PHARMACODYNAMICS

PET power

A new method for non-invasive imaging of the pharmacodynamics of drug action using positron-emission tomography (PET) should allow scientists to determine the most effective strategies for administering the heat-shock protein 90 (HSP90) inhibitor 17-allylaminogeldanamycin (17-AAG), according to research published in the June issue of *Nature Biotechnology*.

Without understanding the potency and kinetics of target inhibition by drugs in patients, it is difficult to determine mechanisms of sensitivity and resistance, and to establish optimal dosing and scheduling parameters. Notwithstanding advances in our understanding of the molecular basis of carcinogenesis, little is known about the pharmacodynamics of therapeutic agents, including successful drugs such as imatinib (Glivec) and retinoic acid. Furthermore, the effects of an inhibitor on a tumour target can only be determined if an assay has been developed and if tumour tissue can be collected before and after therapy, which is difficult in patients with solid tumours.

Smith-Jones *et al.* have developed a new technique to image the pharmacodynamics of 17-AAG, a potent anti-breast-cancer agent, which exerts its effect by indirectly inducing the degradation of the cell-surface protein kinase ERBB2 (also known as HER2/NEU). Members of the HER kinase family, such as epidermal growth factor receptor and ERBB2, are overexpressed, amplified or mutated in various tumour types. 17-AAG, a geldanamycin derivative, binds to HSP90, which is required for the conformational maturation and stability of key signalling molecules, including ERBB2.

To understand the potency and time course of 17-AAG action on ERBB2, the authors attached a positron emitter to a fragment of trastuzumab (Herceptin), an antibody that binds ERBB2, so that the antibody fragment could be detected over time using PET. After injecting the antibody fragment into mice and then treating the mice with 17-AAG, they could repeatedly image the disappearance of ERBB2 over time.

17-AAG is presently in Phase 1 clinical trials for cancer treatment. It is not clear whether the doses and schedules with which the drug is being administered are affecting the target in the tumour optimally. The authors intend to use the technique in patients with breast cancer whose tumours express high levels of ERBB2 to shed light on these questions. The technique also has the potential to screen for patients who might benefit most from this type of therapy.

Other drugs that induce the degradation of a target with an extracellular domain might benefit from this approach.

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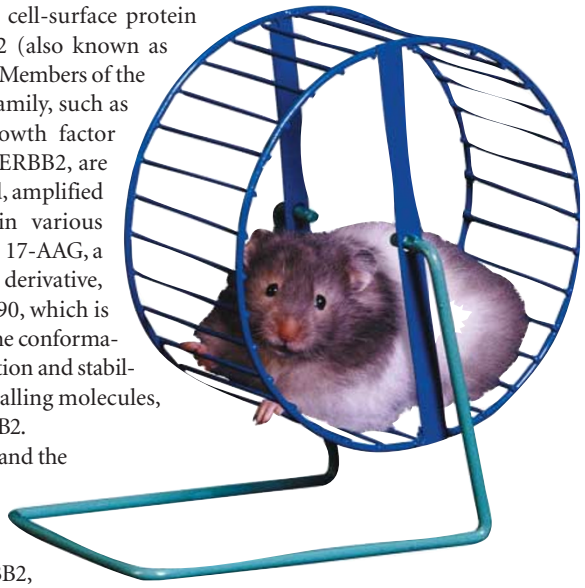
References and links

ORIGINAL RESEARCH PAPER Smith-Jones, P. M. *et al*. Imaging the pharmacodynamics of HER2 degradation in response to Hsp90 inhibitors. *Nature Biotechnol.* 9 May 2004 (doi:10.1038/nbt968)

FURTHER READING Gambhir, S. S. Molecular imaging of cancer with positron emission tomography. *Nature Rev. Cancer* **2**, 683–693 (2002) | Dancey, J. & Sausville, E. A. Issues and progress with protein kinase inhibitors for cancer treatment. *Nature Rev. Drug Discov.* **2**, 296–313 (2003)



TRIAL WATCH

IGF and cancer risk

Epidemiological observations have linked circulating concentrations of insulin-like growth factor 1 (IGF1) and its main binding protein, IGFBP3, to cancer risk. Andrew Renehan *et al.* have published a systematic review and meta-regression analysis of case–control studies, which explores this association further.

IGFs and their binding proteins regulate cell proliferation, differentiation and apoptosis — the biology of the IGF1 axis is complex. IGF1 is mitogenic and anti-apoptotic, and IGFBP3 inhibits growth by sequestering IGF1. IGFBP3 is also possibly antiproliferative and pro-apoptotic independent of IGF1. There are high concentrations of IGFs and IGFBPs in the circulation, and they are dependent on growth-hormone concentrations, age, sex and nutritional status. Their concentrations also vary greatly between individuals. Epidemiological studies have linked high circulating levels of IGF1 with prostate, breast, colorectal and lung cancer, while high IGFBP levels have been associated with decreased risk of cancer. However, findings have been inconsistent.

Renehan *et al.* identified 139 published epidemiological studies that were potentially relevant to IGF assessment and cancer risk. Of these, 21 fulfilled the authors' inclusion criteria — the studies were published as full articles, the findings were expressed as odds ratios (ORs) with 95% confidence intervals and detailed associations of peptide concentrations were reported. Combined, these studies included 3,609 cases and 7,137 controls.

High concentrations of IGF1 were associated with an increased risk of prostate cancer (OR comparing 75th with 25th percentile of circulating peptide concentrations, 1.49) and pre-menopausal breast cancer (OR 1.65). Why IGF1 concentrations, which decrease with increasing age, are associated with prostate cancer, which has peak incidence in older age, is unknown. Also, why IGF1 is associated with pre-menopausal breast cancer risk, but not with post-menopausal breast cancer, requires further investigation.

High concentrations of IGFBP3 were associated with an increased risk of pre-menopausal breast cancer (OR 1.51), but not with any other cancer. However, there was great heterogeneity between studies for associations with IGFBP3 concentrations, in particular for lung cancer. The authors' analysis included the CARET study, which recruited only male heavy smokers and asbestos workers — when this study was excluded, high concentrations of IGFBP3 were associated with a decreased risk of lung cancer (OR 0.53). The link between IGFBP3 and cancer risk is therefore still unclear, but the protective effects of higher concentrations of IGFBP3 for all cancers were not shown.

Although the authors used stringent inclusion criteria, meta-analyses of this type do have some limitations, as they are vulnerable to biases and confounding in the original studies. IGF1 and IGFBP3 concentrations can be measured easily in blood and might therefore be a useful assessment of risk for specific cancer types.

ORIGINAL REFERENCE Renehan, A. G. *et al*. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* **363**, 1346–1353 (2004)