melting of the stripe phase as a whole.

However, an equally credible case was made[8] that the hourglass spectrum could instead be explained in terms of spin excitations in a rather weakly interacting gas of itinerant electrons, and a debate regarding the interpretation of the hourglass spectrum evolved that rages up to the present day. All along, the problem for the dynamical-stripe interpretation was that the modelling of the spin waves involved a lot of assumptions. In this regard, Boothroyd and colleagues' study[1] makes a big difference. The authors perform a neutron-scattering experiment on a material that falls outside the family of cuprate superconductors — a cobalt oxide insulator — and that is known to display stripes[9] in a simple static form[6]. They show that the material exhibits an hourglass spin-fluctuation spectrum (Fig. 1a) strikingly similar to that of the cuprates (Fig. 1b); the only difference is seen at low energies, where the cuprate 'quantum gap' is absent in the cobalt oxide. This similarity lends support to the hypothesis that the hourglass spin-fluctuation spectrum in the cuprate superconductors arises from dynamical stripes[4,5].

Boothroyd and colleagues' results arrive at a time when the reality of complex quantum matter in underdoped cuprates is becoming mainstream wisdom. Perhaps we already know so much about these materials that research should be refocused on the greatest mystery of all[4]: that increased levels of doping make the complex quantum stuff gradually fade away, and that the best superconductors are found at the point where the electron traffic starts to resemble the quantum fog of the simple metals. ■

Jan Zaanen *is at the Instituut-Lorentz for Theoretical Physics, Leiden University, 2300 RA Leiden, the Netherlands.*
e-mail: jan@lorentz.leidenuniv.nl

1. Boothroyd, A. T., Babkevich, P., Prabhakaran, D. & Freeman, P. G. *Nature* **471,** 341–344 (2011).
2. Schrieffer, J. R. *Theory of Superconductivity* (Perseus, 1999).
3. Bednorz, J. G. & Muller, K.A. *Z. Phys. B* **64,** 189–193 (1986).
4. Zaanen, J. in *100 Years of Superconductivity* (eds Rochalla, H. & Kes, P. H.) (Chapman & Hall, in the press); http://arxiv.org/abs/1012.5461 (2011).
5. Kivelson, S. A. *et al. Rev. Mod. Phys.* **75,** 1201–1241 (2003).
6. Zaanen, J. & Gunnarsson, O. *Phys. Rev. B* **40,** 7391–7394 (1989).
7. Tranquada, J. M. *et al. Nature* **429,** 534–538 (1995).
8. Eschrig, M. *Adv. Phys.* **55,** 47–183 (2006).
9. Cwik, M. *et al. Phys. Rev. Lett.* **102,** 057201 (2009).

TRANSLATIONAL MEDICINE

Cancer lessons from mice to humans

New clinical trials report the efficacy of two mechanism-based therapies for treating human pancreatic neuroendocrine tumours. Studies in mouse models have contributed to these success stories, and continue to do so.

DAVID TUVESON & DOUGLAS HANAHAN

Advances in cancer medicine have reset our clinical and social expectations: the aim now is to effectively combat formidable tumours — an effort that was previously deemed improbable. Writing in *The New England Journal of Medicine*, Raymond *et al.*[1] and Yao *et al.*[2] report phase III clinical trials of two drugs that target distinctive cancer-associated signalling pathways. The results suggest an impressive efficacy of both drugs (sunitinib and everolimus) for treating pancreatic neuroendocrine tumours. It is therefore likely that these drugs, which are already standard treatments for other cancers, will become the first new approvals in 25 years by the US Food and Drug Administration (FDA) for treating these cancers, a remarkable milestone.

Pancreatic neuroendocrine tumours (PNET) are uncommon, but difficult to diagnose and treat. These cancers, which originate from the hormone-producing pancreatic islet cells, stand in stark contrast to another type of pancreatic cancer, pancreatic ductal adenocarcinoma, which is much more prevalent and deadly: a larger proportion of patients with PNET undergo surgical excision, and the clinical course of the disease is highly variable. Nonetheless, patients with advanced PNET who are not candidates for surgery have a terminal illness, and their tumours are difficult to manage; the FDA-approved chemotherapeutic agent streptozotocin shows only modest activity in these patients.

A vast number of potential anticancer drugs are currently in the pipelines of biopharmaceutical companies. Indeed, the scope of mechanism-based targeting is broad, often with several potential drugs affecting the same target. Consequently, it is challenging to decide which targets and candidate drugs might be of value in particular forms of human cancer, especially those that are rare but deadly like PNET. There is growing optimism that genetically engineered mouse models, which can mimic the progression of specific types of human cancer at the genomic and tissue levels, can contribute to this prioritization[3]. The hope is that preclinical trials of candidate drugs in representative mouse models could help to motivate and guide clinical trials of targeted therapies in the related human tumours (Fig. 1). The two new papers[1,2] reflect proof of this concept.

The mouse model of PNET, called RIP-Tag2, shows similar tissue-level features to the human tumours[4]. However, the cancer in the animal does not follow the same — currently obscure[5] — initiating events that lead to human PNET; it is instead driven by a viral oncogene that abrogates the function of two generic tumour-suppressor pathways commonly lost in human tumours.

Preclinical trials in this model had predicted that both sunitinib, a pan-specific inhibitor of tyrosine-kinase enzymes, and everolimus,

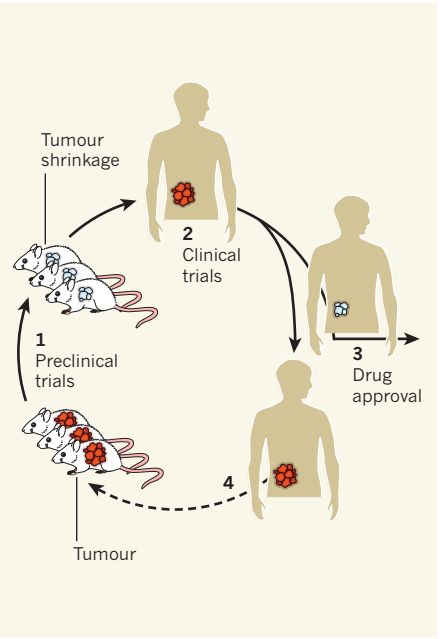

Figure 1 | Linking preclinical and clinical trials. (**1**) Preclinical trials on cohorts of mice engineered to develop a particular type of cancer are a good starting point for evaluating mechanism-based drugs. (**2**) If the mice show detectable therapeutic benefits, such as increased survival and/or tumour shrinkage, the preclinical trials can motivate and guide the design of clinical trials in the same type of cancer. (**3**) Clinical benefit, such as tumour shrinkage, increased progression-free-survival and overall survival, can justify drug approval for clinical use. (**4**) Relapses and clinical failures, however, can be translated back into refined preclinical trials aiming to understand and circumvent the limitation.

which inhibits another kinase, mTOR, would be effective in treating human PNET. Several studies[6–8] showed that sunitinib, and other kinase inhibitors that target signalling associated with angiogenesis through receptors for the growth factors VEGF and PDGF (thus inhibiting angiogenesis), cause tumour shrinkage. Sunitinib also produced increased survival in the animal studies. These results motivated Raymond and colleagues to perform two phase II trials[9,10] and now the phase III trial[1] of sunitinib in patients with PNET (Box 1). Similarly, a separate study[11] reported the efficacy of another mTOR inhibitor, rapamycin, in treating PNET in the mouse model, presaging the clinical success of everolimus, a refined mTOR inhibitor, which Yao *et al.*[2] now describe.

Although drug efficacies seen in the preclinical trials were encouraging, the trials also revealed limitations — in tumour shrinkage and long-term survival of the mice — that may well influence how these drugs are most effectively used to treat human PNET. Yao and colleagues also find that, whereas everolimus delays time to progression of the disease (progression-free survival), it seemingly does not increase overall survival rates. This trial is still ongoing, however, so the lack of effect on overall survival is not yet conclusive.

Pertinent to this clinical observation is an intriguing result with translational potential from preclinical trials of rapamycin in the mouse model of PNET. Rapamycin on its own produced only a modest overall survival benefit, and the animals also showed evidence of rapamycin resistance following treatment, in the form of regrowth of the previously responding tumours[9]. But when rapamycin was given in combination with another approved drug — erlotinib, which inhibits the growth factor receptor EGFR — the animals' overall survival rate improved significantly and there was a decrease in relapse during treatment[11].

These outcomes in the PNET mouse model are consistent with the possibly limited overall survival of patients with PNET following treatment with everolimus only[2]. The preclinical results therefore encourage clinical trials on everolimus in combination with erlotinib (or with other drugs that target downstream effectors in the same signalling pathway). A small clinical trial[12] combining the two drugs to treat PNET is already under way.

For sunitinib, the tumour shrinkage and increased overall survival seen in preclinical trials[8] are recapitulated in the human trial: Raymond *et al.*[1] report improved both progression-free survival and overall survival after administration of this drug. But, as with everolimus, preclinical trials revealed limitations to the effectiveness of sunitinib in the form of adaptive resistance in PNET. In other words, faced with sunitinib's potent effect in blocking angiogenesis, the tumours not only adapt after a period of shrinkage, but also survive the treatment better, inducing alternative pro-angiogenic signalling circuits[13] and becoming more invasive and metastatic[8]; this reflects a phenomenon seen in other preclinical models as well as in clinical trials[14–16].

The mouse data therefore predict eventual failure of therapy with sunitinib alone, and should motivate preclinical and clinical trials to circumvent the evasive resistance — an iterative and bidirectional process of translational therapeutic oncology.

The clinical results with everolimus and sunitinib[1,2] are landmarks for treating PNET. The approach that led to this — aligned preclinical trials in a representative mouse model and human clinical trials — could also be used to test the efficacy of other anticancer drugs and may well replicate this success story. Indeed, this approach heralds a future in which preclinical trials in genetically engineered mouse models, and in other representative animal models, could guide the development of more effective therapies for human cancers, revealing efficacy, beneficial drug combinations and (potentially surmountable) mechanisms of resistance. ■

David Tuveson *is at the Cancer Research UK/Cambridge Research Institute, University of Cambridge, Cambridge CB2 0RE, UK.*

Douglas Hanahan *is at the Swiss Institute for Experimental Cancer Research, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne, Switzerland.*
e-mails: david.tuveson@cancer.org.uk; dh@epfl.ch

BOX 1

A closer look at the trials

Both trials[1,2] enrolled patients with advanced pancreatic neuroendocrine tumours (PNET) who had already received much treatment (including surgery and chemotherapy).

Raymond *et al.*[1] compared the response of 86 randomly selected patients given sunitinib with that of 85 control patients on a placebo drug. Neither the patients nor their doctors were aware of who was receiving which treatment — a double-blind trial.

The median tumour-progression-free survival of patients on sunitinib (11.4 months) was appreciably longer than that of the control group (5.5 months). Moreover, patients treated with sunitinib showed early signs of an increase in overall survival. The side effects were typical of previous experience with sunitinib and included gastrointestinal disturbances and fatigue.

Yao and colleagues[2] compared the response of 207 randomly selected patients on everolimus with that of 203 patients who received only the best supportive care. In this study, the patients and their physicians were aware of the treatment used, with patients who were receiving only supportive care having the option to switch to everolimus if their cancer progressed. Nonetheless, all patients were classified by the treatment they initially received (intention to treat).

Everolimus was beneficial, extending the median time of progression from 4.6 months to 11 months. The incidence of rash, gastrointestinal disturbances, fatigue, anaemia and infections was higher in patients treated with this drug, but these side effects were largely manageable. Although no increase in overall survival of patients treated with everolimus was noted, this conclusion is tentative because of the cross-over of patients and the continuance of the trial for the best responders to everolimus.

It should be determined whether these treatments are also beneficial to other groups of patients with PNET, including those who have just had surgery, those who have early-stage disease and those who were marginally too ill to qualify for these trials[1,2]. **D.T. & D.H.**

1. Raymond, E. *et al. N. Engl. J. Med.* **364,** 501–513 (2011).
2. Yao, J. C. *et al. N. Engl. J. Med.* **364,** 514–523 (2011).
3. Frese, K. K. & Tuveson, D. A. *Nature Rev. Cancer* **7,** 645–658 (2007).
4. Hanahan, D. *Nature* **315,** 115–122 (1985).
5. Jiao, Y. *et al. Science* doi: 10.1126/science.1200609 (2011).
6. Bergers, G., Song, S., Meyer-Morse, N., Bergsland, E. & Hanahan, D. *J. Clin. Invest.* **111,** 1287–1295 (2003).
7. Pietras, K. & Hanahan, D. *J. Clin. Oncol.* **23,** 939–952 (2005).
8. Pàez-Ribes, M. *et al. Cancer Cell* **15,** 220–231 (2009).
9. Faivre, S. *et al. J. Clin. Oncol.* **24,** 25–35 (2006).
10. Kulke, M. H. *et al. J. Clin. Oncol.* **26,** 3403–3410 (2008).
11. Chiu, C., Nozawa, H. & Hanahan, D. *J. Clin. Oncol.* **28,** 4425–4433 (2010).
12. http://clinicaltrials.gov/ct2/show/NCT00843531
13. Casanovas, O., Hicklin, D. J., Bergers, G. & Hanahan, D. *Cancer Cell*. **8,** 299–309 (2005).
14. Bergers, G. & Hanahan, D. *Nature Rev. Cancer* **8,** 592–603 (2008).
15. Azam, F., Mehta, S. & Harris, A. L. *Eur. J. Cancer* **46,** 1323–1332 (2010).
16. Ebos, J. M. L. & Kerbel, R. S. *Nature Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2011.21 (2011).

D.H. declares competing financial interests. See online article for details.