Novel candidate for treatment of haematopoietic disorders

Vida Foubister, freelance writer

A small molecule that targets signalling peptides has been found to stimulate haematopoiesis in human cell cultures and mouse models [1]. PT100, an orally bioavailable amino boronic dipeptide (Val-boro-Pro), increases the levels of key cytokines in the haematopoietic system, including granulocyte colony-stimulating factor (G-CSF), interleukin-6 (IL-6) and interleukin-11 (IL-11).

Point Therapeutics (http://www.pther.com) is currently conducting a Phase I clinical trial to evaluate PT100 as a treatment for neutropenia in cancer patients undergoing chemotherapy. The Boston-based biopharmaceutical company, whose scientists recently discovered that PT100 has anti-tumour activity, has also announced plans to initiate a Phase I clinical trial to study its safety and efficacy in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

Amino boronic dipeptides

PT100 is one of a class of amino boronic dipeptides that was originally developed by researchers at Tufts University School of Medicine (http://www.tufts.edu/med) to inhibit CD26/dipeptidyl aminopeptidase IV. These molecules were later found to stimulate progenitor cell proliferation [2,3].

Scientists at Point Therapeutics have further characterized the activity of one such molecule, PT100 or Val-boro-Pro (Fig. 1). Oral administration of 5 μg PT100, twice daily for five days, to BALB-c mice increased their levels of erythroid and myeloid progenitor cells.

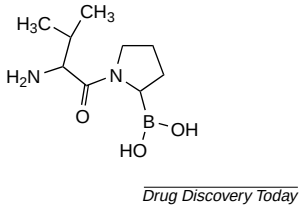

Figure 1. Structure of the amino boronic dipeptide, Val-boro-Pro (PT100). Figure courtesy of Point Therapeutics (http://www.pther.com).

PT100 also increased absolute neutrophil counts and serum levels of G-CSF and IL-6 in these animals, further suggesting that it stimulates granulopoiesis.

'Most interestingly, it could stimulate the generation of neutrophils in mice that had been treated with myeloablative cyclophosphamide chemotherapy,' says Barry Jones, Senior Vice President of Research at Point Therapeutics. BALB-c mice were given 220 mg cyclophosphamide per kg body weight, a dose that reduces their peripheral blood absolute neutrophil count (ANC) by at least 90% in four days, and then treated with 2 μg or 5 μg PT100. This treatment stimulated neutrophil regeneration, with the optimal response following administration of 2 μg PT100 on days three to five following cyclophosphamide treatment.

In vitro studies using human bone-marrow stromal cells further support a role for PT100 in stimulating haematopoiesis through the upregulation of cytokines. These experiments and others done with CD26-deficient mice were also used to determine its mechanism-of-action. PT100 appears to stimulate haematopoiesis through fibroblast activation protein (FAP) and not the structurally similar serine protease CD26.

Existing treatments

Neutropenia, a condition characterized by a low white blood count that can result in severe or even life-threatening infections, is the most common side effect of cancer chemotherapy. 'Patients often end up having their chemotherapy compromised because the oncologist will reduce the dose intensity,' explains Gary Lyman, Professor of Medicine and Oncology at the University of Rochester (http://www.rochester.edu).

Amgen (http://www.amgen.com) markets the two products that are currently available on the market to treat neutropenia: Neupogen®, a recombinant G-CSF, is injected daily for up to two weeks over the course of chemotherapy; Neulasta® is G-CSF that has been modified by the addition of polyethylene glycol to increase the length of time it circulates in the bloodstream and requires only a single dose per chemotherapy cycle.

Unlike Neupogen® and Neulasta®, treatment with PT100 does not directly increase cytokine levels. Instead, it stimulates their production. Effective doses of other cytokines, such as IL-6, are associated with unacceptable toxicities. According to Richard N. Small, Senior Vice President, Chief Financial Officer

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and Treasurer of Point Therapeutics, PT100 has several potential advantages. One is that it is orally bioavailable and therefore does not need to be injected. Secondly, it is inexpensive to manufacture and is thus potentially a cost-effective therapy. Third, it has a broad mechanism-of-action. 'You could get multiple beneficial effects outside of restoring your neutrophils,' he explains.

'The novelty of it is the fact that this is a new therapeutic target,' says Jaroslaw Maciejewski, Section Head of Experimental Hematology and Hematopoiesis at the Cleveland Clinic Cancer Center (http://www.clevelandclinic.org/cancer). Although clinicians are looking for better and less toxic ways to treat neutrophenia, its unclear that PT100 will prove to be as efficacious as conventional treatments. 'The effect that they've demonstrated in mice is quite a bit less than treatment with G-CSF,' says Lyman. 'Perhaps different doses or schedules will prove to be more effective.' He also suggested the possibility of evaluating the effect of PT100 in combination with Neupogen® or Neulasta®.

Other indications

Point Therapeutics released interim results from its Phase I clinical trial evaluating the effects of PT100 in patients with chemotherapy-induced neutropenia on 28 May 2003. 'It's been well tolerated and we've seen some biological effects that correlate with the preclinical animal studies,' Small concludes.

Based on data that PT100 can stimulate the production of cytokines and chemokines to promote acquired and innate immune defenses against certain cancerous tumours, the company is also initiating a clinical trial in patients with hematological malignancies this year [4]. 'In a preclinical mouse model of human B cell lymphoma, PT-100 was shown to enhance the activity of the monoclonal antibody Rituximab (Rituxan®; http://www.rituxan.com), [which] is currently used to treat non-Hodgkin's lymphoma,' says Jones. 'Because both non-Hodgkin's lymphoma and chronic lymphocytic leukaemia express the target antigen, CD20, which is recognized by Rituximab, PT100 could augment its activity in the treatment of both types of cancer.'

References

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An everlasting flu vaccine with none of the pain

Paul D. Thacker, freelance writer

Researchers at the Wistar Institute (http://www.wistar.upenn.edu) are currently devising a prototype mouse influenza vaccine, which promises to last longer and provide increased protection against this rapidly evolving pathogen. The vaccine has three novel features: a synthetic peptide as the vaccine, a nasal delivery system and an immune response to unique protein on the virus.

The World Health Organisation (WHO; http://www.who.org) estimates that five million people are affected by influenza every year and, of those, a quarter to half a million patients die. Although a vaccine for the pathogen exists, the virus mutates rapidly, forcing researchers to constantly search and identify new strains and then ascertain which viruses to incorporate into the annual flu shot.

'Normally against influenza you use an inactivated virus,' says Winstar Institute Associate Professor, Laszlo Otvosz [1]. 'But like many other groups, we are trying to use subunit vaccines which come from proteins or peptides.'

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