Paracrine and endocrine actions of interferon tau (IFNT)

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Abstract

This review focuses on the paracrine and endocrine actions of interferon tau (IFNT) during pregnancy recognition and establishment in ruminants. Pregnancy recognition involves the suppression of the endometrial luteolytic mechanism by the conceptus to maintain progesterone production by the corpus luteum (CL). The paracrine antiluteolytic effects of conceptus-derived IFNT inhibit upregulation of oxytocin receptors in the endometrial epithelia of the uterus, thereby preventing the production of luteolytic prostaglandin F2 alpha (PGF2 α) pulses. In the endometrium, IFNT induces or upregulates a large number of classical IFN-stimulated genes (ISGs) and regulates expression of many other genes in a cell-specific manner that are likely important for conceptus elongation, implantation and establishment of pregnancy. Further, IFNT has endocrine effects on extrauterine cells and tissues. In sheep, IFNT induces luteal resistance to PGF2 α , thereby ensuring survival of the CL for maintenance of pregnancy. The ISGs induced in circulating peripheral blood mononuclear cells by IFNT may also be useful as an indicator of pregnancy status in cattle. An increased knowledge of IFNT and ISGs is important to improve the reproductive efficiency in ruminants.

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Introduction

In domestic ruminants, establishment of pregnancy requires pregnancy recognition signaling followed by implantation and placentation (Guillomot *et al.* 1993, Guillomot 1995, Spencer *et al.* 2004b, 2007, 2008). On days 4–6 post mating, the morula-stage embryo enters the uterus and then forms a blastocyst with an inner cell mass and a blastocoele or central cavity surrounded by a monolayer of trophectoderm cells. Following hatching from the zona pellucida, the blastocyst develops into an ovoid and then tubular conceptus that begins to elongate on day 12 (sheep) or day 15 (cattle) into a filamentous form that eventually occupies the entire length of the uterine horn. Elongation of the conceptus is critical for the production of interferon tau (IFNT), the pregnancy recognition signal, and implantation (Farin *et al.* 1989, Guillomot *et al.* 1990, Gray *et al.* 2002). Proliferation of mononuclear trophoblast cells (Wang *et al.* 2009) primarily drives exponential increases in length of the trophectoderm during conceptus elongation (Wales & Cuneo 1989).

Although blastocysts can be developed entirely *in vitro*, the efficiency and resulting quality is markedly lower than that *in vivo* (Hasler *et al.* 1995). Indeed, a

blastocyst must be transferred into the uterus for it to develop into an elongated filamentous type conceptus (Heyman *et al.* 1984, Flechon *et al.* 1986, Maddox-Hyttell *et al.* 2003). Indeed, the epithelia of the uterus produce embryotrophic factors in response to progesterone that stimulate blastocyst growth and conceptus elongation (Bazer *et al.* 2011, Lonergan *et al.* 2015, Spencer & Hansen 2015, Spencer *et al.* 2016).

Pregnancy recognition: paracrine antiluteolytic effects of IFNT

Maternal recognition of pregnancy can be defined as the physiological process whereby the conceptus signals its presence to the maternal system and prolongs the lifespan of the ovarian corpus luteum (CL) (Bazer *et al.* 1991). This process in ruminants requires that the conceptus elongate to produce sufficient IFNT to signal pregnancy recognition and suppress development of the endometrial luteolytic mechanism (Spencer *et al.* 1996b, Roberts *et al.* 1999, 2008b, Spencer & Bazer 2002). The antiluteolytic effects of IFNT on the endometrium maintain CL function and thus secretion of progesterone, which is essential for conceptus growth and development throughout pregnancy.

Endometrial luteolytic mechanism

Ruminants (sheep, cattle, goats) are spontaneous ovulators that have uterine-dependent oestrus cycles, because the endometrium is the source of the luteolysin, prostaglandin F₂ alpha (PGF₂α) (Wathes & Lamming 1995, McCracken *et al.* 1999, Spencer & Bazer 2002). At the end of the oestrus cycle, the endometrium produces and releases luteolytic pulses of PGF₂α in response to oxytocin that cause functional and structural regression of the CL, a process termed luteolysis. In sheep, the source of luteolytic PGF₂α pulses is the endometrial luminal epithelium (LE) (Gray *et al.* 2000), because those cells express the oxytocin receptor (OXTR) (Wathes & Lamming 1995) and prostaglandin-endoperoxide synthase 2 (PTGS2), an essential enzyme in PG synthesis (Charpigny *et al.* 1997, Simmons *et al.* 2010). Both OXTR and PTGS2 are required for the synthesis and secretion of luteolytic PGF₂α.

As summarized in Fig. 1 for sheep, the luteolytic mechanism of the endometrial LE involves progesterone, oestrogen and oxytocin and their respective receptors (McCracken *et al.* 1984, Spencer *et al.* 1996b, Spencer & Bazer 2002). At oestrus (day 0), oestrogen from ovarian antral follicle(s) increase estrogen receptor alpha (ESR1), progesterone receptor (PGR) and OXTR expression in the endometrium (Wathes & Hamon 1993, Spencer & Bazer 1995); however, the endometrium does not release PGF₂α as a CL is not present to produce oxytocin (OXT). During early diestrus, the newly formed CL produces progesterone that stimulates the accumulation of phospholipids in LE of the uterus, and those phospholipids serve as a source of arachidonic acid for PG synthesis. Progesterone levels then increase and act via PGR to inhibit or 'block' the expression of ESR1 and OXTR in the endometrial LE (McCracken *et al.* 1984). As a result, ESR1 and OXTR expression is not detectable during most of dioestrus (days 5–11). Continuous exposure of the uterus to progesterone for 8–10 days downregulates PGR expression in endometrial LE after day 10 (Spencer *et al.* 1995b), allowing for rapid increases in ESR1 expression on days 12 and 13 followed by OXTR on day 14 in cyclic and nonpregnant ewes (Hixon & Flint 1987, Spencer *et al.* 1995a). The promoter of the ovine OXTR gene contains several SP1 elements that mediate responsiveness to ligand-activated ESR1 (Fleming *et al.* 2006). PTGS2 expression is also upregulated between days 10 and 12 post-oestrus/mating (Charpigny *et al.* 1997, Simmons *et al.* 2010). Oxytocin begins to be secreted from the posterior pituitary and/or CL beginning on day 9 of the oestrus cycle and pregnancy, and it acts on OXTR in the endometrial LE to induce production and release of luteolytic PGF₂α pulses between days 14 and 16 (Wathes & Lamming 1995). As a result, the CL regresses, thereby allowing for the ewe to complete the 17-day oestrus cycle and return to oestrus. The timing of the

Figure 1 Schematic illustrating hormonal regulation of the endometrial luteolytic mechanism and antiluteolytic paracrine effects of conceptus interferon tau (IFNT) on the ovine uterine endometrium. During oestrus and metestrus, expression of oxytocin receptors (OXTR) by uterine luminal and superficial ductal glandular epithelia (LE) increase in response to estrogens from the ovarian follicles that first stimulate the expression of estrogen receptor alpha (ESR1) and estrogens act via ESR1 to increase OXTR. Progesterone receptors (PGR) are expressed by LE during metestrus and diestrus, but low systemic levels of progesterone are insufficient to act via PGR to suppress ESR1 and OXTR gene expression. During early diestrus, endometrial ESR1 and oestrogen are low, but progesterone levels begin to increase with formation of the corpus luteum (CL). Progesterone acts through the PGR to suppress ESR1 and OXTR synthesis for 8–10 days. Continuous exposure of the endometrium to progesterone eventually downregulates PGR gene expression in the endometrial LE by days 11–12 of the oestrus cycle. The loss of PGR terminates the progesterone block to ESR1 and OXTR formation. Thus, ESR1 appears between days 11 and 12 post-oestrus, which is closely followed by increases in OXTR on days 13 and 14. The increase in OXTR expression is facilitated by increasing the secretion of estrogens by ovarian follicles. In both cyclic and pregnant ewes, oxytocin is released from the posterior pituitary and ovarian corpus luteum beginning on Day 9. In cyclic ewes, OXT binds to OXTR on LE and increases the release of luteolytic pulses of prostaglandin F₂α (PGF₂α) to regress the CL through a PTGS2-dependent pathway. In pregnant ewes, IFNT is synthesized and secreted by the elongating conceptus beginning on Day 10 of pregnancy. IFNT binds to type I IFN receptors (IFNAR) on the endometrial LE and inhibits transcription of the ESR1 gene through a signaling pathway involving interferon regulatory factor two (IRF2). These antiluteolytic actions of IFNT on the ESR1 gene prevent OXTR formation, thereby maintaining the CL and progesterone production required for establishment and maintenance of pregnancy. E2, estradiol; ESR1, estrogen receptor alpha; IFNAR, type I IFN receptor; IFNT, interferon tau; IRF2, interferon regulatory factor two; OXT, oxytocin; OXTR, oxytocin receptor; P4, progesterone; PGF, prostaglandin F₂α; PGR, progesterone receptor; PTGS2, prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase).

PGR downregulation by progesterone determines when the luteolytic mechanism develops in the endometrium in both sheep and cattle (Woody *et al.* 1967, Garrett *et al.* 1988, Morgan *et al.* 1993). Thus, progesterone

first suppresses and then induces the development of the endometrial luteolytic mechanism in cyclic ewes. In cattle, oxytocin may have a more modulatory and auxiliary role in luteolysis, as opposed to the mandatory role for oxytocin in sheep (Hansel & Blair 1996, Kotwica *et al.* 1997, Binelli *et al.* 2000).

Pregnancy recognition and IFNT

Embryo transfer experiments initially defined the maternal recognition of pregnancy period in sheep (Moor *et al.* 1969). Moor and Rowson found that a sheep conceptus must be present in the uterus by days 12 or 13 of the cycle in order for a successful pregnancy to be obtained following embryo transfer (Moor & Rowson 1966a,b). Removal of the conceptus from the uterus before day 13 had no effect on oestrus cycle length, whereas removal after day 13 extended CL lifespan past day 17. Similar experiments were conducted in cattle (Betteridge *et al.* 1978). Those studies defined that maternal recognition of pregnancy occurs on days 12–13 in sheep and days 16–17 in cattle and involves a product(s) of the conceptus.

Accordingly, a combination of *in vitro* and *in vivo* experiments resulted in the purification of the pregnancy recognition signal IFNT and discovery that it is a type I IFN and the exclusive antiluteolytic factor secreted by the ruminant conceptus (Roberts *et al.* 2008a, Bazer *et al.* 2015). IFNT is expressed specifically by the mononuclear trophoblast cells of the conceptus and peaks around day 15 (sheep) and day 20 (cattle) (Godkin *et al.* 1984b, Farin *et al.* 1989, Guillomot *et al.* 1990). Although low amounts of IFNT can be detected from day 8 or 10 blastocysts in sheep (Ashworth & Bazer 1989), production of IFNT is maximal by the elongating conceptus on days 14–16 and then declines to undetectable levels by day 25 (Bazer *et al.* 1992, Roberts *et al.* 1999). Thus, IFNT production by the conceptus is initiated prior to the formation of OXTR in the endometrial epithelium in cyclic or nonpregnant ewes and cows.

Antiluteolytic paracrine effects of IFNT

Research in sheep established that IFNT is the antiluteolytic factor produced by the conceptus that inhibits the development of the endometrial luteolytic mechanism (Vallet *et al.* 1988b). Intrauterine injections of purified or recombinant ovine (ro) IFNT into sheep (Godkin *et al.* 1984b, Vallet *et al.* 1988b, Ott *et al.* 1993), cattle (Knickerbocker *et al.* 1986a,b, Thatcher *et al.* 1986, Meyer *et al.* 1995, Thatcher *et al.* 2001) and goats (Newton *et al.* 1996) abrogated development of the endometrial luteolytic mechanism and extended CL lifespan.

The majority of studies on the cellular and molecular effects of IFNT as a pregnancy recognition signal have involved sheep (Fig. 1). A series of *in vivo* studies found that IFNT does not act to affect PGR expression in the endometrial epithelium during pregnancy (Spencer & Bazer 1995, 1996, Spencer *et al.* 1995b). Rather, IFNT acts in a paracrine fashion on endometrial LE to suppress transcription of the ESR1 and OXTR genes (Spencer & Bazer 1996, Spencer *et al.* 1996a, Fleming *et al.* 2001). The increases in ESR1 and OXTR gene expression detected in the uterine LE on days 11–17 post-oestrus in cyclic or nonpregnant sheep do not occur in pregnant sheep (Spencer & Bazer 1995) or in cyclic sheep infused with roIFNT (Spencer *et al.* 1995c). By inhibiting OXTR expression, IFNT prevents the production of luteolytic pulses of PGF2 α by the endometrium. Of note, IFNT does not inhibit basal production of PGF2 α , which is higher in pregnant than cyclic ewes; further, the conceptus and IFNT do not inhibit PTGS2 gene expression or activity in the endometrial LE (Charpigny *et al.* 1997, Kim *et al.* 2003b, Simmons *et al.* 2010, Dorniak *et al.* 2011). Thus, the antiluteolytic actions of IFNT are to prevent the increases in epithelial ESR1 and OXTR gene expression, which are oestrogen responsive, by directly inhibiting transcription of the ESR1 gene. The cellular and molecular mechanisms involved in IFNT inhibitory actions on the ovine ESR1 gene are not fully known, but appears to involve IFN regulatory factor two (IRF2) (Fleming *et al.* 2001). Of note, IFNT can not inhibit OXTR expression once it is initiated in the endometrial epithelium (Vallet & Bazer 1989).

Similar to sheep, PGR decline to undetectable levels in the endometrial LE of both cyclic and pregnant cattle by day 13 post-oestrus, and OXTR do not develop in endometrial LE of pregnant as in cyclic or nonpregnant cattle after day 16 post-oestrus (Robinson *et al.* 1999, Okumu *et al.* 2010). In contrast to sheep, little or no change in ESR1 expression was observed in the uterine epithelia of pregnant as compared to nonpregnant cattle (Robinson *et al.* 1999). Thus, pregnancy and IFNT can inhibit OXTR expression independent of ESR1 in the endometrium of cattle. IRF2 also regulates the expression of the bovine OXTR gene (Telgmann *et al.* 2003), suggesting a common role of IRF2 in the antiluteolytic actions of IFNT on the endometrium to establish pregnancy. The absence of OXTR in the endometrium prevents the release of luteolytic pulses of PGF2 α by the endometrium (Thatcher *et al.* 1989, Spencer *et al.* 2007). However, IFNT does not inhibit expression of PTGS2, which is important for the generation of prostaglandins that regulate endometrial function and conceptus elongation during early pregnancy in sheep (Dorniak *et al.* 2011) and likely cattle (Spencer *et al.* 2013, Ribeiro *et al.* 2016).

Paracrine actions of IFNT to regulate conceptus elongation- and implantation-related genes in the endometrium

Interferon tau is the only known IFN to act as a pregnancy recognition signal in ruminants, but IFNs or ISGs may have a biological role in establishment of pregnancy in other species including mice and humans (Hansen *et al.* 1999, Bazer *et al.* 2009a). The paracrine actions of IFNT on the endometrium stimulates expression of ISGs in the endometrium of both sheep and cattle that are hypothesized to regulate uterine functions important for conceptus elongation, implantation and establishment of pregnancy (Hansen *et al.* 1999, Spencer *et al.* 2008, Bazer *et al.* 2009a, Hansen *et al.* 2010). The interferon (alpha and beta) receptor (IFNAR) mediates IFNT actions (Hansen *et al.* 1989). The elongating ovine conceptus expresses IFNAR1/2 (Rosenfeld *et al.* 2002), and *in vitro* studies with ovine trophectoderm cells found that IFNT stimulates their proliferation and certain ISGs (Wang *et al.* 2013), supporting the idea that IFNT has an autocrine role in conceptus elongation. A recent *in vivo* loss-of-function study challenged that idea. In that study, translation of IFNT or IFNAR1/2 mRNAs was inhibited in the trophectoderm of the ovine conceptus using morpholino antisense oligonucleotides delivered into the uterine lumen via osmotic pumps from days 8 to 14 post mating (Brooks & Spencer 2014). Elongating and filamentous type conceptuses were recovered from day 14 ewes infused with a control morpholino or IFNAR1/2 morpholinos. In contrast, severely growth-retarded and malformed conceptuses were recovered from IFNT morpholino-infused ewes with increased numbers of apoptotic trophectoderm cells. Thus, available studies support the idea that IFNT is a critical regulator of conceptus elongation, but those effects are indirect via paracrine effects on the endometrium, which is similar to the dual roles of the human pregnancy recognition signal, chorionic gonadotropin (Banerjee & Fazleabas 2011).

Classical type I IFN-stimulated genes in the endometrium

A combination of transcriptional profiling and proteomic experiments elucidated genes stimulated or uniquely induced by IFNT in human cells, ovine endometrium, bovine endometrium and bovine peripheral blood mononuclear cells (PBMC) during early pregnancy (Hansen *et al.* 1999, Bauersachs *et al.* 2006, 2012, Spencer *et al.* 2007, 2008, Forde *et al.* 2009, 2011, Mansouri-Attia *et al.* 2009, Cerri *et al.* 2012, Forde & Lonergan 2012, Spencer & Hansen 2015, Biase *et al.* 2016). The vast bulk of genes induced or upregulated by IFNT are classical ISGs also associated with the effects of other type I IFNs, such as IFNA and IFNB, that are activated during innate immune responses to invading

pathogens (RNA viruses, DNA viruses, intracellular bacteria, parasites) (Schneider *et al.* 2014).

A archetypical ISG that responds to IFNT in early pregnant ruminants is ISG15 (ISG15 ubiquitin-like modifier, also known as ubiquitin cross-reactive protein or ISG17). On days 10 or 11 of the oestrus cycle and pregnancy in sheep, ISG15 is expressed in LE of the uterus, but disappears from the LE by days 12–13 of pregnancy (Johnson *et al.* 1999b). As the conceptus begins to elongate on day 12 and secrete more IFNT, ISG15 is upregulated in the upper stroma and GE by days 13–14, while expression extends to the lower stroma, deep glands and myometrium as well as resident immune cells of the ovine uterus by days 15–16 of pregnancy (Johnson *et al.* 1999b, 2000a). As IFNT production by the conceptus declines, expression of ISG15 in the stroma and GE also declines between days 20 and 25 of pregnancy. Similar spatiotemporal alterations in ISG15 expression occur in the bovine uterus during early pregnancy (Johnson *et al.* 1999a, Austin *et al.* 2004).

A combination of studies with bovine endometrium, ovine endometrium and human fibroblast cells found that IFNT activates the canonical janus kinase-signal transducer and activator of transcription-IFN regulatory factor (JAK-STAT-IRF) signaling pathway used by other type I IFNs (Stark *et al.* 1998). All endometrial cell types express IFNAR1 and IFNAR2 subunits in sheep (Rosenfeld *et al.* 2002); however, *in vivo* studies revealed that most classical ISGs are not induced or upregulated by IFNT in the LE of the ovine uterus during early pregnancy (Johnson *et al.* 1999b, 2001, Choi *et al.* 2001, 2003, Song *et al.* 2007). Further studies revealed that IRF2, a potent transcriptional repressor of ISGs (Taniguchi *et al.* 2001), is expressed specifically in the uterine LE and represses activity of IFN-stimulated response element (ISRE)-containing promoters (Spencer *et al.* 1998, Choi *et al.* 2001). Indeed, all components of the ISGF3 transcription factor complex (STAT1, STAT2, IRF9) and most classical ISGs (B2M, GBP2, IFI27, IFIT1, ISG15, MIC, OAS) contain one or more ISRE in their promoters. Thus, constitutive expression of IRF2 in the LE was hypothesized to restrict induction of most classical ISGs by IFNT in the stroma and GE of the uterus (Dorniak *et al.* 2013a). In endometrial LE during pregnancy, the lack of ISG induction and silencing of ISGs, such as MHC and B2M, may be a critical mechanism preventing immune rejection of the semi-allogeneic conceptus (Choi *et al.* 2003). Although type I IFNs are involved in both innate and adaptive immune responses in other species, little information is available on the role of IFNT in the immunology of the uterus and pregnancy.

A significant challenge is to determine which of the classical ISGs induced in the endometrium by IFNT have a biological role in conceptus elongation and/or establishment of pregnancy. CXCL10 (chemokine (C-X-C motif) ligand 10 or IP-10) is one classical ISG

that stimulates trophoblast growth and adhesion *in vitro* (Nagaoka *et al.* 2003a,b). Other chemokines, such as CXCL12 in sheep (Ashley *et al.* 2011) and CCL8 and CCL11 in cattle (Sakamoto *et al.* 2017), may also have a role in conceptus–endometrial interactions. Thus, it is likely that other classical ISGs have biological roles in conceptus elongation and implantation in ruminants, particularly since IFNT has embryotrophic effects mediated by the endometrium (Dorniak *et al.* 2013b, Brooks & Spencer 2015).

Non-classical IFNT-stimulated genes in the endometrium

A number of approaches, including microarray analysis of human U3A (STAT1 null) cells and ovine endometrium and *in situ* hybridization analysis, were used to discover IFNT-regulated genes in the uterine LE during pregnancy (Kim *et al.* 2003a, Song *et al.* 2005, 2006b Gray *et al.* 2006, Satterfield *et al.* 2006). In sheep, IFNT was found to stimulate the expression of a number of genes (CST3, CST6, CTSL, GRP, HSD11B1, IGFBP1, LGALS15, SLC2A1, SLC2A5, SLC5A11, SLC7A2) in the endometrial LE and (or) GE that have biological activities potentially important for conceptus elongation and implantation (Spencer *et al.* 2007, 2008) (Table 1). Of note, none of those genes are classical ISGs induced

by other type I IFNs; thus, they were referred to as ‘non-classical’ IFNT-stimulated genes. Further, those genes must be first induced by progesterone in the endometrial epithelia before IFNT can stimulate their expression. Many non-classical IFNT-stimulated genes identified to date have biological activities that implicate them in trophoblast (proliferation, migration, attachment and (or) adhesion, nutrient transport) (Spencer *et al.* 2004a, 2008, Bazer *et al.* 2011, 2012, Dorniak *et al.* 2013a) (Table 1). For example, knockdown of an amino acid transporter (SLC7A1) in the conceptus trophoblast (Wang *et al.* 2014) and inhibition of HSD11B1 activity in utero or in the conceptus trophoblast compromised conceptus elongation in sheep (Dorniak *et al.* 2013b, Brooks *et al.* 2015). Of note, IFNT actions on the bovine endometrium are not as well understood in terms of non-classical IFNT-stimulated genes, but recent transcriptomic studies have started to uncover them (Forde *et al.* 2011, 2012, Bauersachs *et al.* 2012, Lonergan & Forde 2014, Bauersachs & Wolf 2015).

Critical signaling components of the JAK-STAT signaling system (STAT1, STAT2, IRF9) are not expressed in endometrial LE (Choi *et al.* 2001). Thus, it was reasoned that IFNT regulates the expression of genes in endometrial LE of the ovine uterus using a noncanonical, STAT1-independent signaling pathway. Indeed, other type I IFNs utilize noncanonical mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) cascades (Platanias 2005). In ovine endometrium and LE cells *in vitro*, IFNT activates distinct JAK, epidermal growth factor receptor, MAPK (ERK1/2), PI3K-AKT and (or) Jun N-terminal kinase (JNK) signaling modules to regulate expression of PGE2 receptors (Banu *et al.* 2010, Lee *et al.* 2012a). Additionally, PTGS2-derived prostaglandins and HSD11B1-derived cortisol are part of the noncanonical pathway of IFNT action on the endometrium in sheep (Dorniak *et al.* 2011, 2012, Brooks *et al.* 2015). Available evidence supports the idea that combinatorial paracrine effects of IFNT, via canonical and noncanonical signaling pathways, stimulates biological processes in the endometrium that regulate conceptus elongation for the establishment of pregnancy. Future investigations should focus on understanding the biological roles of classical and non-classical IFNT-stimulated genes as well as genes downregulated by IFNT in pregnancy establishment.

IFNT and the servomechanism regulating uterine gland function in sheep

In ruminants, a servomechanism involving ovarian hormones (oestrogen and progesterone) and placental factors (IFNT and CSH1) has been proposed to regulate endometrial function during pregnancy (Spencer & Bazer 2002, Spencer *et al.* 2004c, Bazer *et al.* 2009b). In sheep, CSH1 (chorionic somatomammotrophin hormone one or placental lactogen) is produced by

Table 1 Effects of ovarian progesterone (P4) and intrauterine infusion of interferon tau (IFNT) or prostaglandins (PGs) on elongation- and implantation-related genes expressed in the endometrial epithelia of the ovine uterus^a.

Gene symbol and general function	P4	IFNT
Transport of glucose		
SLC2A1	↑	+
SLC2A5	n.d.	n.e.
SLC2A12	n.d.	+
SLC5A1	↑	+
SLC5A11	↑	+
Transport of amino acids		
SLC1A5	n.d.	n.d.
SLC7A2	↑	+
Cell proliferation, migration, attachment		
GRP	↑	+
IGFBP1	↑	+
LGALS15	↑	++
SPP1	↑	+
Proteases and their inhibitors		
CTSL	↑	++
CST3	↑	+
CST6		+
Intracellular enzymes		
HSD11B1	↑	+
PTGS2	↑	n.e. ^b
Transcription factors		
HIF1A	↑	+
HIF2A	↑	+

^aEffect of hormone or factor denoted as induction (↑), stimulation (+), no effect (n.e.), decrease (–) or not determined (n.d.).

^bNo effect (n.e.) on gene expression, but increases PTGS2 activity.

binucleate cells of the placenta beginning on days 15–16 of pregnancy, which is coordinate with the onset of expression of several progesterone-induced genes in the uterine glands that include SERPINA14 (serine peptidase inhibitor, clade A (alpha-1 antitrypsin)-like or uterine milk proteins or UTMP), SPP1 (secreted phosphoprotein 1 or osteopontin), GRP (gastrin-releasing peptide) and STC1 (stanniocalcin one) (Ing *et al.* 1989, Whitley *et al.* 1998, Stewart *et al.* 2000, Song *et al.* 2006a). The prolactin receptor, which is involved in CSH1 action, is uniquely expressed in the GE (Cassy *et al.* 1999, Stewart *et al.* 2000, Noel *et al.* 2003). Available evidence supports the idea that sequential exposure of the ovine uterus to oestrogen, progesterone, IFNT and CSH1 activates and maintains endometrial gland differentiation and secretory function during gestation (Spencer & Bazer 2002, Spencer *et al.* 2004c, Bazer *et al.* 2009b). Treatment of ovariectomized ewes with progesterone alone for at least 14 days induces SPP1, UTMP and STC1 expression by GE (Spencer *et al.* 1999b, Johnson *et al.* 2000b, Song *et al.* 2006a). Intrauterine infusions of CSH1 further increased SPP1, STC1 and SERPINA14 expression, but only when ewes received progesterone and intrauterine infusions of IFNT (Spencer *et al.* 1999b, Noel *et al.* 2003). The effects of IFNT may be attributed, in part, to increasing PRLR expression in the GE (Martin *et al.* 2004). The pathways mediating the interactive effects of IFNT and CSH1 on uterine gland function in ruminants remain unknown.

Endocrine actions of IFNT

Embryo transfer and uterine ligation experiments in the late 1960s and 1970s (Moor & Rowson 1966a, Mapletoft *et al.* 1976b) described a local/ipsilateral effect of the conceptus in maintaining the CL during early pregnancy. In those experiments, ligation of the gravid horn protected the CL ipsilateral to the conceptus, while the contralateral CL regressed, suggesting that preservation of the CL did not involve a systemic mediator. This finding was a primary reason why a paracrine action of conceptus secretory proteins on the endometrium was researched since the 1970s. Additional studies did not resolve the mechanism for the resistance of the CL of pregnancy to the lytic effects of PGF2 α (Inskeep *et al.* 1975, Mapletoft *et al.* 1976a, Pratt *et al.* 1977, Silvia & Niswender 1984), particularly considering that more PGF2 α is released from the uterus through the uterine vein in day 13 pregnant as compared to cyclic ewes (Wilson *et al.* 1972, Arosh *et al.* 2016).

Navigation of IFNT beyond the luminal epithelium of the uterus

Methods to detect IFNT expression and bioactivity were developed subsequent to its identification as

the pregnancy recognition signal in sheep and cattle. Radioimmunoassay (RIA) with polyclonal antibody against native IFNT detected 2 ng of IFNT per ml in media from cultured ovine conceptuses (Vallet *et al.* 1988a). In sheep, the release of IFNT from a cultured ovine conceptus was detected as early as day 8 (~1 ng/h) and increased linearly through day 16 (~7 μ g/h) of pregnancy in sheep (Ashworth & Bazer 1989). Another RIA with a sensitivity of 6.1 ng/mL was developed that detected IFNT in uterine luminal fluid of cattle (Takahashi *et al.* 2005). Similarly, IFNT antiviral bioactivity increased appreciably in conceptus culture media from days 12 to 14 (Pontzer *et al.* 1988). Early attempts to detect IFNT in systemic fluids, such as urine and cervical mucus, using western blot analysis with a 1 ng/mL limit of detection were not successful (Kazemi *et al.* 1988). More recently, IFNT was not detected in uterine vein or ovarian artery and vein blood on days 12–16 of pregnancy using western blot and enzyme-linked immunosorbent assays with unknown limits of detection (Lee *et al.* 2012b) or 1 ng/mL limit of detection (Arosh *et al.* 2016). These results, coupled with the lack of detection of radiolabeled ovine IFNT in maternal blood after infusion into the uterine lumen of ewes (Godkin *et al.* 1984), lead to the conclusion that IFNT does not exit the uterus and only exerts paracrine actions on the endometrium.

Indirect evidence to support a role for IFNT outside of the uterus in ruminants includes induction of ISG15 in endometrial cells that are located more distally in the uterus. For example, ISG15 mRNA was localized to the deep epithelial as well as myometrial layers of the early pregnant uterus in cows (Johnson *et al.* 1999a) and ewes (Johnson *et al.* 1999b). Other ISGs, such as MX1 and MX2, had a similar distribution in the uterus during pregnancy in sheep (Ott *et al.* 1998). It was hypothesized that expression of ISGs in the uterine stroma and myometrium was induced directly by IFNT or indirectly via an IFNTomedin (Spencer *et al.* 1996b). The idea that IFNT could cross the endometrial LE was further supported by the observation that the uterine LE lose junctional complex proteins after day 12 of pregnancy, thus making those epithelia 'leaky' (Satterfield *et al.* 2007). Recent studies propose another mechanism of IFNT transport into the endometrium involving extracellular vesicles (exosomes and microvesicles) that are produced by the conceptus. Two studies have identified IFNT in extracellular vesicles recovered from uterine luminal fluid of pregnant ewes (Ruiz-Gonzalez *et al.* 2015, Nakamura *et al.* 2016). Fluorescent-labeled extracellular vesicles, isolated from conceptus-conditioned media and infused into the uterine lumen from days 8 to 14 of the oestrus cycle, were only observed in the uterine LE and not in the deeper glands, stroma or myometrium or other maternal tissues such as the ovary, CL, parametrial lymph nodes or lung (Burns *et al.* 2016). However, the small number and size of the labeled extracellular vesicles may have

precluded their detection in that study. IFNT could also exit the uterus through the lymphatic system, but antiviral activity was not detected in lymph draining the uterus during pregnancy (Lamming *et al.* 1995). Further, iliac and submandibular lymph node ISG15 mRNA concentrations are low in day 15 pregnant ewes and not different from nonpregnant ewes (Antoniuzzi & Hansen, personal communication).

The first indication that IFNT might be released into the uterine vein during early pregnancy and have endocrine effects was reported by Schalue-Francis and coworkers (Schalue-Francis *et al.* 1991). In that study, 58 antiviral units per ml of IFN activity was detected in uterine vein serum from day 15 pregnant ewes, but antiviral activity was not found in sera from the ovarian artery or jugular vein during pregnancy, prompting the conclusion that IFNT might be rapidly cleared from the systemic circulation. A more recent study found significant antiviral activity in uterine vein blood of day 15 pregnant sheep (Oliveira *et al.* 2008). Despite the day 14–15 conceptus producing 20,000,000 antiviral units or about 200 µg IFNT each day, it was determined that the amount of IFNT in the uterine vein blood was only 5–10 ng/mL (Romero *et al.* 2015), which is similar to the amounts of antiviral activity in uterine vein serum (Schalue-Francis *et al.* 1991). Antiviral activity was observed in the uterine vein, but not uterine artery serum, of day 15 pregnant when compared to cyclic sheep (Bott *et al.* 2010). Using a validated RIA, IFNT was detected in the uterine vein serum of ewes on days 15 and 16 of pregnancy (Romero *et al.* 2015).

The affinity of IFNT for the type I IFN receptor is exceptionally high (Kd of 10–11 M) (Hansen *et al.* 1989, Li & Roberts 1994), which means that this receptor can become activated at very low IFN concentrations. Indeed, ISG15 expression can be induced in cultured small, large and mixed luteal cell cultures with as little as 100 pg/mL IFNT in sheep (Antoniuzzi *et al.* 2013) and cattle (Hansen *et al.* 2017). Most of the historical assay sensitivities for IFNT are only 1 ng/mL and would fail to detect IFNT as it circulates below that concentration. Thus, the difficulty in detecting IFNT in peripheral serum may be caused by very low circulating levels of IFNT that are below the limits of detection using current technologies. Alternatively, IFNT may not be detectable because it is not the cytokine released from the uterine vein that induces ISGs in peripheral tissues.

Systemic actions and effects of IFNT

Available correlative studies in sheep support the idea that IFNT from the elongating conceptus exits the uterus via the uterine vein (Oliveira *et al.* 2008, Romero *et al.* 2015), thereby inducing the expression of ISGs in maternal tissues and cells including PBMC, liver and CL (Oliveira *et al.* 2008, Bott *et al.* 2010, Ribeiro *et al.* 2014, Meyerholz *et al.* 2016, Sinedino *et al.* 2017). Examination of PBMC

revealed that ISGs were upregulated in response to early pregnancy in both sheep (Yankey *et al.* 2001) and cattle (Han *et al.* 2006, Gifford *et al.* 2007). This pregnancy-associated induction of ISGs in PBMC was further examined using microarray studies, which revealed many hundreds of genes were upregulated and downregulated in PBMC from cattle in response to pregnancy on day 18 (Hansen *et al.* 2010). Exogenous rolFNT, delivered into the uterine vein of cyclic sheep, upregulated ISG15 in the liver (Antoniuzzi *et al.* 2013). Liver biopsies had increased MX1 and ISG15 mRNA in day 18 pregnant as compared to cyclic Holstein-Friesian heifers (Meyerholz *et al.* 2016), corroborating the idea of systemic release and endocrine actions of IFNT.

In sheep, induction of ISG15 expression was found in the CL following subcutaneous (Spencer *et al.* 1999a) and intramuscular injections (Chen *et al.* 2006) of rolFNT given from days 11–17 of the oestrus cycle. The induction of ISG15 mRNA in the CL occurred in response to uterine luminal infusion or intramuscular injection of 2 mg rolFNT, but not following intramuscular injection of 200 µg rolFNT, suggesting a dose effect of rolFNT with this method of delivery. Successively, rolFNT was directly infused into the uterine vein of sheep using osmotic pumps that delivered 200 µg rolFNT over a 24-h period (Hansen *et al.* 2010) and induced ISG15 mRNA in the ipsilateral and contralateral CL as well as in the endometrium and liver (Oliveira *et al.* 2008, Bott *et al.* 2010). Continuous systemic delivery of rolFNT from days 10 to 17 of the oestrus cycle delayed return to oestrus in sheep. In that study, control (bovine serum albumin)-infused ewes returned to oestrus by day 19, whereas rolFNT-infused ewes had oestrus cycles that were delayed to at least day 32, when presence of the original CL marked in ink at the time of pump installation was confirmed at necropsy. Thus, endocrine delivery of IFNT into the uterine vein blocked endogenously induced luteolysis.

To determine if IFNT could directly protect the CL (Bott *et al.* 2010), 200 µg rolFNT per day was delivered into the uterine vein using miniosmotic pumps beginning on day 10 (prior to endogenous action of PGF2α). After 12 h, the ewes received a single luteolytic pulse of PGF2α (Silvia & Niswender 1984, 1986, Silva *et al.* 2000, Bott *et al.* 2010). The luteolytic pulse of PGF2α caused a decline in serum progesterone in control-infused but not ewes infused with rolFNT (Bott *et al.* 2010, Antoniuzzi *et al.* 2013). When infusion of rolFNT was reduced to only 20 µg/day (833 ng/h) into the uterine vein or jugular vein on days 10–13, the CL was protected from the luteolytic action of PGF2α exogenously administered on day 11 (Antoniuzzi *et al.* 2013). Thus, the induction of ISGs in the CL and resistance to luteolytic PGF2α appears to be maximized with lower doses of rolFNT rather than single or multiple injections of high doses of rolFNT, which likely better reflect conditions *in vivo* during a normal pregnancy.

Induction of ISGs during pregnancy in extrauterine tissues

In sheep, ISGs are induced by pregnancy in extrauterine tissues including the PBMC, CL and liver. For example, ISG15 mRNA and protein are upregulated in CL on day 15 (Oliveira *et al.* 2008, Bott *et al.* 2010, Romero *et al.* 2013). ISG15 and its ISGylated protein targets were predominantly localized to large luteal cells on day 15 of pregnancy with diminished but significant localization to small luteal cells. Pregnancy-associated ISGs are induced in small, large and mixed luteal cells isolated on day 10 of the oestrus cycle and cultured with rIFNT for 24 h (Antoniazzi *et al.* 2013). Moreover, ISGs are upregulated in the CL during the maternal recognition of pregnancy period (Romero *et al.* 2013). Evaluation of physiological responses in the CL lead to the conclusion that pregnancy may provide luteal resistance to PGF2 α through activation or stabilization of gene expression associated with IFN, chemokine, cell adhesion, cytoskeletal and angiogenic pathways. Cell survival genes induced by IFNT in the CL may also play important roles in sustaining luteal steroidogenesis by inhibiting apoptosis of luteal cells (Antoniazzi *et al.* 2013). Collectively, these responses to IFNT direct the luteal environment to continue to produce progesterone and to be resistant to the luteolytic effects of PGF2 α .

In cattle, ISG15 expression also is upregulated in the CL as early as day 16 of pregnancy and continues to be detected in the CL through day 60 of pregnancy (Yang *et al.* 2010, Magata *et al.* 2012). Both free and ISG15-conjugated proteins were upregulated in bovine small luteal and large luteal cells following culture with rIFNT (Nitta *et al.* 2011, Hansen *et al.* 2017). Pregnancy also induces lymphoangiogenesis in the bovine CL via the vascular endothelial growth factor (VEGF) system (Miyamoto *et al.* 2014). Key intraluteal regulators induced by pregnancy may involve influx of neutrophils as well as an increase in interleukin 8 chemokine expression to complement continued steroidogenesis (Shirasuna *et al.* 2015). Pregnancy, via IFNT may also downregulate genes detrimental to CL survival and function. For example, expression of tumor necrosis alpha (TNF α), an inflammatory cytokine secreted mainly by macrophages, was reduced in pregnancy, suggesting qualitative changes in macrophages within the CL (Shirasuna *et al.* 2015). This is consistent with and would complement a general upregulation of cell life genes in ovine CL in response to pregnancy (Romero *et al.* 2013). The specific endocrine effects of IFNT and ISGs on the bovine CL remain to be elucidated.

IFNT, ISGs and pregnancy diagnosis

Diagnosis of pregnancy is integral to management of beef and dairy cattle. The identification of nonpregnant cows as soon as possible following artificial insemination

would allow producers to better manage return to pregnancy and entry into optimal milk (dairy) and meat (dairy and beef) production. Current traditional methods of pregnancy diagnosis focus on per rectum ultrasound on day 32 or transrectal palpation of the reproductive tract around day 40. New indirect chemical methods for pregnancy diagnosis include the detection of pregnancy-associated glycoprotein (PAG or pregnancy specific protein B) in blood on days 24–32 following artificial insemination (AI). Determination of pregnancy status prior to day 32 would have tremendous economic benefit to cattle producers (Hansen & Galligan 2007). If inseminated cows that failed to conceive and maintain pregnancy were identified through lack or suboptimal detection of a conceptus-induced ISG(s) in the maternal circulation at days 18–20, a rapid resynchronization of the oestrus cycle could be performed, thereby reducing the calving interval and improving the profitability of dairy operations (De Vries 2006).

Because IFNT is expressed and induces ISGs in the endometrium during pregnancy recognition, it was reasoned that surrogate markers for pregnancy or IFNT might be present in the blood and provide an indicator of pregnancy status in cattle. Historical assays for IFNT did not have sensitivity beyond the low ng levels, thus studies focused on ISGs. The concept of detecting ISGs in blood as indicators of pregnancy is not new (Hansen & Rueda 1991), but there are currently no ISG-based protein biomarkers in blood that are useful to determine pregnancy status. In sheep, the levels of MX1 mRNA were greater in PBMC from day 15 through day 30 after insemination in pregnant as compared with nonpregnant ewes (Yankey *et al.* 2001). Similar effects of pregnancy on ISGs in PBMC of cattle were observed (Han *et al.* 2006, Gifford *et al.* 2007). Overall, mean blood ISG15 mRNA levels are greater from day 15 to day 32 of gestation, with maximal levels on day 20 in pregnant compared with inseminated, nonpregnant cows. In addition, the detection of ISG15 mRNA in PBMC over several days was more accurate in predicting pregnancy when compared to a single determination. Further studies focusing on cattle under different production systems revealed that ISGs increased in leukocytes in response to pregnancy on day 18 in dairy heifers, but not in lactating dairy cows (Green *et al.* 2010, Monteiro *et al.* 2014). A similar study in beef cows demonstrated an increase in ISG mRNA between days 15 and 22 of pregnancy with a peak concentration on day 20 (Pugliesi *et al.* 2014). That study found that leukocyte ISG mRNA levels are a more accurate predictor of pregnancy when coupled with ultrasound determination of a CL on day 20 of pregnancy.

In cattle, the levels of ISG15 and MX2 mRNA in PBMC are positively correlated with the amount of IFNT infused in the uterus (Matsuyama *et al.* 2012). Interestingly, maternal treatment with recombinant bovine somatotropin during the pre- and

peri-implantation period stimulated conceptus development and increased expression of ISG15 and RTP4 in blood leukocytes of lactating dairy cows (Ribeiro *et al.* 2014). Similar to sheep, conceptus length and IFNT mRNA are correlated (Bertolini *et al.* 2002). Loss of embryos in a model of induced embryo mortality is associated with diminished RTP4 and ISG15 mRNA levels in peripheral blood leukocytes in sheep (Kose *et al.* 2016). Stevenson and coworkers tested the reliability of using the change in one ISG (MX2) from steady-state levels on day 0 to days 18 and 19 after AI for identification of nonpregnant heifers (Stevenson *et al.* 2007). Although, the fold changes in ISG mRNA from day 0 to day 18 were greater for heifers diagnosed pregnant, the low sensitivity (the ability of the test to identify a pregnant cow) and negative predictive value (calculated as the proportion of nonpregnant outcomes generated by the pregnancy test that were from truly nonpregnant cows) precluded this approach for accurately detecting nonpregnant heifers at day 18 after AI. The abundance of ISG mRNA in maternal PBMC progressively increased from day 15 after AI, peaked on day 20 and then decreased to day 22 (Pugliesi *et al.* 2014). In that study, ISG transcript abundance was greater on day 18 than day 15 for all ISGs (OAS1, ISG15, MX1, MX2) in pregnant when compared to nonpregnant beef cows, but the sensitivity and negative predictive value for the pregnancy detection were also low.

In pregnant Holstein–Friesian cows, investigators defined the shortest interval to pregnancy detection by measuring ISGs in blood on days 17 and 18 after AI in nulliparous, primiparous and multiparous cows (Green *et al.* 2010). The greatest amount of ISG was found in primiparous cows on day 20, which correlates with maximal production of IFNT by the elongated conceptus. There was a greater false-positive rate for lactating cows, suggesting that ISG-based diagnostics might be more feasible for nulliparous cows. Similarly, greater PBMC ISG15 and RTP4 levels were observed in primiparous than multiparous Holstein cows on day 19 (Sinedino *et al.* 2017). A possible explanation for the differences in ISG expression between heifers or primiparous and multiparous cows might be related to conceptus length, as it is longer in heifers when compared to cows during pregnancy recognition thus affecting the amount of IFNT produced (Berg *et al.* 2010). Another possible reason for improved peripheral ISG expression in heifers is that they are smaller than multiparous cows, which could affect systemic concentrations of IFNT and, consequently, the response of ISG in leukocytes. Green and coworkers tried to improve the accuracy of early pregnancy diagnosis by using the ratio of ISG expression on day 18 after AI to expression of ISG based on a baseline control blood sample collected before AI (Green *et al.* 2010). This approach improved the overall utility of the test, but would entail more blood sampling and might not be practical for an on-farm test.

Available studies in cattle support the idea that detection of ISGs in blood are a reasonable indicator of pregnancy status in ruminants, but improvements in methodology are needed, with more adequately defined cut-offs and easier on-farm and cost-effective methods. For example, Wiltbank and coworkers summarized 4 studies in which PBMC ISGs were assessed for early pregnancy diagnosis and reported that the false-negative results ranged from 10.1 to 17.5% (Wiltbank *et al.*

Figure 2 Endocrine action of pregnancy in ruminants. IFNT is a major conceptus secretory protein (CSP) that is released by the expanding and elongating blastocyst. IFNT has been shown to suppress the upregulation of ESR1, which leads to suppression of OXTR, disruption of pulsatile PGF2 α release and antiluteolytic action on the corpus luteum. The mechanism disrupting PGF may be slightly different in cattle and only involve effects on the OXTR. Regardless, paracrine action of IFNT alters PGF2 α pulses in both sheep and cattle and, thereby, protects the CL so that it can continue to produce progesterone, which supports production of histotroph and further development and attachment of the conceptus. In addition to activating ISGs in the endometrium, IFNT, in addition to other CSP, may be released into the uterine vein to act in peripheral/endocrine action on immune cells and the corpus luteum. The consequences of activated innate immune responses during establishment of pregnancy in ruminants is unknown and needs to be clarified as functionally important or simply consequential to massive release of IFNT by the developing conceptus. Concerns with utility of detection of ISGs in blood cells as indicators of pregnancy centers on massive induction of these same ISGs in response to viral infections and other inflammatory responses (i.e. bacterial infections such as mastitis in dairy cows). However, the endocrine action of pregnancy and IFNT when inducing ISGs in the CL may be relevant to establishment of luteal resistance to PGF2 α . This is certainly implicated through studies demonstrating resistance of the CL induced by endocrine delivery of IFNT in response to both endogenous and exogenous PGF2 α . CL, corpus luteum; CSP, conceptus secretory protein; ESR1, estrogen receptor alpha; IFNT, interferon tau; ISGs, interferon-stimulated genes; OXTR, oxytocin receptor; PGF2 α , prostaglandin F2 alpha.

2016). Another concern for this approach to pregnancy diagnosis in cattle is the considerable induction of ISGs by other type I IFNs (IFNA, IFNB, IFNW) that occurs in response to viral infections (Hansen *et al.* 2015) and pro-inflammatory stressors (Hansen *et al.* 2010). These false-positive responses might be managed by multiple blood samples including those outside of the maternal recognition window in order to find a baseline of ISG. Regardless, when used with other parameters such as serum progesterone, serum pregnancy-associated glycoproteins (PAGs) and ultrasound, detection of ISGs may be useful to determine pregnancy status and the timing of embryo loss in cattle (Wijma *et al.* 2016).

Conclusions

The antiluteolytic effects of IFNT in ruminants involve paracrine effects on the endometrium and endocrine effects on the CL that culminate in maternal recognition of pregnancy and maintenance of progesterone production, the unequivocal hormone of pregnancy (Fig. 2). The production of sufficient IFNT to establish pregnancy is dependent on conceptus elongation. The individual, additive and synergistic actions of progesterone and IFNT regulate expression of elongation- and implantation-related genes in the endometrium that, in turn, increase substances (e.g., glucose, amino acids, proteins, lipids) in the uterine lumen that govern conceptus survival and elongation. One important area of future research is determining which ISGs and impacted biological pathways are critical determinants of pregnancy establishment and success. Indirect and correlative evidence in sheep and cattle supports the concept that IFNT is released by the conceptus, navigates the endometrium, enters uterine vein blood and is delivered in amounts sufficient to induce ISGs in peripheral tissues (PBMC, CL, liver). Detection of antiviral activity specific to IFNT, immunoreactive IFNT in radioimmunoassay, and mass spectrometry detection of IFNT in uterine vein blood provides evidence that this occurs. The induction of peripheral ISGs is temporally related to the size of the conceptus and production of IFNT. Induction of ISGs in PBMC in response to pregnancy may have critical roles in prompting peripheral innate immune responses. The induction of ISGs in the CL may be important to sustain its function to produce progesterone and prevent the lytic effects of PGF2 α . The development of a blood or milk test to better manage the open or nonpregnant cow is an area of current and future interest. Some focus has recently moved away from the ISGs as surrogate markers for IFNT action because of the false-positive issue in context of maternal infections and stressors during pregnancy. If IFNT is specifically and accurately detectable in peripheral fluids distal to the uterine vein, then it will be an outstanding candidate biomarker for an early pregnancy test.

Declaration of interests

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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