MIG

Joshua Marion Farber*

Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, NIH, 10 Center Drive, Room 11N-228, MSC 1888, Bethesda, MD 0892-1888, USA

* corresponding author tel: 301-402-4910, fax: 301-402-0627, e-mail: joshua_farber@nih.gov

SUMMARY

MIG (monokine induced by IFNγ) is a non-ELR CXC chemokine ligand for CXCR3, a receptor expressed primarily on T cells and NK cells. In contrast to related chemokines, MIG contains a long C-terminal extension that is subject to inactivating proteolytic processing. MIG is induced in a range of cells including macrophages, endothelial cells, and parenchymal cells, primarily in response to IFNγ. MIG is a chemotactic factor for T cells, particularly following T cell activation, and has been shown to induce adhesion of activated T cells to endothelial cells. MIG's primary role *in vivo* is presumed to be in the recruitment of T cells and NK cells to inflammatory sites where IFNγ is being made. MIG has also been found to inhibit colony formation from hematopoietic progenitors *in vitro* and to inhibit tumor growth and angiogenesis *in vivo*.

BACKGROUND

Discovery

MIG was discovered by differential screening of a cDNA library made from the RAW 264.7 mouse macrophage cell line that had been treated with supernatants from concanavalin A-stimulated splenocytes (Farber, 1990, 1992). The mouse MIG (MuMIG) cDNA was used to isolate the human MIG (HuMIG) cDNA by screening a cDNA library made from IFNγ-treated cultures of the THP-1 monocytic cell line (Farber, 1993).

Alternative names

None.

Structure

Only the primary structure of MIG is known, which is that of a CXC chemokine. When aligned with other CXC chemokines, the MIG sequences contain a highly basic region that extends beyond the C-termini of the other chemokines to yield full-length mature proteins of 105 and 103 amino acids for the mouse and human proteins respectively.

Main activities and pathophysiological roles

MIG is a chemotactic factor selective for lymphocytes with greatest activity on activated T cells (Liao *et al.*, 1995). MIG is also active on NK cells (Rabin *et al.*, 1999). MIG has no activity on neutrophils or monocytes. Consistent with its induction by IFNγ MIG shows widespread induction in a range of models of infectious diseases (Amichay *et al.*, 1996) and inflammatory disorders (Goebeler *et al.*, 1998; Spandau *et al.*, 1998) and MIG's primary role *in vivo* is presumed to be in the recruitment of T cells and NK cells to inflammatory sites where IFNγ is being made.

GENE AND GENE REGULATION

Accession numbers

Mouse MIG cDNA: M34815; Mu*mig* gene, promoter region: X58682
Human MIG cDNA: X72755

Chromosome location

Human chromosome 4q21.21 (Lee and Farber, 1996).

Relevant linkages

Humig is closely linked to genes for IP-10 (INP10, SCYB10) (Lee and Farber, 1996) and I-TAC (SCYB9B) (Erdel *et al.*, 1998) (see **Figure 1**), at some distance from the other CXC chemokines on chromosome 4 (Tunnacliffe *et al.*, 1992; Lee and Farber, 1996; Modi and Chen, 1998).

Regulatory sites and corresponding transcription factors

Analysis has been confined to the mouse gene. Regulatory sequences include possible NFκB and AP-2 sites without proven function (Wright and Farber, 1991) and a unique palindromic element, γRE-1, that mediates induction by IFNγ (Wright and Farber, 1991; Wong *et al.*, 1994). γRE-1 binds γRF-1, a factor that differs from other IFNγ-activated transcription factors but which contains a subunit antigenically related to p91/STAT1α (Wong *et al.*, 1994; Guyer *et al.*, 1995; Feghali and Wright, 1995).

Cells and tissues that express the gene

In the mouse, a low and variable level of expression can be detected in the spleen, thymus, and liver of unmanipulated animals. After elicitation by IFNγ or in response to disseminated infections, induction of the mouse gene can be detected in multiple tissues, including brain, heart, kidney, liver, lung, skin, spleen, thymus, ovary, and uterus. Expression is particularly dramatic in the liver. Expression in the liver has been shown by *in situ* hybridization to be in hepatocytes and in the spleen in CD11b+ cells, presumed to be macrophages (Amichay *et al.*, 1996). Induction by IFNγ occurs in mouse peritoneal macrophages (Farber, 1990) as well as in rat microglia and astrocytes treated *ex vivo* (Vanguri, 1995). Expression was seen in thymic stromal cells in a model of induced thymocyte apoptosis (Lerner *et al.*, 1996), in the mouse macrophage cell line RAW 264.7 (Farber, 1990), and in the mouse mammary tumor cell line 66.1 (Sun *et al.*, 1999). For the human gene,

IFNγ-induced expression is seen in monocytes, the monocytic cell line THP-1 (Farber, 1993), endothelial cells, keratinocytes, fibroblasts (Ebnet *et al.*, 1996), and neutrophils (Gasperini *et al.*, 1999). MIG mRNA expression has been shown in the epidermis of skin involved with *cutaneous T cell lymphomas* (Tensen *et al.*, 1998) and *lichen planus* (Spandau *et al.*, 1998).

PROTEIN

Accession numbers

Mouse MIG: AAA39706
Human MIG: CAA51284

Sequence

See Figure 1. The site of signal peptide cleavage in MuMIG has not been verified, but based both on empirically derived rules and on data for HuMIG, it would be predicted to be after the glycine at position 21, so that the mature protein begins with the threonine at position 22. In HuMIG the site of signal peptide cleavage is after the glycine at position 22 so that the mature protein begins with the threonine at position 23.

Description of protein

Structural information is available only by inference from other CXC chemokines.

Important homologies

MIG is most closely related to the CXC chemokines IP-10 and I-TAC at 30–35% amino acid identity over the regions that can be compared. A comparison of the sequences of human and mouse MIG and IP-10 along with the human I-TAC are shown in Figure 1.

Posttranslational modifications

MuMIG is *N*-glycosylated, while HuMIG is not. HuMIG and MuMIG show extensive proteolytic processing of their C-terminal regions with multiple secreted polypeptides (Liao *et al.*, 1995; Amichay *et al.*, 1996). The C-terminal truncated HuMIG shows

Figure 1 Comparison of the predicted sequences of unprocessed human (Hu) and mouse (Mu) MIG, human and mouse (CRG-2) IP-10, and the human I-TAC. N-terminal residues of the secreted proteins that have been established experimentally for HuMIG and IP-10 are indicated in bold type. MuMIG Asn58 (underlined) is predicted to be glycosylated. Numbers at the right indicate the positions of the residues at the end of each line. Solid backgrounds indicate identities among the proteins. Dots mark gaps created to produce optimal alignments. Tildes mark positions without corresponding residues. The alignment was created using the PileUp and PrettyBox programs of the Wisconsin Sequence Analysis Package, Genetics Computer Group, Madison, WI.

```
HuMIG         M K K S G V L F L L   G I I L L V L I G V   Q G T P V V R K G R   C S C I S T N Q G T   I H L Q S L K D L K   Q F A P S   55
MuMIG         ~ M K S A V L F L L   G I I F L E Q C G V   R G T L V I R N A R   C S C I S T S R G T   I H Y K S L K D L K   Q F A P S   54
IP-10         ~ M N Q T A I L I C   C L I F L T L S G I   Q G V P L S R T V R   C T C I S I S N Q P   V N P R S L E K L E   I I P A S   54
CRG-2/MuIP-10 ~ M N P S A A V I F   C L I L L G L S G T   Q G I P L A R T V R   C N C I H I D D G P   V R M R A I G K L E   I I P A S   54
I-TAC         ~ M S V K G M A I A   L A V I L C A T V V   Q G F P M F K R G R   C L C I G P G V K A   V K V A D I E K A S   I M Y P S   54


HuMIG         P S C E K I E I I A   T L . K N G V Q T C   L N P D S A D V K E   L I K K W E K Q V S   Q K K K Q K N G K K   H Q K K .   108
MuMIG         P N C N K T E I I A   T L . K N G D Q T C   L D P D S A N V K K   L M K E W E K K I N   Q K K K Q K R G K K   H Q K N M   108
IP-10         Q F C P R V E I I A   T M K K K G E K R C   L N P E S K A I K N   L L K A V S K E M S   K R S P ~ ~ ~ ~ ~   ~ ~ ~ ~ ~   98
CRG-2/MuIP-10 L S C P R V E I I A   T M K K N D E Q R C   L N P E S K T I K N   L M K A F S Q K R S   K R A P ~ ~ ~ ~ ~   ~ ~ ~ ~ ~   98
I-TAC         N N C D K I E V I I   T L K E N K G Q R C   L N P K S K Q A R L   I I K K V E R K N F   ~ ~ ~ ~ ~ ~ ~ ~ ~   ~ ~ ~ ~ ~   94


HuMIG         K V L K V R K S Q .   R S R Q K K T T 125
MuMIG         K N R K P K T P Q S   R R R S R K T T 126
IP-10         ~ ~ ~ ~ ~ ~ ~ ~ ~ ~   ~ ~ ~ ~ ~ ~ ~ ~ 98
CRG-2/MuIP-10 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~   ~ ~ ~ ~ ~ ~ ~ ~ 98
I-TAC         ~ ~ ~ ~ ~ ~ ~ ~ ~ ~   ~ ~ ~ ~ ~ ~ ~ 94
```

much reduced activity compared with the full-length form, but does not function as a receptor antagonist.

CELLULAR SOURCES AND TISSUE EXPRESSION

Cellular sources that produce

Macrophages, hepatocytes, endothelial cells, keratinocytes, fibroblasts, microglia, astrocytes, thymic stromal cells, lymphocytes, and neutrophils are all sources of MIG.

Eliciting and inhibitory stimuli, including exogenous and endogenous modulators

IFNγ is the primary inducer *in vitro* and *in vivo* (Farber, 1990; Amichay *et al.*, 1996; Ebnet *et al.*,

1996). In human endothelial cells, both IFNγ and TNF have been reported to be necessary, and HuMIG was also induced in these cell by LPS and in fibroblasts by a sonicate of *B. burgdorferi* (Ebnet *et al.*, 1996). Expression in multiple mouse tissues is elicited by disseminated infections with a variety of agents including *Plasmodium yoelii*, *Toxoplasma gondii*, and vaccinia virus (Amichay *et al.*, 1996).

Synergistic inducing activity has been described with IFNγ and hyaluronan fragments (Horton *et al.*, 1998) and by TNF plus IFNγ. IL-4 can diminish induction in macrophages by IFNγ (Ohmori and Hamilton, 1998).

RECEPTOR UTILIZATION

The only known receptor for MIG is CXCR3, which it shares with IP-10 (Loetscher *et al.*, 1996) and with the recently-described I-TAC (Cole *et al.*, 1998). Data on expression and activities for MIG and IP-10 are summarized for comparison in **Table 1**.

Table 1   MIG and IP-10 compared

	MIG	IP-10
Protein structure, human	103 amino acids with proteolytically processed C-terminus	77 amino acids
Gene induction	IFNγ Contributions by TNFα, LPS, hyaluronic acid	IFNγ, IFNγ/β, LPS, anti-CD3 Contributions by TNFα, IL-1, hylauronic acid
Tissue expression in mice	Low level in spleen and thymus constitutively Widespread induction in infection, particularly in liver	Spleen and thymus constitutively Widespread induction in infection
Cell type expression	Monocytes/macrophages, endothelial cells, hepatocytes, keratinocytes, fibroblasts, microglia, astrocytes, thymic stroma, lymphocytes, neutrophils	As for MIG, plus respiratory and intestinal epithelial cells, mesangial cells, and smooth muscle cells
Activities *in vitro*	T cells: chemotaxis, calcium flux, adhesion NK cells: calcium flux CD34+ progenitors: suppression of CFU Endothelial cells: inhibition of chemotaxis	As for MIG, plus chemotaxis of NK cells and monocytes, augmentation of IFNγ production by splenocytes, and inhibition of endothelial cell proliferation and capillary tube formation
Activities in rodents	Suppression of viral infection Suppression of tumor growth Inhibition of angiogenesis	As for MIG, plus recruitment of mononuclear cells to sites where injected, and impaired wound healing when expressed as transgene in the skin
Expression in disease	Widespread tissue expression in experimental infections in mice *Inflammatory skin diseases, multiple sclerosis, sarcoidosis*, and Epstein–Barr virus-positive *lymphoproliferative diseases* in humans	As for MIG, plus inflammatory diseases of kidney and lung and organ transplantation in mice, and leprosy, tuberculosis, glomerulonephritis, and atherosclerosis in humans

IN VITRO ACTIVITIES

In vitro findings

HuMIG produces a calcium flux on tumor-infiltrating lymphocytes (TILs), on peripheral blood T cells after activation *in vitro* and on NK cells (Liao *et al.*, 1995; Rabin *et al.*, 1999). It has chemotactic activity on TILs and some freshly isolated T cells, including naïve CD8+ T cells, as well as on T cells after activation *in vitro*. HuMIG produces a calcium signal on both memory and naïve T cells cells after short-term activation with OKT3 (Rabin *et al.*, 1999). HuMIG can suppress the number of hematopoietic progenitors derived from CD34+ human bone marrow cells (Schwartz *et al.*, 1997). It can also induce rapid adhesion of activated T cells to integrin ligands and to HUVECs (Piali *et al.*, 1998).

Regulatory molecules: Inhibitors and enhancers

Responses of T cells to HuMIG are enhanced after cellular activation through antigen receptors.

Bioassays used

MIG is bioassayed by measuring calcium flux and chemotaxis on activated T cells such as TILs (Liao *et al.*, 1995). Activity can also be measured using calcium flux and chemotaxis on CXCR3-transfected cell lines (Loetscher *et al.*, 1996).

IN VIVO BIOLOGICAL ACTIVITIES OF LIGANDS IN ANIMAL MODELS

Normal physiological roles

MIG is presumed to be involved in the trafficking of activated T cells and NK cells to inflammatory sites where IFNγ is being made.

Knockout mouse phenotypes

The unchallenged knockout mouse is normal.

Interactions with cytokine network

MIG is induced in response to IFNγ, and in some cases induction can be enhanced with TNF and diminished with IL-4. MIG can inhibit the angiogenic activities of growth factors and ELR chemokines in the corneal micropocket assay (Strieter *et al.*, 1995).

PATHOPHYSIOLOGICAL ROLES IN NORMAL HUMANS AND DISEASE STATES AND DIAGNOSTIC UTILITY

Role in experiments of nature and disease states

Evidence from experiments using recombinant vaccinia virus expressing MuMIG suggests that MIG may have a role in host defense against *viral infection* (Mahalingam *et al.*, 1999). A role in human diseases can only be inferred from data on gene and/or protein expression in the dermatologic disorders *psoriasis* (Goebeler *et al.*, 1998) and *lichen planus* (Spandau *et al.*, 1998) and in the malignancies *lymphomatoid granulomatosis* (Teruya-Feldstein *et al.*, 1997) and *cutaneous T cell lymphomas* (Tensen *et al.*, 1998).

IN THERAPY

Preclinical – How does it affect disease models in animals?

MuMIG has been expressed in recombinant *vaccinia virus* used to infect nude mice, and the mice infected with the MuMIG-producing virus showed increased time to death or significantly decreased mortality, depending on the infecting innoculum, as compared with mice infected with the control virus (Mahalingam *et al.*, 1999). The antiviral effects of MuMIG in this model were thought to be mediated by NK cells. MIG has been shown to have direct antitumor effects in a model of *Burkitt's lymphoma* in nude mice with HuMIG-injected tumors showing ischemic necrosis (Sgadari *et al.*, 1997). MuMIG has been shown to be induced in tumor tissue in mouse models during antitumor treatment with IL-12 (Kanegane *et al.*, 1998; Siders *et al.*, 1998; Zilocchi *et al.*, 1998; Tannenbaum *et al.*, 1998) and in tumors of the mouse mammary cell line 66.1 (Sun *et al.*, 1999). Neutralization with antibodies to MuMIG

have been shown to abrogate partially the antitumor effects of IL-12 (Kanegane *et al.*, 1998) and to diminish substantially lymphocyte infiltration of IL-12-treated *renal cell tumors* (Tannenbaum *et al.*, 1998).

References

Amichay, D., Gazzinelli, R. T., Karupiah, G., Moench, T. R., Sher, A., and Farber, J. M. (1996). Genes for chemokines MuMig and Crg-2 are induced in protozoan and viral infections in response to IFN-gamma with patterns of tissue expression that suggest nonredundant roles *in vivo. J. Immunol.* **157**, 4511–4520.

Cole, K. E., Strick, C. A., Paradis, T. J., Ogborne, K. T., Loetscher, M., Gladue, R. P., Lin, W., Boyd, J. G., Moser, B., Wood, D. E., Sahagan, B. G., and Neote, K. (1998). Interferon-inducible T cell alpha chemoattractant (I-TAC): A novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. *J. Exp. Med.* **187**, 2009–2021.

Ebnet, K., Simon, M. M., and Shaw, S. (1996). Regulation of chemokine gene expression in human endothelial cells by pro-inflammatory cytokines and Borrelia burgdorferi. *Ann. N.Y. Acad. Sci.* **797**, 107–117.

Erdel, M., Laich, A., Utermann, G., Werner, E. R., and Werner-Felmayer, G. (1998). The human gene encoding SCYB9B, a putative novel CXC chemokine, maps to human chromosome 4q21 like the closely related genes for MIG (SCYB9) and INP10 (SCYB10). *Cytogenet. Cell. Genet.* **81**, 271–272.

Farber, J. M. (1990). A macrophage mRNA selectively induced by γ-interferon encodes a member of the platelet factor 4 family of cytokines. *Proc. Natl Acad. Sci. USA* **87**, 5238–5242.

Farber, J. M. (1992). A collection of mRNA species that are inducible in the RAW 264.7 mouse macrophage cell line by gamma interferon and other agents. *Mol. Cell. Biol.* **12**, 1535–1545.

Farber, J. M. (1993). HuMIG: a new human member of the chemokine family of cytokines. *Biochem. Biophys. Res. Commun.* **192**, 223–230.

Feghali, C. A., and Wright, T. M. (1995). Ligand-dependent and -independent activation of the transcription factor gamma RF-1 in a cell-free system. *Biochem. J.* **310**, 461–467.

Gasperini, S., Marchi, M., Calzetti, F., Laudanna, C., Vicentini, L., Olsen, H., Murphy, M., Liao, F., Farber, J., and Cassatella, M. A. (1999). Gene expression and production of the monokine induced by IFN-gamma (MIG), IFN-inducible T cell alpha chemoattractant (I-TAC), and IFN-gamma-inducible protein-10 (IP-10) chemokines by human neutrophils. *J. Immunol.* **162**, 4928–4937.

Goebeler, M., Toksoy, A., Spandau, U., Engelhardt, E., Brocker, E., and Gillitzer, R. (1998). The C-X-C chemokine Mig is highly expressed in the papillae of psoriatic lesions. *J. Pathol.* **184**, 89–95.

Guyer, N. B., Severns, C. W., Wong, P., Feghali, C. A., and Wright, T. M. (1995). IFN-γ induces a p91/Stat1α-related transcription factor with distinct activation and binding properties. *J. Immunol.* **155**, 3472–3480.

Horton, M. R., McKee, C. M., Bao, C., Liao, F., Farber, J. M., Hodge-DuFour, J., Pure, E., Oliver, B. L., Wright, T. M., and Noble, P. W. (1998). Hyaluronan fragments synergize with interferon-gamma to induce the C-X-C chemokines mig and

interferon-inducible protein-10 in mouse macrophages. *J. Biol. Chem.* **273**, 35088–35094.

Kanegane, C., Sgadari, C., Kanegane, H., Teruya-Feldstein, J., Yao, L., Gupta, G., Farber, J. M., Liao, F., Liu, L., and Tosato, G. (1998). Contribution of the CXC chemokines IP-10 and Mig to the antitumor effects of IL-12. *J. Leukoc. Biol.* **64**, 384–392.

Lee, H.-H., and Farber, J. M. (1996). Localization of the gene for the human MIG cytokine on chromosome 4q21 adjacent to INP10 reveals a chemokine "mini-cluster". *Cytogenet. Cell. Genet.* **74**, 255–258.

Lerner, A., Clayton, L. K., Mizoguchi, E., Ghendler, Y., van Ewijk, W., Koyasu, S., Bhan, A. K., and Reinherz, E. L. (1996). Cross-linking of T-cell receptors on double-positive thymocytes induces a cytokine-mediated stromal activation process linked to cell death. *EMBO J.* **15**, 5876–5887.

Liao, F., Rabin, R. L., Yannelli, J. R., Koniaris, L. G., Vanguri, P., and Farber, J. M. (1995). Human Mig chemokine: biochemical and functional characterization. *J. Exp. Med.* **182**, 1301–1314.

Loetscher, M., Gerber, B., Loetscher, P., Jones, S. A., Piali, L., Clark-Lewis, I., Baggiolini, M., and Moser, B. (1996). Chemokine receptor specific for IP10 and mig: structure, function, and expression in activated T-lymphocytes [see comments]. *J. Exp. Med.* **184**, 963–969.

Mahalingam, S., Farber, J. M., and Karupiah, G. (1999). The interferon-inducible chemokines MuMig and Crg-2 exhibit antiviral activity *in vivo. J. Virol.* **73**, 1479–1491.

Modi, W. S., and Chen, Z. Q. (1998). Localization of the human CXC chemokine subfamily on the long arm of chromosome 4 using radiation hybrids. *Genomics* **47**, 136–139.

Ohmori, Y., and Hamilton, T. A. (1998). STAT6 is required for the anti-inflammatory activity of interleukin-4 in mouse peritoneal macrophages. *J. Biol. Chem.* **273**, 29202–29209.

Piali, L., Weber, C., LaRosa, G., Mackay, C. R., Springer, T. A., Clark-Lewis, I., and Moser, B. (1998). The chemokine receptor CXCR3 mediates rapid and shear-resistant adhesion-induction of effector T lymphocytes by the chemokines IP10 and Mig. *Eur. J. Immunol.* **28**, 961–972.

Rabin, R. L., Park, M. K., Liao, F., Swofford, R., Stephany, D., and Farber, J. M. (1999). Chemokine receptor responses are achieved through regulation of both receptor expression and signaling. *J. Immunol.* **162**, 3840–3850.

Schwartz, G. N., Liao, F., Gress, R. E., and Farber, J. M. (1997). Suppressive effects of recombinant human monokine induced by IFN-γ (rHuMig) chemokine on the number of committed and primitive hemopoietic progenitors in liquid cultures of CD34+ human bone marrow cells. *J. Immunol.* **159**, 895–904.

Sgadari, C., Farber, J. M., Angiolillo, A. L., Liao, F., Teruya-Feldstein, J., Burd, P. R., Yao, L., Gupta, G., Kanegane, C., and Tosato, G. (1997). Mig, the monokine induced by interferon-gamma, promotes tumor necrosis *in vivo. Blood* **89**, 2635–2643.

Siders, W. M., Wright, P. W., Hixon, J. A., Alvord, W. G., Back, T. C., Wiltrout, R. H., and Fenton, R. G. (1998). T cell- and NK cell-independent inhibition of hepatic metastases by systemic administration of an IL-12-expressing recombinant adenovirus. *J. Immunol.* **160**, 5465–5474.

Spandau, U., Toksoy, A., Goebeler, M., Brocker, E. B., and Gillitzer, R. (1998). MIG is a dominant lymphocyte-attractant chemokine in lichen planus lesions. *J. Invest. Dermatol.* **111**, 1003–1009.

Strieter, R. M., Polverini, P. J., Kunkel, S. L., Arenberg, D. A., Burdick, M. D., Kasper, J., Dzuiba, J., Van Damme, J., Walz, A., Marriott, D., Chan, S.-Y., Roczniak, S., and Shanafelt, A. B. (1995). The functional role of the ELR motif

in CXC chemokine-mediated angiogenesis. *J. Biol. Chem.* **2710**, 27348–27357.

Sun, H., Jackson, M. J., Kundu, N., and Fulton, A. M. (1999). Interleukin-10 gene transfer activates interferon-gamma and the interferon-gamma-inducible genes Gbp-1/Mag-1 and Mig-1 in mammary tumors. *Int. J. Cancer* **80**, 624–629.

Tannenbaum, C. S., Tubbs, R., Armstrong, D., Finke, J. H., Bukowski, R. M., and Hamilton, T. A. (1998). The CXC chemokines IP-10 and Mig are necessary for IL-12-mediated regression of the mouse RENCA tumor. *J. Immunol.* **161**, 927–932.

Tensen, C. P., Vermeer, M. H., van der Stoop, P. M., van Beek, P., Scheper, R. J., Boorsma, D. M., and Willemze, R. (1998). Epidermal interferon-gamma inducible protein-10 (IP-10) and monokine induced by gamma-interferon (Mig) but not IL-8 mRNA expression is associated with epidermotropism in cutaneous T cell lymphomas. *J. Invest. Dermatol.* **111**, 222–226.

Teruya-Feldstein, J., Jaffe, E. S., Burd, P. R., Kanegane, H., Kingma, D. W., Wilson, W. H., Longo, D. L., and Tosato, G. (1997). The role of Mig, the monokine induced by interferon-gamma, and IP-10, the interferon-gamma-inducible protein-10, in tissue necrosis and vascular damage associated with Epstein-Barr virus-positive lymphoproliferative disease. *Blood* **90**, 4099–4105.

Tunnacliffe, A., Majumdar, S., Yan, B., and Poncz, M. (1992). Genes for β-thromboglobulin and platelet factor 4 are closely linked and form part of a cluster of related genes on chromosome 4. *Blood* **79**, 2896–2900.

Vanguri, P. (1995). Interferon-γ-inducible genes in primary glial cells of the central nervous system: comparisons of astrocytes with microglia and Lewis with Brown Norway rats. *J. Neuroimmunol.* **56**, 35–43.

Wong, P., Severns, C. W., Guyer, N. B., and Wright, T. M. (1994). A unique palindromic element mediates gamma interferon induction of mig gene expression. *Mol. Cell. Biol.* **14**, 914–922.

Wright, T. M., and Farber, J. M. (1991). 5′ regulatory region of a novel cytokine gene mediates selective activation by interferon γ. *J. Exp. Med.* **173**, 417–422.

Zilocchi, C., Stoppacciaro, A., Chiodoni, C., Parenza, M., Terrazzini, N., and Colombo, M. P. (1998). Interferon gamma-independent rejection of interleukin 12-transduced carcinoma cells requires CD4+ T cells and granulocyte/macrophage colony-stimulating factor. *J. Exp. Med.* **188**, 133–143.

LICENSED PRODUCTS

PharMingen: Recombinant mouse and human MIGs, anti-HuMIG monoclonal antibodies for ELISA assay and intracytoplasmic staining for flow cytometry.

R&D Systems: Recombinant mouse and human MIGs, anti-HuMIG polyclonal antibodies, anti-HuMIG monoclonal antibody, and anti-MuMIG polyclonal antibodies for ELISA, neutralization, and western blotting.

PeproTech: Recombinant HuMIG, anti-HuMIG polyclonal antibodies.