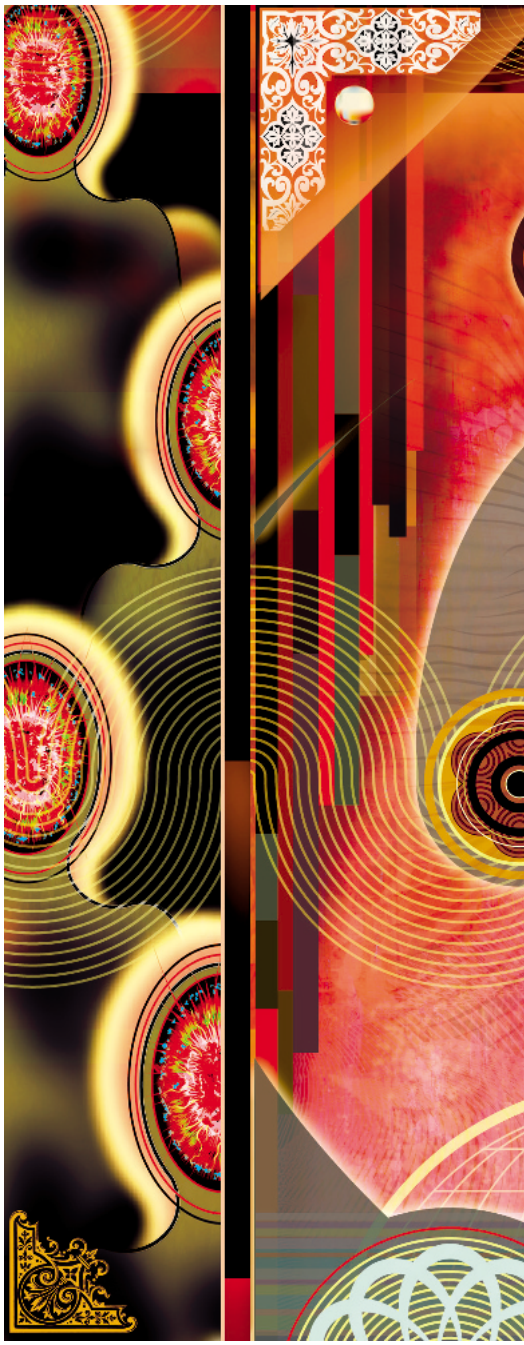
Existing cancer treatments often leave the most dangerous cells untouched. But now doctors have these elusive masterminds in their sights. **Helen Pilcher** reports

The traitors within



FOR years, they've been depicted as the good guys. Stem cells help renew many parts of our bodies and, we're told, with a little coaxing might provide cures for anything from Alzheimer's to diabetes. But stem cells can also turn bad. Very bad.

Rogue stem cells are now known to be involved in at least some cancers, including breast cancer, and they are resilient, relentless killers. They seem immune to most treatments, lurking in the background as the other cancer cells around them die. Then they churn out new cancer cells that can make old tumours regrow or seed new ones – perhaps the reason why so many cancers come back after seeming to have disappeared.

The discovery of cancer stem cells is bringing about a fundamental shift in our understanding of cancer, a shift that includes radically rethinking how we tackle the disease. Most cancer treatments are not designed to kill cancer stem cells, which may be why so many fail so miserably. So some researchers are trying to develop an arsenal of weapons designed specifically to eliminate cancer stem cells, in the hope of ridding patients of their cancer once and for all.

The field is buzzing with excitement, but it's not going to be easy. Cancer stem cells are masters of disguise. They share many similarities with normal stem cells, a feature that makes them hard to spot – and even harder to kill. A lot of painstaking work is needed to establish just what role stem cells play in different cancers, let alone to develop therapies. Nevertheless, a handful of treatments are already nearing trials.

The idea that stem cells are involved in cancer goes back more than half a century. The trouble has been proving it. True stem cells can divide asymmetrically, producing one daughter cell that remains a stem cell and a second, called a progenitor, that is slightly more specialised. The progenitor divides more rapidly and ultimately gives rise to many highly specialised cell types that cannot divide any more. In this way, a relatively small number of blood stem cells, for example, can generate the billions of new blood cells needed by the body every day. With cancer, similarly, the idea was that a few rogue stem cells might churn out the huge number of abnormal cells that form the bulk of a tumour.

The property of "stemness" is elusive, though. Definitive proof that cancer stem cells exist came only in 1994. John Dick's team at the University of Toronto, Canada, took blood samples from patients with acute myeloid leukaemia and used a machine called a flow cytometer to separate them into two types based on their surface proteins. When the cells were injected into mice with deficient immune systems, only one type caused the animals to develop the cancer.

These "cancer stem cells" were incredibly rare. Only one in several hundred thousand cells from the initial blood sample could give rise to a cancer. "These are the real business end of the tumour," says Dick. The study suggested that although the bulk of cancer cells are what do the damage, the evil masterminds are the tiny subset of stem cells that keep the cancer growing. The implication was huge: to cure a person of cancer, these cancer stem cells must be eliminated, something that most treatments don't do.

The reaction was guarded. Many people thought that leukaemia, a cancer of the blood, might be the exception rather than the rule and that cancer stem cells were unlikely to turn up in solid tumours. "But it was the beginning of a paradigm shift," says Stephen Emerson, who studies blood stem cells at the University of Pennsylvania. This shift was completed in 2003 when cancer stem

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cells were found in two different solid tumours – breast and brain cancer.

"This opened the floodgates," says Sean Morrison of the University of Michigan in Ann Arbor, one of the leaders of the breast cancer team. "People suddenly thought: 'Holy cow, this model could change the way we think cancer works and change the way it is treated.'"

Previously, most experts had thought that just about any cancer cell could divide like crazy and keep on dividing indefinitely. This means that any cancer cell left in the body could potentially reignite the disease, so the aim of most treatments is to kill all these dividing cells: standard therapies such as chemotherapy and radiation target rapidly dividing cells.

The cancer stem cell theory, however, says that only cancer stem cells can reignite the disease. These cells divide slowly – unlike the progenitors they give rise to – so they might survive most therapies. In fact, they may be particularly hard to kill. Last month, Jeremy Rich's team at Duke University Medical Center in Durham, North Carolina, showed that cancer stem cells from glioblastoma brain tumours are very good at repairing their own DNA. This helps them survive the DNA damage caused by radiation therapy.

"Lots of people say that a failure to recognise cancer stem cells earlier could explain our inability to treat cancer effectively now," Morrison says. It's certainly a scenario that matches clinical experience. There are numerous cases of chemotherapy or radiation shrinking tumours so much that they become invisible on X-rays, only for the cancer to return later and kill the patient. If the cancer stem cell model is right, these relapses occur when quiescent cancer stem cells regenerate the tumour.

The question then is, how many tumours are like this? Cells with stem-cell-like characteristics have now been found in many other solid tumours, including ovarian, lung and skin cancers, but more work is ▶