New therapies

Haemopoietic growth factors

NJ Ketley, AC Newland

Haemopoietic growth factors (HGFs; box 1) were originally described on the basis of their ability to support haemopoietic colony growth in vitro. The genes for several of these proteins have been cloned and their production engineered by recombinant technology, making them available for widespread clinical use. This review discusses the uses of those HGFs which are licensed for clinical practice, and describes areas of current research in this field.

HGFs and their receptors

Both HGFs and their receptors show considerable structural homology, suggesting that they are derived from a smaller repertoire of factors. HGFs differ as to their target cells, both in lineage and maturity (box 2; figure 1), but there is considerable overlap and some redundancy, the relevance of which is unclear. HGFs also differ as to their glycosylation status, depending on whether a cationic or prokaryotic production system is used (box 3); erythropoietin has been shown to have minimal activity if non-glycosylated, whereas the effect of glycosylation on granulocyte- and granulocyte-macrophage colony-stimulating factor (G- and GM-CSF) function has yet to be clarified. The pathways for signal transduction from the HGF/receptor complexes are currently the subject of intensive research, which will bring greater understanding of the role of HGFs in haematological disease.

HGFs in steady-state and stressed haemopoiesis

HGFs have been thought to control the production of the various cellular elements of the bone marrow, as well as enabling the body to respond to pathological challenges such as infection and bleeding. Production of the various cells from progenitors was thought to proceed along a series of predetermined divisions, each yielding more committed and mature cells of defined type, with limited scope for external modulation (stochastic haemopoiesis). More recent evidence suggests that while HGFs play only a minor role in physiological (unstressed) haemopoiesis, the series of divisions occurs in a random manner (deterministic haemopoiesis),1 which may be influenced by HGFs in response to external stimuli. Autocrine HGF production has been demonstrated in some cases of acute myeloid leukaemia, in which it is associated with a poorer prognosis; this suggests that derangement of HGF production may be involved in the development of the transformed phenotype characteristic of malignant haemopoiesis.2

Reappraisal of HGF usage

The initial enthusiasm for HGFs has been tempered recently. Following five years of ever-expanding indications for their use, guidelines for the use of myeloid HGFs have recently been produced by the American Society of Clinical Oncology3 so that effective evaluation can take place. It is now clear from several large randomised studies that, in some areas of practice, their use conveys no clinical benefit, whilst in others it is generally not cost-effective. However, a number of indications have now been accepted for licensing purposes. These include erythropoietin for hypoproliferative anaemias, GM-CSF and G-CSF to accelerate marrow recovery after marrow transplantation and G-CSF to accelerate marrow recovery after cancer chemotherapy and in the treatment of severe chronic neutropenia.

Other uses are under evaluation and will be considered in more detail. These include (a) collection and transfusion of peripheral blood progenitor cells (PBPC) as an alternative to bone-marrow transplantation, (b) ex-vivo expansion of precursor cells as an alternative to harvesting large numbers of bone marrow cells or PBPCs, and (c) the application of these factors to the treatment of infectious diseases. One observation in this latter area is of particular interest: following the administration of cytokines, particularly GM-CSF, alterations in

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Summary

Haemopoietic growth factors are involved in the production of the various blood cells from progenitors in the bone marrow, making them useful in a range of clinical situations. The genes for several of them have been cloned and their production engineered by recombinant technology, making them available for widespread clinical use. This review discusses the uses of those HGFs which are licensed for clinical practice, and describes areas of current research in this field.

Keywords: haemopoietic growth factors, chemotherapy, cytopenia

<table>
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<tr>
<td>erythropoietin (Epo)</td>
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<td>granulocyte-colony stimulating factor (G-CSF)</td>
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<td>granulocyte/macrophage-colony stimulating factor (GM-CSF)</td>
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<td>interleukin 1 (IL-1)</td>
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<td>interleukin 3 (IL-3)</td>
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<td>interleukin 6 (IL-6)</td>
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<tr>
<td>macrophage-colony stimulating factor (M-CSF)</td>
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<td>stem-cell factor (SCF)</td>
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<td>thrombopoietin (Tpo)</td>
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Box 1

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neutrophil and monocyte kinetics occur, mimicking those seen with endotoxiaemia and bacterial infection. Preclinical studies suggest that stimulation by CSFs can enhance the inflammatory response and lead to a better outcome of infections. In addition to these applications, there have been several trials on the use of erythropoietin and G-CSF in autologous blood banking, these are particularly contentious in cost-benefit analyses. The main areas of reappraisal will be considered in more detail below.

Chemotherapy and bone-marrow transplantation

HODGKIN’S DISEASE AND NON-HODGKIN’S LYMPHOMAS (BOX 4)

Initial concerns that myeloid growth factors might stimulate myeloid leukaemia cells meant that early studies of HGFs in association with chemotherapy and bone marrow transplantation were conducted in lymphomas. HGFs were initially used for cases of Hodgkin’s disease and non-Hodgkin’s lymphomas in relapse where autologous bone marrow transplantation is the treatment of choice. Both G- and GM-CSF, given after conditioning, significantly reduce the duration of neutropenia and hospital stay; there is generally a trend towards fewer infective episodes, less use of antibiotics and less requirement for parenteral feeding; platelet recovery, survival and relapse rates are unaffected.

More recently, HGFs have been used to reduce the haematological toxicity of out-patient remission induction therapy and non-bone-marrow-transplantation salvage regimens. Whilst GM-CSF is effective in reducing periods of neutropenia and associated infections and the duration of resulting hospital admissions, there is again no effect on survival. Some worries remain that non-haematological toxicity may be increased by such strategies and any possible effects mediated through HGF receptors on non-haemopoietic cells (eg, colonic carcinoma) remain ill-defined at present.

The failure of HGFs to reduce post-bone-marrow-transplantation relapse, taken together with some studies showing a poorer outcome on HGFs, and better understanding of drug-resistance mechanisms, suggests that dose escalation alone does not hold the answer to increasing cure rates of lymphomas and other malignancies.

ACUTE MYELOID LEUKAEMIA

Early in vitro data suggested that clonogenic acute myeloid leukaemia cells might be induced to proliferate and differentiate by HGFs, conveying a potential survival advantage. Clinical studies to date have been reassuring in providing no evidence for such an effect impacting on remission, relapse and survival rates; however, although studies have shown a significant acceleration of neutrophil recovery with both G- and GM-CSF, this has not been accompanied by reductions in the rate of overall or fatal infections.

Theoretical and in vitro evidence in favour of HGFs increasing the number of cells in cycle and thus maximising cell kill from chemotherapy has not translated into greater remission rates, and indeed one study has shown a deleterious effect of GM-CSF started two days prior to chemotherapy on remission induction. Current recommendations are therefore for the use of HGFs following chemotherapy in acute myeloid leukaemia for life-threatening infections and in those considered to be high-risk, such as the elderly and those expected to regenerate slowly. A recent large randomised study has, however, failed to show any benefit of GM-CSF following daunorubicin/ctarabine induction chemotherapy in patients over the age of 60.

ALLOGENIC BONE MARROW TRANSPLANTATION

As with autologous bone-marrow transplantation, both G- and GM-CSF have been shown to enhance neutrophil regeneration in allogeneic transplantation; however, neither agent has shown a beneficial effect on platelet recovery, graft-versus-host disease (GVHD) or overall survival. Some concerns remain as to the effects of HGFs on GVHD, which is essentially cytokine-driven, and their use is therefore recommended only for those who experience delayed engraftment.

G-CSF has been shown to have some activity in those with leukaemia relapsing after allogeneic bone-marrow transplantation, a group with a very poor prognosis. Giralt and colleagues reported on seven patients who relapsed within a year of transplant, three of whom achieved a complete remission of more than nine months duration when treated with G-CSF alone. The mechanism was thought to involve both stimulation of the donor (grafted) marrow and differentiation of the relapsed leukaemic clone.
Haemopoietic growth factors in clinical practice

**Growth factors and their target cells**

<table>
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<tr>
<th>Growth factor</th>
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<tr>
<td>G-CSF</td>
<td>Committed granulocyte precursors</td>
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<tr>
<td>GM-CSF</td>
<td>Less mature myeloid precursors and macrophage precursors</td>
</tr>
<tr>
<td>Epo</td>
<td>Erythroid precursors</td>
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Those in routine clinical use

- G-CSF: committed granulocyte precursors
- GM-CSF: less mature myeloid precursors and macrophage precursors
- Epo: erythroid precursors

Those in use in clinical trials and on compassionate basis

- IL-3: immature myeloid precursors, including erythroid & megakaryocytic
- IL-6: megakaryocyte & B-cell precursors

Those in use in vitro

- M-CSF: committed macrophage precursors
- SCF: pluripotent progenitor cells
- Tpo: megakaryocyte precursors

Box 2

**HGFs licensed for clinical use in UK**

- Erythropoietin, Epoetin alpha (Epogen, Eprex, Cilag Biotech) - glycosylated
- Erythropoietin, Epoetin beta (Recormon, Boehringer Mannheim) - glycosylated
- G-CSF, Filgrastim (Neupogen, Amgen) - non-glycosylated, E.coli
- G-CSF, Lenograstim (Granocyte, Chugai) - glycosylated, Chinese hamster ovary
- GM-CSF, Molgramostim (Leucomax, Sandoz) - non-glycosylated, E.coli

Box 3

**Indications in Hodgkin’s disease and non-Hodgkin’s lymphoma**

**Bone marrow transplantation**

- Faster regeneration and reduced hospital stay
- No adverse effects on relapse
- No survival advantage

**Induction or salvage chemotherapy**

- Less neutropenia, may prevent admissions
- Greater non-haematological toxicity

Box 4

CHEMOTHERAPY FOR SOLID TUMOURS

G-CSF has been shown to reduce neutropenia and infection in patients with small-cell lung cancer receiving chemotherapy, with a concomitant reduction in the need for antibiotic treatment and hospital admission. The benefit of using G-CSF is modest, such that it is only recommended where the chemotherapy regimen being used has a greater than 40% chance of inducing febrile neutropenia.

The advent of transplantation using PBPCs has increased the potential for chemotherapy in solid tumours such as lung and breast carcinoma. Although the high dose chemotherapy that can be given with such a strategy is generally associated with a gratifying early response, it remains unclear whether such intensification offers any long-term advantage over conventional dose chemotherapy. In breast carcinoma, response can be predicted based on that seen with conventional dose chemotherapy, however, even in these responsive patients only 15–20% achieve a durable remission with transplantation. Randomised controlled trials are currently underway to establish the appropriate indications for use of these various therapeutic approaches but early results do suggest that high-dose strategies with stem cell support may have a role in the poor prognosis, node-positive group. Similar results have also been reported in lung cancer. Initial results were disappointing but more recent studies with high-dose therapy plus PBPC and local radiotherapy in limited-disease small-cell lung cancer have shown much better results than those receiving conventional chemotherapy. Further controlled studies are underway.

**PBPC mobilisation and transplantation**

PROBLEMS WITH BONE-MARROW TRANSPLANTATION

Despite the encouraging reduction in the duration of neutropenia following autologous bone-marrow transplantation with the use of HGFs, two problems remain: firstly, a 10–14 day period of obligate neutropenia with significant morbidity and, secondly, platelet dependence lasting an average of 4–6 weeks. This prompted the search for alternative sources of progenitor cells, which might lead to more rapid engraftment.

MOBILISATION

Progenitor cells were first demonstrated in the peripheral blood in 1962, and an increase during regeneration following chemotherapy was noted a decade later. It was not until the availability of HGFs, however, that such cells were put to widespread clinical use. Several studies have now confirmed that using PBPCs allows faster regeneration than using bone marrow (typically neutropenia and thrombocytopenia of less than two weeks), due to the presence of a mixture of 'stem-cells' and more committed progenitor cells; this limits morbidity and allows high-dose chemotherapy to be used in patients who were previously ineligible for bone-marrow transplantation. PBPC transplantation is being used increasingly for solid tumours and is rapidly replacing autologous bone marrow transplantation for haematological malignancies.

PBPCs are best mobilised by a combination of myelosuppressive chemotherapy followed by G- or GM-CSF; this effects a 10–100-fold increase in PBPC numbers, which can be collected using cell-separation technology (box 5; figure 2). This harvesting procedure allows transplantation of those who have received previous pelvic radiotherapy and who are unfit for a general anesthetic; it also holds the potential for less tumour contamination of the harvested product, which is currently being investigated prospectively using polymerase chain reaction techniques. There is no additional benefit in using HGFs after transplantation; the minimum period of neutropenia remains seven or eight days.

THE FUTURE OF PBPCS

PBPCs are also increasingly used for allogeneic transplantation, with HGF alone used for the mobilisation phase. Regeneration is faster than bone marrow transplantation, and initial data suggest no adverse effects on GVHD or disease outcome compared with traditional allogeneic bone marrow transplantation.

Remaining issues in using PBPCs are the threshold of cells required for both short-term and long-term reconstitution (current estimates are 2 x 10^6 CD34+ cells/kg or 10 x 10^6 CFU-GM/kg) and the best method of assessing this (CD34 by immunophenotyping or CFU-GM by colony assay). The potential for using cocktails of HGFs for ex vivo expansion of PBPCs will allow the wider application of their use, especially when combined with gene therapy techniques.
Transplantation using PBPCs

- harvest using chemotherapy + HGF
- faster regeneration including platelets; shorter hospital stay
- possible even with bone marrow involvement (outcome here remains under evaluation)
- applicable to allogeneic transplantation (HGF only)
- potential for ex vivo expansion and gene therapy

Box 5

Figure 2 Role of HGFs in normal haematopoiesis

Cytopenia and bone marrow failure

APLASTIC ANAEMIA
Patients with aplastic anaemia generally have high circulating concentrations of HGFs such as G-CSF, GM-CSF and erythropoietin (Epo), and in vitro studies have shown normal HGF production from stromal cells of aplastic patients. Concern has recently been expressed that the use of HGFs in cases of severe aplastic anaemia only delays definitive treatment such as bone marrow transplantation,$^{23}$ with an attendant risk of increased alloimmunisation and greater transformation to acute leukaemia; later use of bone-marrow transplantation in these patients has an ever-decreasing rate of cure. Use of HGFs is currently justified for the treatment of systemic infections and, in the context of clinical trials, especially for those in whom transplantation is not a realistic treatment option.

MYELODYSPLASIA
The cytopenia in myelodysplasia is often less severe than in aplastic anemia, at least initially, and may be restricted to one or two lineages; in addition, these patients are predominantly of an age at which bone marrow transplantation is not a treatment option. HGFs have been used singly, in combination and together with low-dose chemotherapy or differentiating agents. Although overall responses have been disappointing, some studies have shown beneficial effects on haemoglobin levels/transfusion dependency and neutrophil counts; thrombocytopenia is ameliorated much less often. Few of these generally small studies have shown significant impact on quality of life and survival. Better patient selection, for example, using molecular genetics, should allow for improvement of these results in current trials.

HIV INFECTION
Cytopenia in HIV infection is multifactorial, with immune factors, drugs, infection, bone marrow infiltration and HIV infection per se all playing a part; treatment-related myelosuppression is a major limiting factor in therapy of both HIV and its complications. A significant number of patients have been shown to respond to Epo with a decreased transfusion requirement and improved quality of life; a retrospective analysis showed greater response rates in those with low (<500 IU/ml) endogenous Epo levels.

G-CSF has been used with variable dosing intervals to maintain the absolute neutrophil count above 1.5 x 10^9/l,$^2$ enabling continuation of antibiotic treatment or chemotherapy, and controlling bacterial infections. GM-CSF has been shown to correct functional abnormalities in neutrophils and monocytes with no adverse effects on viral replication or p24 antigen levels.$^9$ The thrombocytopenia of HIV has proven more difficult to reverse, with neither G-, GM-CSF nor Epo showing any activity. Zidovudine is sometimes effective, studies with interleukin-3 (IL-3) are ongoing, and thrombopoietin will doubtless be tried soon.
Agranulocytosis and Neutropenia

HGFs have been used for the treatment of drug-induced agranulocytosis with encouraging results: the duration of severe neutropenia is reduced, with a concomitant reduction in mortality to around 5%. The median time to recovery of neutrophils is eight days, however, the wide range (2–56 days) suggests that many patients do not require treatment with HGFs for a successful outcome; initial bone marrow assessment seems to be the best predictor of the need for HGF therapy - those showing white cell aplasia should receive HGF, whilst those showing early regeneration (‘maturation arrest’) will recover without the need for HGF. Congenital agranulocytosis carries a much higher morbidity, with some sufferers dying in childhood. In vitro studies have demonstrated normal numbers of granulocyte precursors, which exhibit decreased maturation and growth; this can be reversed with HGFs in vitro, and their use in vivo has been accompanied by increases of neutrophil counts to within the normal range, resolution of chronic infections, a decrease in new infections and decreased antibiotic usage. The most severely affected children, those with Kostmann’s syndrome, show marrow hyperplasia with inadequate maturation and an increased risk of transformation to myelodysplasia and acute myeloid leukaemia. Such children show a remarkable response to G-CSF, although recent evidence suggests that mutation of the G-CSF receptor may confer a yet further increased risk of malignant transformation.

Cyclic neutropenia is characterised by regular fluctuation in the peripheral blood neutrophil counts, often with a periodicity of 21 days. The disease has been attributed to a defect of progenitor cell regulation, although the precise lesion has not been identified; the disease can be transferred by bone-marrow transplantation in animal models, and responds poorly to standard treatment modalities. G-CSF has been shown to have a beneficial effect on both neutropenia and the resulting symptoms from infectious complications.

A few patients with autoimmune neutropenia have been treated with G-CSF to good effect. Surprisingly, these patients required quite small doses of G-CSF (30 MU twice weekly) to attain neutrophil counts greater than 1 x 10⁹/L, which were associated with reduced morbidity, resolution of oral ulceration and decreased infection rate. Patients with both cyclic and autoimmune neutropenia have been shown to maintain lasting responses (9–18 months) to G-CSF, with no evidence of bone marrow exhaustion.

Anaemia Associated with Malignancy, Chronic Disease and Surgery

Malignancy-Associated Anaemia

Many patients with malignancy have a degree of anaemia, which is a major determinant of their quality of life; the pathogenesis includes chemo- and/or radiotherapy, bleeding, bone-marrow infiltration and immune factors. Where the erythropoietic system is not a part of the malignant clone, the anaemia is often characterised by an Epo level inappropriately low for the degree of anaemia; in many such cases the anaemia will respond to therapy with Epo, with a reduction in transfusion requirements and improved quality of life. The anaemia associated with myeloma responds better than that associated with various solid tumours, with breast and colonic carcinomas showing the poorest response. In cases associated with bone-marrow infiltration, the response is proportional to the degree of infiltration; useful responses may still be obtained.

Anaemia in Chronic Disease States

The demonstration that the multifactorial anaemia associated with end-stage renal failure was largely due to Epo deficiency, and that upwards of 95% of such patients will respond to Epo therapy has transformed the management of this group of patients. It has also highlighted debate about the provision of such undoubtedly efficacious, but expensive treatment within various healthcare systems, and led to a search for other chronic-disease associated anaemias which might show a response to Epo.

Most patients with anaemia of chronic disease are only moderately anaemic and may derive little benefit from Epo therapy; symptoms attributed to anaemia may in fact be due to the underlying condition. Some patients do have symptomatic anaemia, and Epo has been shown to be effective in patients with rheumatoid arthritis when given thrice weekly.

Erythropoietin and Autologous Blood Donation

Autologous donation prior to elective surgery is becoming increasingly popular, and the feasibility of this is much enhanced by Epo therapy. Epo allows the necessary units to be collected over a shorter period of time, and means that patients with some degree of anaemia can still donate without haemodynamic
compromise. However, a recent study has demonstrated that this is a complex issue: some orthopaedic patients required more allogeneic blood if they had donated more autologous units, and many autologous units were wasted. The use of Epo does not currently form part of UK guidelines for autologous transfusion, and advice should be sought from haematologists locally.

Current research and future practice

THROMBOPOIETIN
Advances in growth factor support of patients with haematological malignancy have been hindered by the lack of an effect on platelet recovery with single HGFs; even combinations, such as GM-CSF with IL-3, which have some activity, have unacceptable toxicity for other than compassionate usage. A platelet-specific HGF was postulated but remained elusive until last year when, after many years of searching, thrombopoietin was described. This glycoprotein binds to the previously described c-Mpl ligand on megakaryocytes and has modulatory effects on both proliferation and maturation; its efficacy in conditions with deficient platelet production will soon be tested, and it should prove a valuable member of the recombinant HGF armamentarium.

EX VIVO EXPANSION AND MANIPULATION OF PROGENITOR CELLS
The ability to isolate and grow progenitor cells in long-term culture has raised the possibility of manipulating them to realise therapeutic goals. It has already been demonstrated that progenitor cells can be expanded many-fold by combinations of HGFs, such as stem-cell factor, IL-1, IL-3, IL-6, G-CSF and GM-CSF. Such techniques allow the generation of sufficient cells for transplantation from inadequate initial harvests, or without the need for mobilisation chemotherapy/HGFs, and have already been put to clinical use with good effect. The availability of a rich source of progenitor cells has allowed the development of techniques whereby ‘therapeutic’ genes may be transferred into haemoipoietic stem cells with the opportunity to treat a wide range of human disease. Unfortunately, low efficiency of transfer and limited expression of the transferred gene have largely prevented any beneficial effect so far. There have been few clinical studies but important progress has been achieved in some of the inherited genetic disorders. In cancer therapy there has been less progress, despite considerable effort, but gene marker studies in which the transferred genes are used simply to track the infused components of the stem cell harvest have already shown their utility. Genetic marking has shown that following autologous transplantation cells present within the graft are capable of causing relapse and such approaches may aid adequate purging prior to transplantation.

NOVEL INDICATIONS
Intradermal GM-CSF has been shown to improve wound-healing in patients with lepromatous leprosy, who showed enhanced keratinocyte growth, Langerhans recruitment and increased rate of wound healing. Animal models suggest that these effects do not operate via increased circulating neutrophil or monocyte/macrophage numbers, and that the effect is particular to GM-CSF. Studies are ongoing using local GM-CSF to treat chronic leg ulcers and cutaneous Kaposi sarcoma lesions.
Locally applied GM-CSF has similarly been shown to benefit patients at risk of oral mucositis following myeloablative chemotherapy. Effects such as enhanced chemotaxis, increased cell adhesion and neutrophil and macrophage activation are thought to explain the reduced incidence and severity of oral mucositis associated with the use of GM-CSF mouthwashes.

Conclusion
HGFs have rapidly established a central role in the treatment of a wide range of haematological disorders and randomised studies have confirmed their effectiveness in reducing blood product support and facilitating early discharge from hospital. Although they do not appear to affect survival, their effect on quality of life is undisputed. Their use in non-haematological malignancies is also now becoming established for similar reasons. Initial fears about stimulation of malignant clones have proved largely groundless, although long-term effects in those with bone marrow failure have yet to be excluded. Recent appraisal has centred on appropriate use based on morbidity and mortality analysis and studies are now concentrating on dose intensification and enhanced response. Cost-effectiveness and patient quality of life are also
Haemopoietic growth factors in clinical practice

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important and the findings in recent studies have confirmed the savings associated with shorter in-patient episodes and the improvement in morbidity. 12 Thrombopoietin should soon join the other clinically available HGFs to aid treatment of thrombocytopenia due to inadequate marrow production and the results of the current studies are eagerly awaited.