

# Slit proteins, potential endogenous modulators of inflammation

Necat Havlioglu, Liya Yuan, Hao Tang, and Jane Y Wu

Departments of Pediatrics and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, Missouri, USA

**Recent studies suggest that molecules important for guiding neuronal migration and axon path-finding also play a role in modulating leukocyte chemotaxis. Neuronal migration and leukocyte chemotaxis may share some common regulatory mechanisms. Intracellular signal transduction mechanisms guiding neuronal migration and leukocyte chemotaxis are beginning to be elucidated. Studying molecular mechanisms modulating cell migration may provide new insights into understanding of endogenous inhibitors of inflammation.** *Journal of NeuroVirology* (2002) **8**, 486–495.

**Keywords:** axon guidance; inflammation; neuronal migration; roundabout; signal transduction; slit

## Introduction

Since the discovery of leukocyte chemotaxis by Leber in 1888 (reviewed in McCutcheon, 1946; Harris, 1954), this type of cell migration has been studied extensively (Boyden, 1962; Ramsey, 1972; Zigmond, 1974; Devreotes and Zigmond, 1988; Downey, 1994; Sanchez-Madrid and Angel del Pozo, 1999). Work in the last 20 years has demonstrated the importance of the chemokine family in leukocyte chemotaxis (reviewed in Murphy, 1994; Springer, 1994; Rollins, 1997; Baggiolini *et al*, 1997; Luster, 1998; Locati and Murphy, 1999). There are currently more than 40 chemokines that are structurally related small proteins with 70 to 100 amino acid residues. Chemokines are classified into several families according to their structural features: CXC

chemokines such as IL-8 (interleukin-8) and SDF-1 (stromal cell-derived factor-1), CC chemokines such as RANTES (regulated upon activation in normal T cells expressed and secreted) and MCP-1 (monocyte chemoattractant protein-1), C chemokine (such as lymphotactin), and CX3C chemokine (such as fractalkine). Although many CC chemokines are of broad spectrum, CXC chemokines often are more restricted.

Chemokines play multiple roles, not only in normal development but also in the pathogenesis of a large number of diseases such as atherosclerosis (Yla-Herttuala *et al*, 1991; Nelken *et al*, 1991; Boring *et al*, 1998; Gerszten *et al*, 2000), allogeneic transplant rejection (Pattison *et al*, 1994; Kondo *et al*, 1996), virally induced vascular diseases (Strelow *et al*, 1999), as well as tissue injury repair (Furie and Randolph, 1995) and tumor development (Sharpe *et al*, 1990; Smith *et al*, 1994; Strieter *et al*, 1995; Dilloo *et al*, 1996; Moore *et al*, 1998). In tumorigenesis, both tumor-induced angiogenesis and tumor metastasis involve cell migration (Koch *et al*, 1992b; Smith *et al*, 1994; Strieter *et al*, 1995; Boshoff *et al*, 1997; Tachibana *et al*, 1998; Moore *et al*, 1998). Activation or increased production of chemokines has been found in a number of inflammatory disorders, not only in the organs outside of the nervous system but also in certain neurodegenerative disorders (for example, Koch *et al*, 1992a; reviewed in

---

Address correspondence to Jane Y Wu, Departments of Pediatrics and Molecular Biology and Pharmacology, Washington University School of Medicine, Box 8208, St. Louis, MO 63110, USA. E-mail: jwu@molecool.wustl.edu

The present address of Necat Havlioglu is Department of Pathology, St. Louis University, Missouri, USA.

The authors are grateful to the members of Wu laboratory and Yi Rao for helpful discussions, to the NIH for grant support (to JYW), and to the Leukemia Society of America for scholar award (JYW).

Received 25 January 2002; revised 4 September 2002; accepted 5 September 2002.

Seegerer *et al*, 2000; Luster, 2001, 2002). Inhibition of chemokines has shown therapeutic potentials in animal models (Harada *et al*, 1994; Gong *et al*, 1997; Barnes *et al*, 1998). Therefore, much effort has been directed towards obtaining reagents that can block chemokines or their receptors (Baggiolini and Moser, 1997; Nelson and Krensky, 1998; Baggiolini, 1998; Luster, 2001; Izikson *et al*, 2002).

Extensive studies on chemokines show that these chemotactic factors act through seven-transmembrane receptors coupled to G proteins (GPCRs). Many chemokine receptors signal through Gi-type proteins. Activation of the receptors by chemokines often involves calcium mobilization and stimulation of phosphoinositide-specific phospholipase C (PI-PLC) (for reviews, see Murphy, 1994). However, our understanding of signal transduction pathways downstream of chemokine receptors is still limited. It is not known about how these pathways are regulated by other ligand-receptor pathways. Although some viral-derived chemokine inhibitors have been reported (Smith *et al*, 1997; Kledal *et al*, 1997), very little is known about endogenously produced chemokine inhibitors.

### **Slit: A molecular cue for axon guidance and neuronal migration**

A number of neuronal guidance cues have been found in the nervous system (reviewed in Tessier-Lavigne and Goodman, 1996; Raper and Tessier-Lavigne, 1999). Recent studies on a family of secreted proteins, the Slit proteins, have uncovered molecular cues guiding neuronal migration. First identified in *Drosophila* (Nusslein-Volhard *et al*, 1984; Rothberg *et al*, 1988, 1990), slit gene family in mammals has at least three members, slit1, -2, and -3. They encode secreted proteins containing four leucine-rich repeat (LRR) regions at N-terminal region, followed by nine epidermal growth factor (EGF) repeats, a laminin G domain (previously also known as the a laminin G domain with similarities to agrin, laminin, and perlecan [ALPS] domain), and a cysteine-rich C-terminal region. slit genes have been shown to encode ligands for the Roundabout receptor (Robo) (Battye *et al*, 1999; Brose *et al*, 1999; Kidd *et al*, 1999; Li *et al*, 1999; Nguyen Ba-Charvet *et al*, 1999; Yuan *et al*, 1999). Slit can promote axon branching (Wang *et al*, 1999b) and repel axons in the spinal cord and in the brain (Brose *et al*, 1999; Kidd *et al*, 1999; Li *et al*, 1999; Nguyen Ba-Charvet *et al*, 1999). Slit proteins are capable of guiding the movement of at least two populations of tangentially migrating neurons in the CNS: those migrating from the anterior subventricular zone (SVZa) to the olfactory bulb (Wu *et al*, 1999; Hu, 1999) and those migrating from the striatal primordium to the neocortex (Zhu *et al*, 1999). Slit protein acts as a chemorepellent whose concentration gradient guides neuronal migration (Wu *et al*, 1999). The activities of

Slit in both axon guidance and neuronal migration led to the conclusion that these two phenomena in the nervous system share common guidance mechanisms (Wu *et al*, 1999; Zhu *et al*, 1999).

### **Activities of Slit proteins in the nervous system and in the immune system**

It is not clear whether mechanisms underlying cell migration that operate in the nervous system are conserved in the immune system. At the cellular level, the environment in which leukocytes migrate seems to be different from the tightly packed environment within which axons and neurons navigate. Furthermore, the morphology of migrating neurons with a rather long leading process and a trailing process appears to be distinct from that of the leukocytes. At the molecular level, receptors for all known neuronal guidance cues, including a *C. elegans* homolog of DCC (UNC-5), deleted in colorectal cancer (DCC), Eph, neuropilin, Robo, and plexin, are proteins containing a single transmembrane domain (Leung-Hagesteijn *et al*, 1992; Cheng and Flanagan, 1994; Keino-Masu *et al*, 1996; Chan *et al*, 1996; Tessier-Lavigne and Goodman, 1996; Leonardo *et al*, 1997; Ackerman *et al*, 1997; He and Tessier-Lavigne, 1997; Kolodkin *et al*, 1997; Feiner *et al*, 1997; Chen *et al*, 1998; Giger *et al*, 1998; Winberg *et al*, 1998; Kidd *et al*, 1998, 1999; Zallen *et al*, 1998; Brose *et al*, 1999; Li *et al*, 1999; Yuan *et al*, 1999; Takahashi *et al*, 1999; Tamagnone *et al*, 1999; Bashaw and Goodman, 1999; Mueller, 1999). In contrast, seven-transmembrane GPCRs mediate responses not only to all chemokines but also to other known chemotactic factors in vertebrate animals (Hwang, 1990; Murphy, 1994; Rollin, 1997; Baggiolini *et al*, 1997; Luster, 1998; Locati and Murphy, 1999) and in *Dictyostelium* (Klein *et al*, 1985, 1988; Devreotes and Zigmond, 1988; Parent and Devreotes, 1996, 1999; Chen *et al*, 1996). It is, therefore, not obvious whether neuronal guidance cues can play important roles in the immune system.

We previously reported the expression of Slit and Robo outside the mammalian nervous system (Li *et al*, 1999; Yuan *et al*, 1999) and speculated possible roles for Slit in the immune system (Wu *et al*, 1999; Zhu *et al*, 1999). Our recent studies show that Slit is capable of inhibiting leukocyte migration induced by chemokines (Wu *et al*, 2001). Both human Slit2 and *Xenopus* Slit protein were found to inhibit leukocyte chemotaxis induced by chemokines such as SDF-1, and chemotaxis of differentiated HL-60 cells induced by *N*-formyl peptide f-Met-Leu-Phe (fMLP) was also inhibited by Slit protein. These results demonstrated the functional interaction between Slit-Robo and chemokine-chemokine receptor signal transduction pathways. These studies indicated functional interaction between two distinct families of guidance molecules,

one working through single transmembrane receptors and the other through seven-transmembrane GPCRs. These studies have implications on modulation of pathways involving heterotrimeric G proteins and demonstrate conserved guidance mechanisms for neurons and leukocytes. Furthermore, these findings have biological and therapeutic implications in neuronal migration as well as multiple processes involving chemokines. Our results with Slit and chemokines suggest that modulation of pathways involving heterotrimeric G proteins is important in guiding cell migration.

The observation that functional interaction between Slit and chemokines requires the single-pass transmembrane Robo receptor for Slit and the GPCRs for the chemokines suggests a novel approach to regulate signal transduction pathways activated during inflammation. Chemokines are known to activate a number of downstream components (Downey, 1994; Ganju *et al*, 1998; Rodriguez-Frade *et al*, 1999). Chemokine signaling can be inhibited at any step, beginning from ligand binding (Mashikian *et al*, 1999), receptor polarization or distribution (Nieto *et al*, 1997; Djellas *et al*, 1998; Servant *et al*, 1999), receptor coupling to G proteins (Arai and Charo, 1996; Kuang *et al*, 1996), release of the  $\beta\alpha$  subunits of G proteins (Neptune and Bourne, 1997; Arai *et al*, 1997; Neptune *et al*, 1999), activation of effectors such as  $Ca^{2+}$ , focal adhesion kinase (FAK), MAP kinase, or inositol 1,4,5-triphosphate (PI3) kinase (Bacon *et al*, 1996; Ganju *et al*, 1998), function and distribution of integrins (Lauffenburger and Horwitz, 1996), to the organization of actin cytoskeleton (Mitchison and Cramer, 1996). At present, it is not clear at which step(s) the Slit pathway interacts with the chemokine pathway(s). However, recent studies on the intracellular signaling pathways downstream of the Slit receptor, Robo, have demonstrated an important role of a new family of GTPase-activating proteins (GAP) proteins, Slit-Robo GAP (srGAP), as well as Cdc42 in neuronal guidance (Wong *et al*, 2001, 2002a, 2002b). These genes are also expressed in leukocytes (Wu and Havlioglu, unpublished results). These studies provide potential new target genes for studying functional interaction between Slit and chemokine pathways.

### Potential implication of Slit in inflammatory nervous system disorders

Because Slit is not unique among the neuronal guidance cues, we propose that other neuronal guidance cues may also play a role in modulating migration of other cell types, including leukocyte chemotaxis in the immune system. Chemokines play multiple roles, including inflammatory responses (reviewed in Rollins, 1997; Luster, 1998), leukocyte activation (Bokoch, 1995), lymphocyte trafficking, and lym-

phoid organ homeostasis (Springer, 1994; Forster *et al*, 1996; Mackay, 1996; Baggiolini, 1998; Ward, Bacon and Westwick, 1998; Melchers *et al*, 1999; Jung and Littman, 1999; Cyster, 1999). The potential roles of chemokine activation in the inflammatory disorders outside of the nervous system have been extensively covered by a number of excellent reviews. Here we will discuss the potential implication of Slit protein in the inflammatory responses in the nervous system.

Similar to the eye and testes, the central nervous system (CNS) in mammals has evolved complex mechanisms to protect its structure and function from damaging inflammatory responses. There are several layers of anatomical and physiological barriers. These include the unique organization of the blood-brain barrier (BBB), the lack of conventional lymphatic drainage of the brain, the absence of potent antigen-presenting cells, and the down-regulatory roles of neurons on major histocompatibility complex (MHC) expression in the CNS, with paucity of class I and II MHC molecules on resident cells (Aloisi, 1999; Bradl, 1996; Frohman *et al*, 2001; Lawrence and Kim, 2000).

It is known that immune cells and factors can enter the brain parenchyma in the absence of any pathogen. However, only a very small percentage of peripherally injected cytokines can cross the BBB as demonstrated for IL-2 and chemokines (Lawrence and Kim, 2000). Nonetheless, the CNS is under constant surveillance by the immune system. Perivascular and meningeal macrophages are replaced continuously by blood-derived macrophages that may act as first-line scavengers (Lassman, 1999). Small numbers of dendritic-like cells have been detected in some CNS-associated compartments, such as the meninges and the choroid plexus. Human immunodeficiency virus (HIV)-infected T lymphocytes and monocytes are often found in the stroma, as well as in supraepithelial regions of the choroid plexus (Antel, 2000). Numerous resident cells such as microglia, cerebral endothelial cells, and astrocytes acquire the expression of immune accessory molecules and they function as antigen-presenting cells. Healthy neurons may have a number of mechanisms to escape the recognition by immune cells and avoid autoimmune responses. These may include suppression of MHC expression in neurons. In healthy CNS, MHC class II molecules are only present on perivascular cells, leptomeninges, and choroid plexus. MHC class II is induced on microglia and perivascular cells in response to trauma, ischemia, infection, inflammation, and neurodegeneration. MHC class II expression is controlled by neurons. Neurotrophins (especially nerve growth factor [NGF]) play a role in down-regulating MHC class II on microglia (Aloisi, 1999; McCluskey and Lampson, 2000). Functional damage to neurons and loss of bioelectric activity renders neurons susceptible to recognition and

elimination by cytotoxic CD8+ T lymphocytes (Lassman, 1999).

During viral infection or development of certain autoimmune disorders of the nervous system, activated T cells can cross BBB and initiate both protective and unwanted inflammatory responses. When BBB is damaged, a large number of T cells and other inflammatory cells enter the CNS by encountering perivascular macrophages. Activation of microglia and astrocytes also play an important role in the immune responses in the CNS. Activated microglia has phagocytic activity and they also synthesize cytokines and mediators. Activated microglia express B7, intercellular adhesion molecule (ICAM)-1, and CD40 molecules and astrocytes also may express B7 and CD40 (Aloisi, 1999; Antel, 2000; Aloisi, 2000a, 2000b; Becher *et al*, 2000).

In addition to the role of chemokines in the development of the nervous system (for example, see recent papers by Klein *et al*, 2001; Zhu *et al*, 2002 and references within), accumulating evidence suggests that chemokines and their receptors may play an important role in the inflammatory responses in the CNS (Bajetto *et al*, 2001; Izikson *et al*, 2002). These include encephalitis, encephalomyelitis, meningitis, CNS ischemia, CNS reperfusion injury, CNS trauma, CNS tumors, multiple sclerosis, Alzheimer's diseases, and HIV dementia (reviewed in Karpus, 1999; Glabinski and Ransohoff, 1999; Fujika *et al*, 1999; Hesselgesser and Horuk, 1999; Xia and Hyman, 1999; Mennicken *et al*, 1999). However, little is known about endogenous inhibitors of chemokine activation in the CNS. Our recent studies show that Slit is expressed in the postnatal meninges and active in chemorepulsion (Wu and Rao, unpublished observation), suggesting a potential role of Slit in protective mechanisms against leukocyte infiltration into the CNS. In addition, Slit proteins expressed inside CNS may also play a role in modulating inflammatory responses in the CNS.

In a number of scenarios, it is possible that Slit may be of potential therapeutic benefits. For example, multiple sclerosis is an autoimmune disease mediated by leukocyte infiltration. Chemokine expression is up-regulated in multiple sclerosis and

its animal models (Ransohoff *et al*, 1993, 1996; Miyagishi *et al*, 1995; Godiska *et al*, 1995; Hvas *et al*, 1997; Glabinski and Ransohoff, 1999; Hesselgesser and Horuk, 1999). Inhibition of chemokine receptors is protective against the induction of experimental allergic encephalomyelitis, a mouse model of multiple sclerosis (Karpus *et al*, 1995). An inhibitor such as Slit may thus be of use in ameliorating multiple sclerosis. Because the chemokine receptor CXCR4, in the absence of CD4, has been shown to mediate neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 (Hesselgesser *et al*, 1998; Meucci *et al*, 1998), our results on Slit inhibition of SDF-1 signaling through CXCR4 (Wu *et al*, 2001) suggest that Slit may be used to reduce neuronal apoptosis. Up-regulation of chemokine receptors has also been proposed as a potential player in the pathogenesis of Alzheimer's disease either by exacerbating inflammatory responses or by apoptosis (reviewed in Xia and Hyman, 1999; Hesselgesser and Horuk, 1999), forming a basis for suggesting a beneficial effect of Slit and other chemokine inhibitors in Alzheimer's disease.

Several chemokine receptors, including CXCR4 and CCR5, have been shown to be coreceptors for HIV-1 (Cocchi *et al*, 1995; Feng *et al*, 1996; Oberlin *et al*, 1996; Bleul *et al*, 1996, 1997; Dragic *et al*, 1996; Deng *et al*, 1996; Choe *et al*, 1996; Doranz *et al*, 1996; Simmons *et al*, 1997). Because inhibition of receptor signaling can block HIV infection (Alfano *et al*, 1999; Wang and Oppenheim, 1999), the finding of Slit inhibition of signaling through chemokine receptors, including CCR5 and CXCR4, suggests a possible application of Slit in acquired immunodeficiency syndrome (AIDS). This may open a new avenue in drug research for Slit or its derivatives to be used as a therapeutic reagent in inhibiting HIV infection by inhibiting its coreceptors CXCR4 and CCR5 (Wu, *et al*, 2001). The studies on the interplay between chemokine pathways and other signal transduction pathways are only at the beginning. Mechanisms underlying the complex regulation of chemokine signaling inside and outside the nervous system await further investigation with combined molecular, biochemical and functional approaches.

## References and suggested reading

- Ackerman SL, Kozak LP, Przyborski SA, Rund LA, Boyer BB, Knowles BB (1997). The mouse rostral cerebellar malformation gene encodes an UNC-5-like protein. *Nature* **386**: 838–842.
- Alfano M, Schmidtmayerova H, Amella CA, Pushkarsky T, Bukrinsky M (1999). The B-oligomer of pertussis toxin deactivates CC chemokine receptor 5 and blocks entry of M-tropic HIV-1 strains. *J Exp Med* **190**: 597–605.
- Aloisi F (1999). The role of microglia and astrocytes in CNS immune surveillance and immunopathology. In: *The functional role of glial cells in health and disease: dialogue between glia and neurons*. Mastas R, Tsacopoulos M (eds). Kluwer Academic/Plenum: New York, pp 123–133.
- Aloisi F, Ria F, Adorini L (2000a). Regulation of T-cell responses by CNS antigen presenting cells: different roles for microglia and astrocytes. *Immunol Today* **21**: 141–147.
- Aloisi F, Serafini B, Adorini L (2000b). Glia-T cell dialogue. *J Neuroimmunol* **107**: 111–117.
- Antel J (2000). Antigen and superantigen presentation in the human CNS. *J Neuroimmunol* **107**: 118–123.

- Arai H, Charo IF (1996). Differential regulation of G-protein-mediated signaling by chemokine receptors. *J Biol Chem* **271**: 21814–21819.
- Arai H, Tsou CL, Charo IF (1997). Chemotaxis in a lymphocyte cell line transfected with C-C chemokine receptor 2B: evidence that directed migration is mediated by bg dimers released by activation of Gai-coupled receptors. *Proc Natl Acad Sci USA* **94**: 14495–14499.
- Arenzana-Seisdedos F, Virelizier JL, Rousset D, Clark-Lewis I, Loetscher P, Moser B, Baggiolini M (1996). HIV blocked by chemokine antagonist. *Nature* **383**: 400.
- Asensio VC, Campbell IL (1999). Chemokines in the CNS: plurifunctional mediators in diverse states. *Trends Neurosci* **22**: 504–512.
- Bacon KB, Szabo MC, Yssel H, Bolen JB, Schall TJ (1996). RANTES induces tyrosine kinase activity of stably complexed p125FAK and ZAP-70 in human T cells. *J Exp Med* **184**: 873–882.
- Baggiolini M (1998). Chemokines and leukocyte traffic. *Nature* **392**: 565–568.
- Baggiolini M, Dahinder CA (1994). CC chemokines in allergic inflammation. *Immunol Today* **15**: 127–133.
- Baggiolini M, Dewald B, Moser B (1997). Human chemokines: an update. *Annu Rev Immunol* **15**: 675–705.
- Baggiolini M, Moser B (1997). Blocking chemokine receptors. *J Exp Med* **186**: 1189–1191.
- Bajetto A, et al (2001). Chemokines and their receptors in the central nervous system. *Front Neuroendocrinol* **22**: 147–184.
- Barnes DA, Tse J, Kaufhold M, Owen M, Hesselgesser J, Strieter R, Horuk R, Perez HD (1998). Polyclonal antibody directed against human RANTES ameliorates disease in the Lewis rat adjuvant-induced arthritis model. *J Clin Invest* **101**: 2910–2919.
- Bashaw G, Goodman CS (1999). Chimeric axon guidance receptors: the cytoplasmic domains of Slit and Netrin receptors specify attraction versus repulsion. *Cell* **97**: 917–926.
- Battye R, Stevens A, Jacobs JR (1999). Axon repulsion from the midline of the *Drosophila* CNS requires *slit* function. *Development* **126**: 2475–2481.
- Becher B, Prat A, Antel JP (2000). Brain-immune connection: immuno-regulatory properties of CNS-resident cells. *Glia* **29**: 293–304.
- Berger EA, Murphy PM, Farber JM (1999). Chemokine receptors as HIV coreceptors: roles in viral entry, tropism, and disease. *Annu Rev Immunol* **17**: 657–700.
- Bleul CC, Farzan M, Choe H, Parolin C, Clark-Lewis I, Sodroski J, Springer TA (1996). The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature* **382**: 829–833.
- Bleul CC, Wu L, Hoxie JA, Springer TA, Mackay CR (1997). The HIV coreceptors CXCR4 and CCR5 are differentially expressed and regulated on human T lymphocytes. *Proc Natl Acad Sci USA* **94**: 1925–1930.
- Bokoch GM (1995). Chemoattractant signaling and leukocyte activation. *Blood* **86**: 1649–1660.
- Boring L, Gosling J, Cleary M, Charo IF (1998). Decreased lesion formation in CCR2<sup>-/-</sup> mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* **394**: 894–897.
- Boshoff C, Endo Y, Collins PD, Takeuchi Y, Reeves JD, Schweickart VL, Siani MA, Sasaki T, Williams TJ, Gray PW, Moore PS, Chang Y, Weiss RA (1997). Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. *Science* **278**: 290–294.
- Boyden S (1962). The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leukocytes. *J Exp Med* **115**: 453–466.
- Bradl M (1996). Immune control of the brain. In: *Immunoneurology*. Chofflon M, Steinman L (eds). Springer-Verlag: New York, pp 153–167.
- Brose K, Bland KS, Wang KH, Arnott D, Henzel W, Goodman CS, Tessier-Lavigne M, Kidd T (1999). Evolutionary conservation of the repulsive axon guidance function of Slit proteins and of their interactions with Robo receptors. *Cell* **96**: 795–806.
- Cajal S, Ramon Y (1911). *Histology of the nervous system*. Translated by Swanson N, Swanson LW, 1995. Oxford University Press: New York.
- Chan SS, Zheng H, Su MW, Wilk R, Killeen MT, Hedgecock EM, Culotti JG (1996). UNC-40, a *C. elegans* homolog of DCC (Deleted in Colorectal Cancer), is required in motile cells responding to UNC-6 netrin cues. *Cell* **87**: 187–195.
- Chen H, He Z, Bagri A, Tessier-Lavigne M (1998). Semaphorin-neuropilin interactions underlying sympathetic axon responses to class III semaphorins. *Neuron* **21**: 1283–1290.
- Chen M-Y, Insall RH, Devreotes PN (1996). Signaling through chemoattractant receptors in *Dictyostelium*. *Trends Genet* **12**: 52–57.
- Chen S, Bacon L Li, Garcia GE, Xia Y, Lo D, Thompson DA, Siani MA, Yamamoto T, Harrison JK, Feng L (1998). In vivo inhibition of CC and CX3C chemokine-induced leukocyte infiltration and attenuation of glomerulonephritis in Wistar-Kyoto (WKY) rats by vMIP-II. *J Exp Med* **188**: 193–198.
- Cheng HJ, Flanagan JG (1994). Identification and cloning of ELF-1, a developmentally expressed ligand for the Mek4 and Sek receptor tyrosine kinases. *Cell* **79**: 157–168.
- Choe H, Farzan M, Sun Y, Sullivan N, Rollins B, Ponath PD, Wu L, Mackay CR, LaRosa G, Newman W, Gerard N, Gerard C, Sodroski J (1996). The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* **85**: 1135–1148.
- Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P (1995). Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8<sup>+</sup> T cells. *Science* **270**: 1811–1815.
- Cyster JG (1999). Chemokines and cell migration in secondary lymphoid organs. *Science* **286**: 2098–2102.
- Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, Di Marzio P, Marmon S, Sutton RE, Hill CM, Davis CB, Peiper SC, Schall TJ, Littman DR, Landau NR (1996). Identification of a major co-receptor for primary isolates of HIV-1. *Nature* **381**: 661–666.
- Devreotes PN, Zigmond SH (1988). Chemotaxis in eukaryotic cells: a focus on leukocytes and *Dictyostelium*. *Ann Rev Cell Biol* **4**: 649–686.
- Dilloo D, Bacon K, Holden W, Zhong W, Burdach S, Zlotnik A, Brenner M (1996). Combined chemokine and cytokine gene transfer enhances antitumor immunity. *Nat Med* **2**: 1090–1095.
- Djellas Y, Antonakis K, Le Breton GC (1998). A molecular mechanism for signaling between seven-transmembrane receptors: evidence for a redistribution of G proteins. *Proc Natl Acad Sci USA* **95**: 10944–10948.
- Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, Parmentier M, Collman RG, Doms RWA (1996).

- Dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell* **85**: 1149–1158.
- Downey GP (1994). Mechanisms of leukocyte motility and chemotaxis. *Curr Opin Immunol* **6**: 113–124.
- Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA (1996). HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* **381**: 667–673.
- Duel TF, Keim PS, Farmer M, Heinrikson RL (1977). Amino acid sequence of human platelet factor 4. *Proc Natl Acad Sci USA* **74**: 2256–2258.
- Feiner L, Koppel AM, Kobayashi H, Raper JA (1997). Secreted chick semaphorins bind recombinant neuropilin with similar affinities but bind different subsets of neurons in situ. *Neuron* **19**: 539–545.
- Feng L, Chen S, Garcia GE, Xia Y, Siani MA, Botti P, Wilson CB, Harrison JK, Bacon KB (1999). Prevention of crescentic glomerulonephritis by immunoneutralization of the fractalkine receptor CX3CR1 rapid communication [In Process Citation]. *Kidney Int* **56**: 612–620.
- Feng L, Xia Y, Yoshimura T, Wilson CB (1995). Modulation of neutrophil influx in glomerulonephritis in the rat with anti-macrophage inflammatory protein-2 (MIP-2) antibody. *J Clin Invest* **95**: 1009–1017.
- Feng Y, Broder CC, Kennedy PE, Berger EA (1996). HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* **272**: 872–877.
- Forster R, Kremmer E, Schubel A, Breitfeld D, Kleinschmidt A, Nerl C, Bernhardt G, Lipp M (1998). Intracellular and surface expression of the HIV-1 coreceptor CXCR4/fusin on various leukocyte subsets: rapid internalization and recycling upon activation. *J Immunol* **160**: 1522–1531.
- Forster R, Mattis AE, Kremmer E, Wolf E, Brem G, Lipp M (1996). A putative chemokine receptor, BLR1, directs B cell migration to defined lymphoid organs and specific anatomic compartments of the spleen. *Cell* **87**: 1037–1047.
- Frohman EM, et al (2001). Autonomic regulation of neuroimmunological responses: implications for multiple sclerosis. *J Clin Immunol* **21**: 61–73.
- Fujioka T, Kolson DL, Rostami AM (1999). Chemokines and peripheral nerve demyelination. *J NeuroVirol* **5**: 27–31.
- Furie MB, Randolph GJ (1995). Chemokines and tissue injury. *Am J Pathol* **146**: 1287–1301.
- Ganju RK, Brubaker SA, Meyer J, Dutt P, Yang Y, Qin S, Newman W, Groopman JE (1998). The alpha-chemokine, stromal cell-derived factor-1alpha, binds to the transmembrane G-protein-coupled CXCR-4 receptor and activates multiple signal transduction pathways. *J Biol Chem* **273**: 23169–23175.
- Garcia-Zepeda EA, Combadiere C, Rothenberg ME, Sarafi MN, Lavigne F, Hamid Q, Murphy PM, Luster AD (1996a). Human monocyte chemoattractant protein (MCP)-4 is a novel CC chemokine with activities on monocytes, eosinophils, and basophils induced in allergic and nonallergic inflammation that signals through the CC chemokine receptors (CCR)-2 and -3. *J Immunol* **157**: 5613–5626.
- Garcia-Zepeda EA, Rothenberg ME, Ownbey RT, Celestin J, Leder P, Luster AD (1996b). Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. *Nat Med* **2**: 449–456.
- Gerszten RE, Mach F, Sauty A, Rosenzweig A, Luster AD (2000). Chemokines, leukocytes, and atherosclerosis. *J Lab Clin Med* **136**: 87–92.
- Giger RJ, Urquhart ER, Gillespie SKH, Levengood DV, Ginty DD, Kolodkin AL (1998). Neuropilin-2 is a receptor for semaphorin IV: insight into the structural basis of receptor function and specificity. *Neuron* **21**: 1079–1092.
- Glabinski AR, Ransohoff RM (1999). Chemokines and chemokine receptors in CNS pathology. *J NeuroVirol* **5**: 3–12.
- Godiska R, Chantry D, Dietsch GN, Gray PW (1995). Chemokine expression in murine experimental allergic encephalomyelitis. *J Neuroimmunol* **58**: 167–176.
- Gong JH, Ratkay LG, Waterfield JD, Clark-Lewis I (1997). An antagonist of monocyte chemoattractant protein 1 (MCP-1) inhibits arthritis in the MRL-lpr mouse model. *J Exp Med* **186**: 131–137.
- Gray GE, Leber SM, Sanes JR (1990). Migratory patterns of clonally related cells in the developing central nervous system. *Experientia* **46**: 929–940.
- Gregory WA, Edmondson JC, Hatten ME, Mason CA (1988). Cytology and neuron-glia apposition of migrating cerebellar granule cells in vitro. *J Neurosci* **8**: 1728–1934.
- Grimm MC, Pullman WE, Bennett GM, Sullivan PJ, Pavli P, Doe WF (1995). Direct evidence of monocyte recruitment to inflammatory bowel disease mucosa. *J Gastroenterol Hepatol* **10**: 387–395.
- Gu L, Rutledge B, Fiorillo J, Ernst C, Grewal I, Flavell R, Gladue R, Rollins B (1997). In vivo properties of monocyte chemoattractant protein-1. *J Leukoc Biol* **62**: 577–580.
- Halks-Miller M, Hesselgesser J, Miko IJ, Horuk R (1997). Chemokine receptors in developing human brain. *Methods Enzymol* **288**: 27–38.
- Harada A, Sekido N, Akahoshi T, Wada T, Mukaida N, Matsushima K (1994). Essential involvement of interleukin-8 (IL-8) in acute inflammation. *J Leukoc Biol* **56**: 559–564.
- Harris H (1954). Role of chemotaxis in inflammation. *Physiol Rev* **34**: 529–562.
- Harrison JK, Jiang Y, Chen S, Xia Y, Maciejewski D, McNamara RK, Streit WJ, Salafraanca MN, Adhikari S, Thompson DA, Botti P, Bacon KB, Feng L (1998). Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. *Proc Natl Acad Sci USA* **95**: 10896–10901.
- Hatten ME (1999). Central nervous system neuronal migration. *Ann Rev Neurosci* **22**: 511–539.
- He Z, Tessier-Lavigne M (1997). Neuropilin is a receptor for the axonal chemorepellent semaphorin III. *Cell* **90**: 739–751.
- Hesselgesser J, Halks-Miller M, DelVecchio V, Peiper SC, Hoxie J, Kolson DL, Taub D, Horuk R (1997). CD4-independent association between HIV-1 gp120 and CXCR4: functional chemokine receptors are expressed in human neurons. *Curr Biol* **7**: 112–121.
- Hesselgesser J, Horuk R (1999). Chemokine and chemokine receptor expression in the central nervous system. *J NeuroVirol* **5**: 13–26.
- Hesselgesser J, Taub D, Baskar P, Greenberg M, Hoxie J, Kolson DL, Horuk R (1998). Neuronal apoptosis induced

- by HIV-1 gp120 and the chemokine SDF-1 alpha is mediated by the chemokine receptor CXCR4. *Curr Biol* **8**: 595–598.
- Horuk R (1999). Chemokine receptors and HIV-1: the fusion of two major research fields. *Immunol Today* **20**: 89–94.
- Horuk R, Martin AW, Wang Z, Schweitzer L, Gerassimides A, Guo H, Lu Z, Hesselgesser J, Perez HD, Kim J, Parker J, Hadley TJ, Peiper SC (1997). Expression of chemokine receptors by subsets of neurons in the central nervous system. *J Immunol* **158**: 2882–2890.
- Hu H (1999). Chemorepulsion of neuronal migration by Slit2 in the developing mammalian forebrain. *Neuron* **23**: 703–711.
- Hvas J, McLean C, Justesen J, Kannourakis G, Steinman L, Oksenberg J, Bernard C (1997). Perivascular T-cells express the proinflammatory chemokine RANTES mRNA in multiple sclerosis lesions. *Scand J Immunol* **46**: 195–203.
- Hwang SB (1990). Specific receptors of platelet-activating factor, receptor heterogeneity, and signal transduction mechanisms. *J Lipid Mediat* **2**: 123–158.
- Igarashi M, Strittmatter SM, Vartanian T, Fishman MC (1993). G Protein mediation of signals that cause growth cone collapse. *Science* **259**: 77–79.
- Imai T, Hieshima K, Haskell C, Baba M, Nagira M, Nishimura M, Kakizaki M, Takagi S, Nomiyama H, Schall TJ, Yoshie O (1997). Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell* **91**: 521–530.
- Izikson L, Klein RS, Luster AD, Weiner HL (2002). Targeting monocyte recruitment in CNS autoimmune disease. *Clin Immunol* **103**: 125–131.
- Jung S, Littman DR (1999). Chemokine receptors in lymphoid organ homeostasis. *Curr Opin Immunol* **11**: 319–325.
- Karpus WJ (1999). Chemokine regulation of inflammatory-mediated nervous system diseases. *J Neuro Virol* **5**: 1–2.
- Karpus WJ, Lukacs NW, McRae BL, Strieter RM, Kunkel SL, Miller SD (1995). An important role for the chemokine macrophage inflammatory protein-1 alpha in the pathogenesis of the T cell-mediated autoimmune disease, experimental autoimmune encephalomyelitis. *J Immunol* **155**: 5003–5010.
- Keino-Masu K, Masu M, Hinck L, Leonardo ED, Chan SS, Culotti JG, Tessier-Lavigne M (1996). Deleted in Colorectal Cancer (DCC) encodes a netrin receptor. *Cell* **87**: 175–185.
- Kennedy TE, Serafini T, de la Torre JR, Tessier-Lavigne M (1994). Netrins are diffusible chemotropic factors for commissural axons in the embryonic spinal cord. *Cell* **78**: 425–435.
- Kidd T, Bland KS, Goodman CS (1999). Slit is the midline repellent for the robo receptor in *Drosophila*. *Cell* **96**: 785–794.
- Kidd T, Brose K, Mitchell KJ, Fetter RD, Tessier-Lavigne M, Goodman CS, Tear G (1998). Roundabout controls axon crossing of the CNS midline and defines a novel subfamily of evolutionarily conserved guidance receptors. *Cell* **92**: 205–215.
- Kindt RM, Lander AD (1995). Pertussis toxin specifically inhibits growth cone guidance by a mechanism independent of direct G protein inactivation. *Neuron* **15**: 79–88.
- Kledal TN, Rosenkilde MM, Coulin F, Simmons G, Johnsen AH, Alouani S, Power CA, Lutichau HR, Gerstoft J, Clapham PR, Clark-Lewis I, Wells TNC, Schwartz TW (1997). A broad-spectrum chemokine antagonist encoded by Kaposi's sarcoma-associated herpesvirus. *Science* **277**: 1656–1659.
- Klein PS, Fontana D, Knox B, Theibert A, Devreotes PA (1985). cAMP receptors controlling cell-cell interactions in the development of *Dictyostelium*. *Cold Spring Harbor Symp Quant Biol* **50**: 787–799.
- Klein PS, Sun TJ, Saxe CL 3d, Kimmel AR, Johnson RL, Devreotes PN (1988). A chemoattractant receptor controls development in *Dictyostelium discoideum*. *Science* **241**: 1467–1472.
- Klein RS, Rubin JB, Gibson HD, DeHaan EN, Alvarez-Hernandez X, Segal RA, Luster AD (2001). SDF-1 alpha induces chemotaxis and enhances Sonic hedgehog-induced proliferation of cerebellar granule cells. *Development* **128**: 1971–1981.
- Koch AE, Kunkel SL, Harlow LA, Johnson B, Evanoff HL, Haines GK, Burdick MD, Pope RM, Strieter RM (1992a). Enhanced production of monocyte chemoattractant protein-1 in rheumatoid arthritis. *J Clin Invest* **90**: 772–779.
- Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, Elner SG, Strieter RM (1992b). Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* **258**: 1798–1801.
- Kolodkin AL, Levengood DV, Rowe EG, Tai Y-T, Giger RJ, Ginty DD (1997). Neuropilin is a semaphorin III receptor. *Cell* **90**: 753–762.
- Kondo T, Novick AC, Toma H, Fairchild RL (1996). Induction of chemokine gene expression during allogeneic skin graft rejection. *Transplantation* **61**: 1750–1757.
- Kuang Y, Wu Y, Jiang H, Wu D (1996). Selective G protein coupling by C-C chemokine receptors. *J Biol Chem* **271**: 3975–3978.
- Lassman H (1999). Lymphocyte trafficking in the central nervous system. In: *From basic immunology to immune mediated demyelination*. Martino G, Adorini L (eds). Springer-Verlag: Milan, Italy.
- Lalani AS, Masters J, Zeng W, Barrett J, Pannu, Everett H, Arendt CW, MaFadden G (1999). Use of chemokine receptors by poxviruses. *Science* **286**: 1968–1971.
- Lauffenburger DA, Horwitz AF (1996). Cell migration: a physically integrated molecular process. *Cell* **84**: 359–369.
- Lawrence DA, Kim D (2000). Central/peripheral nervous system and immune responses. *Toxicology* **142**: 189–201.
- Leonardo ED, Hinck L, Masu M, Keino-Masu K, Ackerman SL, Tessier-Lavigne M (1997). Vertebrate homologues of *C. elegans* UNC-5 are candidate netrin receptors. *Nature* **386**: 833–838.
- Leung-Hagesteijn C, Spence AM, Stern BD, Zhou Y, Su MW, Hedgecock EM, Culotti JG (1992). UNC-5, a transmembrane protein with immunoglobulin and thrombospondin type 1 domains, guides cell and pioneer axon migrations in *C. elegans*. *Cell* **71**: 289–299.
- Li HS, Chen JH, Wu W, Fagaly T, Yuan WL, Zhou L, Dupuis S, Jiang Z, Nash W, Gick C, Ornitz D, Wu JY, Rao Y (1999). Vertebrate Slit, a secreted ligand for the transmembrane protein roundabout, is a repellent for olfactory bulb axons. *Cell* **96**: 807–818.

- Locati M, Murphy PM (1999). Chemokines and chemokine receptors: biology and clinical relevance in inflammation and AIDS. *Annu Rev Med* **50**: 425–440.
- Luster AD (1998). Chemokines—chemotactic cytokines that mediate inflammation. *N Engl J Med* **338**: 436–445.
- Luster AD (2001). Antichemokine immunotherapy for allergic diseases. *Curr Opin Allergy Clin Immunol* **1**: 561–567.
- Luster AD (2002). The role of chemokines in linking innate and adaptive immunity. *Curr Opin Immunol* **14**: 129–135.
- Mackay CR (1996). Chemokine receptors and T cell chemotaxis. *J Exp Med* **184**: 799–802.
- Mashikian MV, Ryan TC, Seman A, Brazer W, Center DM, Cruikshank WW (1999). Reciprocal desensitization of CCR5 and CD4 is mediated by IL-16 and macrophage-inflammatory protein-1 beta, respectively. *J Immunol* **163**: 3123–3130.
- McCluskey LP, Lampson LA. Local neurochemicals and site specific immune regulation in the CNS. *J Neuropathol Exp Neurol* **59**: 177–187.
- McCutcheon M (1946). Chemotaxis in leukocytes. *Physiol Rev* **26**: 319–336.
- Melchers F, Rolink AG, Schaneil C (1999). The role of chemokines in regulating cell migration during humoral immune responses. *Cell* **99**: 351–354.
- Mellado M, Rodriguez-Frade JM, Vila-Coro AJ, de Ana AM, Martinez AC (1999). Chemokine control of HIV-1 infection. *Nature* **400**: 723–724.
- Mennicken F, Maki R, de Souza EB, Quirion R (1999). Chemokines and chemokine receptors in the CNS: a possible role in neuroinflammation and patterning. *Trends Pharmacol Sci* **20**: 73–78.
- Meucci O, Fatatis A, Simen AA, Bushell TJ, Gray PW, Miller RJ (1998). Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. *Proc Natl Acad Sci USA* **95**: 14500–14505.
- Meucci O, Fatatis A, Simen AA, Miller RJ (2000). Expression of CX3CR1 chemokine receptors on neurons and their role in neuronal survival. *Proc Natl Acad Sci USA* **97**: 8075–8080.
- Mitchison TJ, Cramer LP (1996). Actin-based cell motility and cell locomotion. *Cell* **84**: 371–379.
- Miyagishi R, Kikuchi S, Fukazawa T, Tashiro K (1995). Macrophage inflammatory protein-1 $\alpha$  in the cerebrospinal fluid of patients with multiple sclerosis and other inflammatory neurological diseases. *J Neurol Sci* **129**: 223–227.
- Mohle R, Bautz F, Rafii S, Moore MA, Brugger W, Kanz L (1998). The chemokine receptor CXCR-4 is expressed on CD34+ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced by stromal cell-derived factor-1. *Blood* **91**: 4523–4530.
- Montell DJ (1999). The genetics of cell migration in *Drosophila melanogaster* and *Caenorhabditis elegans* development. *Development* **126**: 3035–3046.
- Moore BB, Arenberg DA, Addison CL, Keane MP, Strieter RM (1998). Tumor angiogenesis is regulated by CXC chemokines. *J Lab Clin Med* **132**: 97–103.
- Mueller B (1999). Growth cone guidance: first steps towards a deeper understanding. *Annu Rev Neurosci* **22**: 351–388.
- Murphy PM (1994). The molecular biology of leukocyte chemoattractant receptors. *Annu Rev Immunol* **12**: 593–633.
- Nelken NA, Coughlin SR, Gordon D, Wilcox JN (1991). Monocyte chemoattractant protein-1 in human atherosclerotic plaques. *J Clin Invest* **88**: 1121–1127.
- Nelson PJ, Krensky AM (1998). Chemokines, lymphocytes and viruses: what goes around, comes around. *Curr Opin Immunol* **10**: 265–270.
- Neptune ER, Bourne HR (1997). Receptors induce chemotaxis by releasing the  $\beta$ g subunit of Gi, not by activating Gq or Gs. *Proc Natl Acad Sci USA* **94**: 14489–14494.
- Neptune ER, Iiri T, Bourne HR (1999). Gai is not required for chemotaxis mediated by Gi-coupled receptors. *J Biol Chem* **274**: 2824–2828.
- Nguyen Ba-Charvet KT, Brose K, Marillat V, Kidd T, Goodman CS, Tessier-Lavigne M, Sotelo C, Chédotal A (1999). Slit2-mediated chemorepulsion and collapse of developing forebrain axons. *Neuron* **22**: 463–473.
- Nieto M, Frade JM, Sancho D, Mellado M, Martinez AC, Sanchez-Madrid F (1997). Polarization of chemokine receptors to the leading edge during lymphocyte chemotaxis. *J Exp Med* **186**: 153–158.
- Nusslein-Volhard C, Wieschaus E, Kluding H (1984). Mutations affecting the pattern of the larval cuticle in *Drosophila melanogaster*. I. Zygotic loci on the second chromosome. *Roux's Arch Dev Biol* **193**: 267–282.
- Oberlin E, Amara A, Bachelier F, Bessia C, Virelizier JL, Arenzana-Seisdedos F, Schwartz O, Heard JM, Clark-Lewis I, Legler DF, Loetscher M, Baggiolini M, Moser B (1996). The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. *Nature* **382**: 833–835.
- Parent CA, Devreotes PN (1996). Molecular genetics of signal transduction in *Dictyostelium*. *Annu Rev Biochem* **65**: 411–440.
- Parent CA, Devreotes PN (1999). A cell's sense of direction. *Science* **284**: 765–770.
- Pattison J, Nelson PJ, Huie P, von Leutthar I, Farshid G, Sibley RK, Krensky AM (1994). RANTES chemokine expression in cell-mediated transplant rejection of the kidney. *Lancet* **343**: 209–211.
- Pearlman AL, Faust PL, Hatten ME, Brunstrom JE (1998). New directions for neuronal migration. *Curr Opin Neurobiol* **8**: 45–54.
- Püschel AW (1999). Divergent properties of mouse netrins. *Mech Dev* **83**: 65–75.
- Rakic P (1971a). Neuron-glia relationship during granule cell migration in developing cerebellar cortex. *J Comp Neurol* **141**: 283–312.
- Rakic P (1971b). Guidance of neurons migrating to the fetal monkey neocortex. *Brain Res* **33**: 471–476.
- Rakic P (1972). Mode of cell migration to the superficial layers of fetal monkey neocortex. *J Comp Neurol* **145**: 61–84.
- Rakic P (1988). Specification of cerebral cortical areas. *Science* **241**: 170–176.
- Rakic P (1990). Principles of neural cell migration. *Experientia* **46**: 882–891.
- Rakic P (1995). Radial versus tangential migration of neuronal clones in the developing cerebral cortex. *Proc Natl Acad Sci USA* **92**: 11323–11327.
- Ramsey WS (1972). Analysis of individual leukocyte behavior during chemotaxis. *Exp Cell Res* **70**: 129–139.
- Ransohoff RM, Hamilton TA, Tani M, Stoler MH, Shick HE, Major JA, Estes ML, Thomas DM, Tuohy VK (1993). Astrocyte expression of mRNA encoding cytokines



- IP-10 and JE/MCP-1 in experimental autoimmune encephalomyelitis. *FASEB J* **7**: 592–600.
- Raper JA, Tessier-Lavigne M (1999). Growth cones and axon pathfinding. In: *Fundamentals of neuroscience*. Zigmond M, et al (eds). Academic Press: New York, pp 519–546.
- Rice DS, Sheldon M, D'Arcangelo G, Nakajima K, Goldowitz D, Curran T (1998). Disabled-1 acts downstream of Reelin in a signaling pathway that controls laminar organization in the mammalian brain. *Development* **125**: 3719–3729.
- Rio C, Rieff HI, Qi P, Corfas G (1997). Neuregulin and erbB receptors play a critical role in neuronal migration. *Neuron* **19**: 39–50.
- Rodriguez-Frade JM, Vila-Coro AJ, Martin A, Nieto M, Sanchez-Madrid F, Proudfoot AE, Wells TN, Martinez AC, Mellado M (1999). Similarities and differences in RANTES- and (AOP)-RANTES-triggered signals: implications for chemotaxis. *J Cell Biol* **144**: 755–765.
- Rollins BJ (1997). Chemokines. *Blood* **90**: 909–928.
- Rothberg JM, Hartley DA, Walther Z, Artavanis-Tsakonas S (1988). Slit: an EGF-homologous locus of *D. melanogaster* involved in the development of the embryonic central nervous system. *Cell* **55**: 1047–1059.
- Rothberg JM, Jacob JR, Goodman CS, Artavanis-Tsakonas S (1990). Slit: an extracellular protein necessary for the development of midline glia and commissural axon pathways contains both EGF and LRR domains. *Genes Dev* **4**: 2169–2187.
- Sanchez-Madrid F, Angel del Pozo M (1999). Leukocyte polarization in cell migration and immune interactions. *EMBO J* **18**: 501–511.
- Schmidtmayerova H, Sherry B, Bukrinsky M (1996). Chemokines and HIV replication. *Nature* **382**: 767.
- Segeer S, Nelson PJ, Schlondorff D (2000). Chemokines, chemokine receptors, and renal disease: from basic science to pathophysiologic and therapeutic studies. *J Am Soc Nephrol* **11**: 152–176.
- Servant G, Weiner OD, Neptune ER, Sedat JW, Bourne HR (1999). Dynamics of a chemoattractant receptor in living neutrophils during chemotaxis. *Mol Biol Cell* **10**: 1163–1178.
- Sharpe RJ, Byers HR, Scott CF, Bauer SI, Maione TE (1990). Growth inhibition of murine melanoma and human colon carcinoma by recombinant human platelet factor 4. *J Natl Cancer Inst* **82**: 848–853.
- Simmons G, Clapham PR, Picard L, Offord RE, Rosenkilde MM, Schwartz TW, Buser R, Wells TNC, Proudfoot AE (1997). Potent inhibition of HIV-1 infectivity in macrophages and lymphocytes by a novel CCR5 antagonist. *Science* **276**: 276–279.
- Smith CA, Smith TD, Smolak PJ, Friend D, Hagen H, Gerhart M, Park L, Pickup DJ, Torrance D, Mohler K, Schooley K, Goodwin, RG (1997). Poxvirus genomes encode a secreted, soluble protein that preferentially inhibits beta chemokine activity yet lacks sequence homology to known chemokine receptors. *Virology* **236**: 316–327.
- Smith DR, Polverini PJ, Kunkel SL, Orringer MB, Whyte RI, Burdick MD, Wilke CA, Strieter RM (1994). Inhibition of interleukin 8 attenuates angiogenesis in bronchogenic carcinoma. *J Exp Med* **179**: 1409–1415.
- Springer TA (1994). Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* **76**: 301–314.
- Strebblow DN, Soderberg-Naucler C, Vieira J, Smith P, Wakabayashi E, Ruchti F, Mattison K, Altschuler Y, Nelson JA (1999). The human cytomegalovirus chemokine receptor US28 mediates vascular smooth muscle cell migration. *Cell* **99**: 511–520.
- Strieter RM, Polverini PJ, Arenberg DA, Walz A, Opdenakker G, Van Damme J, Kunkel SL (1995). Role of C-X-C chemokines as regulators of angiogenesis in lung cancer. *J Leukoc Biol* **57**: 752–762.
- Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, Kitamura Y, Matsushima K, Yoshida N, Nishikawa S, Kishimoto T, Nagasawa T (1998). The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. *Nature* **393**: 591–594.
- Takahashi T, Fournier A, Nakamura F, Wang L-H, Murakami Y, Kalb RG, Fujisawa H, Strittmatter SM (1999). Plexin-neuropilin-1 complexes form functional semaphorin-3A receptors. *Cell* **99**: 59–69.
- Tamagnone L, Artigiani S, Chen H, He Z, Ming G-I, Song H-J, Chedotal A, Winberg ML, Goodman CS, Poo M-M, Tessier-Lavigne M, Comoglio PM (1999). Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates. *Cell* **99**: 71–80.
- Tessier-Lavigne M, Goodman CS (1996). The molecular biology of axon guidance. *Science* **274**: 1123–1133.
- Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, Hammer RE, Richardson JA, Herz J (1999). Reeler/Disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell* **97**: 689–701.
- Walsh C, Cepko C (1988). Clonally related cortical cells show several migration patterns. *Science* **241**: 1342–1345.
- Walsh C, Cepko C (1990). Widespread dispersion of neuronal clones across functional regions of the cerebral cortex. *Science* **255**: 434–440.
- Wang H, Copeland NG, Gilbert DJ, Jenkins NA, Tessier-Lavigne M (1999a). Netrin-3, a mouse homolog of human NTN2L, is highly expressed in sensory ganglia and shows differential binding to netrin receptors. *J Neurosci* **19**: 4938–4947.
- Wang KH, Brose K, Arnott D, Kidd T, Goodman CS, Henzel W, Tessier-Lavigne M (1999b). Purification of an axon elongation- and branch-promoting activity from brain identifies a mammalian Slit protein as a positive regulator of sensory axon growth. *Cell* **96**: 771–784.
- Wang JM, Oppenheim JJ (1999). Interference with the signaling capacity of CC chemokine receptor 5 can compromise its role as an HIV-1 entry coreceptor in primary T lymphocytes. *J Exp Med* **190**: 591–595.
- Ward SG, Bacon K, Westwick J (1998). Chemokines and T lymphocytes: more than an attraction. *Immunity* **9**: 1–11.
- Winberg ML, Noordermeer JN, Tamagnone L, Comoglio PM, Spriggs MK, Tessier-Lavigne M, Goodman CS (1998). Plexin A is a neuronal semaphorin receptor that controls axon guidance. *Cell* **95**: 903–916.
- Wong K, Ren X-R, Huang Y-Z, Xie Y, Liu G, Saito H, Tang H, Wen L, Brady-Kalnay SM, Mei L, Wu JY, Xiong W-C, Rao Y (2001). Signal transduction in neuronal migration: Roles of GTPase activating proteins and the small GTPase Cdc42 in the Slit-Robo pathway. *Cell* **107**: 209–221.

- Wong K, Wu JY, Rao Y (2002a). Neuronal migration. In *Encyclopedia of life sciences*. New York: Nature Publishing Group. In press.
- Wong K, Park H-T, Wu JY, Rao Y (2002b). Slit proteins: guidance cues for cells ranging from neurons to leukocytes. *Curr Op Genet Dev* **12**: 583–591.
- Wu JY, Feng L, Park HT, Havlioglu N, Wen L, Tang H, Bacon K, Jiang Z, Zhang X, Rao Y (2001). The neuronal repellent slit inhibits leukocyte chemotaxis induced by chemotactic factors. *Nature* **410**: 948–952.
- Wu W, Wong K, Chen JH, Jiang ZH, Dupuis S, Wu JY, Rao Y (1999). Directional guidance of neuronal migration in the olfactory system by the secreted protein Slit. *Nature* **400**: 331–336.
- Xia MQ, Hyman BT (1999). Chemokines/chemokine receptors in the central nervous system and Alzheimer's disease. *J NeuroVirol* **5**: 32–41.
- Yla-Herttuala S, Lipton BA, Rosenfeld ME, Sarkioja T, Yoshimura T, Leonard EJ, Witztum JL, Steinberg D (1991). Expression of monocyte chemoattractant protein 1 in macrophage-rich areas of human and rabbit atherosclerotic lesions. *Proc Natl Acad Sci USA* **88**: 5252–5256.
- Yuan W, Zhou L, Chen J, Wu JY, Rao Y, Ornitz D (1999). The mouse Slit family: secreted ligands for Robo expressed in patterns that suggest a role in morphogenesis and axon guidance. *Dev Biol* **212**: 290–306.
- Zallen JA, Yi BA, Bargmann CI (1998). The conserved immunoglobulin superfamily member SAX-3/Robo directs multiple aspects of axon guidance in *C. elegans*. *Cell* **92**: 217–227.
- Zhu Y, Li HS, Zhou L, Wu JY, Rao Y (1999). Cellular and molecular guidance of GABAergic neuronal migration from the striatum to the neocortex. *Neuron* **23**: 473–485.
- Zhu Y, Yu T, Zhang X, Nagasawa T, Wu JY, Rao Y (2002). Role of the Chemokine SDF-1 as the meningeal attractant for embryonic cerebellar neurons. *Nature Neurosci* **5**: 719–720.
- Zigmond SH (1974). Mechanisms of sensing chemical gradients by polymorphonuclear leukocytes. *Nature* **249**: 450–452.
- Zou YR, Kottmann AH, Kuroda M, Taniuchi I, Littman DR (1998). Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature* **393**: 595–599.