

## **Acknowledgements**

I wish to express my sincere thanks to Messers. Shoji Fukusumi, Ryo Fujii, and Yuji Kawamata, and Drs. Yugo Habata, Yoshihiro Ishibashi, Susumu Honda, Chieko Kitada, Tsutomu Kurokawa, Haruo Onda, Yasuhiro Sumino, Osamu Nishimura, and Masahiko Fujino for their helpful advice and collaboration, and to Dr. Shuji Hinuma for reviewing this manuscript.

## References

- Bohlen, P., Brazeau, P., Benoit, R., Ling, N., Esch, F. and Guillemin, R. (1980) Isolation and amino acid composition of two somatostatin-like peptides from ovine hypothalamus: somatostatin-28 and somatostatin-25. *Biochem. Biophys. Res. Commun.* **96**, 725-734.
- Buck, L. and Axel, R. (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* **65**, 175-187.
- Choe, H., Farzan, M., Konkel, M., Martin, K., Sun, Y., Marcon, L., Cayabyab, M., Berman, M., Dorf, M.E., Gerard, N., Gerard, G. and Sodroski, J (1998) The orphan seven-transmembrane receptor apj supports the entry of primary T-cell-line tropic and dualtropic human immunodeficiency virus type 1. *J. Virol.* **72**, 6113-6118.
- Edinger, A.L., Hoffman, T.L., Sharron, M., Lee, B., Yi, Y., Choe, W., Kolson, D.L., Mitrovic, B., Zhou, Y., Faulds, D., Collman, R.D., Hesselgesser, J., Horuk, R. and Doms, R.W. (1998) An orphan seven-transmembrane domain receptor expressed widely in the brain functions as a coreceptor for human immunodeficiency virus type 1 and simian immunodeficiency virus. *J. Virol.* **72**, 7934-7940.
- Farzan, M., Choe, H., Vaca, L., Martin, K., Sun, Y., Desjardins, E., Huffing, N., Wu, L., Waytt, R., Gerard, N., Gerard, C. and Sodroski, J. (1998) A tyrosine-rich region in the N terminus of CCR5 is important for human immunodeficiency virus type 1 entry and mediates an association between gp120 and CCR5. *J. Virol.* **72**: 1160-1164.

Habata, Y., Kawamata, Y., Fujii, R., Hosoya, M., Fukusumi, S., Hinuma, S., Kitada, C., Kurokawa, T., Murosaki, S., Nishimura, O., Onda, H., Sumino, Y., Tatemoto, K. and Fujino, M. (1999) Apelin, the natural ligand of the orphan receptor APJ, is abundantly secreted in the colostrum. *Biochim. Biophys. Acta* **1452**, 25-35.

Himmelweit, F. (1960) The Collected Papers of Paul Ehrlich. Ed. and compiled by Himmelweit F, Vol. III, Chemotherapy. Pergamon Press (London).

Hinuma, S., Habata, Y., Fujii, R., Kawamata, Y., Hosoya, M., Fukusumi, S., Kitada, C., Masuo, Y., Asano, T., Matsumoto, H., Sekiguchi, M., Kurokawa, T., Nishimura, O., Onda, H., Fujino, M. (1998) A prolactin-releasing peptide in the brain. *Nature* **393**, 272-276.

Hinuma, S., Hosoya, M., Ogi, K., Tanaka, H., Nagai, Y. and Onda, H. (1994) Molecular cloning and functional expression of a human thyrotropin-releasing hormone (TRH) receptor gene. *Biochim. Biophys. Acta* **1219**, 251-259.

Hoffman, T.L., Stephens, E.B., Narayan, O. and Doms, R.W. (1998) HIV type I envelope determinants for use of the CCR2b, CCR3, STRL33, and APJ coreceptors. *Proc. Natl. Acad. Sci. USA* **95**, 11360-11365.

Lee, D.K., Cheng, R., Nguyen, T., Fan, T., Kariyawasam, A.P., Liu, Y., Osmond, D.H., George, S. and O'Dowd, D.F. (2000) Characterization of apelin, the ligand for the APJ receptor. *J. Neurochem.* **74**, 34-41.

Matsumoto, M., Hidaka, K., Akiho, H., Tsuda, S., Okada, M. and Yamaguchi, T. (1996) Low stringency hybridization study of the dopamine D4 receptor revealed D4-like mRNA distribution of the orphan

seven-transmembrane receptor, APJ in human brain. *Neurosci. Lett.* **219**, 119-122.

McConnel, H.M., Owicki, J.C., Perce, J.W., Miller, O.L., Baxter, C.T., Wada, H.G. and Pitchford, S. (1992) The cytosensor microphysiometer: biological applications of silicon technology. *Science* **257**, 1905-1912.

Meunier, J.-C., Mollereau, C., Toll, L., Saudeau, C., Moisand, C., Alvinerie, P., Butour, J.-L., Guillmot, J.-C., Ferrara, P., Monsarrat, B., Mazarguil, H., H., Vassart, G., Parmentier, M., Constatin, J. (1995) Isolation and structure of the endogenous agonist of opioid receptor-like ORL<sub>1</sub> receptor. *Nature* **377**, 532-535.

Neve, K.A., Rosser, M.P. and Barber, D.L. (1995) Regulation of Na<sup>+</sup>-H<sup>+</sup> exchange by G protein-coupled receptors. *Meth. Neurosci.* **25**, 225-241.

O'Dowd, B.F., Heiber, M., Chan., A., Heng, H.H.Q., Tsui, L.-C., Kennedy, J.L., Shi, X., Petronis, A., George, S.R. and Nguyen, T. (1993) A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene* **136**, 355-360.

Ohtaki, T., Watanabe, T., Ishibashi, Y., Kitada, C., Tsuda, M., Gottschall, P.E., Arimura, A. and Fujino, M. (1990) Molecular identification of receptor for pituitary adenylate cyclase activating polypeptide. *Biochem. Biophys. Res. Commun.* **171**, 838-844.

Probst, W.C., Synder, L.A., Scuster, D.I., Brosius, J., Sealfon S.C. (1992) Sequence alignment of the G-protein coupled receptor superfamily. *DNA Cell Biol.* **11**, 1-20.

Reinscheid, R.K., Nothacker, H.P., Bourson, A., Ardati, A., Henningsen,

- R.A., Bunzow, J.R., Grandy, D.K., Langen, H., Monsma Jr., F.J., Civelli, O. (1995) Orphanin FQ: A neuropeptide that activates an opioid-like G protein-coupled receptor. *Science* **270**, 792-794.
- Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R.M., Tanaka, H., Williams, S.C., Richardson, J.A., Kozlowski, G.P., Wilson, S., Arch, J.R.S., Buckingham, R.E., Haynes, A.C., Carr, S.A., Annan, R.S., McNulty, D.E., Liu, W.-S., Terrell, J.A., Elshourbagy, N.A., Bergsma, D.J. and Yanagisawa, M. (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein coupled receptors that regulate feeding behavior. *Cell* **92**, 573-585.
- Scatchard, G. (1949) The attractions of proteins for small molecules and ions. *Ann. N.Y. Acad. Sci.* **51**, 660-672.
- Stadel, J.M., Wilson, S., Bergsma, D.J. (1997) Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery. *Trends Pharmacol. Sci.* **18**, 430-437.
- Strosberg, A.D. (1991) Structure/function relationship of proteins belonging to the family of receptors coupled to GTP-binding proteins. *Eur. J. Biochem.* **196**, 1-10.
- Tatemoto, K., Hosoya, M., Habata, Y., Fujii, R., Kakegawa, T., Zou, M.-X., Kawamata, Y., Fukusumi, S., Hinuma, S., Kitada, C., Kurokawa, T., Onda, H., Fujino, M. (1998) Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem. Biophys. Res. Commun.* **251**, 471-476.
- Wilson, S., Bergsma, D.J., Chamber, J.K., Muir, A.I., Fantom, K.G.M., Ellis, C., Murdock, P.R., Herrity, N.C., Stadel, J.M. (1998) Orphan G-protein

coupled receptors: the next generation of drug target? *Brit. J. Pharmacol.* **125**, 1387-1392.

Zou, Y.-R., Kottmann, A. H., Kuroda, M., Taniuchi, I. and Littman, D.R. (1998) Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature* **393**, 595-599.