Explor. Anim. Med. Res., Vol. 1, Issue - 2, 2012. p- 104-111

CD14 GENE AS A CANDIDATE GENE FOR IMMUNOMODULATION : A REVIEW

Aruna Pal[1], P.N. Chatterjee[2],U.K. Karmakar[3], Sanjoy Datta[4] and A.K. Saren[5]

INTRODUCTION :

Incidences of diseases of milch animals is critical to dairy industry imparting havoc economic thrust in terms of veterinary and treatment costs, reduced milk production in the subsequent lactation, milk disposal due to antibiotic residues, early culling, extra labour involvement and detoriation in milk quality. In order to avoid such circumstances, animals are conventionally treated with antibiotics or vaccinated against the particular disease. But with the emergence of antibiotic resistant organisms, milk disposal due to its residual effect to the end consumers, worldwide concern for organic food production and ethical considerations of sufferings of animals has limited the antibiotic therapy.

Vaccination has also not been proved to be hundred percent efficient against the diseases of multietiological factors specially against diseases involving high morbidity rate. Thus, it seems understanding and subsequent manipulation of the host immune response (immune-modulation) is the most precise and effective tool to lower down the disease incidences and to nullify the limitations associated with antibiotic treatment or vaccination.

The host defense system (immunity) is categorically of two type *i.e.* non-specific or innate immunity and specific immunity. Host immune response represents a highly regulated yet integrated interaction between different types of cells that respond to eliminate the foreign invaders (pathogens). It is the expression of the self for its own well being carried out via an array of several interacting molecules. CD (Cluster of Differentiation) molecules are one such group, conferring self-defense to the host against various pathogens. They are mostly found on various differentiated cell type or types present in the body. CD molecules ranges from 1 to 166 with differential structure and functions (Goldsby *et al.* 2000), of these CD14 is the most important molecule known so far, playing a vital role against several endotoxigenic bacteria.

CD14 molecule :

Cluster of differentiation (CD) molecules are the markers on the cell surface, as recognized by specific sets of antibodies, used to identify the cell type, stage of differentiation and activity of a cell. The CD nomenclature was proposed and established in International Workshop and Conference on Human

[1] *Veterinary Officer, Block Animal Health Centre, Dubrajpur, Birbhum, West Bengal, India.*

[2] *Veterinary Officer, Block Animal Health Centre, Khoirasole, Birbhum, West Bengal, India.*

[3] *Veterinary Officer, ABAHC Dubrajpur, Birbhum, West Bengal, India.*

[4] *Veterinary Officer, ABAHC, Mirik, Darjelling, West Bengal. India.*

[5] *Veterinary Officer, Additional Block Animal Health Centre, Khoirasole. Birbhum, West Bengal. India.*

Leukocyte Differentiation Antigens (HLDA), which was held in Paris in 1982. This system was intended for the classification of many monoclonal antibodies (mAbs), generated by different laboratories around the world, against various surface molecules (antigens) on leukocytes (white blood cells). Since then, the use has expanded to many other cell types and more than 250 CD clusters and sub-clusters have been identified (Annon 2006b). CD14 molecule is considered as 'pattern recognition molecule' in the innate immune response against microorganisms and other exogenous and endogenous stress factors. In human, CD molecules range from 1 to 235 (Annon 2006b).

CD14, an anti bacterial peptide, binds and neutralizes bacterial endotoxins. It is also known as 'myeloid membrane glycoprotein precursor' or 'LPS receptor' and acts as an important mediator of innate immunity. It has been classified as 'pattern recognition receptor', which binds LPS (Lipo-polysaccharide) on gram-negative bacteria such as *E. coli*, Neisseria and Salmonella etc. facilitating the destruction of microbes and induction for secretion of cytokines involved in triggering adaptive immune response (Tizzard 1998). CD14 is a phospho-inositol-glycan linked cell surface receptor on macrophages that binds to LPS. The core carbohydrate and lipidA of LPS are virtually the same for these microbes and hence become the target site for binding by CD14. LPS can not act directly on cell by itself, rather binds to CD14, a plasma protein that is also found on neutrophils and monocytes. Each CD14 molecule binds one or two LPS molecules, which is catalyzed by LBP (Lipo-polysaccharide Binding Protein). Once it binds with lipoproteins, the toxic activities of LPS get lost. Apart from LPS, CD14 also binds to lipoarabinomannans of Mycobacteria, to manuronic acid polymers of *Pseudomonas sp.* and to peptidoglycans of *Staphylococcus aureus*. It is assumed to play a key role in septic shock by interacting with mononuclear phagocytes and stimulating the macrophages to secrete pro-inflammatory cytokines, IL-1, IL-6, IL-12, TNF, several reactive oxygen species, nitrogen metabolites and arachidonic acid metabolites including leukotrienes and prostaglandins, which in turn destroy the pathogens (Tizzard 1998).The polypeptide CD14 is of 40.076 kDa in human, where as in bovine it is 46 kDa. The mature CD14 membrane protein is composed of 356 amino acids with 4 sites for N-linked glycosylation. Additional 19 amino acid sequences are removed during processing. CD14 is anchored to the cell surface by linking with glycosyl-phosphatidyl-inositol (Wright 2006).

CD14 acts as a receptor for both LPS (Lipopolysacchaide) and peptidoglycan, two of the most abundant constituents in the bacterial cell wall. CD14 functions both as a cell membrane receptor and a soluble receptor for bacterial LPS. It has been reported to bind to apoptotic cells (Deviit *et al.* 1998) and phospholipids (Wang *et al.* 1998). CD14 functions as a receptor for endotoxin (LPS) (Wright *et al.* 1990). LPS binds to LBP which facilitates the binding of LPS to CD14 (Hailman *et al.* 1994).

Structure of CD14 molecule :

The primary structure of the bovine CD14 protein deduced from the DNA sequence consists of 374 amino acids. The first is methionine, followed by a stretch of 15 hydrophobic and/or neutral residues, typical of eukaryotic signal peptides. Alignment of the amino acid sequences of bovine CD14 with human and mouse CD14 reveals 73.1% and 62.3% identity, respectively (Julius *et al.* 2002). The polypeptide CD14 is 40.076 kDa in human, whereas it is 46 kDa in bovine. In human, the mature CD14 membrane protein is composed of 356 amino acids with 4 sites for N-linked glycosylation. An additional 19 amino acid sequence is removed during processing. CD14 is anchored to the cell surface by linkage to glycosyl-phosphatidyl-inositol (Wright 2006).

Crystal structure of CD14 depicts a large hydrophobic pocket on the N-terminal side of the horse-

Table 1 : Different species with isolated CD14 cDNA and genomic DNA

Species	Gene Bank Accession Number	Reference
Human (*Homo sapiens*)	NM_000591	Ferrero and Goyert, 1988
Mice (*Mus musculus*)	NM_009841	Matsuura *et al.*, 1989
Rat (*Rattus norvegicus*)	NP 068512	Choi and Lee, 2004
Cattle (*Bos taurus*)	NM_174008	Pal *et al.* 2006c, Pal *et al.* 2006d, Diamond *et al.* 1996
Sheep (*Ovies aries*)	AY289201	Steele *et al.*, 2003
Monkey (*Pan troglodytes*)	XP_517975	NCBI
Goat (*Capra hircus*)	DQ457090	Pal *et al.* 2006
Buffalo (*Bubalus bubalis*)	DQ444324	Pal *et al.* 2006a
	DQ457089.	Pal *et al.* 2006b
	EU370404	Pal and Chatterjee 2008
	GU368103	Pal and Chatterjee 2010
Dog (*Canis familiaris*)	XP_848746	NCBI

CD14 gene have been characterized in *Homo sapiens* (Ferroro and Goyert 1988), *Mus musculus* (Matsuura *et al.* 1989), *Rattus norvegicus* (Choi and Lee 2004), *Bos taurus* (Wang *et al.* 2002), Bubalus bubalis (Pal *et al.* 2008a), *Capra hircus* (Pal and Chatterjee 2009), crossbred cattle (*Bos taurus* X *Bos indicus*, *Pal et al. 2011*) and *Canis familiaris* (Gene bank Accesion no. XP_848746). Molecular characterization of CD14 gene first time evaluated in buffalo by Pal *et al.* (2006a & b), in goat (Pal *et al.* 2006) and also in crossbred cattle (Pal *et al.* 2006, Pal *et al.* 2011).

shoe like structure. Regions involved in the lipo-polysaccharide binding map to the rim and bottom of the pocket indicating that the main component of the lipo-polysaccharide binding site. Mutations that interfere with lipo-polysaccharide signaling but not with lipo-polysaccharide binding, are also clustered in a separate area near the pocket. Ligand diversity of CD14 could be explained by the rim of the pocket, the considerable flexibility of the rim of the pocket and the multiplicity of grooves available for ligand binding (Kim *et al.* 2005).

At least two soluble forms of CD14 (sCD14) have been described. One soluble form is produced by shedding from the cell surface, which results in an approximately 48 kDa molecule (Bazil *et al.* 1986 & 1991, Hazoit *et al.* 1988 & 1993). A second soluble form is released from cells before addition of the GPI anchor at C-terminus, resulting in higher mo-

lecular weight (Bufler *et al*. 1995). CD14 is a member of the family of leucine rich proteins, with 10 leucine rich repeat motifs (LXXLXL), common to both human and mouse CD14 (Ferrero *et al.* 1990). First crystal structure of CD14 to 2.5 A0 resolution has been identified (Kim *et al.* 2005).

Genetic characterization of CD14 gene :

Structure of CD14 gene:

CD14 gene has been explored in various mammalian species including nucleotide sequencing of genomic DNA and mRNA.

Chromosomal localization:

CD14 gene has been mapped at various chromosome locations in different species. It has been found on Chromosome 18 in mouse (Ferrero *et al.* 1990) and rat. But in human and monkey, it is located in chromosome 5. In bovine, it is mapped on chromosome no. 7 (Gautier et al. 2003). In case of dog, CD14 gene is mapped on chromosome number 2 (Gene card 2009).

Phylogenetic analysis of CD14 gene :

Crossbred cattle CD14 gene is 98.1, 96.0, 94.7, 90.5, 81.5, 81.1, 78.2, 78.1, 76.5, 70.6, 68.5, 59.3, 11.0% identical to cattle(exotic, *Bos taurus*), buffalo, sheep, goat, pig, horse, human, dog, rabbit, mouse, rat, monkey, chicken CD14 gene (Pal *et al.* 2011). Phylogenetic analysis reveals that cattle are genetically most similar to buffalo, followed by sheep and goat (Pal *et al.* 2011, Pal and Chatterjee 2009).

CD14 gene and its application in immuno-modulation :

Characterization of CD14 gene is useful in various ways of immuno-modulation-

I. Recombinant protein as antibacterial substance against disease.

II. Transgenic animal production with CD14 gene insert.

III. Somatic gene therapy against diseases.

IV. CD14 gene - used in marker assisted selection.

I. Recombinant protein as antibacterial substance against disease:

The recombinant protein obtained from the phenotypically resistant variety of CD14 gene, may be of therapeutic use against a wide range of diseases. Recombinant CD14 may be incorporated into infant through feeding or incorporating CD14 as part of a vaccination along with antigen. Recombinant protein may also be administered to a patient having T-cell immune deficiency and may also be used in preparation of medicines for activating B-cells (Julius *et al.* 2002).

II. Transgenic animal production with CD14 gene insert :

Transgenic animals may also be produced with the genetically resistant variant fragment of CD14 gene, to enhance disease resistance. The cloned gene for CD14 can also be approached for somatic gene therapy where, intramammary inoculation of CD14 gene construct may prove its worth against mastitis (McBride 2002). Till now transgenic animals against CD14 gene could not be produced, however studies are in progress. Transgenic mice expressing recombinant CD14 from cows have been produced by ARS scientists Bob Wall. They will be challenged with *E. coli* to see the worth of CD14 in mastitis prevention. Eventually, bioengineered cows could be developed with immunity to mastitis (McBride 2002). However, a transgenic cow with bacterial gene insert of lysostaphin has been developed and is claimed to be the first transgenic cow resistant to mastitis (Suszkiw 2001).

III. Somatic gene therapy against diseases :

Somatic gene therapy with the gene inserted in the tissue can be done with the aim of production of protein locally, thus may be helpful for treating the disease. The cloned gene for CD14 was designed and inserted into a cow's mammary gland, so that the protein was secreted only in milk. A delivery system for insertion of CD14 gene construct through intramammary route for the prevention of mastitis is in progress (McBride 2002).

In vivo transfection of mammary gland for the production of high value protein against the pathogens known to be responsible for mastitis, had been found to be effective and foreign protein production into milk was observed 60 days after in vivo transfection into lactating mammary gland of ewes with plasmid DNA (Gagne *et al.* 1997).

IV. CD14 gene - used in marker assisted selection :

Most of the economically important traits of livestock are complex, continuously distributed phenotypes, influenced by environment and multiple polygenes, remain dispersed across the genome. Recent advances in molecular genetics have provided rational basis for the expeditious improvement in complex production traits. Thus, the immune response genes especially the CD14 gene may be exploited for the benefit of mankind. The variability at the nucleotide level of CD14 gene leads to the variability in the CD14 encoded molecule, which in turn gives rise to the phenotypic variability in host immune response. CD14 has been considered as an important candidate gene for its association with various diseases, like mastitis (Lee *et al.* 2003) in dairy animals, treponemiasis (Schroder *et al.* 2000) and glomerulo-nephritis (Yoon *et al.* 2003). Genetic polymorphism study for CD14 gene has been carried out for the first time in any farm animal by us.

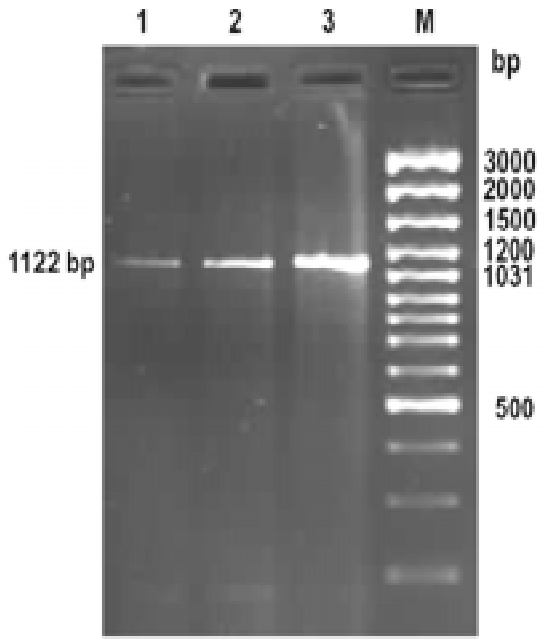

Fig 1: Molecular characterization of CD14 gene in goat depicted in 1% agarose gel electrophoresis. Lane 1, 2, 3 represents amplified product of caprine CD14 gene.
(Source: Pal et al. 2009. Journal of Small Ruminant Research. 82: 84-87)

PCR-SSCP study on CD14 gene has been carried out in buffalo, where eight variants have been identified (Pal *et al.* 2008b, Pal and chatterjee 2006, Pal and chatterjee 2010 Gen bank accession no. EU370398 to EU370403). Association of these variants with economic traits may lead to establishment of marker. Thus, the variants of CD14 gene and their association with the incidences of disease occurrence may be used as a marker for disease resistance. Similar association studies have been conducted with other genes as growth hormone gene (Pal *et al.* 2004, Pal *et al.* 2005).This nucleotide variation can be diagnosed by RFLP/SSCP assay and the markers associated with these quantitative trait loci can be applied as an alternative selection strategy for augmenting disease resistance trait. This is of prime importance for the cases where the traits of interest have

low heritability, difficult to measure and/or expressed late in life. Marker assisted selection (MAS) allows to select the individuals at an early age, independent of its sex. Besides, it also yields a rapid genetic progress than other conventional methods and yet remains sustainable.

With the recent molecular techniques it can be exploited as a therapeutic agent (recombinant product or DNA construct), development of disease resistant transgenics and strategic breeding practises (MAS).

CONCLUSION :

CD14 gene is an important gene for immunomodulation. CD14 molecule and CD14 gene has been characterized in various livestock species. Structural analysis of CD14 molecule and CD14 gene encoding it is helpful for understanding its function for immuno-modulation. CD14 gene has been observed to be highly variable both between and within species, which may be helpful for biodiversity and evolutionary studies. There is a need to ascertain the differential biological potency of different allelic variations of CD14. On the basis of such functional study, the most potent variant can be expressed in vitro for further therapeutic/immunological or immune-competence study. Future scope includes disease resistant transgenic animal production with resistant variety of CD14 gene insert and somatic gene therapy. Marker assisted selection may be helpful for a breeder for selection of disease resistant animals at an early age. The above methods need to be commercialized and applied in field conditions for the ultimate benefit to the farmers.

REFERENCES :

Annonymous.(2005).Gene card for protein coding CD14. GC05M139991. http://genecards.bcgsc.ca

Annonymous. (2006b). www.wikipedia.org/wiki/cluster of differentiation.

Bazil V and Strominger JL. (1991). Shedding as a mechanism of down modulation of CD14 on stimulated human monocytes. J.Immunol. 147:1567-1574.

Bazil V, Horejsi V, Baudys M, Kristofova H, Stromingerm JL, Kostka W and Hilgert I. (1986). Biochemical characterization of a soluble form of the 53 kDa monocyte surface antigen. Eur.J.Immonol. 16: 1583-1589.

Bufler P, Stiegler G, Schuchmann M, Hess S, Kruger C, Stelter F, Eckerskorn C, Schutt C and Engelmann H. (1995). Soluble lipopolysaccharide receptor (CD14) is released via two different mechanisms from human monocytes and CD14 transfectants. Eur. J. Immunol. 25: 604.

Choi HC and Lee KY. (2004). CD14 glycoprotein expressed in vascular smooth muscle cells. J. Pharmacol. Sci. 95 (1): 65-70.

Deviit A, Moffa OD, Raykundalia C, Capra JD, Simmons DL and Gregory CD. (1998). Human CD14 mediates recognition and phagocytosis of apoptotic cells. Nature. 392: 505-509.

Diamond G, Russel JP and Bevins CL. (1996). Inducible expression of an antibiotic peptide gene in lipopolysaccharide-challenged tracheal epithelial cells. J. Proc. Natl. Acad. Sci. U.S.A. 93 (10): 5156-5160.

Ferrero E and Goyert SM. (1988). Nucleotide sequence of the gene encoding the monocyte differentiation antigen, CD14. J. Nucleic Acids Res. 16 (9): 4173.

Ferrero E and Goyert SM. (1988). Nucleotide sequence of the gene encoding the monocyte differentiation antigen. CD14. J. Nucleic Acids Res. 16 (9): 4173.

Ferrero E, Hsieh CL, Francke U and Goyert SM. (1990). CD14 is a member of the family of leucine rich proteins and is encoded by a gene syntenic with multiple receptor genes. J.Immunol. 145(1): 331-336.

Gagne M, Chapdelaine P, Therrienet J and Gagne

D. (1997). Genetically treated animals. Immunova Inc. Cessionnaire. Can. Pat. PCT/CA96/00297.

Gautier M, Hayes H, Bonsdorff T and Eggen A. (2003). Development of a comprehensive comparative radiation map of bovine chromosome 7 (BTA7) versus human chromosomes 1 (HSA1), 5 (HSA5) and 19 (HSA19). Cytogenetic and Genome Research. 102: 25-31.

Goldsby RA, Kindt TJ and Osborne BA. (2000). Kuby Immunology. 4th edn. W.H. Freeman and Company. New York.

Hailman E, Lichenstein HS, Wurfel MM, Miller DS, Johmson DA, Kelley M, Busse LA, Zukowski MM and Wright SD. (1994). Lipopolysaccharide (LPS) binding protein accelerates the binding of LPS to CD14. J. Exp. Med. 179: 269-277.

Hazoit A, Chen S, Ferrero E, Los MG, Silber R and Goyert SM. (1988). The monocyte differentiation antigen, CD14 is anchored to the cell membrane by a phosphatidylinositol linkage. J.Immunol. 141 : 547-552.

Hazoit A, Tsuberi B and Goyert SM. (1993). Neutrophil CD14: Biochemical properties and role in the secretion of tumor necrosis factor-alpha in response to lipopolysaccharide. J.Immunol. 150: 5556-5565.

Julius MH, Fillip D and Khiavi KA. (2002). Bovine lactation associated immunotropic protein (CD14) encoding gene and its application in the B cell activation. Patent: JP 2001504695-A.

Kim JI, Lee CJ, Jin MS, Lee CH, Paik SG, Lee H and Lee JO. (2005). Crystal structure of CD14 and its implication for lipopolysaccharide signalling. J.Biol.Chem. 280(12): 11347-11351.

Kim JI, Lee CJ, Jin MS, Lee CH, Paik SG, Lee H and Lee JO. (2005). Crystal structure of CD14 and its implication for lipopolysaccharide signalling. J.Biol.Chem. 280(12): 11347-11351.

Lee JW, Paape MJ, Elsasser TH and Zhao X. (2003). Recombinant soluble CD14 reduces severity of intramammary infection by *E.coli*. Infection and Immunity. 71(7): 4034-4039.

Matsuura K, Setoguchi M, Nasu N, Higuchi Y, Yoshida S, Akizuki S and Yamamoto S. (1989). Nucleotide and amino acid sequences of the mouse CD14 gene. J. Nucleic Acids Res. 17 (5): 2132.

McBride J. (2002). An udder solution for Bossie's woes. Agriculture Research Magazine - Vol. 50. No. 6. http://www.ars.usda.gov/is/AR/archive/jun02/udder0602.htm

NCBI. (2006). www.ncbi.nlm.nih.gov

Pal A, Sharma A and Chatterjee PN and Bhattacharya TK. (2006a). Bubalus bubalis CD14 (CD14) gene, exon 2 and partial cds.Gene sequence Accession No. DQ444324. http://www.ncbi.nlm.nih.gov

Pal A, Sharma A and Chatterjee PN. (2006b). Bubalus bubalis CD14 (CD14) mRNA, complete cds. Gene sequence Accession No. DQ457089. http://www.ncbi.nlm.nih.gov

Pal A and Chatterjee PN.(2008). Bubalus bubalis CD14 (CD14) mRNA, partial cds. Gene sequence Accession no. EU370404. http://www. ncbi. nlm. nih.gov

Pal A and Chatterjee PN. (2010). Bubalus bubalis breed Murrah myeloid membrane glycoprotein precursor (CD14) mRNA, partial cds. Gene sequence Accession no. GU368103. http://www.ncbi.nlm.nih.gov

Pal A and Chatterjee PN. (2010). *Bos taurus* x *Bos indicus* myeloid membrane glycoprotein precursor (CD14) mRNA. complete cds. Gene sequence Accession no. GU368102. http://www.ncbi.nlm.nih.gov

Pal A Chatterjee PN and Bhattacharya TK. (2006). Capra hircus CD14 mRNA. complete cds. Gene sequence Accession No. DQ457090. http://www.ncbi.nlm.nih.gov

Pal A and Chatterjee PN. (2006). *Bos taurus* CD14 gene Exon-2, partial cds. Molecular Characterization of CD 14 gene in crossbred cattle. Gene se-

quence Accession No. DQ457091. http:// www.ncbi.nlm.nih. gov

Pal A, Sharma A, Bhattacharya TK and Chatterjee PN. (2008). Detection of single nucleotide polymorphism of CD14gene in *Bubalus bubalis* by PCR-SSCP. 96th Indian Science Congress, Shillong.

Pal A, Sharma A and Bhattacharya TK. (2008). Molecular characterization of CD14 cDNA in *Bubalus bubalis* and *Capra hircus*. Conference on Development of Dairy cattle. NDRI. Eastern Regional station.

Pal A and Chatterjee PN.(2009). Molecular cloning and characterization of CD14 gene in goat. J. Small Ruminant Res. 82: 84-87.

Pal A, Sharma A and Chatterjee PN. (2011). Molecular cloning and characterization of CD 14 gene in crossbred cattle. Molecular Biology International. Article ID 507346. 13 pages 2011. doi:10.4061/ 2011/507346

Pal A, Chakravarty AK, Bhattacharya TK, Joshi BK and Sharma A.(2004). Detection of Polymorphism of growth hormone gene for the analysis of relationship between allele type and growth traits in Karan Fries cattle. Asian Aust. J. Anim. Sci. 17(9):1334-1337.

Pal A, Chakravarty AK, Bhattacharya TK and Sharma A.(2005). Polymorphism of growth hormone gene and its association with expected milk production traits in dairy bulls. J. Applied Animal research. 27(9):29-33.

Schroder NW, Opitz B, Lamping N, Michelsen KS, Zahringer U, Gobel UB and Schumann RR. (2000). Involvement of lipo-polysaccharide binding protein, CD14 and Toll-like receptors in the initiation of innate immune responses by Treponema glycolipids. J. Immunol. 165 (5): 2683-2693.

Steele B, Daniel JA and Sartin JL. (2003). Anatomy, Physiology and Pharmacology, Auburn University. Auburn. AL 36849. USA. (Direct submission 02 May, 2003).

Suszkiw. (2001). Scientist develop first transgenic cow clone for mastitis disease resistance. US Department of Agriculture. University of Vermont www.ars.usda.gov

Tizzard, IR. (1998). Veterinary Immunology-An Introduction. 5th edn. Harcourt Brace and Company Asia PTE Ltd. USA.

Wang P, Kitchens R, and Munford R. (1998). Phosphatidyl inositides bind to plasma membrane CD14 and can prevent monocyte activation by bacterial lipo-polysaccharide. J. Biol. Chem. 273: 24309-24313.

Wang Y, Zarlenga DS, Paape MJ and Dahl GE.(2002). Recombinant bovine soluble CD14 sensitizes the mammary gland to lipo-polysaccharide. Vet. Immunopathol. 86: 115-124.

Wright SD. (2006). Protein reviews on the web. http://mpr.nci.nih.gov/PROW/ncbi

Yoon HJ, Shim JH, Yang SH, Chae DW, Kim H, Lee DS, Kim HL, Kim S, Lee JS and Kim YS. (2003). Association of the CD14 gene -159 polymorphism with progression of IgA nephropathy. J.Med.Genet. 40 (2):104-108.