sumoto *et al.*[3] resolves the conflict generated by the proxy evidence for the nutrient status of the Southern Ocean at various times. But assessing the effects of their proposed mechanism on atmospheric levels of CO_2 during glacials, as well as the effects of other ideas that have been put forward[9,10], will require more evidence. We need a more synoptic view of past shifts in nutrient ratios, and a better understanding of the ecological response to such changes. Progress is being made, but the story isn't over yet. ■

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Optics

The light fantastic

Martin Hegner

Optical tweezers use light to manipulate tiny particles — but only one at a time. If the light in the tweezers is a 'Bessel beam', this problem can be overcome, creating some interesting experimental possibilities.

Optical tweezers have become a standard tool in many areas of science, such as colloid research and biological studies. On page 145 of this issue, Garcés-Chávez *et al.*[1] report an extension of this technique that makes it possible to manipulate ensembles of particles simultaneously.

Laser light can exert force on dielectric (polarizable) particles through radiation pressure and refraction[2]: light has momentum, and so light and matter can interact by exchanging momentum. Although these forces are small (of the order of 10^{-12} newtons), they are sufficient to trap and manipulate micrometre-sized particles in a liquid environment[3]. So far, optical manipulation of particles in different places at the same time has been possible only if the particles are in the same optical plane of view[4]. Otherwise, the problem is that the manipulating light beam will diverge around the first trapped particles, and then cannot be brought back to a focus within the short distance to the next set of particles. So experiments must be done in series, and this is very time-consuming. To speed things up, it would be better to work in parallel, manipulating particles held in multiple back-to-back compartments (such as a collection of biological-cell samples) at the same time with a single light beam.

Using a special kind of optical focusing to create a 'Bessel beam' of light, Garcés-Chávez *et al.*[1] now provide the first demonstration of the manipulation of micrometre-sized particles in multiple planes. A Bessel beam (Fig. 1) is so called because the variation of its intensity follows the mathematical pattern known as a zero-order Bessel function. Thanks to its special optical properties, the bright central spot of the beam can re-form after passing an obstruction; the beam does not interfere with the obstruction and re-forms fully only a few micrometres further on. Garcés-Chávez *et al.* show that even when a Bessel beam of light is partially obstructed by an object in the first fluid-filled compartment, particles in a second, spatially separated, fluid compartment can be manipulated using the same light beam and with the same precision. This has been impossible with the conventional optical manipulation techniques used so far.

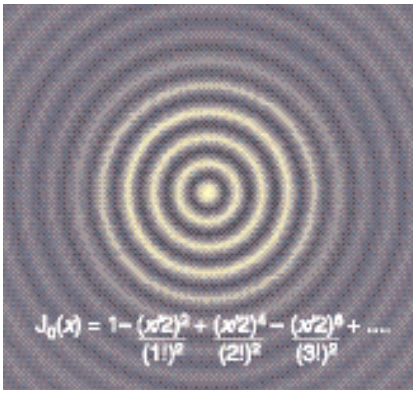

Figure 1 **A Bessel beam. Light passing through a particular scheme of lenses can form a beam of light with a bright central spot and concentric rings of decreasing intensity — known as a Bessel beam, as its varying intensity is described by the zero-order Bessel function shown here. Garcés-Chávez *et al.*[1] have used a Bessel beam to create optical tweezers capable of manipulating many samples at once.**

The authors created a diffraction-free Bessel beam[5] using simple lenses and a special conical lens called an axicon. The bright spot at the beam's centre is a 'non-diffracting' focal line of light and is distinctly different from 'normal' optical trapping beams. The narrow beam has a propagation distance of a few millimetres, which is about 40 times the Rayleigh range (that is, the distance along which particles can be guided) of a normal, or 'gaussian', beam, and this means that optical manipulation can be done in multiple back-to-back compartments at the same time.

The Bessel beam can be imagined as a single rod of light, pushing the trapped particles along its axis. The trapping can extend over a few millimetres, and particles can be held firmly in two dimensions. In contrast, a gaussian beam can hold particles in a stable, three-dimensional configuration[6,7], but the beam diverges quickly, so particles can only be guided for a few micrometres along the axis of such a beam.

Certainly, one of the most impressive applications of (gaussian) optical tweezers is in the study of molecular motors[8,9] and polymer mechanics[10]. These experiments have provided fresh insight into biochemical processes at the single-molecule level and are of great relevance in biology. The key to such experiments is in immobilizing the biological molecule of interest on the surface of a bead and attaching its interacting partner molecule to a second bead, which can then be trapped in three dimensions using infrared laser light[6]. But particles or beads caught in a Bessel beam are constantly pushed along the beam axis, and so comparable studies using Bessel-beam tweezers are not yet possible.

It is foreseeable, however, that if a counter-propagating Bessel beam were applied, the particles' forward motion could be stopped[6]. Like balancing a rod on the tip of another rod, a stable three-dimensional trap between the beams could be established if the power of the beams were adjusted properly. Extending this idea to exploit the Bessel-beam tweezers' ability to work on many particles simultaneously over considerable distance, patterns could be created from interfering Bessel beams, forming arrays of light spots that could be used, for example, to rotate microsystems, or to control lab-on-a-chip microstructures.

In biology, Bessel-beam tweezers could be used to sort the oval-shaped particles produced in the micro-dissection of chromatin (made up of DNA and proteins) through tiny openings or pores. For cell sorting, these tweezers are capable of more accurate guiding than systems used so far[11]. The Bessel-beam technique will no doubt find application across a broad range of science. ■

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Cancer

Stuck at first base

Louise van der Weyden, Jos Jonkers and Allan Bradley

People with the genetic disease Peutz–Jeghers syndrome have many intestinal polyps — benign tissue outgrowths. These seldom become malignant, and the reason may lie in the properties of the affected gene.

Several inherited human diseases are characterized by the formation of polyps in the gut. Polyps are benign outgrowths of tissue with a disordered structure. In some of these diseases, the polyps undergo transformation into malignant gastrointestinal tumours — but this occurs relatively rarely in Peutz–Jeghers syndrome. In an effort to understand why, Bardeesy and colleagues[1] (page 162 of this issue) have produced mice carrying mutations in the mouse counterpart of the *LKB1* gene, which is affected in the human syndrome. The authors' studies of these animals have thrown up some unexpected findings.

Cancer, a disease characterized by unregulated cell proliferation, is caused by the stepwise accumulation of mutations in certain key genes. Every cancer is different, displaying a unique constellation of genetic changes. Yet one can identify some common mutational targets and molecular themes that lie at the heart of the transformation of a normal cell into a potentially deadly cancer cell. Thus, certain genes such as *RAS* and *p53* are often mutated in different cancers, suggesting that some deregulated cellular processes are common to many, if not all, tumours.

On the other hand, as our understanding of the molecular basis of tumour development increases, the richness of the mechanisms that have evolved to control cell growth is becoming more apparent. For example, studies of inherited mutations in tumour-suppressor genes (which usually keep the brakes on cell growth) show that some cell types are highly susceptible to malignant transformation, whereas others with the same mutations seem to be resistant. In addition, different cancer-predisposing mutations in the same cell type can have very different effects on malignancy.

Hereditary polyposis syndromes illustrate these phenomena[2] (Fig. 1). Intestinal polyps are generally composed of two cell types, epithelial and stromal cells; malignant tumours derived from such polyps consist mainly of transformed epithelial cells. Patients with inherited mutations in the *APC* gene develop familial adenomatous polyposis, which is characterized by numerous epithelial-rich polyps that have a propensity to progress to malignant cancer. By contrast, patients with inherited inactivating mutations in *SMAD4* or *BMPR1A* develop juvenile polyposis, and people with *LKB1* mutations develop Peutz–Jeghers syndrome (PJS). Both syndromes are characterized by relatively benign, stromal-rich polyps called hamartomas. In juvenile polyposis, the inactivation of *SMAD4* is limited to the stromal cells, so the epithelial cells are influenced only indirectly[3] (Fig. 1). But the limited malignant potential of polyps in PJS patients must have a different cause, because *LKB1* inactivation occurs in the epithelial, not the stromal, component[4]. Bardeesy *et al.*[1] now provide the first clues to why *LKB1* mutations in the intestinal epithelium produce polyps that rarely become malignant.

To investigate the role of *LKB1* in human PJS, several groups[5–7] have generated mice that lack the relevant mouse gene, *Lkb1*. In all cases, mice lacking both copies of the gene (homozygous animals) die as embryos. Heterozygous mice (with one deleted and one normal copy of the gene) survive, but develop gastrointestinal hamartomas with features akin to those in patients with PJS or juvenile polyposis. These animals are valuable mouse models of PJS. But the molecular basis for the limited malignant potential of PJS polyps has remained a conundrum, as the early death of the homozygous embryos prevents cell lines from being isolated and studied.

To tackle this issue, Bardeesy *et al.* generated mice that lacked one copy of *Lkb1* entirely and also carried a 'conditional' copy of the gene, which is inactivated only under specific experimental conditions (so the animals could develop normally). The authors isolated mouse embryonic fibroblast cells (MEFs) from these animals, and then switched off the conditional *Lkb1* gene in these cells, generating homozygous MEFs in culture.

MEFs are widely used for measuring two hallmarks of cancer: cell immortalization (the ability to multiply indefinitely in culture) and malignant transformation. The propensity of cultured normal MEFs to become immortal is limited by senescence — a programme of cellular 'ageing'. This crucial fail-safe mechanism helps to prevent transformation and is triggered by various

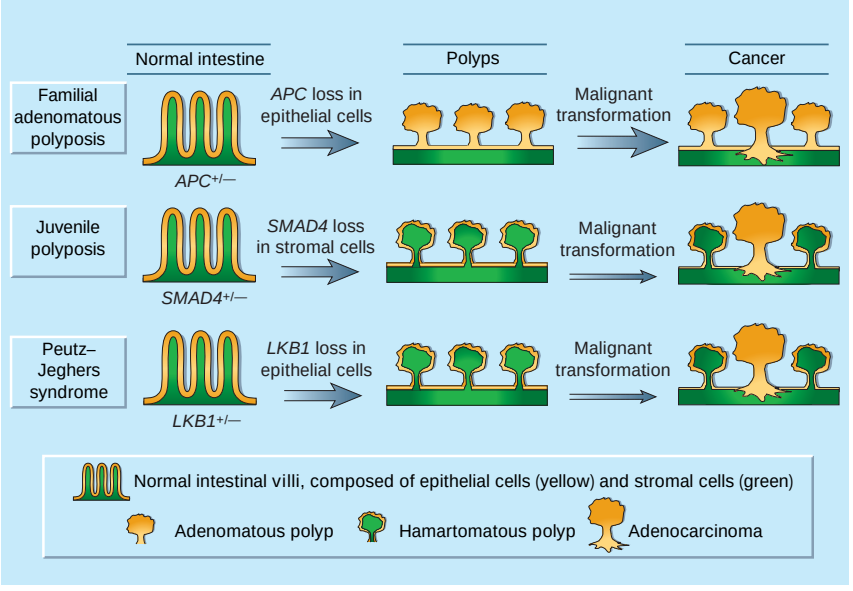

Figure 1 **Development of intestinal cancer from intestinal polyps. Patients with the three diseases indicated on the left carry one normal and one mutant copy of the *APC*, *SMAD4* or *LKB1* tumour-suppressor genes (hence *APC* $^{+/-}$, and so on). Loss of the normal copy of the gene leads to the formation of polyps. Transformation of the epithelial cells in a polyp leads to development of adenocarcinomas, the relative frequency of which is indicated by the thickness of the arrow.**