echanism is the fact that the long-range spatial order of

regenerating protoplasts.<br>Another important feature of the microtubule–tealp<br>mechanism is the fact that the long-range spatial order of Another important feature of the microtubule–tealp<br>mechanism is the fact that the long-range spatial order of<br>a cell is being constantly evaluated. It does not involve<br>the setting up of cellular markers that remain fixed a mechanism is the fact that the long-range spatial order of<br>a cell is being constantly evaluated. It does not involve<br>the setting up of cellular markers that remain fixed, as in<br>the case of growth-site selection in budding a cell is being constantly evaluated. It does not involve<br>the setting up of cellular markers that remain fixed, as in<br>the case of growth-site selection in budding yeast where<br>spatial organization is dependent upon the prev the setting up of cellular markers that remain fixed, as in<br>the case of growth-site selection in budding yeast where<br>spatial organization is dependent upon the previous<br>history of the cell. The microtubule–tealp mechanism the case of growth-site selection in budding yeast where that the medial position of the septum is determined by spatial organization is dependent upon the previous the position of the nucleus. At the onset of mitosis, mid spatial organization is dependent upon the previous<br>history of the cell. The microtubule–tealp mechanism<br>provides more flexibility since the position of the cellular<br>antipodes is under constant surveillance, so should an history of the cell. The microtubule–tealp mechanism<br>provides more flexibility since the position of the cellular<br>antipodes is under constant surveillance, so should an<br>error occur this can be efficiently corrected. This m provides more flexibility since the position of the cellular<br>antipodes is under constant surveillance, so should an<br>error occur this can be efficiently corrected. This may be<br>an important concept in understanding how an ac antipodes is under constant surveillance, so should an<br>error occur this can be efficiently corrected. This may be<br>an important concept in understanding how an accurate<br>cellular shape is specified error occur this can be effic<br>an important concept in ur<br>cellular shape is specified. **2. SPECIFYING POSITION**<br>**3. SPECIFYING POSITION** 

S. SPECIFTING POSITION<br>(GFP)-corset fusion protein has revealed that different<br>regions of the cortical membrane have changed proper-Monitoring the location of a green fluorescent protein<br>(GFP)-corset fusion protein has revealed that different<br>regions of the cortical membrane have changed proper-<br>ties (Sawin et al. 1999). This protein is located in the (GFP)-corset fusion protein has revealed that different<br>regions of the cortical membrane have changed proper-<br>ties (Sawin *et al.* 1999). This protein is located in the<br>central region of the cell closely associated with th regions of the cortical membrane have changed properties (Sawin *et al.* 1999). This protein is located in the central region of the cell closely associated with the cell membrane just under the cell wall. It is excluded f ties (Sawin *et al.* 1999). This protein is located in the not<br>central region of the cell closely associated with the cell<br>membrane just under the cell wall. It is excluded from m<br>the ends of the cell and when a cell divi central region of the cell closely associated with the cell<br>membrane just under the cell wall. It is excluded from<br>the ends of the cell, and when a cell divides there is a<br>clearing of GFP-corset from the new end that is fo membrane just under the cell wall. It is excluded from mechanism in terms of what positions the nucleus in the<br>the ends of the cell, and when a cell divides there is a middle of the cell. The major clue to nuclear position at division. Thus GFP-corset appears to be a marker of clearing of GFP-corset from the new end that is formed<br>at division. Thus GFP-corset appears to be a marker of<br>the cortex in the central region of a cell. There are<br>various mutants that only grow from one end. In most of at division. Thus GFP-corset appears to be a marker of<br>the cortex in the central region of a cell. There are<br>various mutants that only grow from one end. In most of<br>these mutants. GFP-corset is still excluded from both the cortex in the central region of a cell. There are various mutants that only grow from one end. In most of these mutants, GFP-corset is still excluded from both ends of the cell. However mutations in *shkllarh*? a gene various mutants that only grow from one end. In most of<br>these mutants, GFP-corset is still excluded from both<br>ends of the cell. However, mutations in *shk1*/*orb2*, a gene<br>which encodes a p<sup>21</sup>-activated kinase (PAK) kinas these mutants, GFP-corset is still excluded from both<br>ends of the cell. However, mutations in *shkl<sub>l</sub>orb2*, a gene<br>which encodes a p21-activated kinase (PAK) kinase,<br>have a different GFP-corset distribution. In this mutan ends of the cell. However, mutations in  $shkl/orb2$ , a gene<br>which encodes a p2l-activated kinase (PAK) kinase,<br>have a different GFP-corset distribution. In this mutant, which encodes a p21-activated kinase (PAK) kinase,<br>have a different GFP-corset distribution. In this mutant,<br>the fusion protein is now also found at the non-growing<br>end. These observations suggest that there is something have a different GFP-corset distribution. In this mutant,<br>the fusion protein is now also found at the non-growing<br>end. These observations suggest that there is something<br>different about the cortical regions in the middle o the fusion protein is now also found at the non-growing<br>end. These observations suggest that there is something<br>different about the cortical regions in the middle of the<br>cell compared with those at the end which have the end. These observations suggest that there is something different about the cortical regions in the middle of the cell compared with those at the end which have the different about the cortical regions in the middle of the<br>cell compared with those at the end which have the<br>potential to grow. GPF-corset can occupy the middle but<br>not the end cortical regions. The regions are specified cell compared with those at the end which have the<br>potential to grow. GPF-corset can occupy the middle but<br>not the end cortical regions. The regions are specified<br>differently and this specification requires the PAK potential to grow. GPF-corset can occupy the middle but<br>not the end cortical regions. The regions are specified di<br>differently and this specification requires the PAK qu kinase.

The idea of specification of a region is a very familiar concept to developmental biologists. Its application to cells implies that spatially distinct regions within cells concept to developmental biologists. Its application to<br>cells implies that spatially distinct regions within cells<br>have different specifications with significance to under-<br>standing cell morphogenesis cells implies that spatially di<br>have different specifications v<br>standing cell morphogenesis. **4. SEPTUM POSITIONING**

The fission yeast septum is generally placed very close to the middle of the cell. Mutations in two genes, *mid1*/ The fission yeast septum is generally placed very close<br>to the middle of the cell. Mutations in two genes, *midl*<br>*dmf1* and *plo1* result in the septum being misplaced away<br>from the middle (Chang et al. 1996; Sohrmann et from the middle of the cell. Mutations in two genes, *midl| dmfI* and *ploI* result in the septum being misplaced away from the middle (Chang *et al.* 1996; Sohrmann *et al.* 1998). In these mutants the septum can be for from the middle (Chang *et al.* 1996; Sohrmann *et al.* 1996; Bähler *et al.* 1998). In these mutants the septum can be formed at right angles anywhere in the cell, creating 1996; Bähler *et al.* 1998). In these mutants the septum can<br>be formed at right angles anywhere in the cell, creating<br>two unequally sized cells, or in an oblique angle in any<br>position or in a disorganized way throughout t be formed at right angles anywhere in the cell, creating<br>two unequally sized cells, or in an oblique angle in any<br>position, or in a disorganized way throughout the cell. In<br>the former, two situations, a reasonably well-for two unequally sized cells, or in an oblique angle in any<br>position, or in a disorganized way throughout the cell. In<br>the former two situations, a reasonably well-formed<br>sentum is made suggesting that the ability to make a position, or in a disorganized way throughout the cell. In<br>the former two situations, a reasonably well-formed<br>septum is made suggesting that the ability to make a<br>correctly organized septum is intact in these mutants the former two situations, a reasonably well-formed<br>septum is made suggesting that the ability to make a<br>correctly organized septum is intact in these mutants,<br>whilst the global positioning mechanism is defective septum is made suggesting that the ability to make<br>correctly organized septum is intact in these muta<br>whilst the global positioning mechanism is defective.<br>Midln which has a nuclear localization signal an

3. **SPECIFYING POSITION** actin itself might play a role in concentrating midlp into<br>Monitoring the location of a green fluorescent protein midlp, the actin ring and septum can still be formed Mid1p, which has a nuclear localization signal and a pleckstrin homology domain, is found within the nucleus during interphase and in a tight medial ring during pleckstrin homology domain, is found within the nucleus<br>during interphase and in a tight medial ring during<br>mitosis (Sohrmann *et al.* 1996). This ring forms by the<br>coalescence of an initially broad cortical band of midln during interphase and in a tight medial ring during<br>mitosis (Sohrmann *et al.* 1996). This ring forms by the<br>coalescence of an initially broad cortical band of midlp<br>(figure 3) (Bähler *et al.* 1998). Exit of midlp from t mitosis (Sohrmann *et al.* 1996). This ring forms by the coalescence of an initially broad cortical band of midlp (figure 3). (Bähler *et al.* 1998). Exit of midlp from the nucleus requires the plot protein kinase. In a *b* coalescence of an initially broad cortical band of midlp (figure 3). (Bähler *et al.* 1998). Exit of midlp from the nucleus requires the plo1p protein kinase. In a *plo1* mutant, mid1p remains in the nucleus and the septum is nucleus requires the plolp protein kinase. In a *plol* mutant, midlp remains in the nucleus and the septum is misplaced (Bähler *et al.* 1998). These observations suggest that the medial position of the septum is determine mutant, midlp remains in the nucleus and the septum is<br>misplaced (Bähler *et al.* 1998). These observations suggest<br>that the medial position of the septum is determined by<br>the position of the nucleus. At the opset of mito misplaced (Bähler *et al.* 1998). These observations suggest<br>that the medial position of the septum is determined by<br>the position of the nucleus. At the onset of mitosis, midlp<br>is driven out of the nucleus by plot and rel that the medial position of the septum is determined by<br>the position of the nucleus. At the onset of mitosis, midlp<br>is driven out of the nucleus by plolp and relocates into a<br>broad cortical band around the nucleus. Upon nu the position of the nucleus. At the onset of mitosis, midlp<br>is driven out of the nucleus by plolp and relocates into a<br>broad cortical band around the nucleus. Upon nuclear<br>exit midln presumably diffuses out and associates is driven out of the nucleus by plolp and relocates into a broad cortical band around the nucleus. Upon nuclear<br>exit, midlp presumably diffuses out and associates with broad cortical band around the nucleus. Upon nuclear<br>exit, midlp presumably diffuses out and associates with<br>the nearest cortical membrane, which will result in a<br>broad midlp band around the nucleus. The band then exit, midlp presumably diffuses out and associates with<br>the nearest cortical membrane, which will result in a<br>broad midlp band around the nucleus. The band then<br>tightens up into a ring, which co-localizes with the the nearest cortical membrane, which will result in a<br>broad midlp band around the nucleus. The band then<br>tightens up into a ring, which co-localizes with the<br>contractile actin ring in the cell centre (figure 3). The broad midlp band around the nucleus. The band then<br>tightens up into a ring, which co-localizes with the<br>contractile actin ring in the cell centre (figure 3). The<br>actin itself might play a role in concentrating midln into tightens up into a ring, which co-localizes with the contractile actin ring in the cell centre (figure 3). The mid1p, the actin ring and septum can still be formed the ring. It is important to realize that in the absence of midlp, the actin ring and septum can still be formed although they are mislocalized. So, similar to tealp in internhase cells the role of midln is to properly loc midlp, the actin ring and septum can still be formed<br>although they are mislocalized. So, similar to tealp in<br>interphase cells, the role of midlp is to properly locate but<br>not organize the growth machinery during mitosis although they are mislocalized. So, similar to tea<br>interphase cells, the role of midlp is to properly locat<br>not organize the growth machinery during mitosis.<br>This model obviously restates the sentum-positie interphase cells, the role of midlp is to properly locate but<br>not organize the growth machinery during mitosis.<br>This model obviously restates the septum-positioning

not organize the growth machinery during mitosis.<br>This model obviously restates the septum-positioning<br>mechanism in terms of what positions the nucleus in the<br>middle of the cell. The maior clue to nuclear positioning This model obviously restates the septum-positioning<br>mechanism in terms of what positions the nucleus in the<br>middle of the cell. The major clue to nuclear positioning<br>is that again microtubules appear to have a role. In th mechanism in terms of what positions the nucleus in the<br>middle of the cell. The major clue to nuclear positioning<br>is that again microtubules appear to have a role. In the<br>absence of a normal cytoplasmic microtubular cytomiddle of the cell. The major clue to nuclear positioning<br>is that again microtubules appear to have a role. In the<br>absence of a normal cytoplasmic microtubular cyto-<br>skeleton the nucleus is no longer centrally located in t is that again microtubules appear to have a role. In the absence of a normal cytoplasmic microtubular cyto-<br>skeleton the nucleus is no longer centrally located in the<br>cell (Umesono *et al.* 1983) Various models have been absence of a normal cytoplasmic microtubular cyto-<br>skeleton the nucleus is no longer centrally located in the<br>cell (Umesono *et al.* 1983). Various models have been<br>proposed by which microtubules lead to the nucleus being skeleton the nucleus is no longer centrally located in the cell (Umesono *et al.* 1983). Various models have been<br>proposed by which microtubules lead to the nucleus being<br>placed centrally in the cell (Reinsch & Gonczy 199 cell (Umesono *et al.* 1983). Various models have been<br>proposed by which microtubules lead to the nucleus being<br>placed centrally in the cell (Reinsch & Gonczy 1998).<br>One of them is that the nucleus is attached to microproposed by which microtubules lead to the nucleus being<br>placed centrally in the cell (Reinsch & Gonczy 1998).<br>One of them is that the nucleus is attached to micro-<br>tubules, which extend into the cell and where they are placed centrally in the cell (Reinsch & Gonczy 1998).<br>One of them is that the nucleus is attached to micro-<br>tubules, which extend into the cell and where they are One of them is that the nucleus is attached to micro-<br>tubules, which extend into the cell and where they are<br>themselves attached to fixed structures within the cyto-<br>plasm by microtubule motor proteins. The position of the tubules, which extend into the cell and where they are themselves attached to fixed structures within the cyto-<br>plasm by microtubule motor proteins. The position of the<br>nucleus is then determined by the opposing forces gen themselves attached to fixed structures within the cyto-<br>plasm by microtubule motor proteins. The position of the<br>nucleus is then determined by the opposing forces gener-<br>ated by the microtubular motors attached to the fix plasm by microtubule motor proteins. The position of the nucleus is then determined by the opposing forces generated by the microtubular motors attached to the fixed nucleus is then determined by the opposing forces generated by the microtubular motors attached to the fixed sites are sites in the cytoplasm. Assuming that the fixed sites are distributed homogeneously throughout the cell ated by the microtubular motors attached to the fixed<br>sites in the cytoplasm. Assuming that the fixed sites are<br>distributed homogeneously throughout the cell a conse-<br>quence of this mechanism is that a nucleus will become sites in the cytoplasm. Assuming that the fixed sites are<br>distributed homogeneously throughout the cell a conse-<br>quence of this mechanism is that a nucleus will become<br>centrally located within the cytoplasmic volume of the distributed homogeneously throughout the cell a consequence of this mechanism is that a nucleus will become<br>centrally located within the cytoplasmic volume of the

cell. So if a cell is asymmetrically shaped, like a pear for cell. So if a cell is asymmetrically shaped, like a pear for<br>example, then the nucleus will be placed midway<br>between equivalent cytoplasmic volumes rather than example, then the nucleus will be placed midway growing cell tips or the septum. It has become apparent<br>between equivalent cytoplasmic volumes rather than that both of these structures can form perfectly, regardless<br>midway example, then the nucleus will be placed midway<br>between equivalent cytoplasmic volumes rather than<br>midway between the cell ends. Fission yeast morpho-<br>logical mutants with asymmetrical shapes tend to behave between equivalent cytoplasmic volumes rather than<br>midway between the cell ends. Fission yeast morpho-<br>logical mutants with asymmetrical shapes tend to behave<br>like this and the cytoplasmic microtubules are closely midway between the cell ends. Fission yeast morphological mutants with asymmetrical shapes tend to behave like this, and the cytoplasmic microtubules are closely associated with the nucleus making this model and logical mutants with asymmetrical shapes tend to behave<br>like this, and the cytoplasmic microtubules are closely<br>associated with the nucleus, making this model an<br>attractive one to test like this, and the cyt<br>associated with the<br>attractive one to test.<br>Defining the nosition associated with the nucleus, making this model an attractive one to test.<br>Defining the position of septation by the position of the

early mitotic nucleus clearly makes sense as it means that Defining the position of septation by the position of the early mitotic nucleus clearly makes sense as it means that cytokinesis will be initiated in the region of the dividing nucleus maximizing the chance that the two ne early mitotic nucleus clearly makes sense as it means that<br>cytokinesis will be initiated in the region of the dividing<br>nucleus, maximizing the chance that the two newly<br>formed nuclei will be senarated into the two new cell cytokinesis will be initiated in the region of the dividing<br>nucleus, maximizing the chance that the two newly<br>formed nuclei will be separated into the two new cells. It<br>also makes sense to position the nucleus and therefor nucleus, maximizing the chance that the two newly<br>formed nuclei will be separated into the two new cells. It<br>also makes sense to position the nucleus and therefore the formed nuclei will be separated into the two new cells. It<br>also makes sense to position the nucleus and therefore the<br>division site, such that both daughter cells obtain an equal<br>cell volume independently of the overall ce also makes sense to position the nucleus and therefore the<br>division site, such that both daughter cells obtain an equal<br>cell volume independently of the overall cell shape of the<br>mother cell. Again cytoplasmic microtubules division site, such that both daughter cells obtain an equal<br>cell volume independently of the overall cell shape of the<br>mother cell. Again cytoplasmic microtubules may have a<br>central role also in performing the task of spl cell volume independently of the overall cell shape of the<br>mother cell. Again cytoplasmic microtubules may have a<br>central role also in performing the task of splitting the<br>fission yeast cell and its contents into two halve mother cell. Again cytoplasmic microtubules may have a<br>central role also in performing the task of splitting the<br>fission yeast cell and its contents into two halves during<br>mitosis. A combination of extended microtubular po central role also in performing the task of splitting the fission yeast cell and its contents into two halves during mitosis. A combination of extended microtubular poly-<br>mers anchored within the cytoplasm by polarized mot Solution Section yearst cell and its contents into two halves during<br>mitosis. A combination of extended microtubular poly-<br>mers anchored within the cytoplasm by polarized motors<br>provides an elegant mechanism to position or mitosis. A combination of extended microtubular poly-

such as the nucleus. These possibilities have already been provides an elegant mechanism to position organelles<br>such as the nucleus. These possibilities have already been<br>recognized by those studying the mitotic spindle (Hyman<br>& Karsenti, 1996), but have not vet been generally such as the nucleus. These possibilities have already been<br>recognized by those studying the mitotic spindle (Hyman<br>& Karsenti 1996), but have not yet been generally<br>applied to problems of cell morphogenesis recognized by those studying the mitotic spi<br>& Karsenti 1996), but have not yet be<br>applied to problems of cell morphogenesis.<br>A second general concent illustrated by the Karsenti 1996), but have not yet been generally<br>plied to problems of cell morphogenesis.<br>A second general concept illustrated by this work is the<br>rea of approximation as an intermediate step in a posi-

applied to problems of cell morphogenesis.<br>A second general concept illustrated by this work is the<br>idea of approximation as an intermediate step in a positioning mechanism. Formation of a septum requires a idea of approximation as an intermediate step in a posi-<br>tioning mechanism. Formation of a septum requires a<br>number of components including actin to form a very<br>precise thin ring (Gould & Simanis 1997) Generating a tioning mechanism. Formation of a septum requires a<br>number of components including actin to form a very<br>precise, thin ring (Gould & Simanis 1997). Generating a<br>ring from a single point that can extend around the cell number of components including actin to form a very<br>precise, thin ring (Gould & Simanis 1997). Generating a<br>ring from a single point that can extend around the cell<br>and then precisely meet the other end to close the circle precise, thin ring (Gould & Simanis 1997). Generating a<br>ring from a single point that can extend around the cell<br>and then precisely meet the other end to close the circle is<br>a difficult task to perform. In contrast, establ ring from a single point that can extend around the cell<br>and then precisely meet the other end to close the circle is<br>a difficult task to perform. In contrast, establishing a and then precisely meet the other end to close the circle is<br>a difficult task to perform. In contrast, establishing a<br>broad cortical band by exporting midlp from the nucleus<br>is straightforward. This broad band then needs t a difficult task to perform. In contrast, establishing a broad cortical band by exporting midlp from the nucleus<br>is straightforward. This broad band then needs to tighten<br>un to produce the thin ring. How such a tightening is straightforward. This broad band then needs to tighten<br>up to produce the thin ring. How such a tightening up is straightforward. This broad band then needs to tighten<br>up to produce the thin ring. How such a tightening up<br>may occur is not understood, but it could involve yet<br>again some form of positive feedback whereby an increase up to produce the thin ring. How such a tightening up<br>may occur is not understood, but it could involve yet<br>again some form of positive feedback whereby an increase<br>in concentration of a component in the central region of may occur is not understood, but it could involve yet<br>again some form of positive feedback whereby an increase<br>in concentration of a component in the central region of a<br>broad band leads to a further increase by drawing in again some form of positive feedback whereby an increase<br>in concentration of a component in the central region of a<br>broad band leads to a further increase by drawing in components from the lower concentration found in the broad band leads to a further increase by drawing in<br>components from the lower concentration found in the<br>peripheral regions of the broad band. An alternative<br>possibility is a role for actin–myosin in transporting components from the lower concentration found in the<br>peripheral regions of the broad band. An alternative<br>possibility is a role for actin–myosin in transporting<br>components locally within the broad band. Such transperipheral regions of the broad band. An alternative<br>possibility is a role for actin–myosin in transporting<br>components locally within the broad band. Such trans-<br>port could properly concentrate components if the actin possibility is a role for actin–myosin in transporting<br>components locally within the broad band. Such trans-<br>port could properly concentrate components if the actin<br>was polarized towards the central region of the broad components locally within the broad band. Such trans-<br>port could properly concentrate components if the actin<br>was polarized towards the central region of the broad<br>band. A further concent to emerge from these results is port could properly concentrate components if the actin<br>was polarized towards the central region of the broad<br>band. A further concept to emerge from these results is was polarized towards the central region of the broad<br>band. A further concept to emerge from these results is<br>that temporal controls can contribute to spatial order.<br>Triggering the export of midlp from the nucleus at a band. A further concept to emerge from these results is<br>that temporal controls can contribute to spatial order.<br>Triggering the export of midlp from the nucleus at a<br>particular time of the cell cycle, that is the opset of that temporal controls can contribute to spatial order.<br>Triggering the export of midlp from the nucleus at a<br>particular time of the cell cycle, that is the onset of<br>mitosis, has spatial implications for defining the correc Triggering the export of midlp from the nucleus at a particular time of the cell cycle, that is the onset of mitosis, has spatial implications for defining the correct positioning of the septum. particular time of the cell cycle, that is the onset of

A more general point can be made about the roles of the actin and microtubule cytoskeletons in cell morphogenesis. Actin has a very specific distribution within

Fission yeast morphogenesis D. Brunner and P. Nurse 877<br>fission yeast cells, where it is predominantly found at the growing cell tips or the septum. It has become apparent fission yeast cells, where it is predominantly found at the<br>growing cell tips or the septum. It has become apparent<br>that both of these structures can form perfectly, regardless<br>of where they are placed within the cell. Thi growing cell tips or the septum. It has become apparent<br>that both of these structures can form perfectly, regardless<br>of where they are placed within the cell. This raises the<br>general concent that microtubules may play a ro that both of these structures can form perfectly, regardless<br>of where they are placed within the cell. This raises the<br>general concept that microtubules may play a role in<br>more global cellular positioning mechanisms whilst of where they are placed within the cell. This raises the<br>general concept that microtubules may play a role in<br>more global cellular positioning mechanisms whilst actin<br>is used in more local organization. Reverting to the general concept that microtubules may play a role in<br>more global cellular positioning mechanisms whilst actin<br>is used in more local organization. Reverting to the<br>language of developmental biologists: actin-based 'submore global cellular positioning mechanisms whilst actin<br>is used in more local organization. Reverting to the<br>language of developmental biologists: actin-based 'sub-<br>morphogenetic fields' are organized with respect to each is used in more local organization. Reverting to the language of developmental biologists: actin-based 'sub-<br>morphogenetic fields' are organized with respect to each language of developmental biologists: actin-based 'sub-<br>morphogenetic fields' are organized with respect to each<br>other by a microtubular-based global cellular 'morpho-<br>genetic field' morphogenetic<br>other by a mi<br>genetic field'.

## **REFERENCES**

- **REFERENCES**<br>Bähler, J., Steever, A. B., Wheatley, S., Wang, Y.-l., Pringle,<br>I.R. Gould, K. L. & McCollum, D. 1998 Role of Polo ILLET ENERVOLS<br>
J. R., Gould, K. L. & McCollum, D. 1998 Role of Polo<br>
kinase and Midln in determining the site of cell division in ihler, J., Steever, A. B., Wheatley, S., Wang, Y.-l., Pringle, J. R., Gould, K. L. & McCollum, D. 1998 Role of Polo kinase and Midlp in determining the site of cell division in fission veast  $\frac{7}{2}$  Cell Riol 143, 1603– **J. R., Gould, K. L. & McCollum, D. 1998 Role of Polo kinase and Midlp in determining the site of cell division in fission yeast.** *J. Cell Biol.* **<b>143**, 1603–1616. kinaseand Midlp in determining the site of cell division in<br>fission yeast.  $\tilde{J}$ . Cell Biol. **143**, 1603–1616.<br>Chang, F., Woollard, A. & Nurse, P. 1996 Isolation and charac-<br>terization of fission yeast mutants defecti
- fission yeast. *J. Cell Biol*. **143**, 1603–1616.<br>nang, F., Woollard, A. & Nurse, P. 1996 Isolation and charac-<br>terization of fission yeast mutants defective [in the assembly](http://gessler.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0021-9533^28^29109L.131[aid=535154,nlm=8834798])<br>and placement of the contractile actin ring. *T.* and placement of the contractile actin ring. *J. Cell Sci.* **109**, 131–142. andplacement of the contractile actin ring. *J. Cell Sci.* **109**, 131-142.<br>Chant, J. 1996 Generation of cell polarity in yeast. *[Curr. Opin.](http://gessler.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0955-0674^28^298L.557[aid=535155,csa=0955-0674^26vol=8^26iss=4^26firstpage=557,nlm=8791457])*<br>*Cell Biol* **8** 557-565
- 131-142.<br>**Chant, J. 1996 Generation of cell polarity in yeast.** Curr. Opin.<br>*Cell Biol.* **8**, 557-565. Chant,J. 1996 Generation of cell polarity in yeast. Curr. Opin.<br>Cell Biol. 8, 557–565.<br>Gould, K. L. & Simanis, V. 1997 The control of septum forma-<br>tion in fission yeast. Genes Den 11, 2939–2951.
- Gell Biol. **8**, 557–565.<br>
puld, K. L. & Simanis, V. 1997 The control of<br>
tion in fission yeast. *Genes Dev.* **11**, 2939–2951.<br> **Allaman J. M. 1998** The fission yeast microtubule. Gould,K. L. & Simanis, V. 1997 The control of septum formation in fission yeast. *Genes Dev.* **11**, 2939–2951.<br>Hagan, I. M. 1998 The fission yeast microtubule cytoskeleton. *J.*<br>Cell Sci 111 1603–1619
- **CELA SCILL SCILL SCILL SCILL SCILL SCI. 111**, 1603–1612.<br> **111**, 1603–1612.<br> **121 CELA SCI. 111**, 1603–1612. Hagan,I. M. 1998 The fission yeast microtubule cytoskeleton. *J. Cell Sci*. **111**, 1603–1612.<br>Hyman, A. & Karsenti, E. 1996 Morphogenetic properties of microtubules and mitotic spindle assembly *Cell* 84, 401–410.
- Eell Sci. 111, 1603–1612.<br>Hyman, A. & Karsenti, E. 1996 Morphogenetic properties of microtubules and mitotic spindle assembly. *Cell* **84**, 401–410. Hyman,A. & Karsenti, E. 1996 Morphogenetic properties of<br>microtubules and mitotic spindle assembly. *Cell* **84**, 401-410.<br>Marks, J. & Hyams, J. S. 1985 Localization of F-actin<br>through the cell division cycle of *S. bombe*
- microtubules and mitotic spindle assembly. *Cell* **84**, 401–410.<br>
arks, J. & Hyams, J. S. 1985 Localization of F-actin<br>
through the cell division cycle of *S. pombe. Eur. J. Cell Biol.*<br> **39**, 27–32.<br>
ata J. & Nurse, P. 19 through the cell division cycle of *S. pombe. Eur. J. Cell Biol.*<br>**39**, 27–32.<br>Mata, J. & Nurse, P. 1997 teal and the microtubular cyto-<br>skeleton are important for generating global spatial order
- **39**, 27–32.<br>ata, J. & Nurse, P. 1997 teal and the microtubular cyto-<br>skeleton are important for generating global spatial order<br>within the fission yeast cell *Cell* **89**, 939–949 skeleton are important for generating global spatial order<br>within the fission yeast cell. *Cell* **89**, 939–949.
- Mata, J. & Nurse, P. 1998 Discoveringthepoles in yeast.*Trends Cell Biol*. **<sup>8</sup>**, 163^167. Mata,J. & Nurse, P. 1998 Discovering the poles in yeast. Trends<br>Cell Biol. 8, 163–167.<br>Reinsch, S. & Gonczy, P. 1998 Mechanisms of nuclear posi-<br>tioning  $\frac{7}{2}$ Cell Sci 111 2283–2295.
- Cell Biol. **8**, 163–167.<br>
einsch, **S. & Gonczy, P. 1998 Mecl<br>
tioning.** *J. Cell Sci.* **111, 2283–2295.<br>
win K. E. & Nurse, P. 1998 Regu** Reinsch,S. & Gonczy, P. 1998 Mechanisms of nuclear positioning.  $\tilde{j}$ . Cell Sci. 111, 2283–2295.<br>Sawin, K. E. & Nurse, P. 1998 Regulation of cell polarity by microtubules in fission years  $\tilde{\tau}$  Cell Right 142, 457–4
- tioning. *J. Cell Sci.* **111**, 2283–2295.<br>win, K. E. & Nurse, P. 1998 Regulation of cell polar<br>microtubules in fission yeast. *J. Cell Biol*. **142**, 457–471.<br>win, K. E. Nasser Haiibagheri, M. A. & Nurse, P. 1999 Sawin,K. E. & Nurse, P. 1998 Regulation of cell polarity by<br>microtubules in fission yeast. J. Cell Biol. 142, 457–471.<br>Sawin, K. E., Nasser Hajibagheri, M. A. & Nurse, P. 1999 Mis-<br>specification of cortical identity in a
- microtubules in fission yeast. *J. Cell Biol*. **142**, 457–471.<br>win, K. E., Nasser Hajibagheri, M. A. & Nurse, P. 1999 Misspecification of cortical identity in a fission yeast PAK<br>mutant. *Curr. Biol.* **9**, 1335–1338. win, K. E., Nasser Hajibagheri, N<br>specification of cortical identity<br>mutant. *Curr. Biol.* 9, 1335–1338.<br>hrmann M. Eankhauser C. B specificationof cortical identity in a fission yeast PAK<br>mutant. *Curr. Biol.* 9, 1335–1338.<br>Sohrmann, M., Fankhauser, C., Brodbeck, C. & Simanis, V.<br>1996 The *dmfl/midl* gene is essential for correct positioning of
- mutant. *Curr. Biol.* 9, 1335–1338.<br>hrmann, M., Fankhauser, C., Brodbeck, C. & Simanis, V.<br>1996 The *dmf1*/*mid1* gene is essential for correct positioning of<br>the division sentum in fission yeast. *Genes Der*, 10, 2707–271 hrmann, M., Fankhauser, C., Brodbeck, C. & Simanis, V.<br>1996 The *dmfl*/*midl* gene is essential for correct positioning of<br>the division septum in fission yeast. *Genes Dev.* **10**, 2707–2719.<br>Idea T. Umesono, K. Hirata, A. 1996The *dmfl*/midl gene is essential for correct positioning of<br>the division septum in fission yeast. *Genes Dev.* **10**, 2707–2719.<br>Toda, T., Umesono, K., Hirata, A. & Yanagida, M. 1983 Cold-<br>sensitive nuclear division
- the division septum in fission yeast. *Genes Dev.* **10**, 2707–2719.<br>da, T., Umesono, K., Hirata, A. & Yanagida, M. 1983 Cold-<br>sensitive nuclear division arrest mutants of the fission yeast<br>Schizosaccharamyces hambe  $\frac{1}{$ da, T., Umesono, K., Hirata, A. & Yanagida, M. 19<br>sensitive nuclear division arrest mutants of the fiss<br>*Schizosaccharomyces pombe. J. Mol. Biol.* **168**, 251–270.<br>mesono, K. Toda, T. Hayashi, S. & Yanagida, M. sensitivenuclear division arrest mutants of the fission yeast<br> *Schizosaccharomyces pombe.* J. *Mol. Biol.* **168**, 251–270.<br>
Umesono, K., Toda, T., Hayashi, S. & Yanagida, M. 1983 Two
- Schizosaccharomyces pombe. J. Mol. Biol. **168**, 251–270.<br>mesono, K., Toda, T., Hayashi, S. & Yanagida, M. 1983 Two<br>cell division cycle genes *nda2* and *nda3* of the fission yeast<br>Schizosaccharamyces hambe, control, microt mesono, K., Toda, T., Hayashi, S. & Yanagida, M. 1983 Two<br>cell divis[ion](http://gessler.ingentaselect.com/nw=1/rpsv/cgi-bin/linker?ext=a&reqidx=/0022-2836^28^29168L.271[aid=535166,csa=0022-2836^26vol=168^26iss=2^26firstpage=271,nlm=6887245]) cycle genes *nda*2 and *nda3* of the fission yeast<br>*Schizosaccharomyces pombe* control microtubular organization<br>and sensitivity to anti-mitotic benzi cell division cycle genes *nda2* and *nda3* of the fission yeast<br>*Schizosaccharomyces pombe* control microtubular organization<br>and sensitivity to anti-mitotic benzimidazole compounds. *J.*<br>*Mol. Biol* **168** 271–284 *Schizosaccharomyces pombe* control microtubular organization and sensitivity to anti-mitotic benzimidazole compounds. *J. Mol. Biol.* **168**, 271–284.
- Walker,G. M. 1982 Cell cycle specificity of certain antimicrotubular drugs in *Schizosaccharomyces pombe*. *J. Gen. Microbiol*. **<sup>128</sup>**, 61^71.

**BIOLOGICAL**<br>SCIENCES