CARCINOGENESIS

The risk of hanging on

Long-term colonization of the stomach by *Helicobacter pylori* represents the highest known risk for the development of gastric adenocarcinoma, yet only a fraction of the many colonized individuals go on to develop cancer. Richard Peek and colleagues used a rodent model to show that bacterial adhesion to the host cells might be responsible for the increased risk.

The authors infected a gerbil with a human clinical isolate of *H. pylori* and allowed the bacteria to adapt to the host environment for 3 weeks. This produced a highly oncogenic strain, ideal for further study of the carcinogenic process. When a cohort of gerbils was infected with this strain, 75% developed gastric adenocarcinoma after 8 weeks, whereas no carcinoma developed following infection with the parental human isolate.

Using gastric epithelial cells *in vitro*, the authors found that their oncogenic strain increased the amount of β-catenin in the nucleus. In addition, a luciferase assay showed an induction of β-catenin-dependent transcriptional activation. These are key phenomena in the progression of many tumours, and can be caused by other carcinogenic agents. However, the authors were surprised to find that the mechanism by which *H. pylori* induces these changes is not the usual one of blocking the phosphorylation and ubiquitylation of β-catenin. Instead, they found that the *cag* set of pathogenicity genes from *H. pylori* was involved. These genes encode the molecular apparatus for transferring the CagA protein into the host cell, where CagA activates the host phosphatase SHP-2 to cause morphological changes. A series of genetic knockout experiments confirmed that CagA was indeed responsible for the oncogenic strain's pathological properties.

So, how does the oncogenic strain differ from its parent, given that both possess the *cag* genes and no other significant genetic gains or deletions were seen in a microarray comparison? Whereas both strains expressed CagA at similar levels, the oncogenic strain transferred it into the host more efficiently. This was

DRUG DELIVERY

A tiny timely vehicle

The administration of chemotherapy together with anti-angiogenic drugs seems to be a particularly effective way of slowing tumour growth. However, this combination also poses some practical problems — cutting off the tumour blood supply makes it difficult to achieve a high drug concentration, and hypoxia can trigger the expression of chemotherapy-resistance genes. Now, a group led by Ram Sasisekharan has designed a sophisticated delivery system that gets around these complications — a 'nanocell' that localizes to tumours and then shuts down the tumour vasculature before delivering a cytotoxic agent to tumour cells.

Their nanocell consists of a phosopholipid envelope and, inside it, a nanoparticle made of a biodegradable polymer. The researchers incorporated an anti-angiogenic agent — in this case combretastatin — into the liposome, and attached the chemotherapeutic agent doxorubicin to the nanoparticle.

They found that combretastatin escapes rapidly from the lipid envelope, while the conjugated doxorubicin is freed more slowly, degrading into smaller, inactive fragments before breaking down further into free, active doxorubicin. These release kinetics correlate well with the effect of the nanocell combination on the tumour endothelium *in vitro* — the system caused the vasculature to collapse as early as 12 hours post-administration, and tumours to be completely ablated by 30 hours.

The authors tested the therapeutic efficacy of this system *in vivo* using mice with B16:F10 melanomas and mice with Lewis lung carcinoma. They compared the effects of sequential drug delivery using nanocells with several other treatments — one or both drugs delivered simultaneously in simple liposomes, nanocells containing doxorubicin alone or co-administration of doxorubicin-containing nanocells and combrestatin-containing liposomes. Animals treated with nanocells containing both drugs had a better tumour response than any of the other treatment groups. In fact, the increase in survival of mice given the drugs sequentially was about twice that of those given the drugs simultaneously.

Furthermore, the nanocells containing both drugs resulted in the lowest systemic toxicity of all of the treatments. This is probably because the cytotoxic agent is localized to the tumour so effectively — the researchers confirmed this by attaching the dye fluorescein to the nanocell and