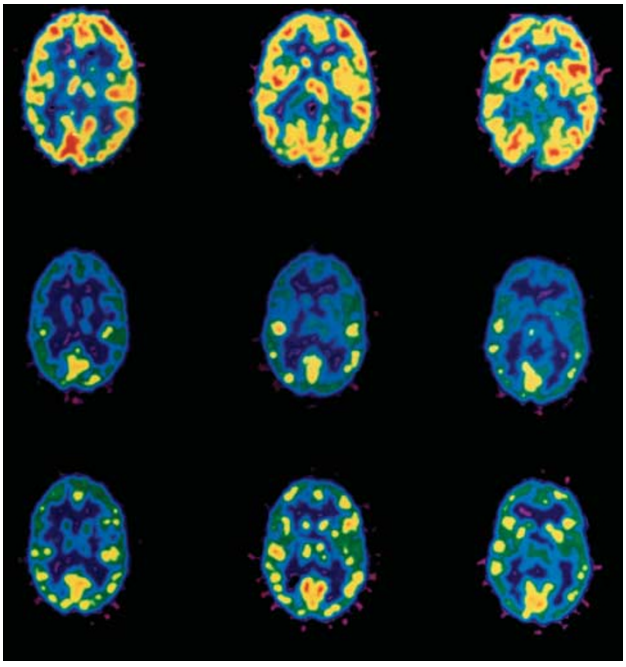
PHARMACODYNAMICS

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 experimental cancer drug 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; Novartis) 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 and colleagues have developed a new technique to image the pharmacodynamics of 17-AAG, a potent anti-breast-cancer agent that exerts its effect by indirectly inducing the degradation of the cell-surface protein kinase HER2. Members of the HER kinase family, such as epidermal growth factor receptor and HER2, are overexpressed, amplified or mutated in a variety of tumour types. 17-AAG, a geldanamycin derivative, binds to heat-shock protein 90 (Hsp90), which is required for the conformational maturation and stability of key signalling molecules, including HER2.

To understand the potency and time course of 17-AAG action on HER2, the authors attached a positron emitter to a fragment of trastuzumab (Herceptin; Genentech), an antibody that binds HER2, so that the antibody fragment could be detected over time using PET. After injecting the antibody fragment into mice and treating them with 17-AAG, the authors could

CHEMICAL BIOLOGY

Building blocks for peptide drugs

The discovery of novel peptide drugs could be simplified by a new protocol for building diverse, mRNA-encoded peptide libraries, according to new work by Merryman and Green. This strategy has been hindered previously by the difficulty of generating sufficient amounts of tRNAs bearing diverse, non-standard amino acid building blocks. However, the recent paper in *Chemistry and Biology* describes how a simple chemical transformation can be used to generate pools of methylated, non-standard aminoacyl (aa)–tRNAs for the convenient synthesis of diverse libraries of drug-like peptides.

Libraries of mRNA-encoded proteins and peptides have been a popular choice for identifying functional peptides that modulate a variety of biological targets. The nature of ribosomal synthesis enables peptides to be encoded with mRNA, making it relatively simple to identify library members with a desired activity. Through iterative rounds of selection and amplification, a diverse population of peptides ultimately evolves into a population dominated by a single desired molecule (a so-called evolutionary method).

Exploiting the highly adaptable nature of the ribosome, which is able to translate randomized pools of mRNA into a variety of products comprising unusual backbones and non-standard amino acids, would enable the creation of a more diverse library. However, chemical aminoacylation protocols are unable to generate bulk amounts of the diverse, non-standard aa–tRNA building blocks required for the ribosome to synthesize these products.

For a starting population of low-molecular-weight peptides that will undergo several rounds of screening, approximately 20 non-standard aa–tRNAs would need to be synthesized in an amount suitable for *in vitro* translation, which for a diverse library of 10^{13} molecules equates to 10–100 mg of non-standard aa–tRNA. Current chemical misacylation techniques used to generate non-standard aa–tRNAs require individually isolated tRNAs, and a multitude of separate reactions, meaning that library complexity is limited by the amount of non-standard aa–tRNA that can be produced.

The authors' solution to this problem is to chemically transform the standard amino acids once they have been loaded onto their cognate tRNA by aminoacyl synthetase. They demonstrated that readily available bulk-acylated tRNA can be subjected to a chemical transformation to generate altered aa–tRNAs that are ready for translation. A transformation reaction consisting of a reductive alkylation, followed by a reductive methylation and photoreversal of the former adduct, was used to generate tRNAs bearing *N*-monomethyl amino acids that are ready for translation.

One additional advantage of this particular transformation reaction is that the resulting poly-*N*-methylated peptide backbones are more resistant to proteases and are able to cross cell membranes, thereby circumventing two of the toughest challenges in the development of peptide drugs. To begin screening with a library of peptides that already have these drug-like qualities would be a distinct advantage.

Joanna Owens

References and links

ORIGINAL RESEARCH PAPER Merryman, C. & Green, R. Transformation of aminoacyl tRNAs for the *in vitro* selection of 'drug-like' molecules. *Chem. Biol.* **11**, 575–582 (2004)

WEB SITE

Rachel Green's Lab: http://www.mbg.jhmi.edu/FacultyDetails.asp?PersonID=366

repeatedly image the disappearance of HER2 over time.

The Hsp90 inhibitor 17-AAG is presently in Phase 1 clinical trials. 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 breast-cancer patients whose tumours express high levels of HER2 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.

Melanie Brazil

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)

COMPUTATIONAL CHEMISTRY

Sifting success

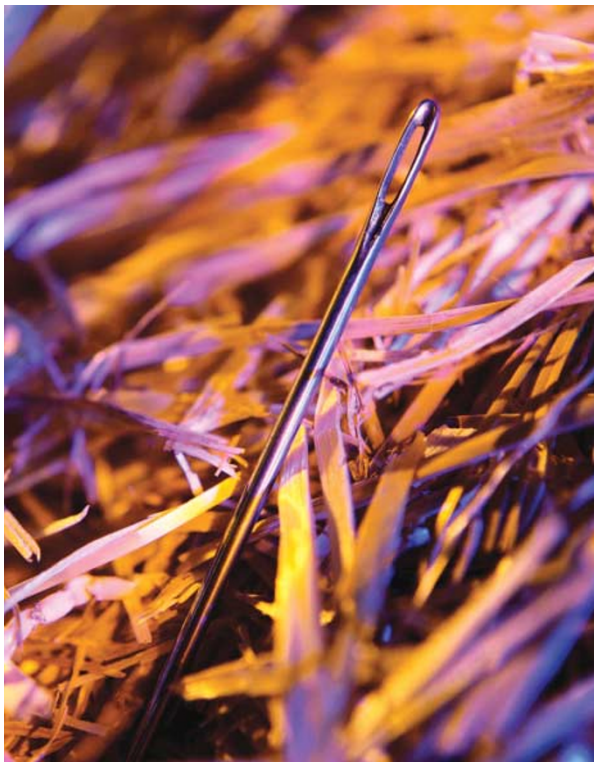
Chemical database mining, in which the structures of molecules known to have a particular activity are used to formulate 'queries' to search for other molecules in the database that are likely to show similar activity, can be a valuable approach for lead discovery, especially when little or no information on the macromolecular target is available. Writing in the *Journal of Medicinal Chemistry*, Tropsha, Kohn and colleagues have recently described a novel general approach to database mining, which integrates rigorously validated quantitative structure–activity relationship (QSAR) models. This approach gave an exceptionally high hit rate in a test of its ability to identify anticonvulsant compounds from a set of 250,000 molecules.

A key determinant of the success of database mining is the way in which the query molecules and those within the database are described computationally. Many types of chemical 'descriptors' can be calculated for a given molecule, and so an important question is how to select descriptors that will maximize the chances of identifying interesting molecules when a database is searched.

Addressing this question was a major focus of the authors' study, which was based on a series of compounds termed functionalized amino acids (FAAs) that were previously shown by Kohn and co-workers to have anticonvulsant activity in animal models of epilepsy (indeed, an FAA was recently designated for Phase III trials). However, the macromolecular targets of FAAs are not known, meaning that ligand-based approaches, such as database mining, represent the most efficient way to rationally discover new chemical entities with anticonvulsant activities that might be structurally dissimilar from FAAs.

Tropsha *et al.* had previously developed several QSAR models for FAAs, and rigorously validated them, which is also a key determinant of the success of the authors' approach in the present study. Each model was built by first using many different types of descriptors to characterize known FAAs and then applying statistical methods to find those descriptors that best correlated the structure of the compounds with their anticonvulsant activity in animals. Several of these models showed strong predictive ability, and the authors reasoned that the descriptors used in the best of the models would be a good choice for use in database mining.

So, the authors computed the descriptors from each of the top ten models for ~250,000 compounds in two publicly available databases.



The FAAs, as described by the descriptors in each of the ten models, were then used as queries to search the two databases, and ~4,000 compounds that met a similarity threshold set by the authors (with respect to the query structures) were identified. However, by only selecting molecules that were found in all ten of the individual 'hit lists' (each corresponding to a particular model/descriptor set), this list could be further reduced to just 50 compounds.

Finally, the authors used the 10 QSAR models to predict the anticonvulsant activity of the 50 compounds, and 22 compounds were selected on the basis of these predictions. Four of these compounds, and five compounds derived by minor modifications, were chosen for synthesis, and seven of the nine compounds were confirmed to have good anticonvulsant activity in animals. This extremely high hit rate suggests that the authors' strategy of integrating rigorously validated QSAR models with database mining could be a valuable general tool in the design and discovery of novel bioactive chemical entities.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Shen, M. *et al.* Application of predictive QSAR models to database mining: identification and experimental validation of novel anticonvulsant compounds. *J. Med. Chem.* **47**, 2356–2364 (2004)

FURTHER READING Shen, M. *et al.* Quantitative structure–activity relationship analysis of functionalized amino acid anticonvulsant agents using *k* nearest neighbor and simulated annealing PLS methods. *J. Med. Chem.* **45**, 2811–2823 (2002) | Tropsha, A. *et al.* The importance of being earnest: validation is the absolute essential for successful application and interpretation of QSPR models. *Quant. Struct. Act. Relat. Comb. Sci.* **22**, 69–77 (2003)