IN THE NEWS

Ready for the end?
A pilot study in America is investigating if the illegal drug ecstasy will help terminally ill cancer patients to cope better with demanding end of life issues.

Anecdotal stories indicate that people who have taken ecstasy when dying from cancer felt able to talk to family and friends about death-related subjects that they were unable to tackle previously, noted John Halpern, the psychiatrist at Harvard Medical School leading the trial (www.telegraph.co.uk, 13 January 2005). The 4 month Food and Drug Administration approved trial will recruit 12 terminally ill cancer patients to assess if taking ecstasy, which is known to give users a euphoric feeling — increased empathy, energy and sexual arousal — helps alleviate a patient's fear of death.

However, concerns have been raised. "There's more research coming in all the time pointing out that there really is adverse effects of using these illicit drugs", stated Jeanette Tait of the Australian Medical Association Queensland public health committee (www.theaustralian.news.com.au, 30 December 2004). Yet others have expressed guarded support for the trial, "…when taken in the context of carefully structured and approved research protocols and facilitated by individuals with expertise, adverse effects can be contained to a minimum", said psychiatrist Charles Grob at Harbour-UCLA Medical Center, Los Angeles (http://seattletimes.nwsource.com/, 28 December 2004).

John Halpern summed up the aim of this trial by saying "This is not about trying to create some sensationalistic storm. This is about trying to help these patients in a meaningful way" (www.cbsnews.com, 27 December 2004).

Nicola McCarthy

CANCER GENETICS

Tumour-suppressor super models

Point mutations in the tumour-suppressor gene *TP53* cause Li–Fraumeni syndrome, which predisposes patients to a broad spectrum of malignancies, particularly sarcomas and carcinomas. However, the range of tumours seen in these patients cannot be explained simply by the loss of wild-type p53 function. Now, two research groups have generated mouse models that closely resemble Li–Fraumeni syndrome and have used these models to investigate why the *TP53* mutations seen in a wide range of human cancers are so oncogenic.

Mice that lack p53 develop lymphomas and sarcomas but not carcinomas, and these tumours tend not to metastasize. Furthermore, p53 is an unusual tumour suppressor because it is commonly altered through missense mutation rather than deletion. So, Kenneth Olive and co-workers produced mice with missense point mutations in two of the most commonly mutated p53 codons in human cancer: $Trp53^{R172H}$ affects the overall structure of the p53 DNA-binding domain, whereas $Trp53^{R270H}$ affects a residue that makes direct contact with DNA. Although $Trp53^{R270H/-}$ and $Trp53^{R172H/-}$ mice developed distinct tumour spectra, both developed different tumour phenotypes compared with *Trp53*-knockout mice, indicating that missense *Trp53* mutants have pro-tumorigenic or oncogenic functions that cannot be explained simply by the loss of wild-type p53. In particular, strains carrying these two mutant alleles developed metastatic carcinomas and are therefore more accurate models of Li–Fraumeni syndrome.

The possibility that mice carrying *Trp53* missense mutations are useful models of Li–Fraumeni syndrome was further supported by work carried out by Gene Lang and

ONCOLYTIC VIRUSES

Export license

Several viruses have been engineered with the capacity to replicate in and exclusively kill cancer cells, although the precise molecular mechanism behind the selectivity of these oncolytic viruses has not always been clear. While studying the oncolytic adenovirus ONYX-015, O'Shea and colleagues have found that tumour cells have alterations in RNA export pathways, revealing a previously unidentified and therapeutically interesting target that governs the selectivity of this virus.

Cells seem to have evolved a defence mechanism to deal with virus infection — stabilization and activation of the tumour suppressor p53 can provoke the premature apoptosis of the infected cell, limiting both viral replication and spread. Therefore, many viruses have evolved mechanisms to subvert the host p53 response. Given that the p53 pathway is mutated in a wide range of cancers, ONYX-015 was designed to specifically replicate in tumour cells that lacked a functional p53 pathway — the E1B-55K viral gene product that targets the tumour suppressor p53 for degradation is deleted in this virus. Surprisingly though, ONYX-015 has efficacy in tumour cells irrespective of their p53 status, prompting O'Shea and colleagues to investigate further.

Initially the authors looked at ONYX-015 infection in normal primary human epithelial lines with a wild-type p53 pathway. As expected, ONYX-015 was unable to successfully replicate and p53 was stabilized in the nucleus. Surprisingly though, this stabilized form of p53 was not active and did not induce apoptosis, indicating that viral products other than E1B-55K can restrict p53 activation. So, the authors next addressed the p53-independent functions of E1B-55K, which include the shutdown of host protein synthesis allowing late viral protein production. By using a set of adenoviruses that were deficient in specific functions of E1B-55K, the authors found that ONYX-015 was unable to induce late viral protein production due to a defect in late viral RNA export from the nucleus. But why should this be different in cancer cells? All the tumour cells that support the full lytic viral replication of ONYX-015 compensated for the defect in late viral RNA export, showing that normal and tumour cells differ markedly in this respect.

These data provide not only a further opportunity to understand how p53 can be inactivated, but also indicate a need to investigate whether the export of late viral RNA shares some characteristics with the export of RNAs important in growth control and tumorigenesis.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER O'Shea *et al.* Late viral RNA export, rather than p53 inactivation, determines ONYX-015 tumor selectivity. *Cancer Cell* **6**, 611–623 (2004)

FURTHER INFORMATION
ONYX pharmaceuticals web site: http://www.onyx-pharm.com/products/onyx_015.html