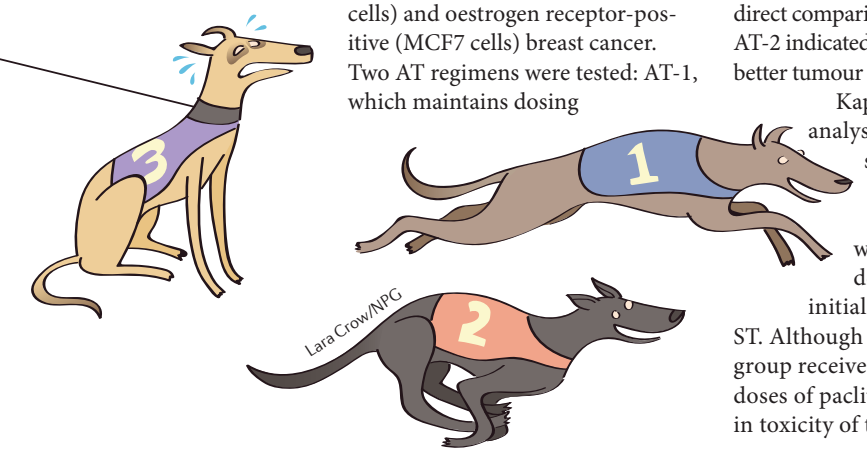
CHEMOTHERAPY

Preventing competitive release

> AT-1 significantly improved progression-free survival over ST

Systemic chemotherapies typically use the maximum tolerated dose to cause maximum tumour cell death. However, this paradigm has been challenged by theoretical models of tumour evolution, which suggest that removal of all cells that are sensitive to chemotherapy permits unopposed proliferation of any remaining resistant cells — a phenomenon called 'competitive release'. Based on this model, an evolution-based treatment strategy that maintains a residual population of chemotherapy-sensitive cells should suppress growth of resistant cells when therapy is withdrawn, as the drug-sensitive cells have a fitness advantage in this condition.

Enriquez-Navas *et al.* designed an evolution-based treatment strategy using paclitaxel (adaptive therapy (AT)), and compared this with standard paclitaxel therapy (ST) in orthotopic xenograft mouse models of triple-negative (MDA-MB-231 cells) and oestrogen receptor-positive (MCF7 cells) breast cancer. Two AT regimens were tested: AT-1, which maintains dosing frequency but decreases paclitaxel dose as a tumour responds, and AT-2, which uses the same doses of paclitaxel but doses are skipped when a tumour has responded. The treatment algorithms relied on tumour volume measurements determined by magnetic resonance imaging (MRI), as this could be used clinically.



In both mouse models, ST initially suppressed tumour growth, but exponential growth resumed following treatment cessation. AT-1 had the same effect as ST initially, but was able to maintain a stable tumour burden similar to the initial tumour volume throughout the experiment (~2 months). This allowed continued reduction of the paclitaxel dose, and eventually treatment withdrawal in some cases. Interestingly, AT-2 controlled tumour volume for longer than ST, but unlike AT-1, tumours treated using AT-2 eventually progressed. A direct comparison between AT-1 and AT-2 indicated that AT-1 provided better tumour growth control.

Kaplan–Meier survival analysis indicated that AT-1 significantly improved progression-free survival over ST, whereas AT-2 did not, despite achieving better initial tumour control than ST. Although mice in the AT-1 group received greater cumulative doses of paclitaxel, no differences in toxicity of the regimens were observed. Overall, these data suggest that AT strategies might be clinically viable.

The authors conducted MRI throughout the treatment protocols and immunohistochemistry (IHC) analyses at the end of each experiment to examine levels of necrosis and tumour blood flow. In mice treated using AT-1, the level of necrotic tissue remained below that of AT-2- and ST-treated tumours. MRI indicated that blood flow was increased in all mice treated with AT-1 relative to ST, and IHC of CD31 (indicating vascular density) and smooth muscle actin (SMA, indicating vessel integrity) indicated that AT-1-treated mice had a higher density of functional vasculature. This might have increased paclitaxel delivery, thus contributing to tumour growth control by lower doses during AT-1, but other mechanisms are likely to also underlie the efficacy of this treatment plan.

It is possible that similar evolution-based strategies could be applicable to other non-chemotherapeutic treatments. However, it remains to be determined whether the results would be similar in other preclinical models (including those that use immunocompetent mice) and whether AT would improve treatment outcomes in patients.

Sarah Seton-Rogers

ORIGINAL ARTICLE Enriquez-Navas, P. M. *et al.* Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. *Sci. Transl Med.* **8**, 327ra24 (2016)