'However, the result needs to be extended to actual tumours, and the functional consequences of this translocation on neuregulin expression and/or structure remain to be determined, as does the partner gene for *NRG1* in the translocation. As the authors discuss, this may be as important as *NRG1* for oncogenesis.'

The therapeutic potential

Edwards and Chaffanet are tackling these outstanding questions and agree that for now neuregulin can only be a tentative therapeutic target for breast cancer. 'However, we already know that one breast cancer cell line secretes a fused neuregulin that is a stimulatory ligand for the ERBB family of receptors,' says Edwards [4], and Lupu recently reported that breast cancer tumorigenicity and metastasis can be inhibited by blocking neuregulin expression [5], results that indicate that targeting neuregulin function might be useful therapeutically.

More immediately, these new results might prompt a rethink in how Herceptin® is used. At present, says Lupu, 'only patients whose tumours overexpress ERBB2 are known to benefit from Herceptin® treatment.' However, if alterations in neuregulin, possibly caused by chromosome translocations, lead to activation of ERBB2, then additional patients might benefit. To test this, Lupu is retrospectively measuring not only the expression of ERBB2 but also its activation and neuregulin expression in patient samples to see whether either of these additional parameters correlates with a good response to Herceptin®. Edwards, meanwhile, wants to examine gene expression patterns in tumours with chromosomal breakpoints within *NRG1*. 'We may find that these tumours look very much like ERBB2 overexpressors but have normal levels of ERBB2, and patients with this type of tumour may benefit from Herceptin® treatment,' he speculates.

Finally, it seems likely that recurrent chromosomal breakpoints will also occur only in other solid tumours. Indeed, Edwards and Chaffanet discovered *NRG1* specific translocations in two pancreatic cancer cell lines during their studies. 'Given our results,' says Edwards, 'I am sure more people will start to look for and find this type of chromosome rearrangement in other carcinomas,' the hope being that this new information will uncover new therapeutic targets.

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Promoting proteasomes: trash to treasure

Hillary E. Sussman, freelance writer

Until recently, proteasomes were either on or off. Now, however, researchers have discovered a novel class of proteasome inhibitors with a unique mechanism-of-action that offers the potential for more substrate-specific regulation of proteasome activity. This could lead to the development of new drugs for treating heart disease, stroke and inflammation [1].

Not just a trash can

Proteasomes are large, multisubunit protease complexes that have long been considered to be simple intracellular waste disposal units, merely gobbling and chewing up proteins that are old, damaged or no longer useful. The 26S assembly is comprised of a 20S cylinder, containing four stacked rings, with two 19S 'lids' (see Figure 1).

The lids perform a regulatory function by recognizing those proteins that have been marked for degradation with ubiquitin and granting them entrance into the cylinder. Inside the cylinder, β-subunits form the proteolytic core where active centres actually digest the proteins, resulting in short peptide fragments; outside, α-subunits maintain the shape of the cylinder.

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Although even the structure might be reminiscent of a trashcan, the proteasome is now taking on an elevated role – as a molecular factory in which the degradation of proteins is an intricate and highly regulated process, according to Maria Gaczynska, Assistant Professor of Molecular Medicine at the University of Texas Health Science Center at San Antonio (http://www.uthscsa.edu) and lead author of the study.

Allosteric shape shifters

Many physiologically relevant proteins are processed by the proteasome, including cell cycle regulators, antigenic proteins and transcription factors. Therefore, it has recently been acknowledged as an attractive target for the development of drugs for the treatment of cancer, autoimmune diseases and inflammation [2]. In fact, proteasome inhibitors are already in clinical trials and in May 2003 the Food and Drug Administration (http://www.fda.gov) approved Velcade™ for the treatment of multiple myeloma.

Velcade™ and other competitive inhibitors block the active centres of the proteasome, thereby irreversibly arresting all proteasome-dependent degradation, triggering apoptosis and, ultimately, killing the cell. 'Somehow cancerous cells are more susceptible to apoptosis than normal cells,' says Gaczynska, 'but you may imagine that this is quite a brute force.' Alternatively, she and her colleagues have characterized a novel class of proline- and arginine-rich peptides (PR peptides) that do not block the active centres of the proteasome but instead act allosterically and are 'much more gentle in regulating proteasome function'.

The peptide PR39 and its truncated derivatives make up this new class of proteasome inhibitors. They are unique in that they act noncompetitively by binding to the α subunits and changing the shape of the proteasome such that the cylinder appears 'squished and sort of bulging at the sides,' says co-investigator Michael Simons, Professor of Pharmacology and Toxicology, Chief of Cardiology, and Director of the Angiogenesis Research Center at Dartmouth Medical School (http://www.dartmouth.edu). However, this structural change does not shut down the entire assembly but, instead, affects the degradation of only a small subset of proteins, and the effect is reversible.

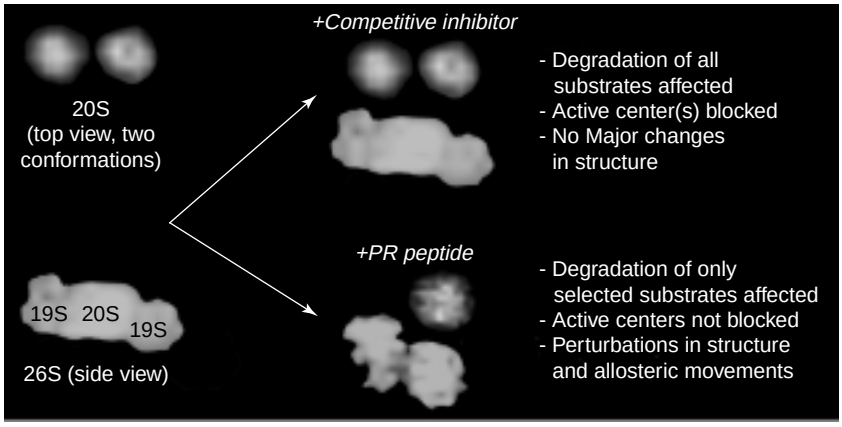

Figure 1. Atomic force micrographs (AFM) of human proteasomes treated with a competitive inhibitor or allosteric PR peptide *in vitro*. PR peptide-treated proteasomes exhibit dramatic changes in surface topography, which is accompanied by degradation of only selected substrates. The top-view 20S particle does not show the typical 'open' or 'closed' conformation but, instead, seems to be 'paralyzed' in a single, shaky conformation. The 26S particle after treatment with PR39 peptide also seems to be 'paralyzed': its length is about a third less than the length of the control (~20 nm versus ~30 nm.) Figure courtesy of Maria Gaczynska, Assistant Professor of Molecular Medicine at the University of Texas Health Science Center at San Antonio (http://www.uthscsa.edu). Abbreviation: PR, proline- and arginine-rich peptides.

Bypassing blockages

PR peptides are slated to be templates for cardiovascular drugs or for stroke because, unlike protease inhibitors developed to treat cancer, they inhibit the degradation of transcription factor HIF-1α, which is 'in essence, activation of angiogenesis'. According to Simons, the current medications for people with arterial blockages mitigate symptoms but many do not induce the growth of vessels. PR peptides 'would bypass the blockage by natural angiogenesis, so to speak,' he says. In addition, they might be useful in the treatment of diseases like rheumatoid arthritis because they also prevent the degradation of the inhibitor of NFκB – IκBα – thereby forestalling the activation of an inflammatory response.

Matthew Grisham, Professor of Molecular and Cellular Physiology at Louisiana State University Health Sciences Center in Shreveport, LA, USA (http://www.lsuhsc.edu), and an expert in inflammatory tissue, injury thinks that PR peptide drugs could become important in acute inflammatory situations, such as ischaemia reperfusion, where NFκB is activated.

'Proteasome inhibitors have not been widely used because, although efficacious, they are exceedingly toxic and must be used very sparingly,' cautions J. Steven Alexander, Associate Professor, also at Louisiana State University Health Sciences Center. '[They] are still 'twitchy' agents when I think of them clinically… and some kill cells at doses frighteningly close to the toxic dosage.' But it is expected that PR

peptides like PR39 will be significantly less toxic than conventional competitive proteasome inhibitors because they are much more specific. 'If it [PR39] constitutes a 'novel' and less toxic proteasome inhibitor, it could be great,' says Alexander. 'What I would like to see is how they will be able to deliver a small molecular weight inhibitor *in vivo*,' wonders Grisham, 'that is always, of course, the bugaboo in drug discovery.'

Peptoids, perhaps

The next step for investigators will be to learn exactly why PR peptides are substrate-specific *in vivo*. Knowing more about the molecular mechanism-of-action will enable them to model even better compounds. Gaczynska anticipates that peptoids, derivatives of peptides, can be made to bind to the proteasome even faster, stronger and with better specificity. This might still be a long way off, she says, but 'it is very promising, and what is important here is it is a new idea of proteasome inhibition'.

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Pharmacists seek the solution of a shaman

Marcus Anhäuser, BMN News

A traditional healer's prescription from the highlands of Mexico could make an effective addition to the therapeutic armament against diabetes, claims a German phytopharmacist.

Traditional healers in the highlands of Mexico can taste whether a patient has diabetes. If a patient shows typical symptoms, like strong thirst, the urge to urinate, tiredness and loss of weight, the healer will taste the blood or urine of the patient. 'If it is sweet, he knows what to do,' said Helmut Wiedenfeld, a Phytopharmacist at the University of Bonn (http://www.uni-bonn.de).

It's all in the blood

Sweet blood, better known in Western medicine as diabetes, is not rare in the Mexican highlands. 'In some villages, eight in ten adults suffer from diabetes mellitus,' Wiedenfeld said. A high sugar diet has recently spread to the region, particularly since sweet soft drinks entered villages in most remote valleys.

'It is tremendous, the kids drink it like water, sometimes two liters a day,' he said. Diabetes mellitus is recognized as the fourth highest cause of mortality globally. Mexico itself is the country with the fourth highest frequency of the disorder in the world.

According to World Health Organization predictions (http://www.who.org), there will be 11.7 million diabetic patients in Mexico by 2025, which means every seventh Mexican will have the disorder. But a shaman would be a hopeless healer if he did not provide medicine. The Mexican healers prescribe a drink called 'Agua de Uso,' meaning water for daily use, Wiedenfeld has found. Patients have to drink half a litre of this liquid per day, and Wiedenfeld is busy working out what it contains.

The magic ingredient

The healers, called curanderos, use local plants that have been used for generations to treat diabetes. About 880 plants worldwide are believed to possess hypoglycemic activity, 343 of which have been reported in the scientific literature. 'But most are just anecdotal stories or poorly tested,' said Wiedenfeld. In Mexico, an estimated 400 plants are used in the treatment against diabetes.

Wiedenfeld knows three of these that work. Shamans always use one plant, no mixtures, which made it easier for the German to investigate. At first he tested a plant called *Equisetum myriochaetum*, the traditional name of which is 'cola de caballo', the Mexican word for the English family name it belongs to – horsetail. Ethnopharmacologically it is reported to show activity against kidney disease.

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