Chapter 1

THE ROLE OF LEUKEMIA INHIBITORY FACTOR IN CANCER AND CANCER METASTASIS

Farhad Ravandi and Zeev Estrov
Department of Bioimmunotherapy, The University of Texas, M. D. Anderson Cancer Center, Houston, Texas, U.S.A

Key words: Leukemia inhibitory factor (LIF), Cancer, Metastasis

Abstract: Leukemia inhibitory factor (LIF) is a cytokine that exerts pleiotropic activities. LIF is a member of the interleukin-6 family of cytokines which share a similar receptor complex and signal through the gp 130 receptor subunit. Several neoplastic cells originating from various tissues express either LIF, its receptor, or both and respond to this cytokine. Data accumulated thus far provide a complex picture of LIF activities with LIF being stimulatory, inhibitory or having no effect, depending on the system in which it is studied. LIF appears to play an important role in stimulating the growth of certain tumours, and in affecting the surrounding tissue and the target organ of tumour metastases, particularly bone and skeletal tissue. Overproduction of LIF is likely to have significant constitutional effects. Studies using animal models have shown that LIF induces cachexia, metastatic-type bone calcifications, thrombocytosis, and an abnormal immune response. It is therefore possible that suppression of LIF activity might have a beneficial effect in some cancer patients.

1. INTRODUCTION

Leukemia inhibitory factor (LIF) is a pluripotent cytokine with pleiotropic activities. LIF is a member of a family of cytokines that includes the ciliary neurotrophic factor (CNTF), interleukin (IL)-6, IL-11, oncostatin-M (OSM), and cardiotropin-1 (1,2). These cytokines are grouped as a family because of their shared helical bundle structure (3-7), shared subunits of their receptor complexes, and in some cases, overlapping functions (8,9). As other members of this family, LIF can either induce proliferation, inhibit proliferation or cause apoptosis, depending on the system in which this cytokine is studied. Several studies have shown that LIF's divergent physiological effects have been adopted by a variety of neoplastic cells and that LIF takes part in the pathophysiology of cancer. In many neoplasms LIF, produced by either normal tissue or tumour cells, provides the cancerous process with growth and survival advantage.

LIF was initially characterized by its ability to induce differentiation of the

W.G. Jiang et al. (eds.), Growth Factors and their Receptors in Cancer Metastasis, 1–25.

murine myeloid leukemia cell line M1 (10-15) and was cloned from a murine T-cell library (12,16). Independently, a human molecule in the supernatant of T-cell clones was identified and termed human interleukin for DA cells (HILDA) (17-20). Once cloned, this molecule was found to be homologous to its murine counterpart (21-23). Subsequently, additional characteristics of LIF were described, and it was given several other names, including differentiation factor (D-factor) (24-25), differentiation-inducing factor (DIF) (26), differentiation inhibitory activity (DIA) (27), differentiation-retarding factor (DRF) (27,28), hepatocyte-stimulating factor III (HSF III) (29), melanoma-derived lipoprotein lipase inhibitor I (MLPLI) (34), cholinergic neural differentiation factor (31), and osteoclast-activating factor (OAF) (26,32) (Table 1). However, because LIF exerts a broad spectrum of activities and despite its diverse and sometimes opposing effects on different leukemia cell lines (21,26,27,29,32,33-35), LIF has become the official name of this cytokine (1).

The effects of LIF on various tissues provide several clues to its possible role in cancer. For example, LIF stimulates embryonic stem cell proliferation (36-40). It affects blastocyst implantation (36-41) and influences the development of peripheral nerves from their precursors in the embryonic neural crest (32,42), which implies that LIF can stimulate immature cells and probably tumour cells with immature cell characteristics. In addition, LIF was shown to induce a catabolic state and cachexia in nude mice and in primates (43-45). It stimulated the release of acute-phase proteins from hepatocytes, (45-47) and affected bone metabolism by inducing both osteoblastic and osteoclastic activities (48-52). These effects are characteristic clinical features of patients with neoplastic diseases likely to be induced by various cytokines including LIF.

In this chapter we describe the physiological characteristics and the pathophysiological role of LIF in cancer and cancer metastasis.

2. MOLECULAR AND CELLULAR CHARACTERISTICS

2.1 LIF Distribution in Cells

LIF is expressed in cells of different tissues, including osteoblasts, keratinocytes, thymic epithelium, T cells, monocytes, skin fibroblasts, embryonic stem cells, bone marrow stroma cells, central nervous system cells, hepatocytes, and a number of tumour cell lines that have become a source for this cytokine (1,20,21,26,37,53-57) (Table 2).

2.2 Structure and Genetics

Naturally occurring LIF appears as a monomeric glycoprotein with a molecular weight is between 40 and 70 kDa despite a polypeptidic core of 22 kDa (3,21,58). This is due to the presence of several putative sites of N-glycosylation in the primary structure of the molecule allowing extensive post-translational modifications (29).

Abbreviations: LIF, leukemia inhibitory factor; LIFR, LIF receptor; TNF, tumour necrosis factor; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; OSM, oncostatin M; IFN, intrerferon; IL, interleukin; IFN, interferon, CNTF, ciliary neurotrophic factor; CFU, colony forming unit; MM, multiple myeloma; TGF, transforming growth factor; G-CSF, granulocyte colony-stimulating factor; HSF, hepatocyte stimulating factor; SP, neuropeptide substance P; CNS, central nervous system

Table 1. Different names of the leukemia inhibitory factor

Name	Reference
Leukemia inhibitory factor (LIF)	10-15
Differentiation factor (D-factor)	24-25
Differentiation inhibitory activity (DIA)	27
Differentiation-inducing factor (DIF)	26
Differentiation-retarding factor (DRF)	27-28
Human interleukin for DA cells (HILDA)	17-20
Hepatocyte stimulating factor III (HSFIII)	2
Melanoma-derived lipoprotein lipase inhibitor I (MLPLI)	34
Cholinergic Neuronal Differentiation Factor	32
Osteoclast-activating factor	26,31

Table 2. Human cell sources of LIF

Source of LIF	Reference
Bone marrow stromal cultures	53
Thymic epithelial cells	55
T cell clones (alloreactive from lymphocytes rejecting) kidney allografts	20,21,56
Cultured keratinocytes	57
Phytohemagglutinin-stimulated T-cells	26,55
Activated monocytes	54

LIF is encoded by genes localized at chromosome 11A1 in mice and chromosome 22q12 in humans (59,60). Although the location of the human gene and the high incidence of a translocation involving t(11;22)(q24q12) in Ewing's sarcoma stimulated considerable interest, further analysis using somatic cell hybrids and pulse-field gel electrophoresis has shown that the gene is located distal to the breakpoint and is not involved in this translocation (61).

The sequences of cloned LIF genes from four mammalian species are highly conserved in the coding regions (62,63). Murine and human LIF have the complete nucleotide sequence of 8.7 and 7.6 kilobase pairs, respectively (12,14,16, 64,65). Both genes consist of three exons, two introns, and an unusually large 3'-untranslated region that is 3.2 kilobase pairs (65). The LIF transcript is 4.2 kilobases in length and predicts a sequence with 179 residues for the mature protein and a 79% homology between the murine and human products (12,14,64). This is the primary and biologically active form of LIF. The promoter region of the *LIF* gene contains four highly conserved TATA elements, with two identified start sites of transcription (62). Three regions within the 5' flanking region have been identified as important to the function of the LIF promoter (21,62).

The structure of LIF has been determined (66). The main chain fold comprises four α-helices linked by two loops. There are two regions of the LIF molecule involved in receptor interaction and biological function. The first is located within the D helix and comprises residues 161-180, and the second is located between residues 150 and 160 at the C-terminus of the CD loop.

2.3 Biological Forms of LIF

Two forms of LIF were detected: the "diffusible" (D) LIF glycoprotein and an "immobilized" (M) form incorporated into the extracellular matrix (67). Both D- and M-LIF forms are produced by the expression of alternative transcripts that diverge throughout the first exon and use different promoters. The two LIF forms are encoded by mRNAs that are spliced differently at the exon 1/exon 2 boundary. The transcript D encodes the diffusible form and the transcript M encodes the matrix-associated form. Splicing a 5' exon to exons 2 and 3 of the LIF transcription unit produces the latter. The two transcripts co-migrate on agarose gel and therefore can be distinguished by ribonuclease protection analysis but not by Northern blot analysis. The molecular organization of the gene for LIF can explain the different localization of its two forms. Exons 2 and 3 produce the core hydrophobic secretory sequences, whereas the extracellular localization is determined by the first exon. Therefore, changes in the amino terminal of the translocation product direct the formation of a mature, functional LIF with extracellular matrix localization (reviewed in 1 and 2).

Although the reported molecular weight of LIF ranges from 38 to 67 kDa, this heterogeneity can be explained by variable glycosylation of the protein (35,64). Recombinant forms of LIF displaying varying patterns of glycosylation (yeast-derived and *Escherichia coli*-derived) are active (12,64).

2.4 LIF Receptors and Their Signaling

The IL-6 cytokine family members share common signaling components i.e. the LIF receptor (LIFR) and the receptor

subunit gp130 (68). The LIFR was first isolated and found to be structurally related to the gp130 component of the IL-6 receptor and the granulocyte colony-stimulating factor (G-CSF) (69). This receptor is now termed LIFRβ. It binds with low affinity to gp130, whereas LIF binds with high affinity to the LIFRß/gp130 complex, initiating its signal trasduction (70). Other components of this receptor complex, used by other members of the IL-6 cytokine family, have been identified. For example, the receptor component CTNFRα is utilized by CTNF(71,72).

LIF binds to a variety of cells from different tissues (24,33,56,73,74). Following receptor binding, signaling pathways involving both protein tyrosine and serine/threonine kinases are activated. Both the Janus-kinase-signal transducer and activator of transcription (JAK-STAT) and mitogen-activated protein kinase (MAPK) pathways are activated (39,72,75) (Figure 1). Activated STAT molecules dimerize and translocate to the nucleus. Although there are at least six STAT proteins, STAT3 tends to be the protein that is activated by LIF (76). The LIFRß is essential for motor neuron development as demonstrated in studies with the LIFRß knockout mouse model (77) (see below).

3. BIOLOGICAL EFFECTS OF LIF

3.1 Effects on the Reproductive System and Embryogenesis

The mammalian embryo develops from a quasi-stem cell system controlled by regulatory factors, one of which is LIF (13,32,78,79). LIF is expressed in both embryonic and maternal tissue. LIF transcripts were also detected in mouse blastocysts, implying its role as a regulator of embryonic stem cells and a mediator of the trophoblast development (36,74).

In the LIF knockout mouse model, homozygous and heterozygous null mice for a functional LIF gene enabled investigating the role of LIF in the reproductive system (80). Male -/- LIF mice were fertile, but female mice, although able to produce viable blastocytes, failed to implant and were therefore sterile. However, the injection of LIF into homozygous -/- female restored blastocyte implantation (81). Male mice engrafted with a LIF-producing cell line showed complete absence of spermatogenesis, whereas female mice had reduction or complete absence of corporae luteae (47). Recent data confirm the crucial role of LIF during implantation and pregnancy in primates such as monkeys (82) and western spotted skunk (83). In addition, it has been demonstrated that LIF has a crucial role in the maintenance of pregnancy in humans (84,85).

3.2 Effects on Bone Metabolism

Several studies have clearly demonstrated the role of LIF in bone remodeling (86). Both osteoclast and osteoblast activities are either stimulated or suppressed by LIF depending on the developmental stage of the respective cells. When the local effect of LIF was studied in mice by injecting the cytokine over one hemicalvaria, two major effects were observed: 1) increased osteoclastic activity and bone resorption in the injected right hemicalvaria and 2) increased total mineralization, including the periosteal area in the non-injected left hemicalvaria (87). Additional studies using an array of laboratory assays showed that LIF inhibited osteogenic calcification (88), affected osteoclast migration (89), increased osteoclast differentiation (90),

Figure 1. The LIF receptor (LIFR) and selected other members of gp130 family. Following ligand binding, dimerization of the cytoplasmic component of the receptor initiates intracellular signaling pathways such as the Jak-STAT pathway. Interaction of Jak proteins with the gp130 component induces their tyrosine kinase activity. This in turn results in the phosphorylation and activation of downstream targets such as STATs, which then induce their target genes.

inhibited bone module formation (91), and reduced bone calcification (92). Engraftment of mice with LIF-producing cells yielded results similar to those described above (87). The engrafted mice had increased calcifications in both skeletal and extra-skeletal tissues such as the myocard (47).

In vitro stimulation of bone resorption by LIF was accompanied by the release of calcium from prelabelled mouse calvaria. This effect, caused by an increase in the number of osteoclasts, could be inhibited by indomethacin, indicating that it is mediated through the activation of prostaglandins. The prostaglandin-dependent bone-resorptive effect of LIF is similar to that of other cytokines such as IL-1, tumour necrosis factor (TNF), and transforrming growth factor (TGF)-ß (93,94).

3.3 Effects on Lipid Metabolism

LIF, like TNF, IL-1, and interferon (IFN)-γ, can inhibit the enzyme lipoprotein lipase, which is a key enzyme in triglyceride metabolism (95,96). High levels of LIF induced a fatal catabolic state with cachexia in mice and monkeys (12,33,43-45,97). It is likely that this effect of LIF is mediated by its ability to suppress adipogenic processes through its enzyme inhibitory effect. Thus, the inhibition of lipoprotein lipase is likely to reduce the intake of fatty acids by adipocytes and lead to cachexia.

3.4 Role of LIF in Inflammation and Tissue Injury

A number of studies demonstrated the role of LIF in inflammation. LIF was found to have both a pro- and an anti-inflammatory role in a variety of inflammatory disorders (98). LIF mRNA increased in various mouse tissues during systemic inflammation triggered by the injection of either endotoxin or lipopolysaccharide (LPS) (99). Interestingly, passive immunisation against LIF prior to LPS injection protected the mice from the lethal effect of high-dose LPS (100), indicating that LIF is one of the agents associated with the lethality of septic shock. Surprisingly, LIF injection prior to a challenge with high dose LPS protected against the lethal dose of LIF (101,102). This dual effect of LIF was found in different diseases in humans, such as rheumatoid arthritis (103,104). LIF is highly elevated in the synovial tissue and fluids of patients with rheumatoid arthritis. In addition, human articular chondrocytes and synovial tissue produce LIF that in turn may upregulate proinflammatory cytokines (105-109). Injection of LIF-binding proteins into a goat joint atenuates the inflammatory reaction caused by a prior injection with LIF (110). LIF has also been detected in the pleural effusion of patients with tuberculosis (111) and in the broncho-alveolar lavage fluid of patients with acute respiratory distress syndrome (112).

Local inflammatory processes have been shown to be mediated by LIF (113-115). On the other hand, the response to injection of complete Freud's adjuvant is significantly augmented in adult LIF knock-out mice (116). Some of the differences among these studies could be explained by dissimilar experimental designs, dose of LIF, and species and age of the studied animals. However, divergent effects of LIF on the thymus and on T and B lymphocytes (see below) may also contribute to dissimilar results in various experimental models.

LIF also plays a role in tissue repair in cases such as stab wound injury and injury to the central and peripheral nervous systems (117-120). LIF mRNA was shown to be upregulated after muscle

crash injury (121) consistent with LIF's role as a stimulator of human muscle precursor-cell proliferation (122,123). In LIF knock-out mice, infiltration by neutrophils, macrophages, and mast cells is delayed in lesions of both the central and peripheral nervous systems (124), suggesting that LIF could be chemotactic for inflammatory cells.

3.5 Effects on Hepatic Function

The hepatocyte-stimulating factor (HSF) III initially detected in cultured keratinocytes and squamous carcinoma cell lines was found to be identical to LIF (29,125). The liver secretes acute-phase proteins into the circulation upon various stimuli including those induced by several cytokines including LIF (126). Injection of LIF into rhesus monkeys strongly increased the levels of acute-phase proteins (127). This molecule is able to induce the production of a number of acute-phase proteins by the hepatocytes, an ability that it shares with other cytokines including IL-6 and TNF. Thus hepatocytes produce LIF which is capable of inducing the production of acute-phase proteins by the liver, suggesting an autocrine role for LIF.

3.6 Effects on the Nervous System

Cholinergic neuronal differentiation factor, a protein acting on sympathetic neurons to induce acetylcholine synthesis and cholinergic function, is now known to be identical to LIF (32). LIF affects the development of peripheral neurons from their precursors in the embryonic neural crest (42). LIF also participates in the regulation of the neuropeptide substance P (SP) in sympathetic neurons, increasing SP in both neuronal cell cultures and cultures containing a mixture of neuronal and non-neuronal cells (126). LIF acts as a survival factor on mature sensory neurons (127). Neuronal differentiation of spinal-cord precursors is dependent on a functioning LIFRß (128). In the LIFRß knock-out mouse model, LIFRß -/- mice die shortly after birth, and they reveal a profound loss of astrocytes in the brain stem and spinal cord, and neurons with pycnotic nuclei and cytoplasmic vacuoles (77,129). These findings and the distribution of the LIFR mRNA in the brain and spinal cord suggests that LIF affects neuronal cells in the adult as well as during development (128). LIF can prevent the death of axotomised sensory and motor neurons (129,130). In the Wobbler mouse model, the animals develop lower-motor neuropathy. Injection of LIF has a sparing effect, improving the neuropathy (131), further demonstrating the complex effects of LIF in the nervous system.

3.7 Effects on the Hematopoietic System

LIF has been characterized by its ability to induce differentiation and suppress the growth of M1 myeloid leukemia cells (12-15,48,132). However, in subsequent studies, LIF stimulated, inhibited or had no effect on leukemia cells, depending on the cell line or the system in which LIF's activity was investigated (133-137). Similarly, LIF induces a divergent effect on normal hematopoietic progenitors. Exposure to LIF reduces the proliferative capability and survival of normal hematopoietic progenitors (138). Although LIF had no effect on CD34+ human bone marrow cells, it enhanced the stimulating effect of IL-3 (139). In another study, LIF stimulated the growth of colony-forming units granulocyte-erythroid-macrophage-megakaryocyte (CFU-GEMM) and CFU-eosinophil (CFU-Eo), and burst-forming units-erithroid (BFU-E) colony-forming cells (140). Similar results were obtained

with CD34+ cells stimulated with IL-3 and IL-6. LIF augmented the effect of megakaryocyte colony-forming cell stimulators and enhanced a chemoattractant effect on human and mouse eosinophils (19,20,73).

Bone marrow stroma cells constitutively express LIF mRNA (53). Exposure of hematopoietic stroma to either IL-1α, IL-1β, TNF-α, or TGF-β increased the level of LIF mRNA (53,141). Stroma obtained from marrow cells of patients with chronic myelogenous leukemia who had high levels of IL-1β expressed high levels of LIF (53,142).

The first clue of the role LIF plays in normal hematopoiesis in vivo came from experiments carried out in mice (47,48). Mice tranfected with LIF-producing cells exhibited thymic atrophy and extramedullary hematopoiesis (47). Daily injection of LIF caused granulocytosis and an increase in megakaryocytes and platelets (46). Transgenic mice constitutively expressing diffusible LIF displayed B-cell hyperplasia, profound disorganization of the thymus, and loss of cortical CD4+ and CD8+ lymphocytes. Transplantation of transgenic bone marrow into wild-type mice recipients transferred the thymic and lymph node defects (143).

Knock-out of the LIF gene significantly impaired the hematopoietic system (80). Both early and mature hematopoietic progenitors were dramatically reduced and a dose effect was seen because heterozygotes were less affected. However, mature hematopoietic elements in the marrow, spleen, and peripheral blood were normal, indicating that the defect was in the stem cell pool rather than in differentiation as found in other studies (144-149). Homozygous null mice for gp130 die mainly of cardiac defects due to the elimination of cardiotrophin-1 signaling (3). In this mutant, the number of mononuclear cells in fetal liver was drastically reduced, as were the numbers of both early and mature CFUs. The thymuses were 50 percent smaller, consistent with other studies showing LIF's role in hematopoiesis.

4. ROLE OF LIF IN CANCER

Several tumour cell lines and neoplastic cells from various tissues produce LIF and express LIF receptors. However, the functional significance of either LIF or LIFR in human neoplasia is not fully understood. LIF can stimulate growth, induce differentiation, or trigger apoptotic cell death of various tumour cells (1,141,150,151) and data on the mechanisms controlling this diverse array of effects are scanty.

Results of in vivo animal trials shed light on some of the possible roles of LIF in cancer and cancer metastasis. Cachexia (43,44), subcutaneous and abdominal fat loss, and elevated leukocyte and platelet counts often found in patients with metastatic cancer were induced by LIF in both mice and monkeys (46-48). In addition, at a high dose, LIF induced myelosclerosis whereas a low dose induced megakaryocytosis, reduced marrow cellularity and caused lymphopenia (48) suggesting a possible role for LIF in the pathogenesis of myeloproliferative disorders such as myelofibrosis and in marrow sclerosis. Furthermore, mice engrafted with FDS-P1 cells that produce high levels of LIF developed a fatal syndrome with cachexia, atrophy of liver and kidney, and excess bone formation with increased osteoblastic activity that resulted in metastatic-type calcifications (47) implying a role for LIF in bone tumours and neoplasms metastasizing to bone.

Table 3. Effect of LIF on Various Tumours

Tumour	Effect
Leukemia and MDS	LIF induces differentiation of the mouse leukemia cell line M1(13-15). LIF stimulates the murine leukemia cell line DA-1 (19,66,152). LIF is produced by the human monocytic leukemia cell line THP-1 (153). LIF is expressed in leukemia cells (140,154) and in long-term bone marrow cultures from patients with AML and MDS (155). LIF stimulates normal marrow progenitor proliferation (139,140) but inhibits leukemia cell growth (156,157).
Lymphoma	Lymphoma cell lines produce LIF (158), and LIF production is upregulated by IL-1 (66). Human T-cell leukemia virus-infected cells produce LIF (159). and LIF probably serves in these cells (160).
Multiple myeloma	Human myeloma cell lines (161) and plasmacytoma cells express LIF (162) and LIF receptors (163). LIF may act as an autocrine growth factor in multiple myeloma (163,164).
Bone Tumours	LIF is constitutively expressed in bone tumour cell lines (165) and is produced by bone tumour cells (166). LIF and LIFR were found in giant tumour cells (167,168). LIF-stimulated growth of giant tumour cells and they exhibit osteoclastic activity (167,168). LIF was detected in the urine of patients with bone tumours (166).
Breast Cancer	LIF stimulates the proliferation of the estrogen-dependent MCF-7 and T47-D and the estrogen-independent SK-BR-3 and BT20 cell lines (169-171). In one study (172), LIF inhibited MCF-7 cell growth. MCF-7 cells bind LIF and like breast cancer cells express the gp130 receptor subunit (169,173). MDA-MB-231 cells produce LIF but do not proliferate in response to this cytokine (170). LIF was detected in the supernatant of the SV40-transformed mammary epithelial cell line HBL 100 (58) but had no effect on normal mammary epithelial cell growth (169,171). Tumours from breast cancer patients express LIF transcripts (174) and LIF mRNA (172). LIF and LIF receptors were detected in the vast majority of breast cancer tumour tissue (173). LIF stimulates fresh breast cancer cell proliferation (169).
Kidney Cancer	The kidney cancer cell lines A-498 and ACHN produce LIF (170). Anti-LIF antibodies inhibit A-498 and ACHN cell proliferation (170), suggesting an autocrine role for LIF in these cells.

Table 3 continued on next page..

Table 3. continuing

Tumour	**Effect**
Prostate Cancer	The hormone-independent prostate cancer cell lines TSH, PC-3 and DV145 produce LIF and express gp130 (170,175). Anti-LIF antibodies suppress DV145 cell growth (170).
Melanoma	The melanoma cell line SEK1 produces LIF (34,176). LIF mRNA is expressed in several melanoma cell lines (177). LIF was detected in > 60% of human melanoma specimens (178). LIF increased the expression of the intracellular adhesion molecule-1 (178).
Hepatoma	The hepatoma cell lines HuH-1 and Hep-G2 express LIF (179). LIF stimulated the expression of acute-phase proteins in the H-35 rat hepatoma line (180). Activation of LIFR initiates the JAK signaling pathway (181).
Gastrointestinal Cancer	LIF, LIFR, and gp130 mRNA were detected in esophageal, gastric, colon, gall bladder, and pancreatic cancer cell lines (58,179). LIF induced apoptosis, growth inhibition, or growth stimulation of different cell lines (179). LIF stimulated the growth of human colon cancer cell lines (182).
Central Nervous System Tumours	LIF either inhibited (183) or had no effect (184) on glioma cell lines. LIF, LIFR, and gp130 were detected in neuroblastoma tumour cells (185). LIF antisense inhibited medulloblastoma cell proliferation (186).
Lung Cancer	LIF is produced by the lung adenocarcinoma cell line NCI-H23 (58), and it stimulated the growth of the lung giant cell carcinoma cell line PG (187).
Oral Cavity Cancer	The oral cavity carcinoma cell line OCC-IC produces LIF (188).
Uterine Cancer	Progestine-stimulated SKUT-1B cells express LIF (189).
Choriocarcinoma	The choriocarcinoma line NJG expresses LIF and LIFR (190).
Germ Cell Tumour	Human germ cell tumour cell lines express LIF and LIFR (191).

Several in vitro studies were performed to delineate the effects of LIF on various tumours from different tissues. Though studies of cell lines often yielded conflicting results, experiments with fresh tissue confirmed LIF's role in tumour growth, disease progression, and tumour metastasis (Table 3).

4.1 Hematological Malignancies

LIF was originally characterized by virtue of its ability to induce differentiation in the murine myeloid leukemia cell line M1, a property that it shares with IL-6 (13-15). However, LIF had no effect on the murine leukemia WEHI 3BD+ cell line that differentiates in response to IL-6 (150,192) whereas it stimulated the growth of the murine IL-3-dependent DA-1 myeloid leukemia cell line (19,152). When injected into mice that had been implanted with T-22 cells, a subclone of the M1 cell line, it prolonged the animals' survival by inducing differentiation (157). LIF is also produced by the THP-1 human monocytic leukemia cell line (58).

LIF was found to be expressed in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) cultured bone marrow stroma cells (155) and in human leukemia cell lines (140,154). Although LIF stimulated human normal marrow hematopoietic progenitor cell growth (139,140,193) and stroma-derived macrophage proliferation (194), it inhibited human leukemia cell growth (156,157).

LIF also affects cells of the lymphoid lineage. T-cell clone (alloreactive) from lymphocytes rejecting kidney allografts and thymic epithelial cells (55) were found to produce LIF (reviewed in 1 & 2). Whereas normal human T lymphocytes did not bind radio-iodinated LIF (164), cells infected with human T-cell leukemia virus (HTLV)-I and –II expressed LIF (159) and proliferated in response to this cytokine (160). Similarly, various lymphoma cell lines were found to produce LIF (158), and LIF production was upregulated by IL-1 (66).

Similar to IL-6, LIF plays a role in multiple myeloma (MM) cell proliferation. Human MM cell lines (161) and myeloma and plasmacytoma cells express LIF (162), LIFR, and the gp130 receptor subunit (163) and proliferate when exposed to LIF (163,164). Thus, similarly to IL-6 LIF may act as an autocrine growth factor for MM cells. The capability of LIF to induce both lytic and osteogenic effects in skeletal tissue, suggest that the osseous abnormalities typically found in MM are induced, among other factors, by LIF-producing myeloma cells.

4.2 Bone Tumours

The effects of LIF on bone remodeling with LIF inducing both osteoclastic and osteoblastic activities suggest that LIF-producing tumour cells may significantly alter bone and skeletal tissue. Because the *LIF* gene was found to be mapped to chromosome 22q11-q12.2 (60), a question arose whether this site might be affected by chromosomal translocations that are related to tumours of neural-crest origin such as Ewing's sarcoma and peripheral neuroepithelioma cytogenetically characterized by t(11;22)(q24;q12). It was found that the *LIF* gene is located far away from the Ewing's sarcoma translocation (61,195).

Nevertheless, bone tumours were found to produce high levels of LIF. Marusic et al. tested various rodent and human immortalized malignant bone tumour cell lines and found that LIF is constitutively expressed in several cell lines and is cytokine-inducible in others (165). LIF

and LIFR were found in the cytoplasm of multinucleated giant tumour cells. Furthermore, LIF-stimulated giant tumour cells displayed osteoclast immuno-cytochemical features and resorbed large amounts of dentin (167,168). Additional indirect evidence for the role of LIF in bone tumours was provided by Gouin et al. who detected LIF in 34.7% of urine samples obtained from patients with a variety of bone tumours. They also found high LIF protein levels in supernatants of both neoplastic and benign bone tumour cells (166).

Although LIF provides various bone tumours with a proliferation advantage and modulates their effects on bone tissue in either an autocrine or paracrine fashion, several studies showed that tumour cells that metastasize to bone may utilize similar mechanisms.

4.3 Breast Cancer

Because LIF affects bone tissue and is produced by marrow stroma cells (86,155), several investigators asked whether LIF has a role in tumours such as breast cancer which metastasizes to this site (196). This was further emphasized by the study of Akatsu et al. who showed that the mouse mammary cell line MMT060562 produces LIF and supports osteoclast formation via a stroma cell-dependent pathway (197).

Studies in breast cancer cell lines showed that some of these cells produce LIF, others express LIFR, and the cells may or may not respond to LIF. The diversity of cell lines and cell line clones that may have different features in different laboratories present a wide array of complex biological characteristics. For example, the estrogen-dependent breast cancer cell lines MCF-7 and T47-D do not produce LIF however their growth is stimulated by this cytokine (169-171). MCF-7 cells bind LIF and, like several other breast cancer cell lines (172), express the gp130 subunit (169). In contrast, MDA-231 cells that express neither estrogen nor progesterone receptors produce LIF but their growth is not affected by this cytokine (170). Interestingly, progesterone treatment of MDA-231 cells co-transfected with both estrogen and progesterone induced the expression of LIF's promoter (198). LIF also stimulated the estrogen-dependent T-47D and the estrogen-independent SK-BR3 and BT20 cell lines; inhibited, according to one study, MCF-7 cells (172), but had not effect on normal mammary epithelial cell growth (169,171). Interestingly, the SV40-transformed mammary epithelium cell line HBL 100 was found to produce LIF (58).

Breast cancer cells from 6 of 6 tumour samples expressed LIF transcripts (174) and widespread LIFR mRNA expression was found in primary breast tumours (172). Immunostaining of tumour samples obtained from 50 breast cancer patients detected LIF in 78% and LIFR in 80% of the samples. The presence of LIF correlated with a low S-phase fraction of the cell cycle and diploidy, whereas the presence of LIFR correlated with dipoidy, low S-phase fraction, and of estrogen receptor positivity. LIF and LIFR were also expressed in normal breast epithelium in 87% and 77% of the specimens, respectively (173). LIF stimulated colony formation of breast cancer cells obtained from five different patients in a dose-dependent fashion (169) and the growth stimulation correlated with the presence of LIFR in these specimens (173).

Taken together the data suggest a complex role of LIF and LIFR in breast cancer growth regulation. Because the bone marrow stroma produces LIF (155) and other cytokines such as stem cell

factor that stimulate breast cell proliferation (169), cells that express LIFR and respond to these cytokines may have a growth advantage in the bone marrow microenvironment.

4.4 Kidney Cancer

Renal carcinoma, like breast cancer, frequently metastasizes to bone. In addition, systemic symptoms, such as weight loss and fever, are common in kidney cancer and likely to result from overproduction of inflammatory cytokines. Moreover, the process of mouse nephrogenesis involves at least two distinct stages that can be blocked by LIF (199), and rat and human mesangial cells produce LIF and respond to this cytokine by transiently expressing the immediate-early genes c-*fos, jun*-B, and *Egr*-1 (200). These data suggest that LIF affects renal cell proliferation.

Studies with cell lines have shown that both the primary kidney cancer line A-498 and the ACHN cell line established from pleural effusion of metastatic renal carcinoma produce LIF. Anti-LIF antibodies suppressed the cells' growth and the inhibitory effect was reversed by exogenous LIF. These data suggest that the endogenously produced LIF stimulated kidney cancer cell line proliferation (170).

4.5 Prostate Cancer

Prostate cancer cells selectively metastasize to the axial skeleton to produce osteolytic lesions. Laboratory data suggest that LIF plays a role in this disease. Paracrine-mediated growth factors may play a role in prostate cancer growth and development (201). In addition, IL-6, often expressed in parallel with LIF (202), was found to be expressed in prostate tissue (175) and might stimulate prostate cancer growth during disease progression (203). The hormone-independent cancer cell lines TSU, PC-3 (204), and DU 145 (170) produce LIF and express gp130 (204). DU 145 cells did not proliferate in response to this cytokine (170,204) however, anti-LIF antibodies inhibited the cells' growth (170). Thus, although only a few studies investigated the effect of LIF on prostate cancer cells and no data on binding of LIF to cellular LIFR are available, results from the above-described studies suggest that LIF plays a role in prostate cancer.

4.6 Malignant Melanoma

In 1989, Mori et al. found that a factor produced by the melanoma cell line SEKI induced cachexia in tumour-bearing nude mice and inhibited lipoprotein lipase. This factor designated melanoma-derived lipoprotein lipase inhibitor was found to be identical to LIF (34,176). Subsequent studies found that LIF mRNA is expressed in various melanoma cell lines of which several produce the protein (58,177). Interestingly, oncostatin-M, another member of the IL-6 cytokine family, significantly increased LIF production by melanoma cells (205).

LIF was detected in more than 60% of human melanoma samples and was found to enhance the expression of the intracellular adhesion molecule (ICAM)-1 in melanoma cells (177). Shedding of the soluble form of ICAM-1 from tumour cells impairs immune recognition and leads to tumour escape. Therefore, LIF may provide melanoma cells with a survival advantage. Furthermore, melanoma cells transfected with LIFR showed increased tumour growth suggesting that LIF may directly stimulate the growth of melanoma cells that express LIFR and provide them with a survival and growth advantage.

4.7 Hepatoma

Only a few groups studied the effects of LIF in hepatoma. It was found that LIF is expressed in the HuH-7 and Hep-G2 hepatoma cell lines (179). LIF upregulated the expression of acute-phase proteins in the rat H-35 hepatoma cells (180) and activation of LIFR initiated signaling through the JAK pathway in Hep-G2 cells (181).

4.8 Gastrointestinal Malignancies

The mRNA of LIF, LIFRß, and gp130 was detected in six stomach cancer, two colon cancer, one esophageal cancer, one gall bladder cancer, and seven pancreatic cancer cell lines (179). LIF induced apoptosis in the AZ-521 gastric and the GBK-1 gall bladder cancer cell lines and was detected in the MIA PACA pancreatic carcinoma cells (58). LIF did not affect the growth of either stomach or cancer cell lines; however, it stimulated the proliferation of two of seven pancreatic cancer cell lines (171). LIF is produced by the colon carcinoma cell lines SW948 and HRT18 (58). It has been shown to enhance human colon carcinoma HT24 cell proliferation suggesting that LIF facilitates the transition from ulcerative colitis to colon cancer (182).

Because the results of cell line studies are inconsistent and since patient tumour tissue has not been studied yet, the biological significance of the cell line studies remains to be determined.

4.9 Central Nervous System Tumours

Considering the variety of effects induced by LIF in the central nervous system (CNS), its involvement in CNS tumour growth is not surprising. LIF, LIFR, and the gp130 receptor subunit were detected in medulloblastoma tumour cells. Twelve of 12 tumour samples expressed LIF, and more than 90% of the samples expressed LIFR and gp130. (185). In addition, LIF antisense inhibited medulloblastom cell proliferation (186). Taken together these data suggest that LIF acts as an autocrine growth factor in medulloblastoma.

LIF was also studied in other CNS tumours. It either inhibited (183) or had no effect (184) on glioma cell lines. Meningioma cells expressed LIF transcripts; however, LIF did not affect the cells' growth in vitro (206).

4.10 Other Neoplasms

Several groups have reported LIF's expression, production, and function in a variety of tumour cell lines. These studies implicate LIF's role in the proliferation of neoplastic cells from several malignancies.

Little is known about the role of LIF in tumours of the lung and the oral cavity. LIF is localized in the human airway mainly in fibroblasts, and IL-1ß can upregulate the expression of LIF's mRNA and the release of LIF protein (207). LIF stimulated the growth of the metastatic human lung giant cell carcinoma PG cell line (187) and was found to be produced by the lung adenocarcinoma NCI-H23 cells (58) and the oral cavity carcinoma cell line OCC-1C (188).

Because of LIF's crucial role in the reproductive system, its effects on neoplasms originating from this system are of special interest. To our surprise, we were able to find only a limited number of studies addressing this issue. Bamberger et al. reported that LIF's transcription is upregulated upon exposure of the SKUT-1B uterine tumour cell line to a progesterone agonist (189). A soluble form of LIFR was detected in the supernatant of the choriocarcinoma cell line NJG, which also expressed LIF cDNA (190). Interestingly, human germ

tumour cell lines express two forms of LIFR. Overexpression of LIFR of either form generated different levels of LIF protein activity, suggesting an autocrine role for LIF during germ cell tumourigenesis (191).

LIF is also expressed in several other human tumour cell lines. Those include the bladder carcinoma line 5637, the epidermal carcinoma cell line HLFa (58) the squamous carcinoma line COLO-16 (29), and the SV40-transformed keratinocyte cell line SVK14 (58). The significance of these findings is yet to be determined.

5. CONCLUSION

Similar to its diverse physiological effects, LIF exerts a broad spectrum of activities in various neoplastic cells, their surrounding tissues, and the cancer patient's body as a whole. Although the accumulating data are incomplete and far from being conclusive, they indicate that LIF plays a major role in the pathophysiology of neoplasia. Tumours of bone, breast, kidney, the CNS, and other tissues, benefit from the presence of this cytokine. LIF, produced endogenously or by the tumours' surrounding tissue, stimulates the cancer cells in an autocrine or paracrine fashion. In addition, LIF-producing tumour metastases, especially those metastasizing to bone, cause local distortion by inducing either blastic or lytic lessions. Moreover, overproduction of LIF is likely to be responsible for constitutional reactions such as an abnormal immune response; inflammatory and anti-inflammatory reactions, production of acute-phase proteins; abnormal responses of the hematopoietic system, including thrombocytosis; and neutrophilia and cachexia.

Several groups worldwide have investigated the role LIF plays in normal physiology and in pathophysiology of cancer. These studies have revealed a wide array of complex effects that are not fully understood. Nevertheless, at least in a limited number of tumours, LIF appears to accelerate the cancerous process. Whether inhibition of LIF would be beneficial as an anticancer therapy remains to be seen.

References

1. Kurzrock R, Estrov Z, Wetzler M, Gutterman JU, Talpaz M. LIF: not just a leukemia inhibitory factor. Endocr Rev 1991;12(3):208-17
2. Taupin JL, Pitard V, Dechanet J, Miossec V, Gualde N, Moreau JF. Leukemia inhibitory factor: part of a large ingathering family. Int Rev Immunol 1998;16(3-4):397-26
3. Robinson RC, Grey LM, Staunton D. The crystal structure and biological function of leukemia inhibitory factor: implications for receptor binding. Cell 1994;77:1101-16
4. McDonald NQ, Panayotatos N, Hendrickson WA, Crystal structure of dimeric human ciliary neurotrophic factor determined by MAD phasing EMBO J 1995;14:2689-99
5. Somers W, Stahl M, Seehra JS. 1.9 A crystal structure of interleukin 6: implications for a novel mode of receptor dimerization and signaling. EMBO J 1997;16:989-97
6. Xu GY, Yu HA, Hong J. Solution structure of recombinant human interleukin-6. J Mol Biol 1997;268:468-81
7. Hinds MG, Maurer T, Zhang JG. Solution structure of leukemia inhibitory factor. J Biol Chem 1998;273:13738-45
8. Taga T. Gp130, a shared signal transducing receptor component for menatopoietic and neuropoietic cytokines. J. Neurochem 1996;67:1-10
9. Nakashima K, Taga T. gp130 and the IL-6 family of cytokines: signaling mechanisms and thrombopoirtic activities. Semin Hematol 1998;35:210-21
10. Ishikawa Y. Differentiation of a cell line of myeloid leukemia. J Cell Physiol 1969;74:223-34
11. Tomida M, Yamamoto-Yamaguchi Y, Hozumi M. Purification of a factor inducing

differentiation of mouse myeloid leukemic M1 cells from conditionedmedium of mouse fibroblast L929 cells. J Biol Chem 1984;259:10978-82
12. Gearing DP, Gough NM, King JA, Hilton DJ, Nicola NA, Simpson RJ, Nice EC, Kelso A, Metcalf D. Molecular cloning and expression of a cDNA encoding a murine myeloid Leukemia Inhibitory Factor. EMBO J 1987;6:3995-02
13. Hilton DJ, Nicola NA, Metcalf D. Purification of a murine leukemia inhibitory factor from Krebs ascites cells. Anal Biochem 1988;173(2):359-67
14. Gough NM, Gearing DP, King JA, Willson TA, Hilton DJ, Nicola NA, et al. Molecular cloning and expression of the human homologue of the murine gene encoding myeloid leukemia-inhibitory factor. Proc Natl Acad Sci U S A 1988;85(8):2623-27
15. Hilton DJ, Nicola NA, Gough NM, Metcalf D. Resolution and purification of three distinct factors produced by Krebs ascites cells which have differentiation-inducing activity on murine myeloid leukemic cell lines. J Biol Chem 1988;263(19):9238-43
16. Gearing DP, King JA, Gough NM. Complete sequence of murine leukemia inhibitory factor. Nuleic Acid Res 1988;16:9857
17. Ythier A, Abbud-Filho M, Williams JM, Loertscher R, Schuster MW, Nowill A, Hansen JA, Maltezos D, Strom T. Interleukin 2 dependent release of IL3 activity by T4+ human T-cell clones. Proc Natl Acad Sci USA 1985;82:7020-24
18. Moreau JF, Bonneville M, Peyrat MA, Jacques Y, Soulillou JP. Capacity of alloreactive human T cell clones to produce factor(s) inducing proliferation of the IL3-dependent DA-1 murine cell line. Ann Inst Pasteur Immunol 1986;137C:25-37
19. Moreau JF, Bonneville M, Godard A, Gascan H, Gruart V, Moore MA, et al. Characterization of a factor produced by human T cell clones exhibiting eosinophil-activating and burst-promoting activities. J Immunol 1987;138(11):3844-49
20. Godard A, Gascan H, Naulet J, Peyrat MA, Jacques Y, Soulillou JP, et al. Biochemical characterization and purification of HILDA, a human lymphokine active on eosinophils and bone marrow cells. Blood 1988;71(6):1618-23
21. Moreau JF, Donaldson DD, Bennett F, Witek-Giannotti J, Clark SC, Wong GG. Leukaemia inhibitory factor is identical to the myeloid growth factor human interleukin for DA cells. Nature 1988;336(6200):690-92
22. Smith AG, Heath JK, Donaldson DD, Wong GG, Moreau JF, Stahl M, Rogers D. Inhibition of pluripotential embryonic stem cells differentiation by purified polypeptides. Nature 1988;336:688-90
23. Gough NM, Gearing DP, King JA, Wilson TA, Hilton DJ, Nicola NA, Metcalf D. Molecular cloning and expression of the human homologue of the murine gene encoding myeloid Leukemia Inhibitory Factor. Proc Natl Acad Sci USA 1988;88:2623-27
24. Yamamoto-Yamaguchi Y, Tomida M, Hozumi M. Specific binding of a factor inducing differentiation to mouse myeloid leukemic M1 cells. Exp Cell Res 1986;164(1):97-02
25. Lowe DG, Nunes W, Bombara M, McCabe S, Ranges GE, Henzel W, et al. Genomic cloning and heterologous expression of human differentiation- stimulating factor. DNA 1989;8(5):351-59
26. Abe E, Tanaka H, Ishimi Y, Miyaura C, Hayashi T, Nagasawa H, et al. Differentiation-inducing factor purified from conditioned medium of mitogen-treated spleen cell cultures stimulates bone resorption. Proc Natl Acad Sci U S A 1986;83(16):5958-62
27. Smith AG, Hooper ML. Buffalo rat liver cells produce a diffusible activity which inhibits the differentiation of murine embryonal carcinoma and embryonic stem cells. Dev Biol 1987;121(1):1-9
28. Koopman P, Cotton RG. A factor produced by feeder cells which inhibits embryonal carcinoma cell differentiation. Characterization and partial purification. Exp Cell Res 1984;154(1):233-42
29. Baumann H, Wong GG. Hepatocyte-stimulating factor III shares structural and functional identity with leukemia-inhibitory factor. J Immunol 1989;143(4):1163-67
30. Mori M, Yamaguchi K, Abe K. Purification of a lipoprotein lipase-inhibitory protein produced by a melanoma cell line associated with cancer cachexia. Biochem Biophys Res Commun 1989;160:1085-92
31. Cornish J, Gallon K, King A, Edgar S, Reid IR. The effect of leukemia inhibitory factor on bone in vivo. Endocrinology 1993;132:1359-66
32. Yamamori T, Fukada K, Aebersold R, Korsching S, Fann MJ, Patterson PH. The cholinergic neuronal differentiation factor from heart cells is identical to leukemia inhibitory factor (published erratum appears in Science 1990 Jan 19;247(4940):271). Science 1989;246(4936):1412-16
33. Williams RL, Hilton DJ, Pease S, Willson TA, Stewart CL, Gearing DP, et al. Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. Nature 1988;336(6200):684-87
34. Mori M, Yamaguchi K, Abe K. Purification of a lipoprotein lipase-inhibitory protein produced by

a melanoma cell line associated with cancer cachexia. Biochem Biophys Res Commun 1989;160:1085-92
35. Gough NM, Williams RL. The pleiotropic actions of leukemia inhibitory factor. Cancer Cells 1989;1(3):77-80
36. Conquet F, Brulet P. Developmental expression of myeloid leukemia inhibitory factor gene in preimplantation blastocysts and in extraembryonic tissue of mouse embryos. Mol Cell Biol 1990;10(7):3801-05
37. Rathjen PD, Nichols J, Tom S, Edwards DR, Heath JK, Smith AG. Developmentally programmed induction of differentiation inhibiting activity and the control of stem cell populations. Genes Dev 1990;4(12B):2308-18
38. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature 1981;292(5819): 154-56
39. Pease S, Williams RL. Formation of germ-line chimeras from embryonic stem cells maintained with recombinant leukemia inhibitory factor. Exp Cell Res 1990;190(2):209-11
40. Burgess AW. Life after LIF? Bioessays 1989;10(5):166-69
41. Shellard J, Perreau J, Brulet P. Role of leukemia inhibitory factor during mammalian development. Eur Cytokine Netw 1996;7(4):699-12
42. Murphy M, Reid K, Hilton DJ, Bartlett PF. Generation of sensory neurons is stimulated by leukemia inhibitory factor. Proc Natl Acad Sci U S A 1991;88(8):3498-01
43. Billingsley KG, Fraker DL, Strassmann G, Loeser C, Filot HM, Alexander HR. Macrophage-derived tumor necrosis factor and tumor-derived of leukemia inhibitory factor and interleukin-6: possible cellular mechanisms of cancer cachexia. Ann Surg Oncol 1996; 3:29-35
44. Mori M, Yamaguchi K, Honda S, Nagasaki K, Ueda M, Abe O, Abe K. Cancer cachexia syndrome developed in nude mice bearing melanoma cells producing leukemia-inhibitory factor. Cancer Res 1991; 51(24):6656-59
45. Ryffel B. Pathology induced by leukemia inhibitory factor. Int Rev Exp Pathol 1993; 34 PT B:69-72
46. Metcalf D, Nicola NA, Gearing DP. Effects of injected leukemia inhibitory factor on hematopoietic and other tissues in mice. Blood 1990;76(1):50-6
47. Metcalf D, Gearing DP. Fatal syndrome in mice engrafted with cells producing high levels of the leukemia inhibitory factor. Proc Natl Acad Sci U S A1989;86(15):5948-52
48. Metcalf D, Gearing DP. A myelosclerotic syndrome in mice engrafted with cells producing high levels of leukemia inhibitory factor (LIF). Leukemia 1989;3(12):847-52
49. Allan EH, Hilton DJ, Brown MA, Evely RS, Yumita S, Metcalf D, et al. Osteoblasts display receptors for and responses to leukemia-inhibitory factor. J Cell Physiol 1990;145(1):110-29
50. Noda M, Vogel RL, Hasson DM, Rodan GA. Leukemia inhibitory factor suppresses proliferation, alkaline phosphatase activity, and type I collagen messenger ribonucleic acid level and enhances osteopontin mRNA level in murine osteoblast-like (MC3T3E1) cells. Endocrinology 1990;127(1):185-90
51. Rodan SB, Wesolowski G, Hilton DJ, Nicola NA, Rodan GA. Leukemia inhibitory factor binds with high affinity to preosteoblastic RCT-1 cells and potentiates the retinoic acid induction of alkaline phosphatase. Endocrinology 1990;127(4):1602-08
52. Reid LR, Lowe C, Cornish J, Skinner SJ, Hilton DJ, Willson TA, et al. Leukemia inhibitory factor: a novel bone-active cytokine. Endocrinology 1990; 126(3): 1416-20
53. Wetzler M, Talpaz M, Lowe DG, Baiocchi G, Gutterman JU, Kurzrock R. Constitutive expression of leukemia inhibitory factor RNA by human bone marrow stromal cells and modulation by IL-1, TNF-alpha, and TGF-beta. Exp Hematol 1991;19(5):347-51
54. Anegon I, Moreau JF, Godard A, Jacques Y, Peyrat MA, Hallet MM, et al. Production of human interleukin for DA cells (HILDA)/leukemia inhibitory factor (LIF) by activated monocytes. Cell Immunol 1990;130(1):50-65
55. Le PT, Lazorick S, Whichard LP, Yang YC, Clark SC, Haynes BF, Singer KH. Human thymic epithelial cells produce IL-6, granulocyte-monocyte-CSF, and leukemia inhibitory factor. J Immunol 1990; 145:3310
56. Hilton DJ, Nicola NA, Metcalf D. Specific binding of murine leukemia inhibitory factor to normal and leukemic monocytic cells. Proc Natl Acad Sci USA 1988;85:5971-75
57. Baumann H, Jahreis GP, Saunder DN, Koj A. Human keratinocytes and monocytes release factors which regulate the synthesis of major acute phase plasma proteins in hepatic cells from man, rat, and mouse. J Biol Chem 1984;259:7331
58. Gascan H, Anegon I, Praloran V, Naulet J, Godard A, Soulillou JP, Jacques Y. Constitutive production of human interleukin for DA cells/leukemia inhibitory factor by human tumor cell lines derived from various tissues. J Immunol 1990;144:2592

59. Kola I, Davey A, Gough NM. Localization of the murine leukemia inhibitory factor gene near the centromere on chromosome 11. Growth Factors 1990;2(2-3):235-40
60. Sutherland GR, Baker E, Hyland VJ, Callen DF, Stahl J, Gough NM. The gene for human leukemia inhibitory factor (LIF) maps to 22q12. Leukemia 1989;3(1):9-13
61. Budarf M, Emanuel BS, Mohandas T, Goeddel DV, Lowe DG. Human differentiation-stimulating factor (leukemia inhibitory factor, human interleukin DA) gene maps distal to the Ewing sarcoma breakpoint on 22q. Cytogenet Cell Genet 1989;52(1-2): 19-22
62. Gough NM, Wilson TA, Stahl J, Brown MA. Molecular biology of the leukaemia inhibitory factor gene. Ciba Found Symp 1992;167:24-38
63. Gough NM. Molecular genetics of leukemia inhibitory factor (LIF) and its receptor. Growth Factors 1992;7(3):175-79
64. Tomida M, Yamamoto-Yamaguchi Y, Hozumi M. Purification of a factor inducing differentiation of mouse myeloid leukemic M1 cells from conditioned medium of mouse fibroblast L929 cells. J Biol Chem 1984;259(17):10978-82
65. Stahl J, Gearing DP, Willson TA, Brown MA, King JA, Gough NM. Structural organization of the genes for murine and human leukemia inhibitory factor. Evolutionary conservation of coding and non-coding regions. J Biol Chem 1990;265(15):8833-41
66. Gascan H, Godard A, Ferenz C, Naulet J, Praloran V, Peyrat MA, Hewick R, Jacques Y, Moreau JF, Soulillou JP. Characterization and amino-terminal aminoacid sequence of natural human interleukin of DA cells/leukemia inhibitory factor. J Biol Chem 1989;264:21509-15
67. Rathjen PD, Toth S, Willis A, Heath JK, Smith AG. Differentiation inhibiting activity is produced in matrix-associated and diffusible forms that are generated by alternate promoter usage. Cell 1990;62(6):1105-14
68. Turnley AM, Bartlett PF. Cytokines that signal through the leukemia inhibitory factor receptor-(beta) complex in the nervous system. J Neurochem, 2000;74:889-99
69. Gearing DP, Thut CJ, VandeBos T, Gimpel SD, Delaney PB, King J, Price V, Cosman D, Beckmann MP. Leukemia inhibitory factor receptor is structurally related to the IL-6 signal transducer, gp130. EMBO J 1991;10:2839-48
70. Gearing DP, Bruce AG. Oncostatin M binds the high-affinity leukemia inhibitory factor receptor. New Biol 1992;4:61-65
71. Davis S, Aldrich TH, Valenzuela DM, Wong VV, Furth ME, Squinto SP, Yancopoulos GD. The receptor for ciliary neurotrophic factor. Science 1991;253:59-63
72. Stahl N, Yancopoulos GD. Thr tripartite CNTF receptor complex: activation and signalling involve components shared with other cytokines. J Neurobiol 1994;25:1454-66
73. Metcalf D, Hilton D, Nicola NA. Leukemia inhibitory factor can potentiate murine megakaryocyte production in vitro. Blood 1991;77(10):2150-53
74. Murray R, Lee F, Chiu CP. The genes for leukemia inhibitory factor and interleukin-6 are expressed in mouse blastocysts prior to the onset of hemopoiesis. Mol Cell Biol 1990;10(9):4953-56
75. Bartoe JL, Nathanson NM. Differential regulation of leukemia inhibitory factor-stimulated neuronal gene expression by protein phosphatases SHP-1 and SHP-2 through mitogen-activated protein kinase-dependent and -independent pathways. J Neurochem 2000;74(5):2021-32
76. Zhong Z, Wen Z, Darnell JE Jr. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. Science 1994;264:95-98
77. Ware CB, Horowitz Md, Renshaw BR, Hunt JS, Liggitt D, Koblar SA, Gliniak BC, McKenna HJ, Papayannopoulou T, Thoma B, Cheng L, Donovan PJ, Peschon JJ, Bartlett PF, Willis CR, Wright BD, Carpenter MK, Davison BL, Gearing DP. Targeted disruption of the low-affinity leukemia inhibitory factor receptor gene causes placental, skeletal, neural and metabolic defects and results in perinatal death. Development 1995;121:1283-99
78. Heath JK, Smith AG, Hsu LW, Rathjen PD. Growth and differentiation factors of pluripotential stem cells. J Cell Sci Suppl 1990;13:75-85
79. Vogiagis D, Salamonsen LA. Review: The role of leukaemia inhibitory factor in the establishment of pregnancy. J Endocrinol 1999; 160(2): 181-90
80. Escary JL, Perreau J, Dumenil D, Ezine S, Brulet P. Leukaemia inhibitory factor is necessary for maintenance of haematopoietic stem cells and thymocyte stimulation. Nature 1993; 363:361-64
81. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, Kontgen F, Abbondanzo SJ. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature 1992;359:76-79
82. Yue ZP, Yang ZM, Wei P, Li SJ, Wang HB, Tan JH, Harper MJ. Leukemia inhibitory factor, leukemia inhibitory factor receptro, and glycoprotein 130 in rhesus monkey uterus during

menstrual cycle and early pregnancy. Biol Reprod 2000;63(2);508-12
83. Passavant C, Zhao X, Das SK, Dey SK, Mead RA. Changes in uterine expression of leukemia inhibitory factor receptor gene during pregnancy and its Up-regulation by prolactin in the western spotted skunk. Biol Reprod 2000;63(1):301-07
84. Piccinni MP, Maggi E, Romagnani S. Role of hormone-controlled T-cell cytokines in the maintenance of pregnancy . Biochem Soc Trans 2000;28(2):212-15
85. Hsieh YY, Tsai HD, Chang CC, Hsu LW, Chang SC, Lo HY. Prolonged culture of human cryopreserved embryos with recombinant human leukemia inhibitory factor. J Assist Reprod Genet 2000;17(3):131-34
86. Martin TJ, Allan EH, Evely RS, Reid IR. Leukaemia inhibitory factor and bone cell function. Ciba Foundation Symposium 1992;167:141-50
87. Cornish J, Gallon K, King A, Edgar S, Reid IR. The effect of leukemia inhibitory factor on bone in vivo. Endocrinology. 1993;132(3):1359-66
88. Malaval L, Gupta AK, Aubin JE. Leukemia inhibitory factor inhibits osteogenic differentiation in rat calvaria cell cultures. Endocrinology. 1995;136(4): 1411-18
89. Chandrasekhar S, Harvey AK. Modulation of PDGF mediated osteoblast chemmotaxis by leukemia inhibitory factor (LIF). J Cell Physiol 1996;169(3):481-90
90. Sabokbar A, Fujikawa Y, Brett J, Murray DW, Athanasou NA. Increased osteoclastic differentiation by PMMA particle-associated macrophages. Inhibitory effect by interleukin 4 and leukemia inhibitory factor. Acta Orthopaedica Scandinavica 1996;67(6): 593-98
91. Malaval L, Gupta AK, Liu F, Delmas PD, Aubin JE. LIF, but IL-6, regulates osteoprogenitor differentiation in rat calvaria cell cultures: modulation by dexamethasone. J Bone Miner Res 1998;13(2):175-84
92. Bohic S, Rohanizadeh R, Touchais S, Godard A, Daculsi G, Heymann D. Leukemia inhibitory factor and oncostatin M influence the mineral phases formed in a murine heterotopic calcification model: a Fourier transform-infrared microspectroscopic study. J Bone Miner Res 1998;13(10):1619-32
93. Thomson BM, Saklatvala J, Chambers TJ. Osteoblasts mediate interleukin 1 stimulation of bone resorption by rat osteoclasts. J Exp Med 1986;164(1):104-12
94. Thomson BM, Mundy GR, Chambers TJ. Tumor necrosis factors alpha and beta induce osteoblastic cells to stimulate osteoclastic bone resorption. J Immunol 1987;138(3):775-79
95. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. N Engl J Med 1987;316(7):379-85
96. Beutler BA, Cerami A. Recombinant interleukin 1 suppresses lipoprotein lipase activity in 3T3-L1 cells. J Immunol 1985;135(6):3969-71
97. Metcalf D. Disease states induced by hemopoietic growth factor excess: their implications in medicine. Int J Cell Cloning 1990;8 Suppl 1:374-87; discussion 387-90
98. Gadient RA, Patterson PH. Leukemia inhibitory factor, Interleukin 6, and other cytokines using the GP130 transducing receptor: roles in inflammation and injury. Stem Cells 1999;17(3):127-37
99. Brown MA, Metcalf D, Gough NM. Leukaemia inhibitory factor and interleukin 6 are expressed at very low levels in the normal adult mouse and are induced by inflammation. Cytokine 1994:6:300-09
100. Block MI, Berg M, McNamara MJ. Passive immunization of mice against D factor blocks lethality and cytokine release during endotoxemia. J Exp Med 1993;178:1085-90
101. Alexander HR, Wong GG, Doherty GM. Differentiation factor/leukemia inhibitory factor protection against lethal endotoxemia inmice: synergistic effect with interleukin 1 and tumor necrosis factor. J Exp Med 1992; 175:1139-42
102. Waring PM, Waring LJ, Billington T. Leukemia inhibitory factor protects against experimental lethal *Escherichia coli* septic shock in mice. Proc Natl Acad Sci USA 1995;92:1337-41
103. Carroll G, Bell M, Wang H. Antagonism of the IL-6 cytokine subfamily—a potential strategy for more effective therapy in rheumatoid arthritis. Inflamm Res 1998;47:1-7
104. Hui W, Bell M, Carroll G. Oncostatin M (OSM) stimulates resorption and inhibits synthesis of proteoglycan in porcine articular cartilage explants. Cytokine 1996;8:495-00
105. Lotz M, Moats T, Villiger PM. Leukeamia inhibitory factor is expressed in cartilage and synovium and can contribute to the pathogenesis of arthritis. J Clin Invest 1992;90:888-96
106. Okamoto H, Yamamura M, Morita Y. The synovial expression and serum levels of interleukin-6, interleukin-11, leukemia inhibitory factor, and oncostatin M in rheumatoid arthritis. Arthritis Rheum 1997;40:1096-05
107. Waring PM, Carroll GJ, Kandiah DA. Increased levels of leukemia inhibitory factory in synovial fluid from patients with rheumatoid arthritis and other inflammatory arthritides. Arthritis Rheum 1993;36:911-15
108. Henrotin YE, De GD, Labasse AH. Effects of exogenous IL-1 beta, TNF alpha, IL-6, IL-8

and LIF on cytokine production by human articular chondrocytes. Osteoarth Cart 1996;4:163-73

109. Chabaud M, Fossiez F, Taupin JL. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. J Immunol 1998;161:409-14

110. Bell M, Carroll GJ, Chapman H. Leukemia inhibitory factor (LIF) binding protein attenuates the phlogistic and abolishes the chondral effects of LIF in goat joints. J Rheumatol 1997;24:2394-02

111. Heymann D, Her E, Nguyen JM. Leukaemia inhibitory factor (LIF) production in pleural effusions: comparison with production of IL-4, IL-8, IL-10 and macrophage-colony stimulating factor (M-CSF). Cytokine 1996;410-16

112. Jorens PG, De JR, Bossaert LL. High levels of leukaemia inhibitory factor in ARDS. Cytokine 1996;8:873-76

113. Szepietowski JC, McKenzie RC, Keohane SG. Leukaemia inhibitory factor: induction in the early phase of allergic contact dermatitis. Contact Dermatitis 1997; 36:21-25

114. McKenzie RC, Paglia D, Kondo S. A novel endogenous mediator or cutaneous inflammation: leukemia inhibitory factor. Acta Derm Venerol 1996;76:111-14

115. Thompson SW, Dray A, Urban L. Leukemia inhibitory factor induces mechanical allodynia but not thermal hyperalgesia in the juvenile rat. Neuroscience 1996;71:1091-94

116. Banner LR, Patterson pH, Allchorne A. Leukemia inhibitory factor is an anti-inflammatory and analgesic cytokine. J Neurosci 1998;18:5456-62

117. Banner LR, Patterson PH. Major changes in the expression of the mRNAs for cholinergic differentiation factor/leukemia inhibitory factor and its receptor after injury to adult peripheral nerves and ganlia. Proc Natl Acad Sci USA 1994;91:7109-13

118. Banner LR, Moayeri NN, Patterson PH. Leukemia inhibitory factory is expressed in astrocytes following corticla brain injury. Exp Neurol 1997;147:1-9

119. Curtis R, Scherer SS, Somogyi R. Retrograde axonal trnsport of LIF is increased by peripheral nerve injury: correlation with increased LIF expression in distal nerve. Neuron 1994;12:191-04

120. Kurek JB, Ausin L, Cheema SS. Up-regulation of leukaemia inhibitory factor and interleukin-6 in transected sciatic nerve and musce following denervation. Neuromuscul Disord 1996;6:105-14

121. Kurek JB, Austin L, Cheema SS, Bartlett PF, Murphy M. Upregulation of leukaemia inhibitory factor and interleukin-6 in transected sciatic nerve and denervated muscle. Neuromusc Disor 1996;6:105-14

122. Austin L, Burgess AW. Stimulation of myoblast proliferation in culture by leukaemia inhibitory factor. J Neurol Sci 1991;101:193-97

123. Austin L, Bower J, Kurek J, Vakakis N. Effects of leukaemia inhibitory factor and other cytokines on murine and human myoblast proliferation. J Neurol Sci 1992;112:185-91

124. Patterson PH, Kou S-Y, Sugiura S. LIF coordinates neuronal and inflammatory response to nerve injury. Soc Neurosci Abstr 1997;23:393-33

125. Baumann H, Jahreis GP, Sauder DN, Koj A. Human keratinocytes and monocytes release factors which regulate the synthesis of major acute phase plasma proteins in hepatic cells from man, rat, and mouse. J Biol Chem 1984;259(11):7331-42

126. Kordula T, Rokita H, Koj A. Effects of interleukin-6 and leukemia inhibitory factor on the acute phase response and DNA synthesis in cultured rat hepatocytes. Lymphokine Cytokine Res 1991:10:23-26

127. Mayer P, Geissler K, Ward M. Recombinant human leukemia inhibitory factor induces acute phase proteins and raises the blood platelet counts in nonhuman primates. Blood 1993;81:3226-33

128. Richards LJ, Kilpatrick TJ, Dutton R, Tan S-S, Gearing DP, Bartlett PF, Murphy M. Leukaemia inhibitory factor (LIF) and related factors promote the differentiation of neuronal and astrycytic precursors within the developing murine spinal cord. Eur J Neurosci 1996;8:291-99

129. Li M, Sendtner M, Smith A. Essential function of LIF receptor in motor neurones. Nature 1995;378:724-27

130. Cheema SS, Richards LR, Murphy M, Bartlett PF. Leukemia inhibitory factor rescues motorneurones from axotomy-induced cell death. Neuroreport 1994;5:989-92

131. Ikeda K, Iwasaki Y, Shiojima T, Kinoshita M. Neuroprotective effect of cholinergic differentiation leukaemia inhibitory factor on Wobbler murine motor neurone disease. Muscle Nerve 1995:18:1344-47

132. Metcalf D. The induction and inhibition of differentiation in normal and leukaemic cells. Philos Trans R Soc Lond B Biol Sci 1990;327(1239):99-109

133. Shabo Y, Lotem J, Rubinstein M, Revel M, Clark SC, Wolf SF, et al. The myeloid blood cell

differentiation-inducing protein MGI-2A is interleukin-6. Blood 1988;72(6):2070-73
134. Metcalf D. Suppression of myeloid leukemic cells by normal hemopoietic regulators. Recent Prog Cytokine Res 1989;10:11-19
135. Maekawa T, Metcalf D. Clonal suppression of HL60 and U937 cells by recombinant human leukemia inhibitory factor in combination with GM-CSF or G-CSF. Leukemia 1989;3(4):270-76
136. Maekawa T, Metcalf D, Gearing DP. Enhanced suppression of human myeloid leukemic cell lines by combinations of IL-6, LIF, GM-CSF and G-CSF. Int J Cancer 1990;45(2):353-58
137. Wang C, Lishner M, Minden MD, McCulloch EA. The effects of leukemia inhibitory factor (LIF) on the blast stem cells of acute myeloblastic leukemia. Leukemia 1990;4(8):548-52
138. Metcalf D, Hilton DJ, Nicola NA. Clonal analysis of the actions of the murine leukemia inhibitory factor on leukemic and normal murine hemopoietic cells. Leukemia 1988;2(4):216-21
139. Leary AG, Wong GG, Clark SC, Smith AG, Ogawa M. Leukemia inhibitory factor differentiation-inhibiting activity/human interleukin for DA cells augments proliferation of human hematopoietic stem cells. Blood 1990;75(10):1960-64
140. Verfaillie C, McGlave P. Leukemia inhibitory factor/human interleukin for DA cells: a growth factor that stimulates the in vitro development of multipotential human hematopoietic progenitors. Blood 1991;77(2):263-70
141. Estrov Z, Talpaz M, Wetzler M, Kurzrock R. The modulatory hematopoietic activities of leukemia inhibitory factor. Leuk Lymphoma 1992;8(1-2):1-7
142. Wetzler M, Kurzrock R, Lowe DG, Kantarjian H, Gutterman JU, Talpaz M. Alteration in bone marrow adherent layer growth factor expression: a novel mechanism of chronic myelogenous leukemia progression. Blood 1991;78(9):2400-06
143. Shen MM, Skoda RC, Cardiff RD, Campos-Torres J, Leder P, Orntiz DM. Expression of LIF in transgenic mice results in altered thymic epitehlium and apparent interconversion of thymic and lymph node morphologies. EMBO J 1994;1375-85
144. Schaafsma MR, Falkenburg JH, Duinkerken N, Moreau JF, Soulillou JP, Willemze R, Fibbe WE. Human interleukin for DA cells (HILDA) does not affect the proliferation and differentiation of hematopoietic progenitor cells in human long-term bone marrow cultures. Exp Hematol 1992;20:6-10
145. Firkin FC, Birner R, Farag S. Differential action of diffusible molecules in long-term bone marrow culture on proliferation of leukaemic and normal haemopoietic cells. Br J Haematol 1993;84:8-15
146. Debili N, Masse JM, Katz A, Guichard J, Breton-Gorius J, Vainchenker W. Effects of the recombinant hematopoietic growth factors intermegakayocytic differentiation of CD34+ cells. Blood 1993;82:84-95
147. Gabutti V, Timeus F, Ramenghi U, Crescenzio N, Marranca D, Miniero R, Cornaglia G, Bagnara GP. Expansion of cord blood progenitors and use for hemopoietic reconstitution. Stem Cells 1993;11 Suppl: 105-12
148. Szilvassy SJ, Cory S. Efficient retroviral gene transfer to purified long-term repopulating hematopoietic stem cells. Blood 1994;84:74-83
149. Szilvassy SJ, Weller K.P, Kin W, Sharma AK, Ho AS, Tsukamoto A, Hoffman R, Leiby KR, Gearing DP. Leukemia inhibitory factor upregulates cytokine expression by a murine stromal cell line enabling the maintenance of highly enriched competitive repopulating stem cells. Blood 1996;87:4618-28
150. Metcalf D. Leukemia inhibitory factor – a puzzling poly-functional regulator. Growth Factors 1992; 7:169-73
151. Kamohara H, Sakamoto K, Ishiko T, Masuda Y, Abe T, Ogawa M. Leukemia inhibitory factor induces apoptosis and proliferation of human carcinoma cells through different oncogene pathways. Int J Cancer 1997;72(4):687-95
152. Moreau JF, Bonneville M, Peyart MA, Jacques Y, Soulillou JP. Capactiy of alloreactive human T clones to produce factor(s) inducing proliferation of the IL3-dependent DA-1 murine cell line. I. Evidence that this production is under IL2 control. Ann Inst Pasteur Immunol 1986; 137C(1):25-37
153. Abe T, Murakami M, Sato T, Kajiki M, Ohno M, Kodaira R. Macrophage differentiation inducing factor from human monocytic cells is equivalent to murine leukemia inhibitory factor. J Biol Chem 1989;264:8941
154. Xie P, Chan FS, Ip NY, Leung MF. Induction of gp130 and LIF by differentiation inducers in human myeloid leukemia K562 cells. Leuk Res 1999;23(12):1113-19
155. Wetzler M, Estrov Z, Talpaz M, Kim KJ, Alphonso M, Srinivasan R, Kurzrock R. Leukemia inhibitory factor in long-term adherent layer cultures: increased levels of bioactive protein in leukemia and modulation by IL-4, IL-1ß, and TNF-α. Cancer Res 1994; 54:1837-42
156. Maekawa T, Metcalf D, Gearing DP. Enhanced suppression of human myeloid

leukemic cell lines by combinations of IL-6, LIF, GM-CSF and G-CSF. Int J Cancer 1990;45(2):353-58
157. Yamamoto-Yamaguchi Y, Tomida M, Hozumi M. Prolongation by differentiation-stimulating factor/leukemia inhibitory factor of the survival time of mice implanted with mouse myeloid leukemia cells. Leuk Res 1992;16(10):1025-29
158. Godard A, Heymann D, Raher S, Anegon I, Peyrat MA, Le Mauff B, Mouray E, Gregoire M, Virdee K, Soulillou JP et al. High and low affinity receptors for human interleukin for DA cells/leukemia inhibitory factor on human cells. Molecular characterization and cellular distribution. J Biol Chem 1992;267(36):3214-22
159. Umemiya-Okada T, Natazuka T, Matsui T, Ito M, Taniguchi T, Nakao Y. Expression and regulation of the leukemia inhibitory factor/D factor gene in human T-cell leukemia virus type 1 infected T-cell lines. Cancer Res 1992;52(24):6961-65
160. Lal RB, Rudolph D, Buckner C, Pardi D, Hooper WC. Infection with human T-lymphotropic viruses leads to constitutive expression of leukemia inhibitory factor and interleukin-6. Blood 1993;81(7):1827-32
161. Gu ZJ, Zhang XG, Hallet MM, Lu ZY, Wijdenes J, Rossi JF, Klein B. A ciliary neurotrophic factor-sensitive human myeloma cell line. Exp Hematol 1996; 24:1195-00
162. Portier M, Zhang XG, Ursule E, Lees D, Jourdan M, Bataille R, Klein B. Cytokine gene expression in human multiple myeloma. Br J Haematol 1993; 85:514-20
163. Nishimoto N, Ogata A, Shima Y, Tani Y, Ogawa H, Nakagawa M, Sugiyama H, Yoshizaki K, Kishimoto T. Oncostain M, leukemia inhibitory factor, and interleukin 6 induce the proliferation of human plasmacytoma cells via the common signal transducer, gp130. J Exp Med 1994; 179(4): 1343-47
164. Zhang XG, Gu JJ, Lu ZY, Yasukawa K, Yancopoulos GD, Turner K, Shoyab M, Taga T, Kishimoto T, Bataille R. et al. Ciliary neurotropic factor, interleukin 11, leukemia inhibitory factor, and oncostatin M are growth factors for human myeloma cell lines using the interleukin 6 signal transducer gp130. Institute for Molecular Genetics, CNRS BP5051, Montepellier, France.
165. Marusic A, Kalinowski JF, Jastrzebski S, Lorenzo JA. Production of leukemia inhibitory factor mRNA and protein by malignant and immortalized bone cells. J Bone Miner Res 1993;8(5):617-24
166. Gouin F, Heymann D, Raher S, De Groote D, Passuti N, Daculsi G, Godard A. Increased levels of leukaemia inhibitory factor (LIF) in urine and tissue culture supernatant from human primary bone tumors. Cytokine 1998;10(2):110-14
167. Soueidan A, Gan OL, Gouin F, Godard A, Heymann D, Jacques Y, Daculsi G. Culturing of cells from giant cell tumour of bone on natural and synthetic calcified substrata: the effect of leukaemia inhibitory factor and vitamin D3 on the resorbing activity of osteoclast-like cells. Virchows Archiv 1995;426(5):469-77
168. Gouin F, Couillaud S, Cottrel M, Godard A, Passuti N, Heymann D. Presence of leukaemia inhibitory factor (LIF) and LIF-receptor chain (gp190) in osteoclast-like cells cultured from human giant cell tumour of bone. Ultrastructural distribution. Cytokine 1999;11(4):282-89
169. Estrov Z, Samal B, Lapushin R, Kellokumpu-Lehitinen P, Sahin AA, Kurzrock R, Talpaz M, Aggarwal BB. Leukemia inhibitory factor binds to human breast cancer cells and stimulates their proliferation. J Interferon Cytokine Res 1995;15(10):905-13
170. Kellokumpu-Lehtinen P, Talpaz M, Harris D, Van Q, Kurzrock R, Estrov Z. Leukemia-inhibitory factor stimulates breast, kidney and prostate cancer cell proliferation by paracrine and autocrine pathways. Int J Cancer 1996;66(4):515-19
171. Liu J, Hadjokas N, Mosley B, Estrov Z, Spence MJ, Vestal RE. Oncostatin M-spccific receptor expression and function in regulating cell proliferation of normal and malignant mammary epithelial. Cytokine 1998;10(4):295-02
172. Douglas AM, Goss GA, Sutherland RL, Hilton DJ, Berndt MC, Nicola NA, Begley CG. Expression and function of members of the cytokine receptor superfamily on breast cancer cells. Oncogene 1997;14(6):661-69
173. Dhingra K, Sahin A, Emami K, Hortobagyi GN, Estrov Z. Expression of leukemia inhibitory factor and its receptor in breast cancer: a potential autocrine and paracrine growth regulatory mechanism. Breast Cancer Res Treat 1998;48(2):165-74
174. Crichton MB, Nichols JE, Zhao Y, Bulun SE, Simpson ER. Expression of transcripts of interleukin-6 and related cytokines by human breast tumors, breast cancer cells, and adipose stromal cells. Cell Endocrinol 1996;120(2):215
175. Tatoud R, Desgrandchamps F, Gegeorges A, Thomas F. Peptide growth factors in the prostate. Pathol Biol 1993 ;41:731-40
176. Mori M, Yamaguchi K, Honda S, Nagasaki K, Ueda M, Abe O, Abe K. Cancer cachexia syndrome developed in nude mice bearing

melanoma cells producing leukemia-inhibitory factor. Cancer Res 1991;51(24):6656-59

177. Paglia D, Oran A, Lu C, Kerbel RS, Sauder DN, McKenzie RC. Expression of leukemia inhibitory factor and interleukin-11 by human melanoma cell lines: LIF, IL-6, and IL-11 are not coregulated. J Interferon Cytokine Res 1995;15(5):455-60
178. Heymann D, Godard A, Raher S, Ringeard S, Lassort D, Blanchard F, Harb J. Human interleukin for DA cells/leukemia inhibitory factor and oncostatin M enhance membrane expression of intercellular adhesion molecule-1 on melanoma cells but not the shedding of its soluble form. Cytokine 1995;7(2):111
179. Kamohara H, Sakamoto K, Ishiko T, Mita S, Masuda Y, Abe T, Ogawa M. Human carcinoma cell lines produce biologically active leukemia inhibitory factor (LIF). Res Commun Mol Pathol Pharmacol 1994
180. Baumann H, Ziegler SF, Mosley B, Morella KK, Pajovic S, Gearing DP. Reconstitution of the response to leukemia inhibitory factor, oncostatin M, and ciliary neurotrophic factor in hepatoma cells. J Biol Chem 1993;268(12):8414-17
181. Hermanns HM, Radtke S, Haan C, Schmitz-Van de Leur H, Tavernier J, Heinrich PC, Behrmann I. Contributions of leukemia inhibitory factor receptor and oncostatin M receptor to signal transduction in heterodimeric complexes with glycoprotein 130. J Immunol 1999;163(12):6651-58
182. Guimbaud R, Abitbol V, Bertrand V, Quartier G, Chauvelot-Moachon L, Giroud J, Couturier D, Chaussade DC. Leukemia inhibitory factor involvement in human ulcerative colitis and its potential role in malignant course. Eur Cytokine Netw 1998;9(4):607-12
183. Halfter H, Kremerskothen J, Weber J, Hacker-Klom U, Barnekow A, Ringelstein EB, Stogbauer F. Growth inhibition of newly established human glioma cell lines by leukemia inhibitory factor. J Neuro Oncol 1998, 39(1):1-18
184. Halfter H, Lotfi R, Westermann R, Young P, Ringelstein EB, Stogbauer FT. Inhibition of growth and induction of differentiation of glioma cell lines by oncostatin M (OSM). Growth Factors 1998;15(2):135-47
185. Liu J, Li H, Moreau JF. Expression of LIF as autocrinal growth factor in human medulloblastomas. Chung Hua Ping Li Hsueh Tsa Chih 1996;25(l):24-26
186. Liu J, Li H, Hamou MF. Inhibitory effect of antisense LIF oligonucleotide on the outgrowth of human medulloblastoma cells. Chung Hua Ping Li Hsueh Tsa Chih 1996;25(3): 132-34
187. Fu J, Zheng J, Fang W, Wu B. Effect of interleukin-6 on the growth of human lung cancer cell line. Chin Med J 1998;111(3):265-68
188. Kajimura N, Iseki H, Tanaka R, Ohue C, Otsubo K, Gyoutoku M, Sasaki K, Akiyama Y, Yamaguchi K. Toxohormones responsible for cancer cachexia syndrome in nude mice bearing human cancer cell lines. Cancer Chemother Pharmacol 1996;38 Suppl:S48-52
189. Bamberger AM, Jenatschke S, Erdmann I, Schulte HM. Progestin-dependent stimulation of the human leukemia inhibitory factor promoter in SKUT-1B uterine tumor cells. J Reprod Immunol 1997;33(3):189-01
190. Tomida M. Presence of mRNAs encoding the soluble D-factor/LIF receptor in human choriocarcinoma cells and production of the soluble receptor. Biochem Biophys Res Commun 1997;232(2):427-31
191. Voyle RB, Haines BP, Pera MF, Forrest R, Rathjen PD. Human germ cell tumor cell lines express novel leukemia inhibitory factor transcripts encoding differentially localized proteins. Exp Cell Res 1999;249(2): 199-11
192. Shabo Y, Lotem J, Rubinstein M, Revel M, Clark SC, Wolf SF, Kamen R, Sachs L. The myeloid blood cell differentiation-inducing protein MG1-2A is interleukin-6. Blood 1988; 72:2070-73
193. Keller JR, Gooya JM, Ruscetti FW. Direct synergistic effects of leukemia inhibitory factor on hematopoietic progenitor cell growth: comparison with other hematopoietins that use the gp130 receptor subunit. Blood 1996;88(3):863-69
194. Heymann D, Gouin F, Guicheux J, Munevar JC, Godard A, Daculsi G. Upmodulation of multinucleated cell formation in long-term human bone marrow cultures by leukaemia inhibitory factor. Cytokine 1997;9(l):46-52
195. Zucman J, Delattre O, Desmaze C, Plougastel B, Joubert I, Melot T, Peter M, De Jong P, Rouleau G, Aurias A. et al. Cloning and characterization of the Ewing's sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints. Genes Chromosome Cancer 1992;5(4):271-77
196. Mansi JL, Berger U, McDonnell T, Pople A, Rayter Z, Gazet JC, Coombes RC. The fate of bone marrow micrometastases in patients with primary breast cancer. J Clin Oncol 1989;7:445-49
197. Akatsu T, Ono K, Katayama Y, Tamura T, Nishikawa M, Kugai N, Yamamoto M, Nagata N. The mouse mammary tumor cell line, MMT060562, produces prostaglandin E2 and

leukemia inhibitory factor and supports osteoclast formation in vitro via a stromal cell-dependent pathway. J Bone Miner Res 1998;13(3):400-08

198. Bamberger AM, Thuneke I, Schulte HM. Differential regulation of the human 'leukemia inhibitory factor' (LIF) promoter in T47D and MDA-MB231 breast cancer cells. Breast Cancer Res Treat 1998;47(2):153-61
199. Bard JB, Ross AS. LIF, the ES-cell inhibition factor, reversibly blocks nephrogenesis in cultured mouse kidney rudiments. Development 1991;113(l):193-98
200. Hartner A, Sterzel BR, Reindi N, Hocke GM, Fey GH, Gopplet-Struebe M. Cytokine-induced expression of leukemia inhibitory factor in renal mesangial cells. Kidney Int 1994;45:1562-71
201. Gleave ME, Hsieh JT, von Eschenbach AC, Chung LW. Prostate and bone fibroblasts induce human prostate cancer growth in vivo: implications for bidirectional tumor-stromal cell implication in prostate carcinoma growth and metastasis. J Urol 1992;147:1151-59
202. Hirano T, Matsuda T, Nakajima K. Signal transduction through gp130 that is shared among the receptors for the interleukin 6 related subfamily. Stem Cells 1994;12:262-77
203. Chung TD, Yu JJ, Spiotto MY, Bartkowski M, Simons JW. Characterization of the role of IL-6 in the progression of prostate cancer. Prostate 1999;38:199-207
204. Mori S, Murakami-Mori K, Bonavida B. Oncostatin M (OM) promotes the growth of DU 145 human prostate cancer cells, but not PC-3 or LNCaP, through the signaling of the OM specific receptor. Anticancer Res 1999;19:1011-5
205. Heymann D, Blanchard F, Raher S, De Groote D, Godard A. Modulation of LIF expression in human melanoma cells by oncostatin M. Immunol Lett 1995;46(3):245-51
206. Schrell UM, Koch HU, Marschalek R, Schrauzer T, Anders M, Adams E, Fahlbusch R. Formation of autocrine loops in human cerebral meningioma tissue by leukemia inhibitor factor, interleukin-6, and oncostatin M: inhibition of meningioma cell growth in vitro by recombinant oncostatin M. J Neurosurg 1998,88(3):541-48
207. Knight DA, Lydell CP, Zhou D, Weir TD, Schellenberg R, Bai TR. Leukemia inhibitory factor (LIF) and LIF receptor in human lung. Distribution and regulation of LIF release. Am J Respir Cell Mol Biol 1999;20(4);834-41
208. Freidin M, Kessler JA. Cytokine regulation of substance P expression in sympathetic neurons. Proc Natl Acad Sci U S A 1991;88(8):3200-03
209. Murphy M, Reid K, Hilton DJ, Bartlett PF. Generation of sensory neurones is stimulated by leukaemia inhibitory factor. Proc Natl Acad Sci USA 1991;88:3498-01
210. Yamakuni H, Minami M, Satoh M. Localisation of mRNA for leukaemia inhibitory factor receptor in the adult brain. J Neuroimmunol 1996;70:45-43
211. Cheema SS, Richards L, Murphy M, Bartlett PF. Leukemia inhibitory factor prevents the death of axotomised sensory neurones in the dorsal root ganglion of the neonatal rat. J Neurosci Res 1994;37:213-18