Drugs of the Future 2005, 30(5): 521-540

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Annual Update 2004/2005 - Treatment of Hematological Disorders

As in previous issues, the goal of this section is to present a balanced picture of the current status of therapies for hematological disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. The therapeutic classification has changed since the publication of the last review and, as also explained in the previous issue of the journal, conditions previously included in this group of drugs, *i.e.*, thrombosis, acute coronary syndrome, myocardial infarction, pulmonary embolism, coronary surgeries, peripheral and arterial vascular disorders and shock, now belong to the group of cardiovascular drugs. A table of oncolytic drugs for hematological/blood cancers is included at the end of this review.

J.R. Prous
Editor

Treatment of Hematological Disorders by Condition

Condition	Phase	Drug	Source
Anemia	II	FG-2216	FibroGen/Astellas Pharma
Anemia, renal failure	III	Ferumoxytol	Advanced Magnetics
	III	R-744	Roche
	II	R-744	Chugai
	I	Hematide™	Affymax
Anemia, secondary	Prereg. (US)	Hemoglobin glutamer-250 (bovine)	Biopure
	Discontinued	Hemoglobin raffimer	Hemosol
Anemia, secondary (chemotherapy-induced)	II	R-744	Roche
	I/II	AMG-114	Amgen
	I	Hematide™	Affymax
Anemia, secondary (heart failure)	II	Darbepoetin alfa[1,2]	Amgen
Anemia, sickle cell	III	ICA-17043[2]	ICAgen/McNeil
	III	NIX-0699	Xechem
	III	Poloxamer-188	SynthRx/CytRx
	I/II	Decitabine[2]	SuperGen/MGI Pharma
Coagulation factor VIIa deficiency	L-2004	Eptacog alfa (activated)[1]	Novo Nordisk
Coagulation factor VIII deficiency (hemophilia A)	II	OBI-1	Octagen/Ipsen
Coagulation factor XIII deficiency	I	Recombinant human factor XIII	Novo Nordisk
Disseminated intravascular coagulation	III	ART-123	Asahi Kasei
Hemorrhage	Prereg.	Eptacog alfa (activated)[1]	Novo Nordisk/ZymoGenetics
	II	rhThrombin	ZymoGenetics
Hemorrhage, subarachnoid	Prereg.	Nicaraven[2]	Chugai
	II/III	Clazosentan sodium	Actelion

Continuation

Treatment of Hematological Disorders by Condition

Condition	Phase	Drug	Source
Idiopathic thrombocytopenic purpura	III	AMG-531	Amgen
Leukopenia	Prereg.	Recombinant human GM-CSF	Cangene/Apotex
Neutropenia	I	KRN-125	Kirin Brewery
Neutropenia, chemotherapy-induced	I	CTCE-0214	Chemokine Therapeutics/Pharmaceutical Product Development
Paroxysmal nocturnal hemoglobinuria	III	Eculizumab[2]	Alexion
Thrombasthenia	L-2004	Eptacog alfa (activated)[1]	Novo Nordisk
Thrombocytopenia	II I	497115 *N*-Acetylcysteine[1,2]	GlaxoSmithKline/Ligand Adherex

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of Hematological Disorders by Source

Source	Condition	Drug	Phase
Actelion	Hemorrhage, subarachnoid	Clazosentan sodium	II/III
Adherex	Thrombocytopenia	*N*-Acetylcysteine[1,2]	I
Advanced Magnetics	Anemia, renal failure	Ferumoxytol	III
Affymax	Anemia, renal failure	Hematide™	I
	Anemia, secondary (chemotherapy-induced)	Hematide™	I
Alexion	Paroxysmal nocturnal hemoglobinuria	Eculizumab[2]	III
Amgen	Anemia, secondary (chemotherapy-induced)	AMG-114	I/II
	Anemia, secondary (heart failure)	Darbepoetin alfa[1,2]	II
	Idiopathic thrombocytopenic purpura	AMG-531	III
Apotex	Leukopenia	Recombinant human GM-CSF	Prereg.
Asahi Kasei	Disseminated intravascular coagulation	ART-123	III
Astellas Pharma	Anemia	FG-2216	II
Biopure	Anemia, secondary	Hemoglobin glutamer-250 (bovine)	Prereg. (US)
Cangene	Leukopenia	Recombinant human GM-CSF	Prereg.
Chemokine Therapeutics	Neutropenia, chemotherapy-induced	CTCE-0214	I
Chugai	Anemia, renal failure	R-744	II
	Hemorrhage, subarachnoid	Nicaraven[2]	Prereg.
CytRx	Anemia, sickle cell	Poloxamer-188	III
FibroGen	Anemia	FG-2216	II
GlaxoSmithKline	Thrombocytopenia	497115	II
Hemosol	Anemia, secondary	Hemoglobin raffimer	Discontinued
ICAgen	Anemia, sickle cell	ICA-17043[2]	III
Ipsen	Coagulation factor VIII deficiency (hemophilia A)	OBI-1	II
Kirin Brewery	Neutropenia	KRN-125	I
Ligand	Thrombocytopenia	497115	II
McNeil	Anemia, sickle cell	ICA-17043[2]	III
MGI Pharma	Anemia, sickle cell	Decitabine[2]	I/II
Novo Nordisk	Coagulation factor VIIa deficiency	Eptacog alfa (activated)[1]	L-2004
	Coagulation factor XIII deficiency	Recombinant human factor XIII	I
	Hemorrhage	Eptacog alfa (activated)[1]	Prereg.
	Thrombasthenia	Eptacog alfa (activated)[1]	L-2004
Octagen	Coagulation factor VIII deficiency (hemophilia A)	OBI-1	II
Pharmaceutical Product Development	Neutropenia, chemotherapy-induced	CTCE-0214	I
Roche	Anemia, renal failure	R-744	III
	Anemia, secondary (chemotherapy-induced)	R-744	II
SuperGen	Anemia, sickle cell	Decitabine[2]	I/II
SynthRx	Anemia, sickle cell	Poloxamer-188	III
Xechem	Anemia, sickle cell	NIX-0699	III
ZymoGenetics	Hemorrhage	rhThrombin	II
	Coagulation factor XIII deficiency	Recombinant human factor XIII	I

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Treatment of Hematological Disorders

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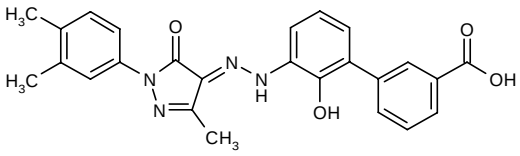
497115



497115 (SB-497115) is an oral, small-molecule drug that mimics the activity of thrombopoietin (TPO) and the first product to move into phase II studies from Ligand and GlaxoSmithKline's growth factor collaboration. The phase II studies are designed to evaluate 497115 in patients with chemotherapy-induced thrombocytopenia and in thrombocytopenia associated with disease states such as immune (idiopathic) thrombocytopenic purpura (ITP) and chronic liver disease. 497115 is the first, and most advanced in human development, nonpeptide small-molecule TPO receptor agonist with demonstrated activity in *in vitro* assays in human bone marrow and pharmacological activity in humans. Data from a phase I study in healthy volunteers show that 497115 increased platelet counts in a dose-dependent fashion when administered orally. An NDA submission is targeted for 2006. The GSK-Ligand collaboration began in 1995 to discover small-molecule drugs to control hematopoiesis to treat patients with cancer, anemia or platelet deficiencies. The research phase of the collaboration ended in 2001. GSK is responsible for the development and registration of products resulting from the collaboration, and Ligand may earn milestone payments of up to USD 8 million as a product moves through development. GSK has exclusive worldwide marketing rights to products resulting from the research, and will pay Ligand royalties. If 497115 is approved and marketed, Ligand could receive double-digit royalties on product sales (1).

1. *Ligand earns milestone for initiation of phase II for SB-497115*. DailyDrugNews.com (Daily Essentials) Feb 9, 2005.

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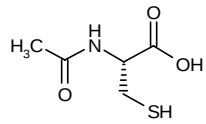
Jenkins, J. et al. *An oral, non-peptide, small molecule thrombopoietin receptor agonist increases platelet counts in healthy subjects*. Blood 2004, 104(11, Part 1): Abst 2916.

N-Acetylcysteine



Adherex is developing *N*-acetylcysteine (NAC) as a bone marrow protectant to prevent blood platelet loss caused by chemotherapy. The company licensed certain rights to the use of NAC for various indications, including the prevention of chemotherapy-induced platelet loss, from the Oregon Health & Science University (OHSU). The university is preparing to initiate a phase I clinical trial in the U.S. under an investigator IND for the use of NAC for protecting bone marrow in patients undergoing platinum-based chemotherapy.

Original monograph – Drugs Fut 1995, 20(6): 559.

AMG-114

A hyperglycosylated analogue of darbepoetin alfa (Aranesp®; see below), AMG-114, developed at Amgen, is currently undergoing phase I/II clinical trials for the treatment of chemotherapy-induced anemia. The compound has shown greater *in vivo* potency than epoetin alfa or darbepoetin alfa in preclinical studies.

AMG-531

Amgen has received fast track designation for AMG-531, the company's first peptibody and a potential new approach to treating immune (idiopathic) thrombocytopenic purpura (ITP). AMG-531 received orphan drug designation in 2003. As an investigational platelet growth factor, AMG-531 appears to directly stimulate platelet production and may offer physicians a way to shift the treatment focus from preventing platelet destruction to boosting platelet production in patients with ITP. The engineered protein therapeutic provides targeted action on the thrombopoietin (TPO) receptor. Like TPO, AMG-531 binds to the TPO receptor and stimulates megakaryocytes to mature into platelets. In recently reported phase I and II studies, AMG-531 appeared to enhance platelet production in patients diagnosed with ITP, and phase III trials have commenced (1, 2).

AMG-531 was tested for safety, tolerability, pharmacodynamics and pharmacokinetics in healthy individuals in a single-center, double-blind, randomized, placebo-controlled study of single doses (0.3-10 μg/kg i.v. or 0.1-2.0 μg/kg s.c.). A total of 48 subjects entered and completed the study. Administration of AMG-531 induced a dose-dependent increase in platelet counts, peaking on days 12-16. The mean platelet count was 1380 x 10^9/l and the dose of 10 μg/kg i.v. produced a 6-fold increase in platelet count from baseline levels. Platelet counts returned to baseline by day 28 of the study. Treatment was well tolerated, with the most common complaint being headache and sore throat (3).

1. *Fast track status for AMG-531 in immune thrombocytopenic purpura*. DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

2. *Amgen first quarter 2005 adjusted earnings per share increased 28 percent to 72 cents*. Amgen Press Release 2005, April 21.

3. Wang, B., Nichol, J.L., Sullivan, J.T. *Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand*. Clin Pharmacol Ther 2004, 76(6): 628.

Additional References

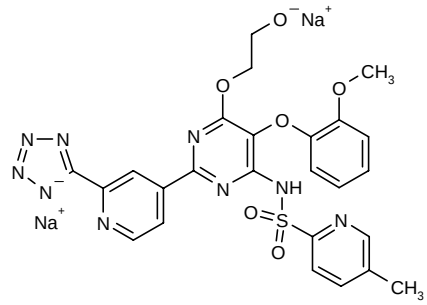
Kuter, D. et al. *A phase 2 placebo controlled study evaluating the platelet response and safety of weekly dosing with a novel thrombopoietic protein (AMG531) in thrombocytopenic adult patients (pts) with immune thrombocytopenic purpura (ITP)*. Blood 2004, 104(11, Part 1): Abst 511.

Newland, A. et al. *An open-label, unit dose-finding study evaluating the safety and platelet response of a novel thrombopoietic protein (AMG531) in thrombocytopenic adult patients (pts) with immune thrombocytopenic purpura (ITP)*. Blood 2004, 104(11, Part 1): Abst 2058.

ART-123

ART-123, or recombinant human soluble thrombomodulin, is an anticoagulant developed at Asahi Kasei and currently in phase III trials for the treatment of disseminated intravascular coagulation, as well as phase II trials for the treatment of deep venous thrombosis. It inhibits thrombin generation via activation of protein C and subsequent inactivation of factor Va and prothombinase. ART-123 prevents clot extension by inhibiting thrombin generation on clots, in contrast to other anticoagulants which inhibit clot formation.

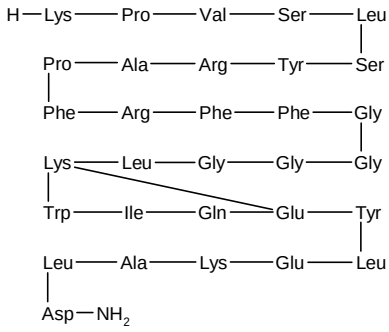
Clazosentan Sodium



Actelion has initiated a comprehensive global phase IIb/III development program for clazosentan sodium (formerly Ro-61-1790, VML-588, AXV-034343), an intravenous endothelin receptor antagonist. The international, double-blind, randomized, placebo-controlled, parallel-group, dose-finding study, known as CONSCIOUS-1 (Clazosentan to Overcome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage), will analyze the efficacy of three dose levels of clazosentan in preventing the occurrence of cerebral vasospasm following subarachnoid hemorrhage, assessed by angiography. As a secondary endpoint, the study will also assess the ability of clazosentan to reduce the occurrence of early morbidity/mortality, as well as the effect of clazosentan on clinical outcome and overall tolerability. The study is expected to recruit 400 patients in 65 centers worldwide and results are expected in the first half of 2006. These results will determine the need, size and duration of a potential phase III study. An earlier placebo-controlled phase IIa study in 34 patients showed that there were significantly fewer and less severe cases of vasospasm reported in the clazosentan group compared to placebo. There were also fewer patients with new cerebral infarcts in the clazosentan group. Infusions of clazosentan were generally well tolerated, with no effects on blood pressure or other vital signs. Full data from this study will become available in the first half of 2005. Actelion acquired clazosentan through its acquisition of Axovan in the fall of 2003 (1).

1. *Actelion begins global phase IIb/III program for clazosentan*. DailyDrugNews.com (Daily Essentials) Dec 28, 2004.

CTCE-0214



Chemokine Therapeutics has completed enrollment and drug administration in its U.S. phase I trial evaluating the safety, pharmacodynamics and pharmacokinetic profile of CTCE-0214, its immune recovery drug candidate for the mobilization of hematopoietic stem and progenitor cells into peripheral blood for collection by leukapheresis. The randomized, double-blind, dose-escalating trial was conducted in 24 healthy adult volunteers at a single U.S. site. CTCE-0214 is a stable small peptide agonist of stromal cell-derived factor-1 (SDF-1), a key signaling molecule in the proliferation, homing, engraftment and expansion of hematopoietic stem cells. The compound has been shown to bind competitively with SDF-1 to cells bearing the SDF-1 receptor CXCR4. Upon binding, CTCE-0214 induces a host of cellular activation responses similar to those of the natural ligand, including mobilization and release of intracellular calcium, chemotaxis, as well as growth and expansion of human stem and progenitor cells. CTCE-0214 has the potential to decrease the time of mobilization and the number of leukapheresis sessions required in the mobilization and collection of stem cells from related and unrelated healthy donors for transplant. The current procedure requires the donor to be administered G-CSF (granulocyte colony-stimulating factor) for 5 days prior to leukapheresis. As a result of its mode of action, CTCE-0214 may help to mobilize stem cells in those people who do not respond to G-CSF. Preclinical work demonstrated that CTCE-0214 is active in significantly raising the levels of circulating hematopoietic stem cells and white blood cells with no untoward effects on bone marrow cells, neutrophil chemotaxis, platelet aggregation and red blood cell integrity. The compound may also have potential for reducing neutropenia following chemotherapy (1-4). Pharmaceutical Product Development (PPDI) has an option to license the compound at the end of phase I.

1. *Chemokine Therapeutics submits IND for CTCE-0214*. DailyDrugNews.com (Daily Essentials) May 20, 2004.

2. *FDA accepts IND for stem cell mobilizing drug CTCE-0214*. DailyDrugNews.com (Daily Essentials) June 17, 2004.

3. *CTCE-0214 enters phase I studies for stem cell mobilization*. DailyDrugNews.com (Daily Essentials) Oct 25, 2004.

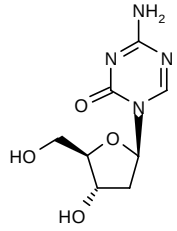
4. *Enrollment completed in phase I study of CTCE-0214*. DailyDrugNews.com (Daily Essentials) March 16, 2005.

Darbepoetin Alfa

Darbepoetin alfa (NESP, KRN-321, Aranesp®) is a recombinant erythropoietic protein launched in 2001 by Amgen for the treatment of chemotherapy-induced anemia and anemia due to chronic renal failure. The product is approved for these indications in several countries, including the U.S., Canada, the E.U. and Australia. Amgen is currently evaluating darbepoetin alfa in phase II trials for the treatment of anemia in congestive heart failure (CHF) patients. Kirin Brewery holds the manufacturing, development and marketing rights to darbepoetin alfa in China, Korea, Japan and several other Asian countries, and it is in phase III clinical development in Japan for renal anemia and phase II for cancer anemia.

Original monograph – Drugs Fut 2000, 25(3): 246.

Decitabine



SuperGen and MGI Pharma have signed a definitive agreement granting the latter exclusive worldwide rights to the development, manufacture, commercialization and distribution of decitabine (Dacogen™), SuperGen's investigational anticancer therapeutic for the treatment of patients with myelodysplastic syndrome (MDS). SuperGen will continue with its filing of the MDS applications for regulatory approval in the U.S. and Europe with assistance from MGI Pharma. SuperGen completed phase III trials of decitabine in patients with MDS in March 2004 and began a rolling submission in the U.S. later in the year. Both the NDA and a European MAA for the drug were subsequently accepted for review. The NDA included clinical data from a phase III trial of decitabine injection in MDS patients, in addition to two phase II studies. The coprimary endpoints of the phase III study were response rate and time to AML transformation or death. The phase III trial, conducted in 170 patients, 89 randomized to decitabine plus supportive care and 81 to supportive care only, achieved the coprimary endpoint of overall response rate. Patients in the decitabine arm had a response rate

of 17% as determined by intent-to-treat (ITT) analysis, compared to a 0% response rate for patients who received supportive care. Responses were durable and lasted a median of 9 months, and all patients who responded to decitabine therapy remained or became transfusion-independent. Median time to progression to AML or death was 340 days for patients treated with decitabine compared to a median of 219 days for patients in the supportive care arm, which was not statistically significant. Additional subset analysis of investigators' evaluation of clinical responses indicated an average patient objective response rate (partial and complete) of 25%. Further subset analysis showed that treatment with decitabine achieved the following positive responses in all specific subtypes of MDS: 17% of patients with chronic myelomonocytic leukemia (CMML); 25% of patients with refractory anemia (RA); 26% of patients with RA with excess blasts (RAEB); 29% of patients with RAEB in transformation (RAEB-T); and 14% of those with RA with ringed sideroblasts (RARS). Adverse events were observed in patients receiving decitabine more frequently than patients randomized to receive supportive care alone. Overall adverse events for decitabine-treated patients were similar to in previously reported phase II studies in MDS. MGI plans to evaluate decitabine for further development in several additional indications, including acute myeloid leukemia (AML), for which a phase III trial is expected to begin this year, chronic myelogenous leukemia (CML) and sickle cell anemia (phase I/II), as well as its use in combination with other anticancer agents for the treatment of various solid tumors. Alternative dosing schedules for decitabine, including subcutaneous administration and more rapid intravenous infusions, are being evaluated in clinical studies. Decitabine, a DNA methyltransferase inhibitor which holds fast track status for the submitted indication, belongs to a class of drugs called hypomethylating agents, with a unique mechanism of action (1-13).

1. *SuperGen clarifies interim data from phase III study of Dacogen in MDS*. DailyDrugNews.com (Daily Essentials) March 12, 2004.

2. *Additional analysis of response data from phase III Dacogen study in MDS*. DailyDrugNews.com (Daily Essentials) May 26, 2004.

3. *MGI Pharma and SuperGen sign license agreement for Dacogen*. DailyDrugNews.com (Daily Essentials) Sept 3, 2004.

4. *SuperGen to submit Dacogen NDA on rolling basis*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

5. *SuperGen reports Q1 R&D highlights*. SuperGen Press Release 2004, April 23.

6. *SuperGen reports Q2 R&D highlights*. SuperGen Press Release 2004, July 22.

7. *MGI Pharma and SuperGen announce closing of stock purchase agreement and effectiveness of license agreement*. MGI Pharma Press Release 2004, Sept 22.

8. *Dacogen MAA accepted for review*. DailyDrugNews.com (Daily Essentials) Oct 27, 2004.

9. *Dacogen NDA accepted for filing*. DailyDrugNews.com (Daily Essentials) Jan 5, 2005.

10. *European submission seeks approval of Dacogen for MDS*. DailyDrugNews.com (Daily Essentials) Oct 6, 2004.

11. Saba, H., Rosenfeld, C., Issa, J.-P. et al. *First report of the phase III North American trial of decitabine in advanced myelodysplastic syndrome (MDS)*. Blood 2004, 104(11, Part 1): Abst 67.

12. *SuperGen reports results from Dacogen™ phase III study in myelodysplastic syndromes (MDS): Company anticipates completing 'rolling' NDA submission by end of third quarter*. SuperGen Press Release 2004, March 31.

13. *SuperGen announces interim data from Dacogen™ phase III clinical study in myelodysplastic syndrome*. SuperGen Press Release 2004, Feb 13.

Original monograph – Drugs Fut 1990, 15(1): 19.

Eculizumab

Alexion has initiated the treatment phase in its pivotal phase III TRIUMPH and SHEPHERD trials, evaluating eculizumab (h5G1.1), a complement C5-blocking antibody, in patients with the chronic orphan blood disorder paroxysmal nocturnal hemoglobinuria (PNH). The TRIUMPH trial will examine the effects of eculizumab on the coprimary endpoints of hemoglobin stabilization and blood transfusion in hemolytic, transfusion-dependent PNH patients during 6 months of therapy. The multicenter, double-blind, randomized, placebo-controlled trial is expected to enroll approximately 75 patients in the U.S., Canada, Europe and Australia. The study includes an observation phase for each patient prior to treatment. TRIUMPH is designed to be a single pivotal efficacy trial for eculizumab in PNH. Randomization and treatment of patients in TRIUMPH are expected to be completed in 2005. The SHEPHERD companion safety trial will be primarily aimed at generating additional safety data with eculizumab in hemolytic PNH patients with a history of transfusion. The multicenter, open-label, nonrandomized, non-placebo-controlled study will enroll approximately 75 patients in the U.S., Canada, Europe, Australia and New Zealand, and will begin after commencement of the TRIUMPH study. Alexion reached agreement with the FDA on the design for the TRIUMPH trial and the companion SHEPHERD safety trial under the FDA's special protocol assessment (SPA) process. Successful outcomes from the trials should serve as a solid basis to support a BLA for PNH. The first study performed with eculizumab in transfusion-dependent PNH patients was an open-label study conducted at 2 sites in England and included 11 patients treated with eculizumab (600 mg i.v. once weekly for 4 weeks, followed by 900 mg i.v. once weekly for 8 weeks) for an initial 3-month period. Results showed that

Table I: Clinical studies of eculizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Paroxysmal nocturnal hemoglobinuria	Open	Eculizumab, 600 mg i.v. 1x/wk x 4 wks → 900 mg i.v. 1x/wk x 8 wks	11	Eculizumab was well tolerated and effective in blocking serum hemolytic activity in patients with paroxysmal nocturnal hemoglobinuria. This activity was associated with reductions in mean transfusion rates and the incidence of paroxysms and improvements in quality of life	4

patients treated with eculizumab experienced a substantial decrease in the destruction of PNH red blood cells, as lactate dehydrogenase (LDH) levels fell from a mean of 3111 IU/l to 594 IU/l and the mean percentage of PNH red blood cells increased from 36.7% of the total red cell population to 59.2%. This reduction in PNH red blood cell destruction led to a reduction in patient transfusion rates from a median of 1.8 units per patient per month to 0.0 units per patient per month. Episodes of hemoglobinuria were reduced by an average of 96% and quality-of-life measurements, assessed using the EORTC QLQ C-30, substantially improved during treatment. Eculizumab could become the first of a new class of antiinflammatory therapeutics called terminal complement inhibitors, and the first drug available specifically for patients suffering from PNH. Eculizumab was awarded orphan drug status for PNH in 2003 in the U.S. and the E.U. (1-4) (see Table I). Eculizumab is also undergoing phase II clinical evaluation for rheumatoid arthritis.

1. *Agreement on phase III program for eculizumab for PNH*. DailyDrugNews.com (Daily Essentials) July 22, 2004.

2. *Treatment phase begins in pivotal TRIUMPH study of eculizumab for PNH*. DailyDrugNews.com (Daily Essentials) Nov 4, 2004.

3. *Treatment phase begins in SHEPHERD study of eculizumab for PNH*. DailyDrugNews.com (Daily Essentials) Jan 12, 2005.

4. Hillmen, P., Hall, C., Marsh, J.C.W. et al. *Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria*. New Engl J Med 2004, 350(6): 552.

Original monograph – Drugs Fut 2004, 29(7): 673.

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Hillmen, P., Hall, C., Marsh, J.C.W., Elebute, M., Richards, S.J., Rollins, S.A., Mojcik, C.F., Rother, R.P. *Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy*. Br J Haematol 2004, 125(Suppl. 1): Abst 5.

Sah, A. et al. *Eculizumab, a C5 complement-blocking antibody, controls haemolysis in paroxysmal nocturnal haemoglobinuria (PNH) with responses maintained over a prolonged period of therapy*. 9th Congr Eur Hematol Assoc (June 10-13, Geneva) 2004, Abst 320.

Eptacog Alfa (Activated)

Novo Nordisk's eptacog alfa (activated) (recombinant factor VIIa, NovoSeven®) was first introduced a number of years ago in Europe as a hemostatic agent for the treatment of hemophilia. Just last year it was also approved for use in Glanzmann's thrombasthenia and coagulation factor VIIa deficiency. The company filed for approval of NovoSeven® in the E.U. in January for its use in hemorrhage related to trauma and clinical trials are being conducted in intracerebral hemorrhage, for which phase IIb trials have been completed and filing in the E.U. is anticipated for mid-2005, as well as variceal bleeding, traumatic brain injury and bleeding related to spinal and cardiac surgery (1-4).

The potential benefits of eptacog alfa for reducing hematoma growth and thus improving outcome of patients with acute intracerebral hemorrhage were determined in a multicenter, double-blind, randomized, placebo-controlled clinical trial. A total of 399 adult patients with acute spontaneous intracerebral hemorrhage confirmed by computerized tomography scanning within 3 h of symptom onset were randomly given a single dose of placebo or eptacog alfa (40, 80 or 160 μg/kg i.v.) at no more than 4 h after symptom onset. The average increase in the volume of intracerebral hemorrhage during the first 24 h after treatment was greater with placebo (29%) than with eptacog alfa (16%, 14% and 11%, respectively, at doses of 40, 80 and 160 μg/kg). The effects were greater in a subgroup of 269 patients who were given study treatment within 3 h of symptom onset; in these patients, the 24-h increase in volume of intracerebral hemorrhage was 34% with placebo and 13% with all eptacog alfa doses. The total volume of the lesion (*i.e.*, including intracerebral hemorrhage, intraventricular hemorrhage and edema) measured at 72 h was 11.0 ml lower with eptacog alfa compared to placebo. Eptacog alfa also reduced the mortality rate (18% *vs*. 29%) and the percentage of patients who died or were severely disabled (53% *vs*. 69%) at 3 months after treatment. Patients given eptacog alfa showed a higher incidence of serious thromboembolic adverse events (7% *vs*. 2% with placebo), but most patients recovered from these complications and the incidence of fatal or disabling thromboembolic events was similar in the different study groups (5) (Table II).

Table II: Clinical studies of eptacog alfa (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hemorrhage, intracerebral	Randomized Double-blind Multicenter	Eptacog alfa (activated), 40 μg/kg i.v. (n=108) Eptacog alfa (activated), 80 μg/kg i.v. (n=92) Eptacog alfa (activated), 160 μg/kg i.v. (n=103) Placebo (n=96)	399	Compared to placebo, eptacog alfa administered within 4 h of symptom onset limited the growth of hematoma, reduced mortality and improved outcomes at 90 days in patients with acute intracerebral hemorrhage	5

1. *NovoSeven approved in Europe for factor VII deficiency and thrombasthenia*. DailyDrugNews.com (Daily Essentials) Feb 23, 2004.

2. *Novo Nordisk reports 2003 year-end R&D highlights*. Novo Nordisk Press Release 2004, Feb 5.

3. *Novo Nordisk updates program progress*. DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

4. *Novo Nordisk makes progress with NovoSeven*. DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

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Ferumoxytol

Advanced Magnetics has initiated two multicenter phase III studies for ferumoxytol, its investigational intravenous iron replacement therapeutic. The two identical studies will involve anemic chronic kidney disease (CKD) patients who are not yet on dialysis. The company has also commenced a multicenter phase III study in anemic CKD patients who are on hemodialysis, and a phase III safety study in anemic CKD patients whether or not on dialysis. The latter double-blind, placebo-controlled, crossover study represents the last study in the phase III iron therapy program for ferumoxytrol. An NDA submission for ferumoxytol in iron replacement therapy for CKD patients, whether or not on dialysis, is expected during the first half of 2006. Ferumoxytol consists of intravenously administered bioavailable iron, allowing more efficient replenishment of the body's iron stores than oral iron supplements, without the common side effects. Ferumoxytol also provides greater flexibility in the administration and dosage amount compared to other available intravenous iron replacement products (1-4). The company, in conjunction with the National Cancer Institute and Cytogen, is also developing ferumoxytol as a contrast agent for magnetic resonance angiography in oncology applications (5).

A study in 29 patients with anemia receiving chronic hemodialysis compared ferumoxytol 128 mg i.v. given for 8 doses, ferumoxytol 510 mg i.v. given for 2 doses and ferrous sulfate 325 mg p.o. t.i.d. given for 2 weeks. Ferumoxytol was administered as a rapid infusion (up to 30 mg/ml/s) within the first 30 min of dialysis. Patients had also received erythropoietin for at least 4 weeks. Greater increases in hemoglobin and transferrin saturation (TSAT) were seen in the ferumoxytol groups than in the ferrous sulfate group, and the increase from baseline TSAT to maximum TSAT was significant with the highest ferumoxytol dose. The treatment was also safe and did not affect blood pressure (6).

1. *Advanced Magnetics reports Q1 R&D highlights*. DailyDrugNews.com (Daily Essentials) Jan 28, 2004.

2. *First two phase III trials for ferumoxytol commence*. DailyDrugNews.com (Daily Essentials) April 30, 2004.

3. *Phase III study of ferumoxytol as intravenous iron replacement therapy*. DailyDrugNews.com (Daily Essentials) Jan 18, 2005.

4. *New phase III hemodialysis trial for ferumoxytol iron replacement therapy*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

5. *First clinical study of ferumoxytol under NCI clinical trial agreement*. DailyDrugNews.com (Daily Essentials) June 3, 2004.

6. Spinowitz, B.S., Schwenk, M.H., Jacobs, P., Kline Bolton, W., Kaplan, M., Finkelstein, F. *Comparison of two intravenous ferumoxytol dosing regimens with oral iron therapy in anemic hemodialysis (HD) patients*. Natl Kidney Found Clin Meet (April 28-May 2, Chicago) 2004, Abst.

FG-2216

FibroGen has reported results of a phase I study and early results of a phase IIa study of FG-2216, its investigational oral anemia therapy. The phase I results provide the first demonstration in humans of an erythropoietic response due to stabilization of hypoxia-inducible factor (HIF) induced by FG-2216, a member of a novel class of small molecules that inhibit HIF-prolyl hydroxylase (HIF-PH). All doses of FG-2216 (0.3-20 mg/kg) administered orally to a total of 54 healthy male subjects were well tolerated and no serious adverse events or dose-limiting toxicities were observed. A dose-dependent elevation in the serum level of erythropoietin (EPO) was seen in response to treatment with FG-2216. Repeated dosing (2 or 3 times weekly) for 3 weeks was associated with a consistent increase in EPO production and in the number of circulating reticulocytes compared to the control group, with no evidence of desensitization to the study drug. Ongoing multicenter phase IIa trials of FG-2216 include single-blind, placebo-controlled studies designed to evaluate the safety and efficacy of FG-2216 in anemic CKD patients (protocol defined as hemoglobin < 10 g/dl), who have not received dialysis. One study is enrolling CKD patients not receiving recombinant EPO therapy for anemia (recombinant EPO-naïve), and the second study is enrolling CKD patients who are treated with recombinant EPO therapy for anemia and switched to FG-2216 or placebo (recombinant EPO-withdrawn). Patients in each study are randomized to either a treatment group which receives FG-2216 (6 or 20 mg/kg) administered orally 3 times a week (Monday, Wednesday and Friday) for 4 weeks, or a placebo group, followed by 2 weeks of observation. In the recombinant EPO-naïve study, the ability of FG-2216 to stimulate increases in circulating levels of hemoglobin is being evaluated. In the recombinant EPO-withdrawn study, the ability of FG-2216 to maintain hemoglobin levels is being evaluated. Early results from the first completely enrolled dose group (6 mg/kg) of the recombinant EPO-naïve study demonstrate that after 3 weeks of oral therapy, patients who received FG-2216 experienced a mean increase in hemoglobin from baseline of 1.0 g/dl (range = 0.1-2.2 g/dl), whereas patients who received placebo experienced a mean decrease in hemoglobin from baseline of 0.6 g/dl (range = 0.3-1.0 g/dl), a statistically significant difference. An analysis of

hemoglobin levels from the last available measurement of the planned 42-day study period demonstrated a mean hemoglobin increase of 1.4 g/dl (range = 0.4-2.7 g/dl) for the FG-2216 group and a mean hemoglobin decrease of 0.5 g/dl (range = 0-1.0 g/dl) for the placebo group. The baseline hemoglobin was 9.6 and 9.8 g/dl for the FG-2216 and the control groups, respectively. FibroGen intends to continue to explore the use of HIF-PH inhibitors in CKD, as well as in other clinical settings, such as chemotherapy-induced anemia, anemias of chronic disease (ACD) in various settings, iron deficiency anemia and anemia associated with congestive heart failure, senescence and menstruation. FG-2216 is designed to stabilize HIF and selectively activate the body's natural process of HIF-2-mediated erythropoiesis, including the induction of endogenous EPO, the mobilization and utilization of iron stores, and the suppression of inflammatory cytokines essential to the formation of new oxygen-carrying red blood cells and the treatment of anemia. FG-2216, a small molecule that stimulates the body's natural process of erythropoiesis, is expected to become the first drug in the world that can be administered orally for the treatment of anemia. In 2004, FibroGen entered an agreement to license FG-2216 (and other compounds) to the former Yamanouchi, now Astellas Pharma, for development and sale in Japan for the treatment of anemia. FibroGen retains rights to FG-2216 for the rest of the world (1, 2).

1. *FibroGen licenses FG-2216 to Yamanouchi for Japan*. DailyDrugNews.com (Daily Essentials) Sept 29, 2004.

2. *FibroGen reports positive findings for oral anemia therapy FG-2216*. DailyDrugNews.com (Daily Essentials) Dec 10, 2004.

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Urquilla, P., Fong, A., Oksanen, S., Leigh, S., Turtle, E., Flippin, L., Brenner, M., Muthukrishnan, E., Fourney, P., Lin, A., Yeowell, D., Molineaux, C. *Upregulation of endogenous erythropoietin (EPO) in healthy subjects by inhibition of hypoxia inducible factor (HIF) prolyl hydroxylase*. 37th Annu Meet Am Soc Nephrol (ASN) (Oct 27-Nov 1, St. Louis) 2004, Abst SU-PO062.

Hematide™

Positive findings have been reported from a placebo-controlled phase I dose-finding study of Affymax's lead product candidate Hematide™, a synthetic, peptide-based erythropoiesis-stimulating agent (ESA) which is being developed to stimulate the production of red blood cells for the treatment of anemia in patients with CKD and cancer. In the study, healthy volunteers were randomized to receive single doses of Hematide™ or placebo in cohorts at increasing dose levels until a pharmacologically active dose was observed. The study was initiated in August 2004 and 3 cohorts were enrolled in a consecutive manner at increasing doses. A fourth cohort was also enrolled at the same dose as in the third cohort. Study results demonstrated that single doses of Hematide™ resulted in dose-dependent increases in circulating reticulocytes in healthy volunteers. At the highest dose tested, Hematide™ also achieved a clinically and statistically significant increase in hemoglobin from baseline that was sustained for at least a month. Single intravenous doses of Hematide™ were well tolerated, with a safety profile similar to placebo. Based on these results, Affymax expects to initiate phase II studies of Hematide™ for the treatment of anemia in patients with CKD before mid-2005 and in cancer patients later in the year. Hematide™ has a completely novel amino acid sequence that is unrelated to erythropoietin or any other known naturally occurring human sequences. In animal and laboratory studies, Hematide™ has demonstrated an excellent safety and efficacy profile, superior stability and an extended duration of action compared to currently marketed recombinant protein products. It is the first nonprotein erythropoiesis-stimulating agent to enter clinical trials (1, 2).

1. *Phase I study for Hematide*. DailyDrugNews.com (Daily Essentials) Oct 7, 2004.

2. *Hematide stimulates production of red blood cells in phase I study*. DailyDrugNews.com (Daily Essentials) March 16, 2005.

Hemoglobin Glutamer-250 (Bovine)

Biopure's hemoglobin glutamer-250 (bovine) (Hemopure®, HBOC-201) is a universally compatible, room temperature-stable pharmaceutical candidate that is administered intravenously to deliver oxygen to the body's tissues. Each bag of Hemopure® contains 30 g of stabilized bovine hemoglobin in 250 ml of a balanced salt solution. These polymerized hemoglobin molecules circulate in the plasma when infused and are smaller, have lower viscosity and more readily release oxygen to tissues than red blood cells. Unlike stored blood, Hemopure® is ultra-purified, compatible with all blood types and stable for 3 years without refrigeration. The product is currently approved in South Africa for the treatment of acutely anemic surgical patients (secondary anemia) and for the elimination, delay or reduction of red blood cell transfusions in these patients, whereas it is an investigational product in the U.S. and Europe.

Biopure and the FDA have met at Biopure's request to discuss its reply to the FDA complete response letter

regarding the company's BLA for Hemopure® for the treatment of acutely anemic orthopedic surgery patients and the elimination or reduction of allogeneic red blood cell transfusions in these patients. The company's clinical development plan was also discussed. The FDA expressed concerns about the current BLA based on safety and efficacy questions arising from the phase III orthopedic surgery trial, beyond those cited in the complete response letter. The agency agreed to a continuing dialogue on these matters. For BLA evaluation, the FDA requested the results of three previously requested preclinical studies. These studies are also a prerequisite for further U.S. clinical trials. Biopure has submitted the protocols and the FDA will review them promptly. The studies, designed to assess the product's effect on tissue perfusion, tissue oxygenation and volume hemodynamics at high doses in conscious swine, are expected to take 6 months to complete after the FDA and Biopure agree on the protocols. The FDA will determine whether additional clinical trials are required after a review of the preclinical studies and Biopure's responses to the agency's issues (1).

Hemopure® has entered a phase II trial in trauma patients at the Johannesburg Hospital Trauma Unit, South Africa. The single-center, randomized, single-blind, parallel-group, standard therapy-controlled study is designed to assess the safety and tolerability of Hemopure® in a hospital setting for emergency treatment of unstable patients who have significant blood loss as a result of blunt or penetrating trauma. The secondary objective is to assess efficacy parameters. Approximately 50 trauma patients will be randomized to receive either standard therapy resuscitation fluids (crystalloids, colloids and/or blood) or up to 10 bags of Hemopure® plus standard therapy. The treatment period for administering Hemopure® is up to 4 h from the first infusion. Patients will be monitored until discharged from the hospital and at 28 days postinfusion. Efficacy data from the study could help confirm the design of a planned phase III trauma trial of Hemopure® in the out-of-hospital setting, being developed by the U.S. Naval Medical Research Center under a research agreement with Biopure. In Europe, Biopure is also conducting a phase II trial of Hemopure® as a potential cardioprotective agent in patients undergoing coronary angioplasty (2).

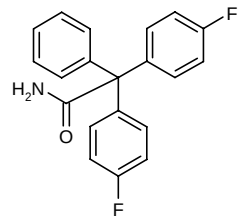
1. *Biopure and the FDA discuss complete response letter for Hemopure BLA*. DailyDrugNews.com (Daily Essentials) Jan 12, 2004.

2. *New South African phase II study for Hemopure in trauma patients*. DailyDrugNews.com (Daily Essentials) Aug 2, 2004.

Hemoglobin Raffimer

Hemosol was developing hemoglobin raffimer (Hemolink®), a purified human hemoglobin solution, as a blood substitute initially for use during CABG surgery. However, following a series of preclinical studies largely completed last year and a recent meeting with the FDA, the company decided instead to pursue HRC-101 as a more cost-effective product.

ICA-17043



ICAgen has initiated enrollment in a pivotal phase III trial of ICA-17043 for the treatment of sickle cell disease. The randomized, double-blind, placebo-controlled ASSERT (A Stratified Sickle Event Randomized Trial) study will enroll 300 patients. Patients must have a diagnosis of sickle cell disease, be aged 16-65 and have a history of at least 2 vaso-occlusive crises requiring a visit to a medical facility in the year prior to enrollment. Patients will be randomized to either a treatment arm or a placebo arm, each consisting of approximately 150 patients, and will receive treatment for a period of 1 year. The primary endpoint is the vaso-occlusive crisis rate and secondary endpoints will include the hemoglobin level. The study will be conducted at approximately 60 sites across the U.S. and in selected other countries. In the recently completed phase II trial in 90 patients with sickle cell anemia, ICA-17043 was shown to improve the hemolytic anemia that is characteristic of the disease. ICA-17043 was well tolerated, with no serious drug-related adverse events. ICA-17043 is a novel small molecule that represents a novel approach to the treatment of sickle cell disease by targeting the Gardos ion channel located on the membrane of red blood cells. It is being developed for once-daily oral administration and has orphan drug designation and fast track status. In the summer of 2004, ICAgen and McNeil entered into a collaborative agreement for the development and commercialization of ICA-17043. The companies will jointly develop the product in the U.S. and McNeil will have rights in most international markets; the agreement also provides for joint development in Canada (1-4).

1. *McNeil and ICAgen enter agreement for ICA-17043 for sickle cell anemia*. DailyDrugNews.com (Daily Essentials) July 14, 2004.

2. *Icagen receives milestone payment for ICA-17043 progress*. DailyDrugNews.com (Daily Essentials) Sept 6, 2004.

3. *Johnson & Johnson reports Q2 R&D highlights*. Johnson & Johnson Press Release 2004, July 13.

4. *Enrollment begins in phase III study of ICA-17043 for sickle cell disease*. DailyDrugNews.com (Daily Essentials) Feb 24, 2005.

Original monograph – Drugs Fut 2003, 28(9): 854.

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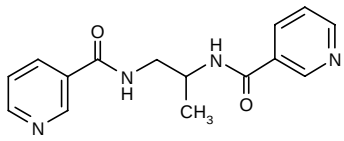
Ataga, K.I. et al. *Efficacy and safety of the Gardos channel inhibitor, ICA-17043, in patients with sickle cell anemia*. Blood 2004, 104(11, Part 1): Abst 103.

KRN-125

KRN-125, a second-generation filgrastim product that requires less frequent administration, is being developed by Kirin Brewery (as a Kirin-Amgen project) for the treatment of neutropenia. It is currently in phase I clinical trials (1).

1. *Kirin announces phase I clinical trial of KRN-125 and other recent developments*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

Nicaraven



Nicaraven (Antevas® injection) is a free radical scavenger developed at Chugai and under regulatory review in Japan for the treatment of subarachnoid hemorrhage.

Original monograph – Drugs Fut 1983, 8(6): 485.

NIX-0699

NIX-0699 (Nicosan™/Hemoxin™, formerly Niprisan™), a nontoxic phytopharmaceutical comprised of four different traditional plant extracts, is in late-stage development by Xechem for the treatment of sickle cell anemia in Nigeria, with launch expected there later this year. The compound, developed by the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, government of Nigeria, was licensed on an exclusive worldwide basis to Xechem in 2002. In 2003 the FDA granted orphan drug status for NIX-0699 (1, 2).

1. *Xechem presents update on Niprisan – NIX-0699 - at Annual Meeting of the National Sickle Cell Disease Program – Projects filing IND before year end.* Xechem Press Release 2004, April 27.

2. *Xechem announces significant progress in the development of its sickle cell disease drug (Nicosan™/Hemoxin™).* Xechem Press Release 2005, Feb 17.

OBI-1

A genetically engineered recombinant porcine coagulation factor VIII (rpfVIII), OBI-1 is being codeveloped by Octagen and licensee Ipsen for the treatment of congenital and acquired hemophilia A in patients with neutralizing antibodies to human factor VIII. OBI-1 was discovered by Emory University. In 1998, Emory granted Octagen an exclusive worldwide license for the commercialization rights to the drug. The same year, Octagen and Ipsen established a research partnership for the development of OBI-1. The product is currently entering phase II trials (1).

1. *Ipsen and Octagen advance OBI-1, recombinant porcine factor VIII, to phase II human trials*. Octagen Press Release 2004, Nov 18.

Poloxamer-188

Poloxamer-188 (CRL-5861, Flocor) is a nonionic surface-active copolymer which has demonstrated clinical benefits in phase II and an initial phase III trial for the treatment of sickle cell anemia. The drug interacts with cell membranes to repair damaged membranes, block cellular adhesion and improve microvascular blood flow. In sickle cell disease, it acts as a blood “lubricant”, decreasing blood viscosity and enabling the rigid sickle cells to become more flexible, thereby allowing easier passage through narrow blood vessels and shortening the episodes of vaso-occlusive crises. Originally developed at CytRx, the drug has been licensed exclusively to SynthRx.

R-744

Development of the innovative anemia treatment R-744, also known as CERA for Continuous Erythropoiesis Receptor Activator, for worldwide use in anemic patients with cancer or renal disease is moving ahead as planned at Roche. Phase III studies in renal patients are under way in Europe and the U.S. and phase III trials in cancer patients are also scheduled to commence (1-3). Chugai is conducting phase II clinical evaluation in Japan in renal anemia.

CERA has been found to improve anemia in previously untreated CKD patients not on dialysis when administered once every week, once every 2 weeks or once every 3 weeks. The extended dosing intervals were evaluated in a multicenter phase II study in 65 patients

randomized to doses of 0.15, 0.30 or 0.60 µg/kg s.c. At 6 weeks, mean hemoglobin increases were 0.30, 0.71 and 1.76 g/dl in patients given 0.15, 0.30 and 0.60 µg/kg/week, respectively. Such dose-dependent increases were also seen with administration every 2 or 3 weeks. Hemoglobin increases were sustained throughout the study. The treatment was generally well tolerated and was not associated with antibody development (4).

1. *Roche reports 2003 year-end R&D highlights*. Roche Press Release 2004, Feb 4.

2. *Roche reports Q1 R&D highlights*. Roche Press Release 2004, April 21.

3. *Roche reports Q2 R&D highlights*. Roche Press Release 2004, July 21.

4. Provenzano, R., Besarab, A., Macdougall, I.C., Dougherty, F.C., Beyer, U. *CERA (continuous erythropoietin receptor activator) administered up to once every 3 weeks corrects anemia in patients with chronic kidney disease not on dialysis*. J Am Soc Nephrol 2004, 15: Abst SU-PO056.

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Locatelli, F., Villa, G., Arias, M., Marchesi, D., Dougherty, F.C., Beyer, U. *CERA (Continuous Erythropoietin Receptor Activator) maintains hemoglobin levels in dialysis patients when administered subcutaneously up to once every 4 weeks*. 37th Annu Meet Am Soc Nephrol (ASN) (Oct 27-Nov 1, St. Louis) 2004, Abst SU-PO051.

Reigner, B., Pannier, A., Jordan, P. *Bioavailability of subcutaneously administered CERA (continuous erythropoiesis receptor activator): An innovative erythropoietic agent for the management of renal anaemia*. Nephrol Dial Transplant 2004, 19(5, Suppl.): Abst MP279.

Recombinant Human GM-CSF

Cangene's first recombinant biopharmaceutical product Leucotropin®, or recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), was filed for approval in Canada in 2003 for the treatment of leukopenia, *i.e.,* for enhancing mature white blood cell production in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing stem cell transplant. The company has an agreement with Apotex for marketing the product in that country.

Recombinant Human Factor XIII

ZymoGenetics has signed a license agreement granting Novo Nordisk exclusive worldwide rights to its recombinant factor XIII (rFXIII) portfolio, including all related intellectual property. Under the agreement, Novo Nordisk will gain the right to develop and commercialize rFXIII on a worldwide basis. ZymoGenetics has been developing rFXIII for the prevention and treatment of bleeding complications and abnormalities in blood clotting associated with factor XIII deficiencies, both congenital and acquired. Factor XIII is the terminal enzyme in the clotting cascade and is responsible for stabilizing blood clots. Its primary function is to crosslink individual fibrin molecules into a strong fibrin mesh. ZymoGenetics has completed phase I studies to evaluate the safety and pharmacokinetics of rFXIII in patients with congenital factor XIII deficiency and to evaluate the safety and pharmacokinetics in healthy volunteers. Scientific evidence suggests there may be expanded potential for factor XIII and factor VIIa to work synergistically in certain bleeding conditions (1, 2).

1. *ZymoGenetics licenses rFactor XIII to Novo Nordisk*. DailyDrugNews.com (Daily Essentials) Oct 7, 2004.

2. *Novo Nordisk updates program progress*. DailyDrugNews.com (Daily Essentials) Oct 13, 2004.

rhThrombin

ZymoGenetics' recombinant human thrombin (rhThrombin) is being developed for the control of bleeding associated with surgical procedures. Four randomized, controlled phase II clinical trials have provided new data on the efficacy and safety profile of rhThrombin as a novel topical surgical hemostat. A total of 130 patients who underwent peripheral artery bypass surgery, spinal surgery, arteriovenous graft construction or liver resection surgery and showed intraoperative bleeding were treated with gelatin sponges containing rhThrombin or placebo. Compared to placebo, rhThrombin was more effective in inducing hemostasis at 10 min and was associated with a shorter mean time to hemostasis. Evidence also suggested that rhThrombin was well tolerated and did not induce the synthesis of anti-thrombin antibodies. The company intends to use these data to design a phase III pivotal trial with rhThrombin, which should begin during the second half of 2005. A BLA filing is anticipated for 2006 (1-3).

1. *rhThrombin enters phase II*. DailyDrugNews.com (Daily Essentials) April 21, 2004.

2. *ZymoGenetics updates pipeline progress*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

3. *Update on the efficacy of rhThrombin in the management of surgery-associated bleeding*. DailyDrugNews.com (Daily Essentials) Feb 15, 2005.

Annual Update 2004/2005 - Treatment of Hematological/Blood Cancers

The hematological/blood cancer group includes leukemia, lymphoma and multiple myeloma. Leukemia is characterized by an abnormal production of white blood cells and can be either chronic or acute, depending on how quickly the disease develops. Leukemia can also be grouped as lymphoid or myeloid, depending on the type of white blood cell that is affected. Hairy cell leukemia is a rare type of chronic leukemia.

Almost 35,000 new cases of leukemia are expected in the U.S. in 2005, with slightly more acute (approximately 16,000) than chronic (approximately 14,000) cases. Leukemia is diagnosed 10 times more often in adults than in children. The most common types in adults are acute myeloid leukemia (AML; approximately 11,000 new cases) and chronic lymphocytic leukemia (CLL; approximately 9,000 new cases). An estimated 22,500 deaths are expected to occur in the U.S. in 2005 due to leukemia. Leukemia occurs more commonly in men than in women and the 5-year survival rate in general ranges from 20% in AML to 73% in CLL.

Lymphoma refers to cancer that develops in the lymphatic system. Hodgkin's disease is an uncommon lymphoma; all other lymphomas are grouped together and are referred to as non-Hodgkin's lymphoma (NHL). In patients with lymphoma, cells in the lymphatic system become abnormal, and since the lymphatic system is ubiquitous, lymphoma may occur almost anywhere in the body. The incidence of NHL has increased dramatically over the last several decades and has gone from being relatively rare to being the fifth most common cancer in the U.S. Lymphoma accounts for about 5% of all cases of cancer in the U.S., with 64,000 new cases estimated in 2005, including 7,000 cases of Hodgkin's lymphoma and 56,000 cases of NHL. An estimated 20,500 deaths will occur in 2005 due to lymphoma (Hodgkin's lymphoma: 1,400; NHL: 19,000). Survival rates vary depending on the stage of the disease. The 5-year survival rates are 85% and 59%, respectively, for Hodgkin's disease and NHL.

Multiple myeloma (MM) is a cancer that begins in plasma cells, a type of white blood cells involved in antibody production. Approximately 16,000 new cases of MM are estimated for 2005, and 11,000 deaths are expected to occur in 2005 as a result of MM (1, 2).

In the table that follows, drugs under active development for the treatment of hematological/blood cancer are shown (*Source: Prous Science Integrity®*).

References

1. NCI website (www.cancer.gov)

2. Cancer Statistics 2005 (American Cancer Society, Inc., www.cancer.org)

Itziar Escudero

Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Leukemia	II	Galarubicin hydrochloride	DNA topoisomerase II	Dong-A
	II	Lonafarnib	Farnesyltransferase	Schering-Plough
	II	AP-23573	mTOR	M.D. Anderson Cancer Center
	I/II	Cord blood stem cells		Gamida-Cell/M.D. Anderson Cancer Center
	I/II	CB-001		Viacell
	I/II	HSV-TK		MolMed

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Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Leukemia	I	Triapine	Ribonucleoside-diphosphate reductase	Vion/National Cancer Institute
	I	AZD-2171	VEGFR-1, -2 and -3	AstraZeneca
	I	STA-5312	Tubulin	Synta Pharmaceuticals
	I	MGCD-0103	HDAC1	MethylGene
	I	Aplidine	VEGFR-1	PharmaMar
Lymphocytic leukemia	II	(*R*)-Roscovitine	CDK1, 2, 7 and 9	Cyclacel
Acute lymphocytic leukemia	L-2005	Clofarabine	Ribonucleoside-diphosphate reductase	Genzyme
	III	Nelarabine		GlaxoSmithKline
	II/III	Imatinib mesilate[1]	Bcr-Abl kinase, KIT, PDGFR	Novartis
	II	Carboplatin[1]	DNA	National Cancer Institute
	II	Alemtuzumab[1]	CD52	National Cancer Institute
	II	Aplidine	VEGFR-1	PharmaMar
	I/II	Annamycin	DNA topoisomerase II	Callisto Pharmaceuticals
	I/II	Epratuzumab	CD22	National Cancer Institute
	I/II	Liposomal vincristine	Tubulin	Inex
	I	Dolastatin 10	Tubulin	National Cancer Institute
	I	Bryostatin 1	PKC	National Cancer Institute
	I	B43-genistein	CD19, Lyn kinase	Parker Hughes Institute
Acute promyelocytic leukemia	Prereg.	Tamibarotene		Nippon Shinyaku
Chronic lymphocytic leukemia	III	Rituximab[1]	CD20	Biogen Idec/Roche/ Genentech
	III	Oblimersen sodium	Bcl-2	Genta
	II	Dexamethasone[1]		Peter MacCallum Cancer Centre
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	Bryostatin 1	PKC	National Cancer Institute
	II	Denileukin diftitox[1]	IL-2 receptor	Ligand
	II	Motexafin gadolinium		Pharmacyclics
	II	Temsirolimus	mTOR	National Cancer Institute
	II	Anti-Tac(Fv)-PE38	CD25	National Cancer Institute
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	OSI-461	Phosphodiesterase 2A and 5A	OSI Pharmaceuticals
	II	Talabostat	DPP IV, FAPα	Point Therapeutics
	II	(*R*)-Etodolac		Salmedix
	I/II	Clofarabine[1]	Ribonucleoside-diphosphate reductase	Bioenvision/Genzyme
	I/II	Gemtuzumab ozogamicin[1]	CD33	M.D. Anderson Cancer Center
	I/II	IDM-4	CD20	IDM
	I/II	Xcellerated T-cells		Xcyte
	I/II	HuMax-CD20	CD20	Genmab
	I/II	GX-015-070	Bcl-2 protein family	Gemin X Biotechnologies
	I	UCN-01	PDK1, CDK1, 2, 4 and 6, CHK1 and 2	National Cancer Institute
	I	BL22	CD22	National Cancer Institute
	I	Lumiliximab	CD23	Biogen Idec
Myeloid leukemia	I	Dolastatin 10	Tubulin	National Cancer Institute
Acute myeloid leukemia	Prereg.	Tipifarnib	Farnesyltransferase	Johnson & Johnson/Janssen-Cilag
	Prereg.	Clofarabine[1]	Ribonucleoside-diphosphate reductase	Bioenvision/Genzyme
	III	Flt3 ligand	Flt3	National Cancer Institute
	III	Histamine dihydrochloride[1]	Histamine receptor	Maxim
	II	Amifostine hydrate[1]		MedImmune Oncology
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	Lestaurtinib	Flt3, RET, TRKA	Cephalon
	II	Topotecan hydrochloride[1]	DNA topoisomerase I	National Cancer Institute
	II	Midostaurin	PKC, Flt3	Novartis
	II	Bryostatin 1	PKC	National Cancer Institute
	II	Temsirolimus		National Cancer Institute
	II	Zosuquidar trihydrochloride	MDR-1	Lilly
	II	101M	DNA	Vion

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Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Acute myeloid leukemia	II	GVAX Leukemia		Cell Genesys
	I/II	Annamycin	DNA topoisomerase II	Callisto Pharmaceuticals
	I/II	Troxacitabine	DNA polymerase	Structural GenomiX
	I/II	Vatalanib succinate	VEGFR-1, -2 and -3	Novartis
	I/II	PR1		National Cancer Institute
	I/II	Tandutinib	Flt3, PDGFRα and β, cKIT	Millennium
	I/II	Pixantrone maleate	DNA topoisomerase II	Cell Therapeutics
	I	Suberanilohydroxamic acid	HDAC	Merck & Co.
	I	MS-27-275	HDAC	National Cancer Institute
	I	MG-98	DNA methyltransferase	MGI Pharma/MethylGene
Chronic myeloid leukemia	R-1998	Lobaplatin	DNA	Hainan Chang An
	II	Homoharringtonine	DNA	M.D. Anderson Cancer Center/ ChemGenex Pharmaceuticals
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	Decitabine	DNA methyltransferase	SuperGen
	II	Topotecan hydrochloride[1]	DNA topoisomerase I	National Cancer Institute
	II	Temsirolimus		National Cancer Institute
	II	Bortezomib[1]	Proteasome	National Cancer Institute
	II	AG-858	HSP70	Antigenics
	I/II	PR1		National Cancer Institute
	I/II	AMN-107	Bcr-Abl kinase, KIT, PDGFR	Novartis
	I	GTI-2040	RRM2	National Cancer Institute
	I	LR-3001	MYB	Genta
	I	17-AAG	HSP90	Kosan/National Cancer Institute
	I	MS-27-275	HDAC	National Cancer Institute
	I	Arsenic sulfide		Shanghai Second Medical University
	I	BMS-354825	Src kinase, Bcr-Abl kinase	Bristol-Myers Squibb/National Cancer Institute
Hairy cell leukemia	II	BL22	CD22	National Cancer Institute
	I	CNF-1010	HSP90	Conforma Therapeutics
Lymphoma	II	AP-23573	mTOR	M.D. Anderson Cancer Center
	I/II	β-Alethine		LifeTime
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan
	I	UCN-01	PDK1, CDK1, 2, 4 and 6, CHK1 and 2	National Cancer Institute
	I	Carboxyamidotriazole		National Cancer Institute
	I	Bryostatin 1		National Cancer Institute
	I	CYC-682	DNA polymerase	Cyclacel
	I	Anti-Tac(Fv)-PE38	CD25	National Cancer Institute
	I	Cilengitide	Integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$	National Cancer Institute
	I	MS-27-275	HDAC	National Cancer Institute
	I	COL-3	MMP-2 and MMP-9	National Cancer Institute
	I	AZD-2171	VEGFR-1, -2 and -3	AstraZeneca
	I	17-DMAG	HSP90	National Cancer Institute
	I	Cord blood stem cells		Gamida-Cell
	I	STA-5312	Tubulin	Synta Pharmaceuticals
	I	Clearazide		Yaupon Therapeutics
Hodgkin's lymphoma	II	Dexamethasone[1]		Peter MacCallum Cancer Centre
	II	Gemcitabine[1]	Ribonucleoside-diphosphate reductase	National Cancer Institute
	II	Liposomal vincristine	Tubulin	Inex
	II	ABT-510		Abbott
	II	SGN-30	CD30	Seattle Genetics
	IND filed	MPC-2130		Myriad Genetics
Non-Hodgkin's lymphoma	Prereg.	Liposomal vincristine	Tubulin	Inex/Enzon
	III	Gemcitabine[1]	Ribonucleoside-diphosphate reductase	Lilly
	III	Carboplatin[1]	DNA	National Cancer Institute
	III	Plerixafor hydrochloride		AnorMED
	III	Pixantrone maleate	DNA topoisomerase II	Cell Therapeutics
	III	Myvax		Genitope

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Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Non-Hodgkin's lymphoma	III	Id-KLH vaccine		Favrille
	II	MDX-060	CD30	Medarex
	II	Dexamethasone[1]		Peter MacCallum Cancer Centre
	II	Antineoplaston A10		Burzynski Research Institute
	II	Pentostatin[1]	ADA	SuperGen/National Cancer institute
	II	Elsamitrucin	DNA topoisomerase I and II	Spectrum Pharmaceuticals
	II	Gallium nitrate[1]		Genta
	II	Amrubicin hydrochloride[1]	DNA topoisomerase II	Sumitomo Pharmaceuticals
	II	Dolastatin 10	Tubulin	National Cancer Institute
	II	Aldesleukin[1]		Chiron
	II	Bryostatin 1		National Cancer Institute
	II	Denileukin diftitox[1]	IL-2 receptor	Ligand
	II	Galiximab	CD80	Biogen Idec
	II	Motexafin gadolinium		Pharmacyclics
	II	Epratuzumab	CD22	Immunomedics
	II	Aplidine	VEGFR-1	PharmaMar
	II	Oncophage		Antigenics
	II	Ortataxel	Tubulin	Bayer
	II	Ixabepilone	Tubulin	National Cancer Institute
	II	ABT-510		Abbott
	II	TRAIL-R1 MAb	TRAIL-R1	Human Genome Sciences
	II	Xcellerated T-cells		Xcyte
	I/II	Alemtuzumab[1]	CD52	Ilex Oncology/National Cancer Institute
	I/II	4,5-Dibromorhodamine 123		Celmed BioSciences
	I/II	Theralux		Celmed BioSciences
	I/II	Talabostat	DPP IV, FAPα	Point Therapeutics
	I/II	HuMax-CD20	CD20	Genmab
	I	*O*^{6}-Benzylguanine	*O*-6-Alkylguanine-DNA-alkyltransferase	National Cancer Institute
	I	Flt3ligand		National Cancer Institute
	I	B43-genistein	CD19, Lyn kinase	Parker Hughes Institute
	I	BL22	CD22	National Cancer Institute
	I	ISS-1018		Dynavax
	I	Yttrium Y90 epratuzumab	CD22	Immunomedics
	I	MT-103	CD19, CD3	Micromet/Medimmune
	I	VEGF Trap	VEGF	Regeneron/Sanofi-Aventis
	I	TACI-Ig	TACI	ZymoGenetics/Serono
	I	PPI-2458	Methionine aminopeptidase-2	Praecis
	I	Inotuzumab ozogamicin	CD22	Wyeth/Celltech Group (UCB)
	I	IMMU-106	CD20	Immunomedics
	I	SGN-40	CD40	Seattle Genetics
	IND filed	RN-321	CD22	Alfacell/National Cancer Institute
B-cell lymphoma	II/III	Suberanilohydroxamic acid	HDAC	Merck & Co.
	II	Liposomal vincristine	Tubulin	Inex
	II	Enzastaurin hydrochloride	PKC	Lilly/National Cancer Institute
	I/II	Ad-IFNγ		Transgene
	I	17-AAG	HSP90	National Cancer Institute/Kosan
	I	R-1594	CD20	Roche
	I	HuCAL-derived antibody	MHC class II	GPC Biotech
Mantle cell lymphoma	III	Temsirolimus	mTOR	Wyeth
	II	Antineoplaston A10		Burzynski Research Institute
	II	Enzastaurin hydrochloride	PKC	Lilly
	II	Bortezomib[1]	Proteasome	Millennium/National Cancer Institute
	IND filed	Anti-CD40 MAb	CD40	Chiron
T-cell lymphoma	III	Nelarabine	Purine nucleotides	GlaxoSmithKline
	II	(*R*)-Roscovitine	CDK1, 2, 7 and 9	Cyclacel
	II	UCN-01	PDK1, CDK1, 2, 4 and 6, CHK1 and 2	National Cancer Institute
	II	Zanolimumab	CD4	Genmab
	I	Siplizumab	CD2	MedImmune

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Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Cutaneous T-cell lymphoma (mycosis fungoides)	III	Depsipeptide	HDAC	Gloucester Pharmaceuticals
	II/III	Suberanilohydroxamic acid	HDAC	Merck & Co.
	II	Alemtuzumab[1]	CD52	National Cancer Institute
	II	Temozolomide[1]	DNA	National Cancer Institute
	II	Anti-Tac(Fv)-PE38	CD25	National Cancer Institute
	II	Zanolimumab	CD4	Genmab/Medarex
	II	SGN-30	CD30	Seattle Genetics
	II	CpG-7909	TLR9	Coley Pharmaceutical
	II	Forodesine hydrochloride	Purine-nucleoside phosphorylase	BioCryst
	I/II	Ad-IFNγ		Transgene
	I	Forodesine hydrochloride	Purine-nucleoside phosphorylase	BioCryst
	I	*O*^{6}-Benzylguanine	*O*-6-Alkylguanine-DNA-alkyltransferase	National Cancer Institute
Sezary syndrome	II/III	Suberanilohydroxamic acid	HDAC	Merck & Co.
	I	Etanercept[1]	TNF-α receptor	M.D. Anderson Cancer Center
Systemic anaplastic large cell lymphoma	II	Alemtuzumab[1]	CD52	National Cancer Institute
	II	MDX-060	CD30	Medarex
Follicular lymphoma	II	SGN-30	CD30	Seattle Genetics
Primary central nervous system lymphoma	II	Antineoplaston A10		Burzynski Research Institute
	I/II	HuMax-CD20	CD20	Medarex
Multiple myeloma	R-2003	Thalidomide[1]	TNF-α	Pharmion
	Prereg.	Thalidomide[1]	TNF-α	Celgene/Fujimoto
	III	Plerixafor hydrochloride		AnorMED
	III	^{166}Ho-DOTMP		NeoRx
	III	Oblimersen sodium	Bcl-2	Genta
	III	Lenalidomide	TNF-α	Celgene
	II	Antineoplaston A10		Burzynski Research Institute
	II	Lexidronam Sm 153		Cytogen
	II	Motexafin gadolinium		Pharmacyclics
	II	Temsirolimus	mTOR	National Cancer Institute
	II	Aplidine	VEGFR-1	PharmaMar
	II	PI-88	Heparanase, VEGF, FGF-2	Progen
	II	CC-4047	TNF-α	Celgene
	II	Arsenic trioxide		Cell Therapeutics
	II	Tocilizumab		Chugai
	II	2-Methoxyestradiol		EntreMed
	II	(*R*)-Roscovitine	CDK1, 2, 7 and 9	Cyclacel
	II	Xcellerated T-cells		Xcyte
	II	PXD-101	HDAC	TopoTarget/CuraGen
	I/II	Atiprimod hydrochloride		Callisto Pharmaceuticals
	I/II	β-Alethine		LifeTime
	I/II	AR20.5	CD227 (MUC1)	AltaRex
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan
	I/II	GVAX Myeloma		Cell Genesys
	I/II	Temozolomide[1]	DNA	National Cancer Institute
	I	17-AAG	HSP90	National Cancer Institute/Kosan
	I	2-Methoxyestradiol		National Cancer Institute
	I	TACI-Ig	TACI	ZymoGenetics/Serono
Myelodysplasia	L-2004	Azacitidine	DNA methyltransferase	Pharmion
	Prereg.	Decitabine	DNA methyltransferase	SuperGen/MGI Pharma
	III	Zosuquidar trihydrochloride	MDR-1	National Cancer Institute
	II	Homoharringtonine	DNA	M.D. Anderson Cancer Center/ ChemGenex Pharmaceuticals
	II	Thalidomide[1]	TNF-α	National Cancer Institute
	II	TER-199	Glutathione transferase	Telik
	II	Vatalanib succinate	VEGFR-1, -2 and -3	National Cancer Institute
	II	Arsenic trioxide		Cell Therapeutics
	II	Lenalidomide	TNF-α	Celgene
	I/II	Midostaurin	PKC, Flt3	National Cancer Institute

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Treatment of Hematological/Blood Cancers

Condition	Phase	Drug	Target	Source
Myelodysplasia	I/II	Gemtuzumab ozogamicin[1]	CD33	M.D. Anderson Cancer Center
	I/II	Tipifarnib	Farnesyltransferase	National Cancer Institute
	I/II	PR1		National Cancer Institute
	I/II	CB-001		Viacell
	I	17-AAG	HSP90	National Cancer Institute/Kosan
	I	MS-27-275	HDAC	National Cancer Institute
	I	MG-98	DNA methyltransferase	MGI Pharma/MethylGene
	I	MGCD-0103	HDAC1	MethylGene
	I	SGN-40	CD40	Seattle Genetics
	I	Triapine	Ribonucleoside-diphosphate reductase	National Cancer Institute/Vion

[1]Launched for another indication. mTOR: mammalian target of rapamycin; VEGFR: Vascular endothelial growth factor receptor; HDAC: Histone deacetylase; CDK: Cyclin-dependent kinase; PDGFR: Platelet-derived growth factor receptor; PKC: Protein kinase C; TNF: Tumor necrosis factor; IL: Interleukin; DPP: Dipeptidyl-peptidase; FAPα: Fibroblast activation protein-α; PDK: Phosphoinositide-dependent kinase; CHK: Checkpoint kinase; MDR1: Multidrug resistance 1; RRM2: Ribonucleotide reductase M2; HSP: Heat shock protein; MMP: Matrix metalloproteinase; ADA: Adenosine deaminase; TRAIL: TNF-related apoptosis-inducing ligand; TACI: transmembrane activator and calcium-modulating and cyclophilin ligand interactor; MHC: Major histocompatibility complex; TLR: Toll-like receptor; FGF: Fibroblast growth factor; MUC1: Mucin 1