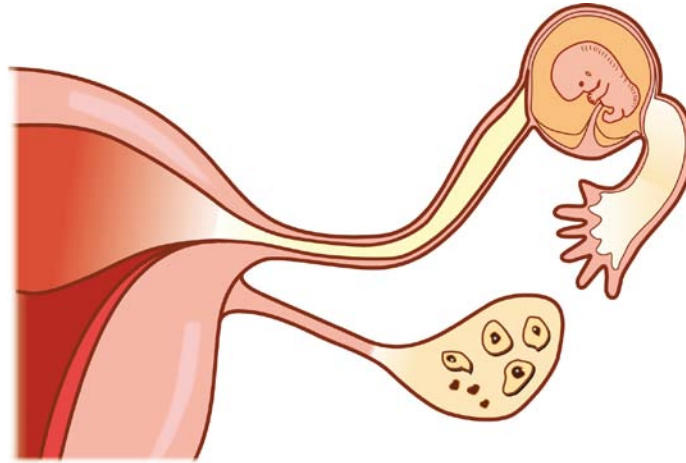


Pelvic injury due to infection



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Centre for
Reproductive
Health

Pelvic inflammatory disease (PID)

- Spectrum of upper genital tract infections that include endometritis, salpingitis, tubo-ovarian abscess, and/or pelvic peritonitis
- ~1 in 250 women worldwide have an episode of PID each year
- Polymicrobial aetiology
- Understanding hindered by two factors:
 - most studies have used specimens obtained from lower genital tract not actual site of infection
 - most research has focused on sexually transmitted pathogens and not non-STD pathogens

C. trachomatis

M. tuberculosis

Insidious presentation

2-10% develop ascending pelvic infection

~1% women worldwide

~8% women worldwide

Prevalence falling

Prevalence rising

Pelvic *M. Tuberculosis* infection and adverse reproductive outcome

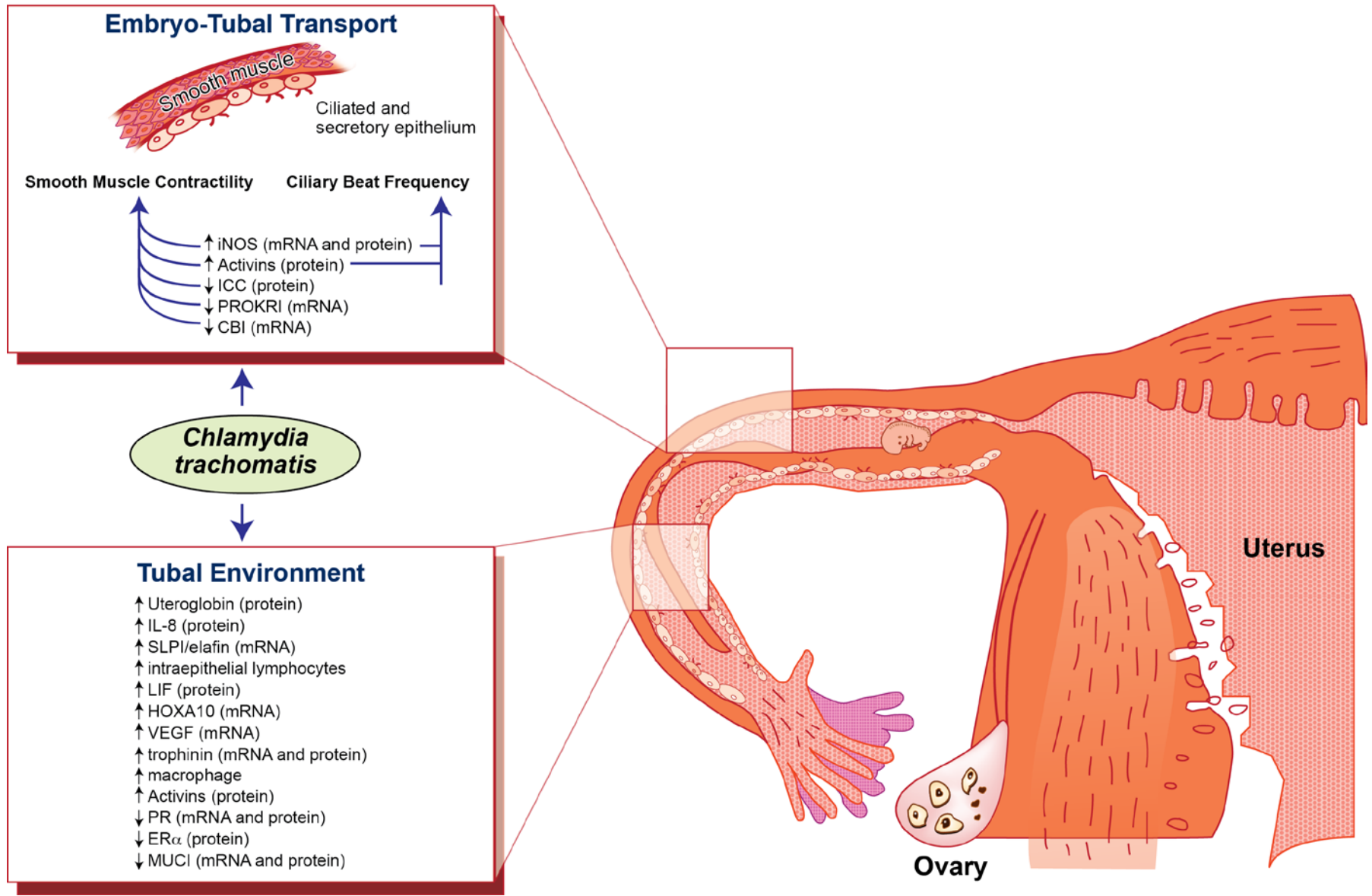
“A successful pregnancy ending in live birth at term is very rare following genital tuberculosis, in spite of effective medical treatment for tuberculosis.”

Pelvic *C. trachomatis* infection and adverse reproductive outcome

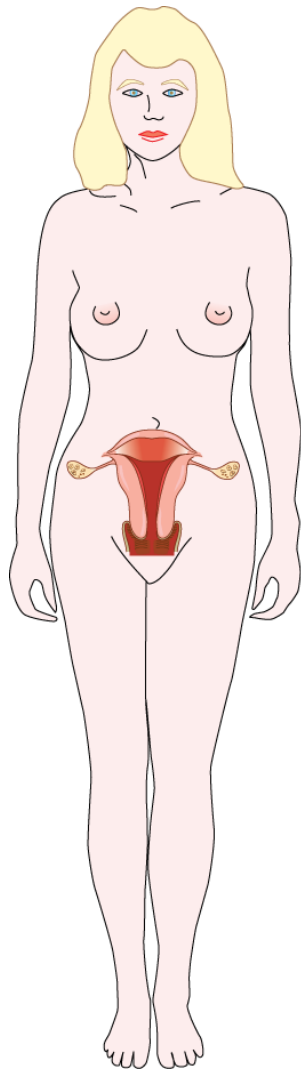
- Difficult to determine true effect
- Lack of reliable method for confirming past pelvic infection
- Much of assumptions based on retrospective case-control studies
- Many studies performed on populations where reproductive outcome common (or rare)
- Studies not taken into account of effect of confounding variables, e.g. age, previous surgery or smoking

The role of *C. trachomatis* in the aetiology of tubal ectopic pregnancy

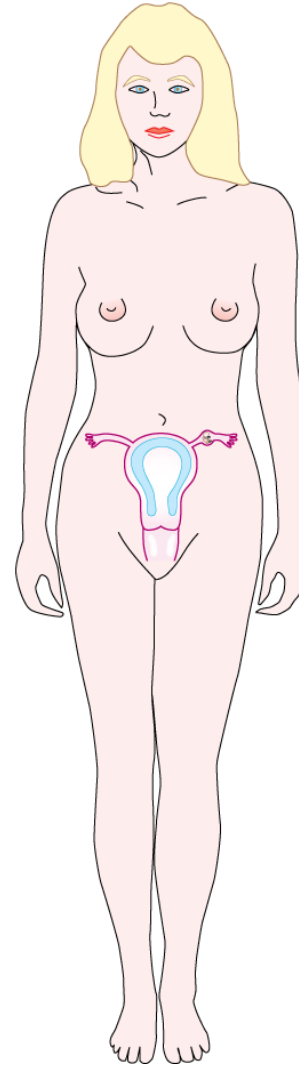
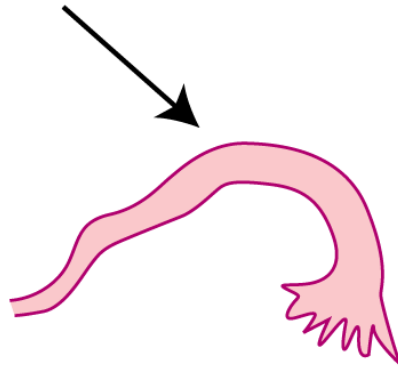
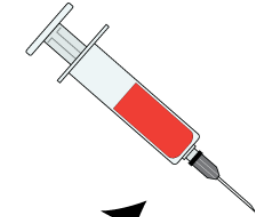
- Gross fibrosis in the pelvis following chlamydial infection is rarely seen at time of surgery for ectopic pregnancy
- Histological examination of Fallopian tube from women with ectopic pregnancy demonstrates an absence of associated structural changes in proximal tubal epithelial cells
- The exact mechanism leading from chlamydial infection to tubal implantation is not known



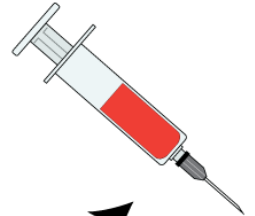
Human tissue resources



Woman
undergoing
hysterectomy



Woman
undergoing
surgery for
ectopic pregnancy



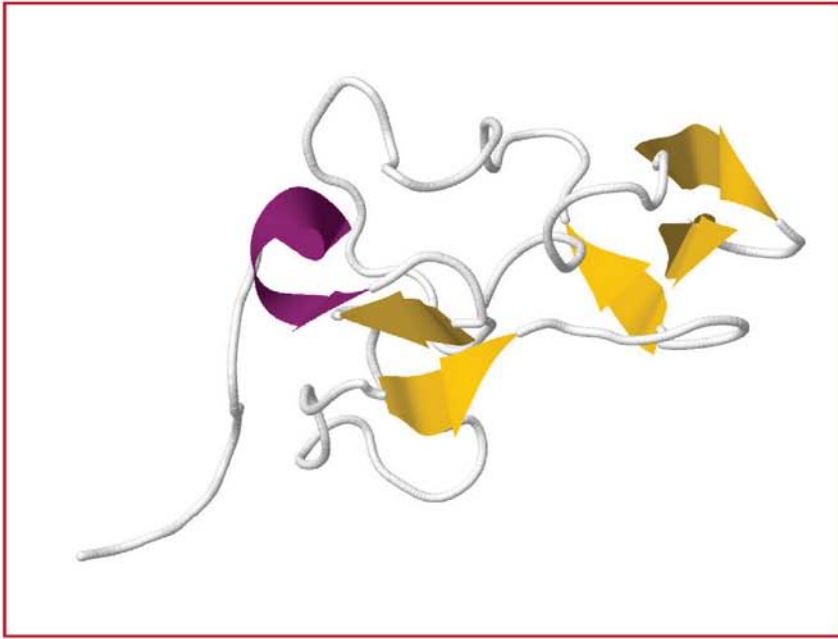
Analysis of past chlamydial infection

- Nucleic acid amplification tests used to identify infection when organism is present but are unable to provide information on past exposure
- Past exposure can be explored serologically
- Commercial ELISAs based on peptides of outer membrane protein
- None of these current ELISAs rigorously evaluated in large well-defined populations
- Cross-react with other bacteria and *C. pneumoniae*
- 'Pgp3 assay' (protein expressed by chlamydial plasmid)

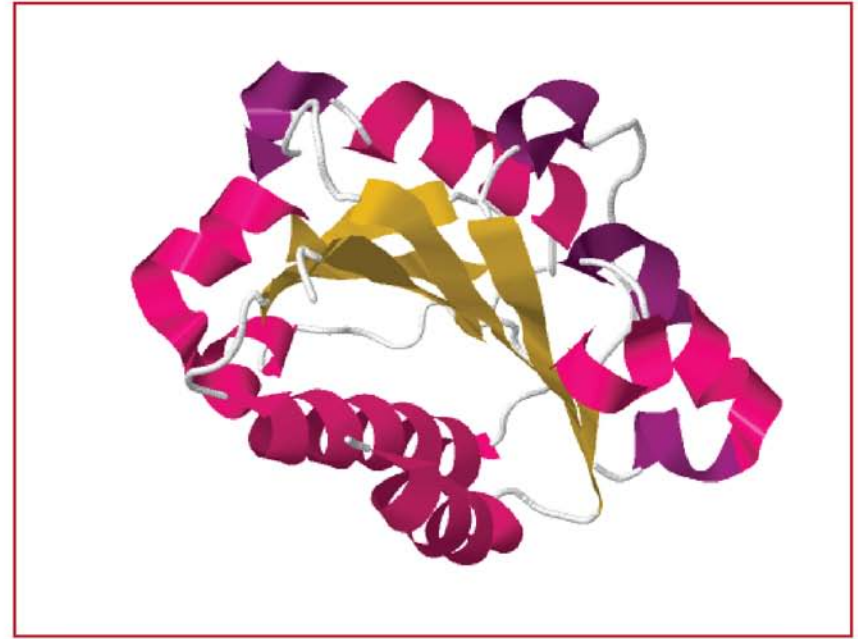
Pgp3 assay for past chlamydial infection

Assay	Sensitivity		Sensitivity difference between pgp3 and commercial assays	
	No. of Samples from <i>C.trachomatis</i> positive patients	No. positive/no. tested (%) (95% CI)	Difference pgp3%-test% (95% CI)	McNemar's <i>P</i> -value
All patients				
pgp3	356	57.9 (52.7 to 62.9)		
Anilab	356	49.2 (44.0 to 54.3)	8.7 (2.9 to 14.5)	0.003
SeroCT	356	47.2 (42.1 to 52.4)	10.7 (4.9 to 16.5)	<0.0005
Medac	356	44.4 (39.3 to 49.6)	13.5 (7.0 to 20.0)	<0.0005
Female ^a				
pgp3	164	73.8 (66.5 to 79.9)		
Anilab	164	59.8 (52.1 to 67.0)	14.0 (5.5 to 22.5)	0.001
SeroCT	164	55.5 (47.8 to 62.9)	18.3 (10.1 to 26.5)	<0.0005
Medac	164	45.7 (38.3 to 53.4)	28.0 (18.9 to 37.2)	<0.0005
Male ^a				
pgp3	190	44.2 (37.3 to 51.3)		
Anilab	190	40.5 (33.8 to 47.6)	3.7 (-4.5 to 11.8)	0.42
SeroCT	190	40.0 (33.3 to 47.1)	4.2 (-4.1 to 12.6)	0.36
Medac	190	43.7 (36.8 to 50.8)	0.5 (-8.6 to 9.6)	1.00

Factors important for a tubal environment conducive to ectopic implantation

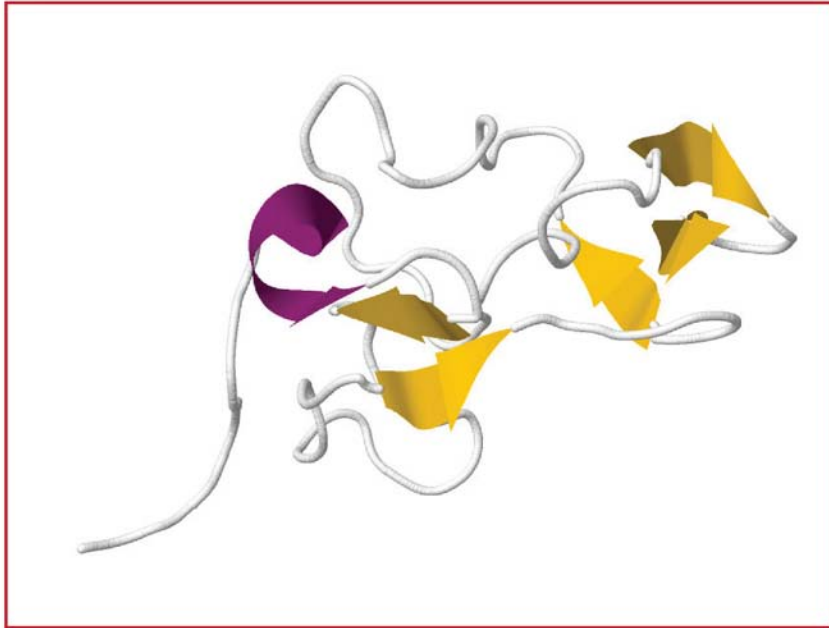


Prokineticins



Integrins

Factors important for a tubal environment conducive to ectopic implantation

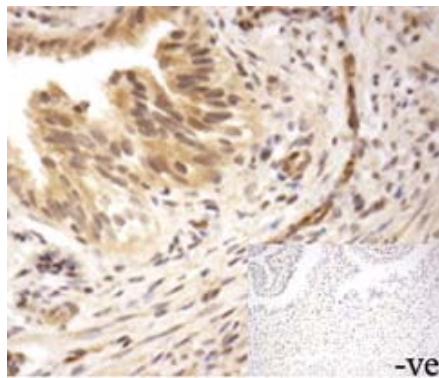


Prokineticins

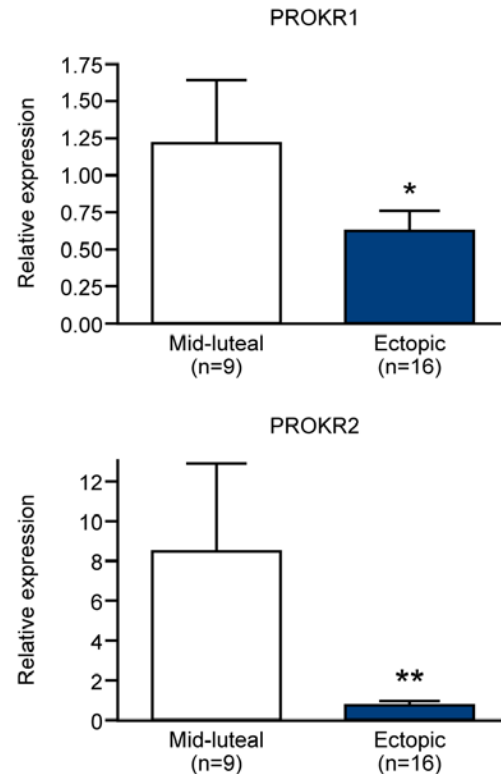
Prokineticins

- Multifunctional secreted proteins
- Ligands for two G-protein coupled receptors PROKR1 and PROKR2
- Roles
 - originally identified as regulators of intestinal contraction
 - shown to affect vascular function
 - also known for regulating genes that are important in implantation
- PROK1 has been shown to induce expression of LIF in human endometrium and LIF is known to play a crucial role in successful intrauterine implantation in mice

Prokineticin receptors in human FT

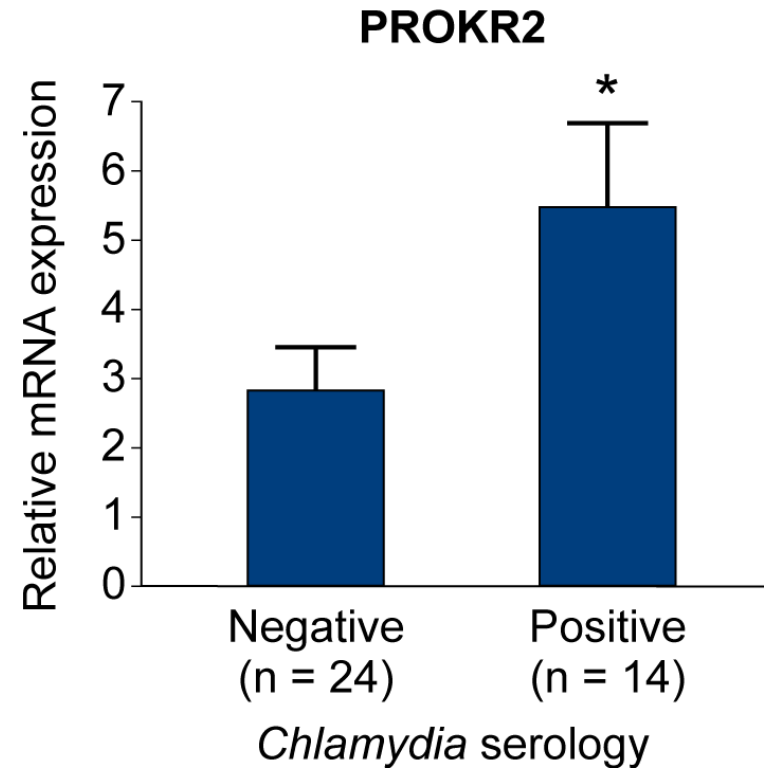
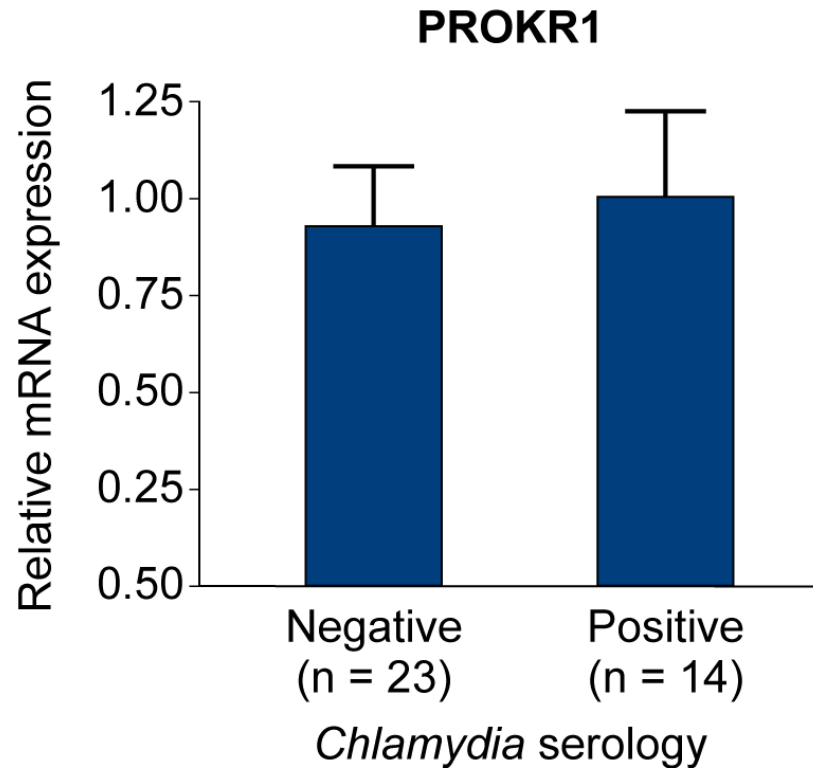


PROKR2

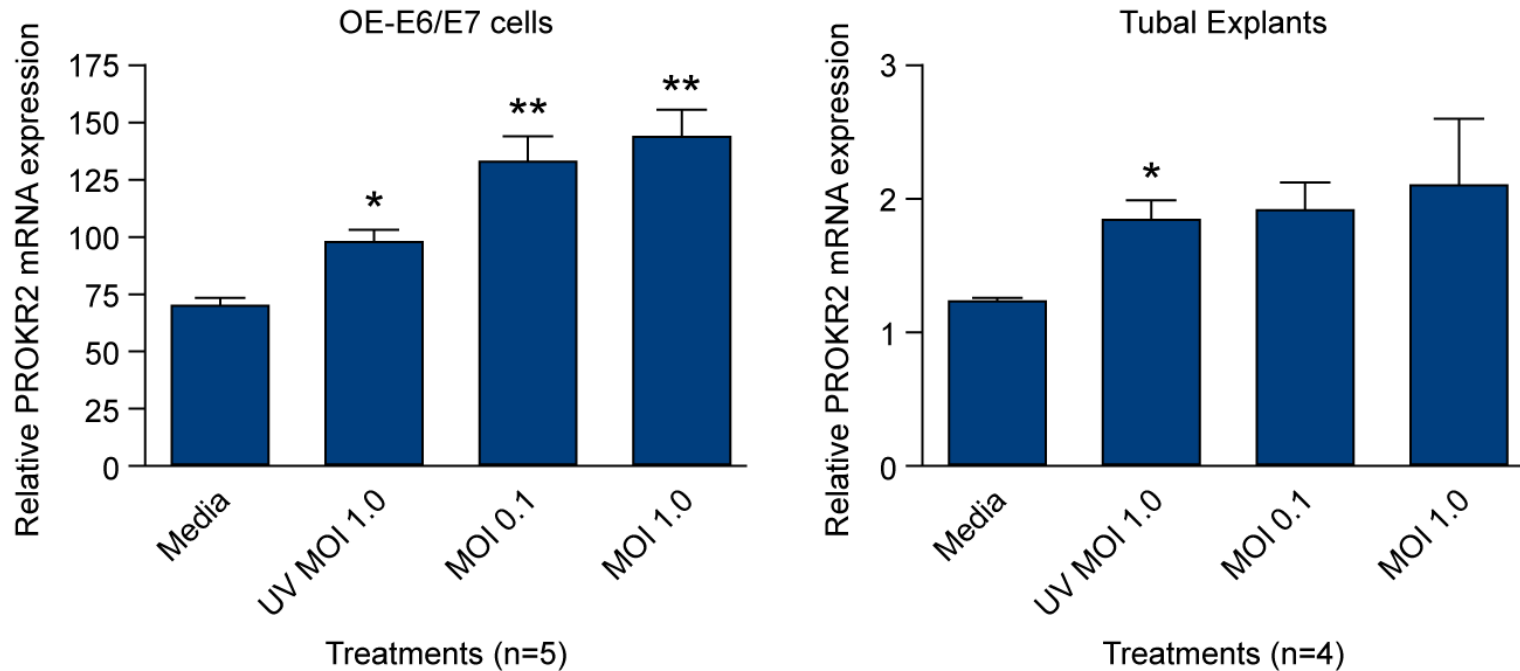


- PROKR1 and 2 expressed in epithelium and smooth muscle of non-pregnant FT
- Decreased in FT from women with ectopic pregnancy where implantation has occurred

Prokineticins and *C. trachomatis*



Prokineticins and *C. trachomatis*

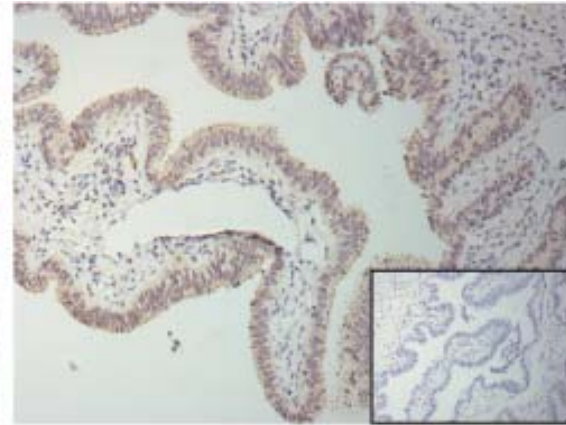
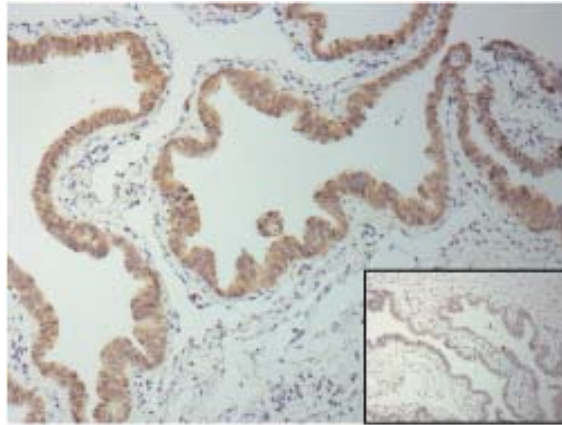


PROKR2 mRNA expression levels were significantly increased in OE-E6/E7 cells treated with live *C. trachomatis* and UV-killed *C. trachomatis* after eight hours of treatment

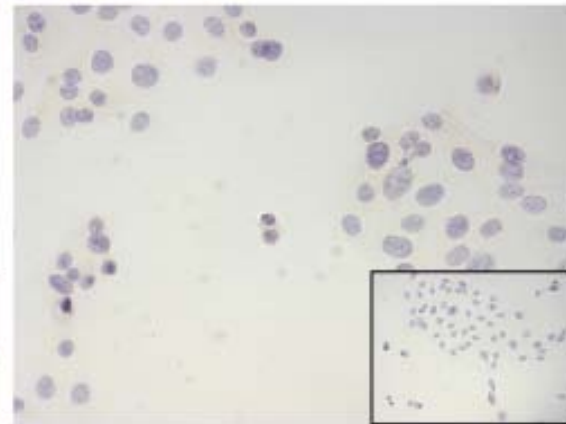
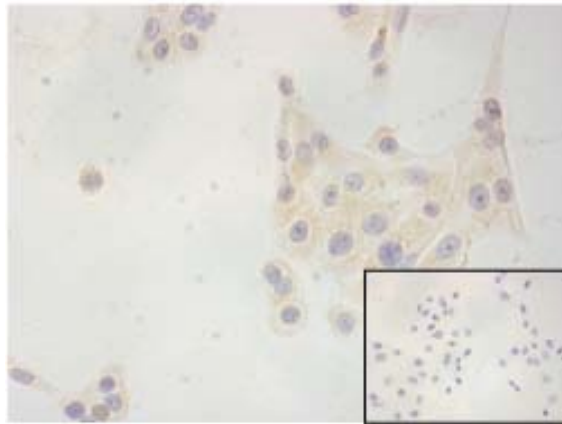
TLR2

TLR4

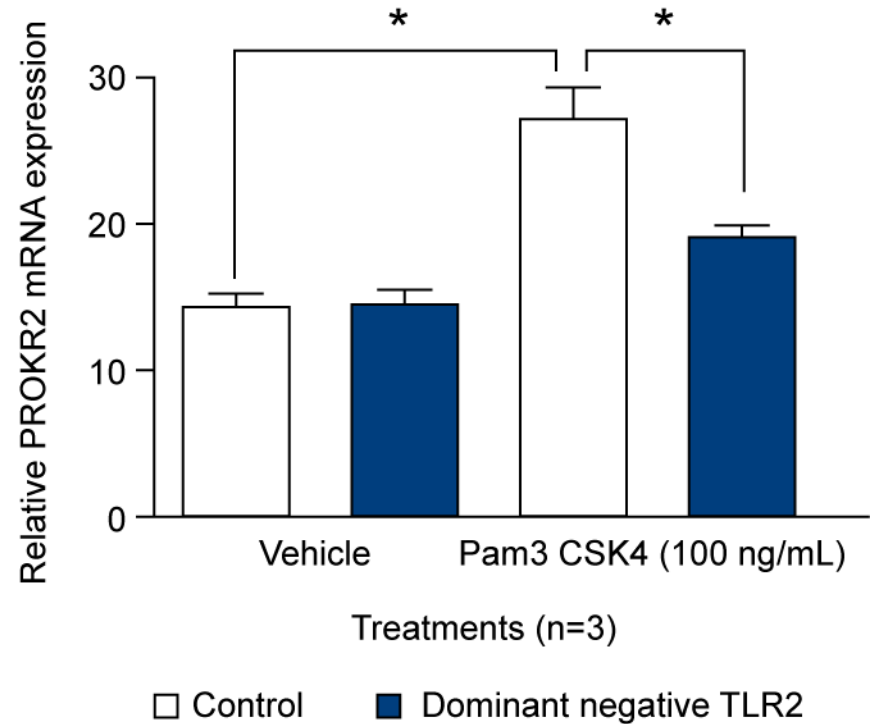
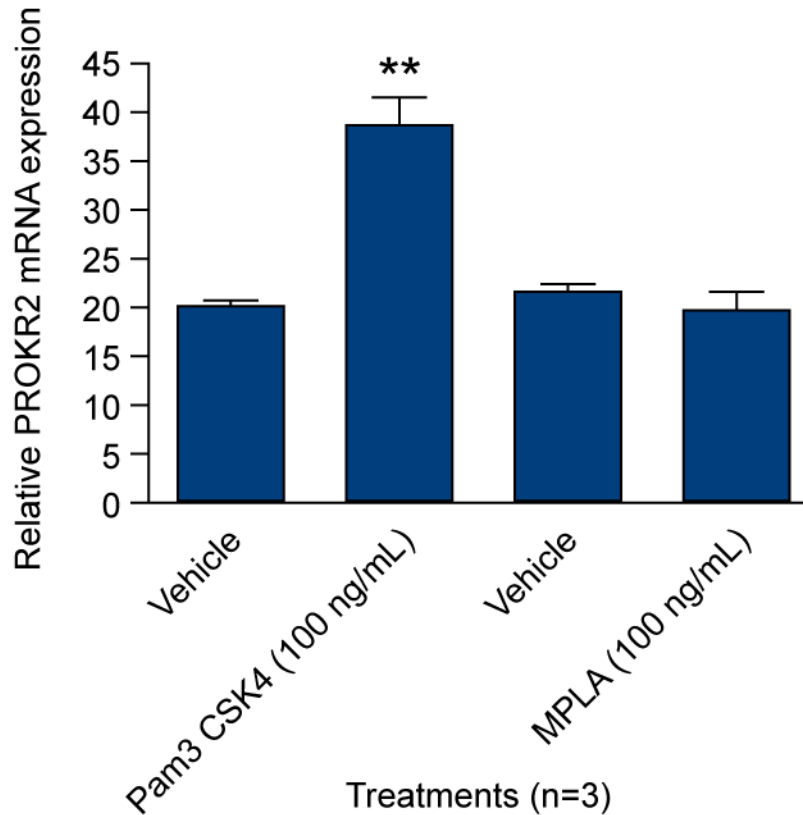
**Fallopian
tube**



OE-E6/E7 cells

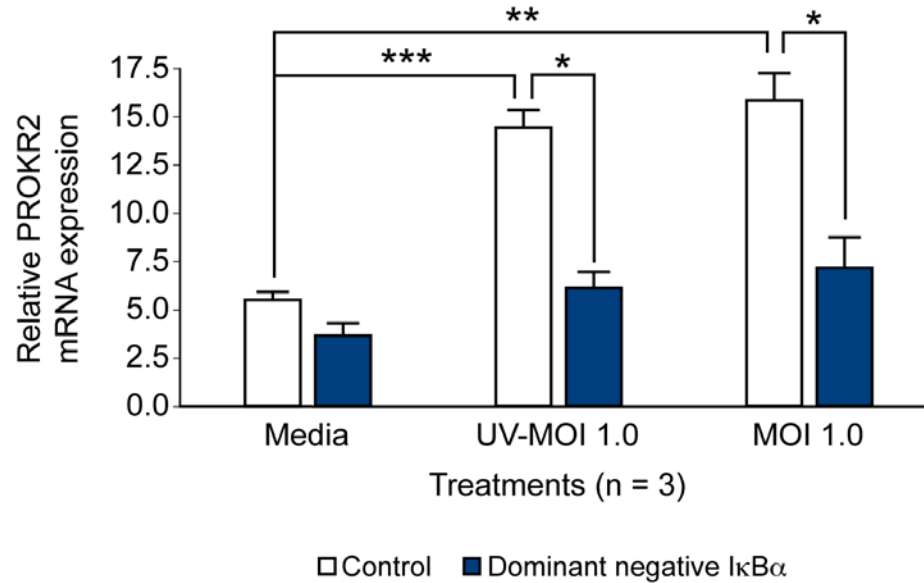
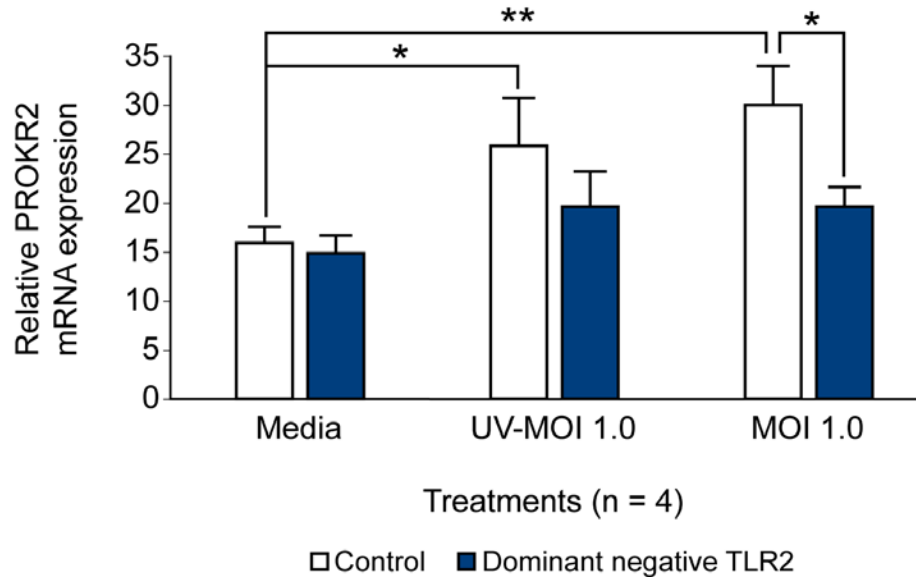


Toll-like receptors are expressed in
Fallopian tube epithelium and
oviductal epithelial cells

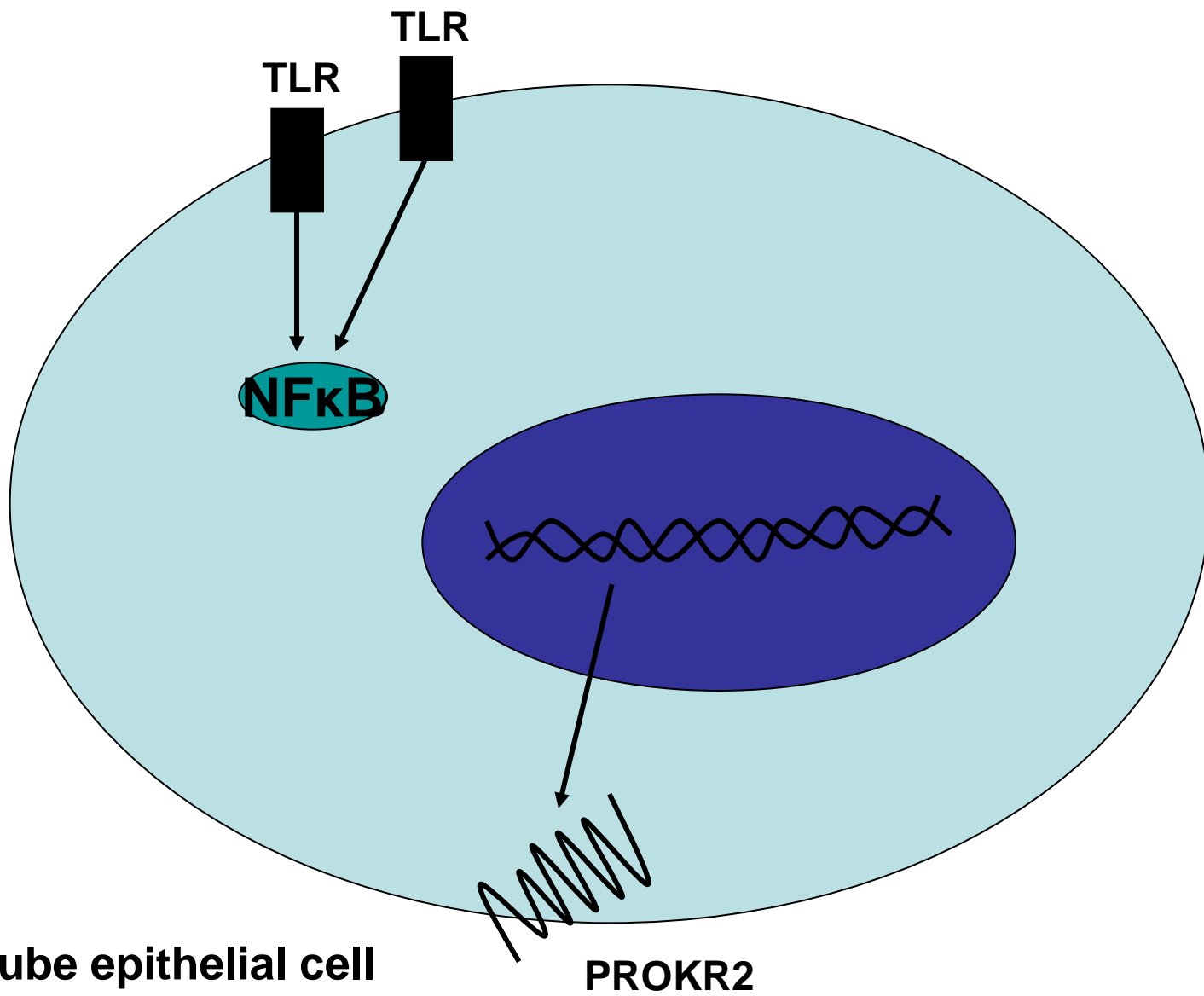
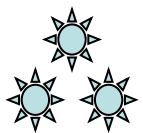


PROKR2 mRNA expression in OE-E6/E7 cells
can be induced by TLR2 activation

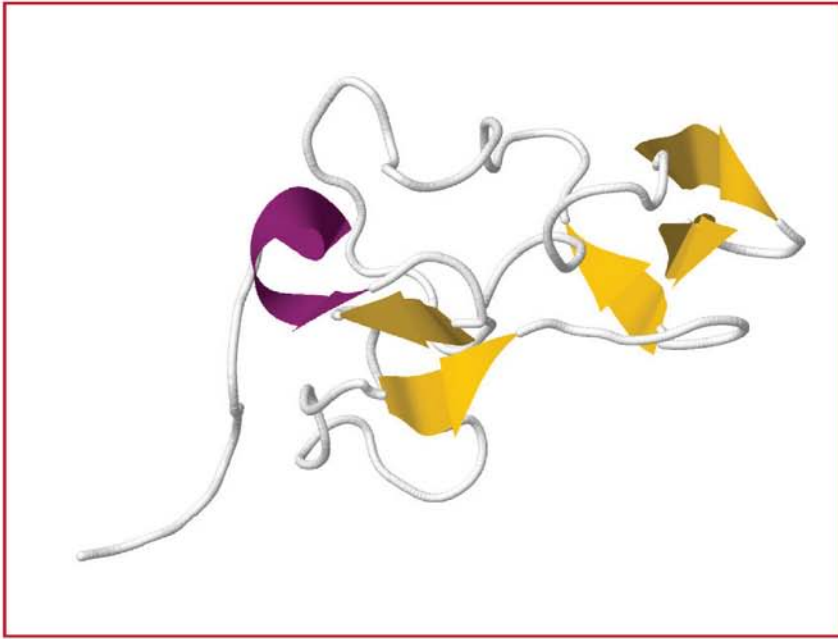
Prokineticins and *C. trachomatis*



Transfection of OE-E6/E7 cells with dominant-negative TLR2 or IκBα abrogated the *C. trachomatis*-induced PROKR2 expression



Factors important for a tubal environment conducive to ectopic implantation

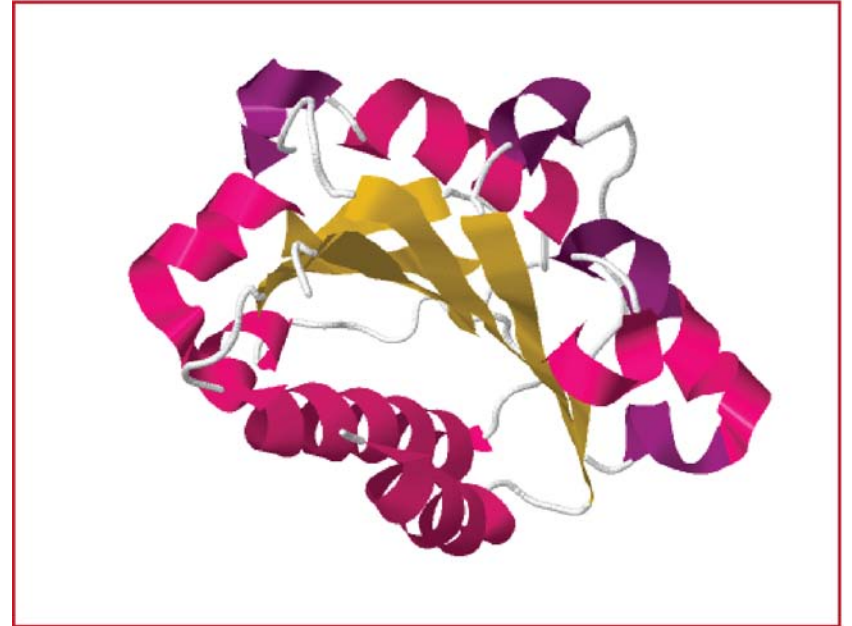


Prokineticins



Integrins

Factors important for a tubal environment conducive to ectopic implantation

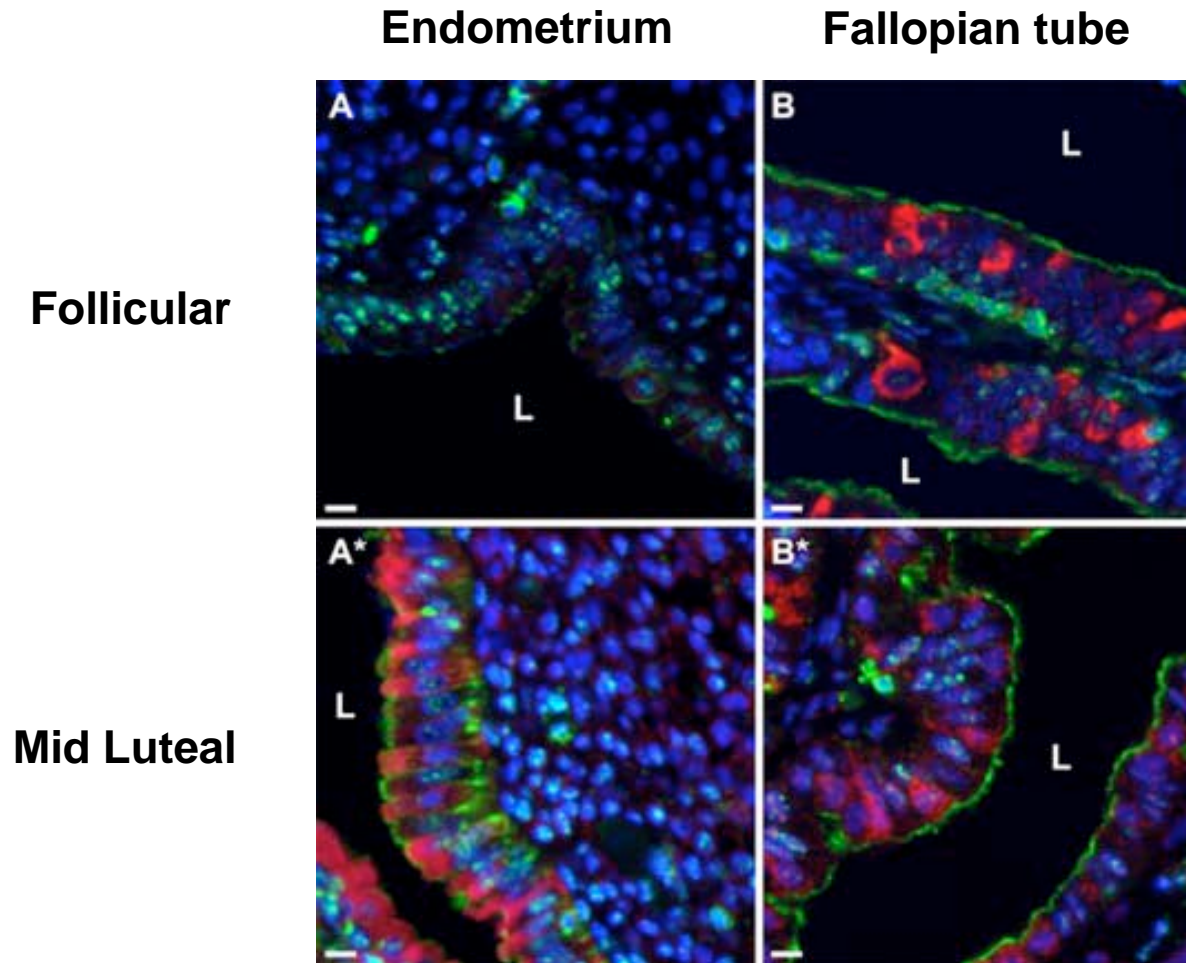


Integrins

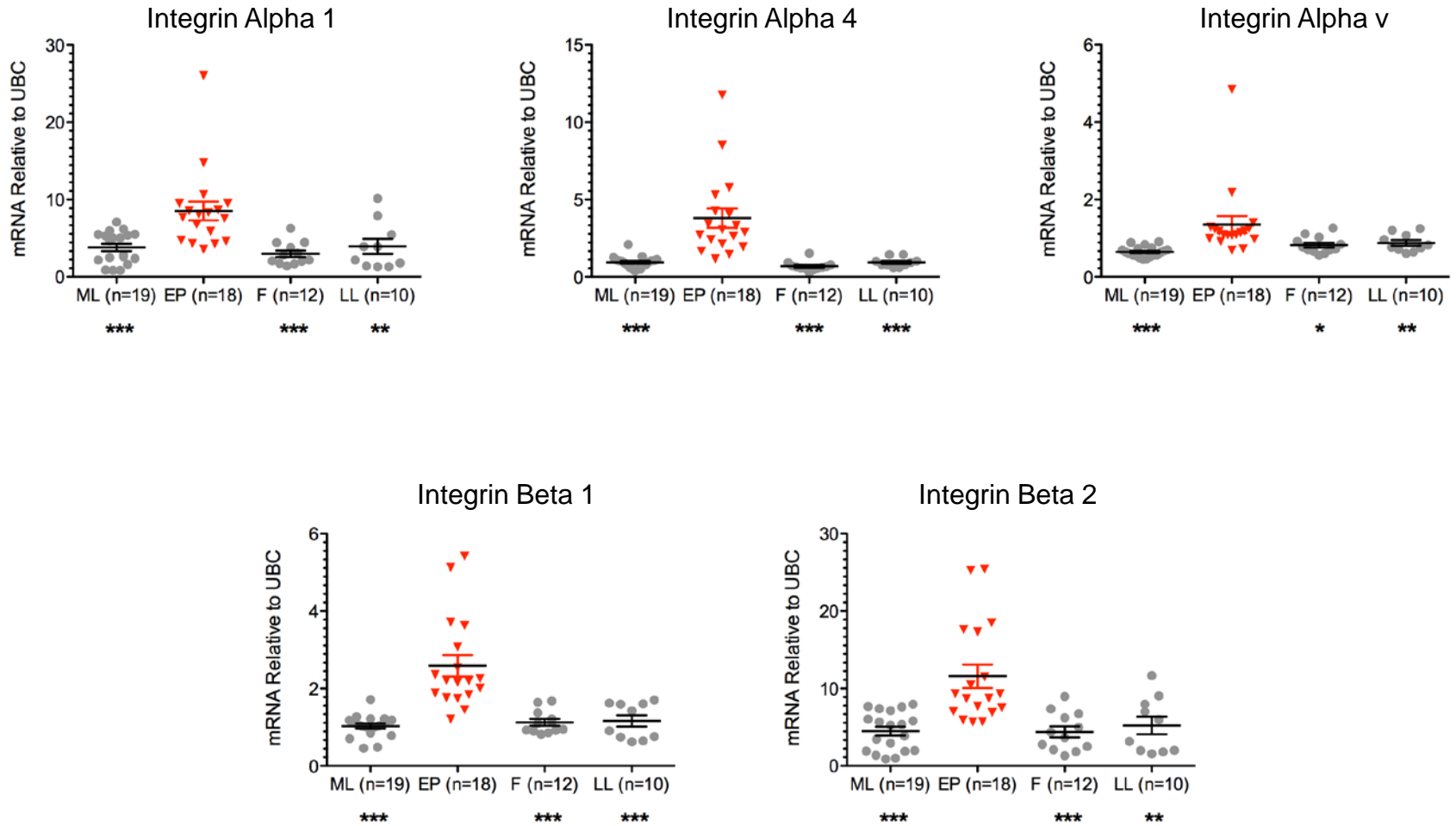
Integrins

- Heterodimeric cell surface receptors that mediate cell-cell and cell-extracellular matrix interactions
- Integrins (alpha 1 beta 1, alpha 4 beta 1, alpha v beta 3) have now been largely accepted as markers of receptivity to the presenting embryo in the uterus
- Functional data limited as homozygous beta1 and alpha4 mutations are embryonic lethal and 80% of alphav -/- mice die *in-utero*

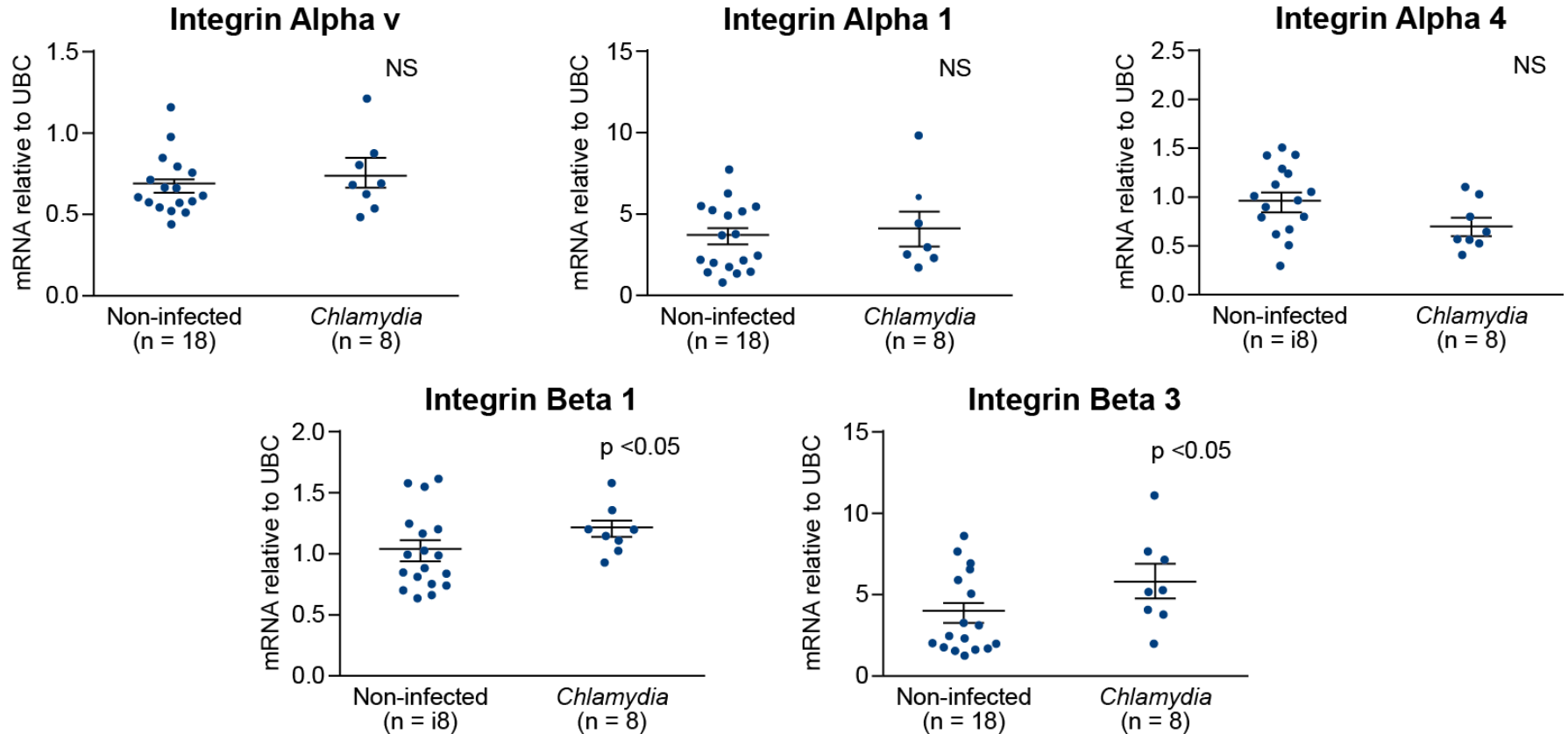
Integrins in human FT



Integrins in human FT



Integrins and *C. trachomatis*

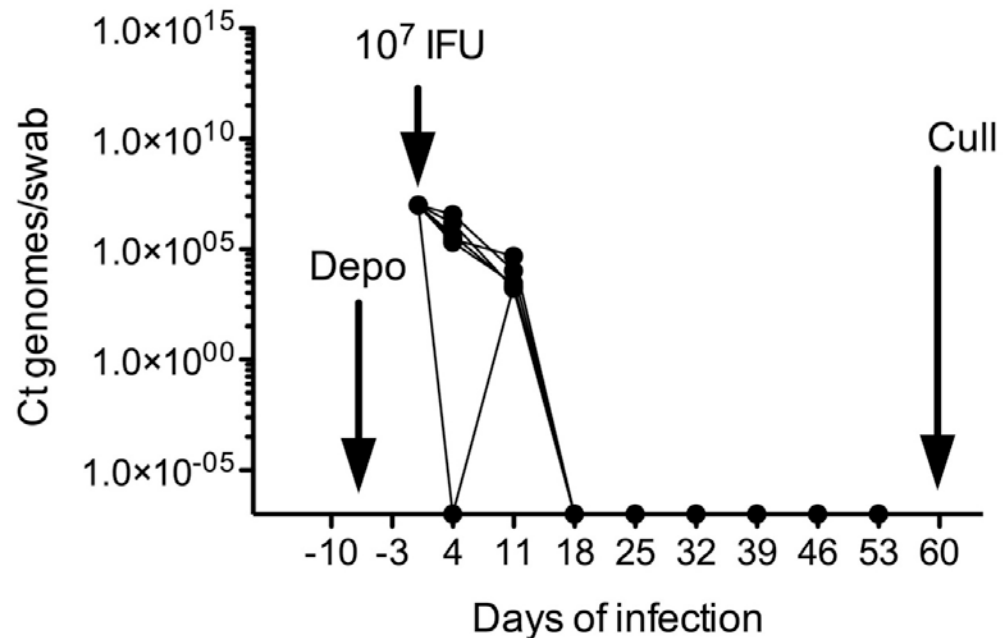


Integrins beta 1 and beta 3 are increased in women with past exposure to chlamydial infection

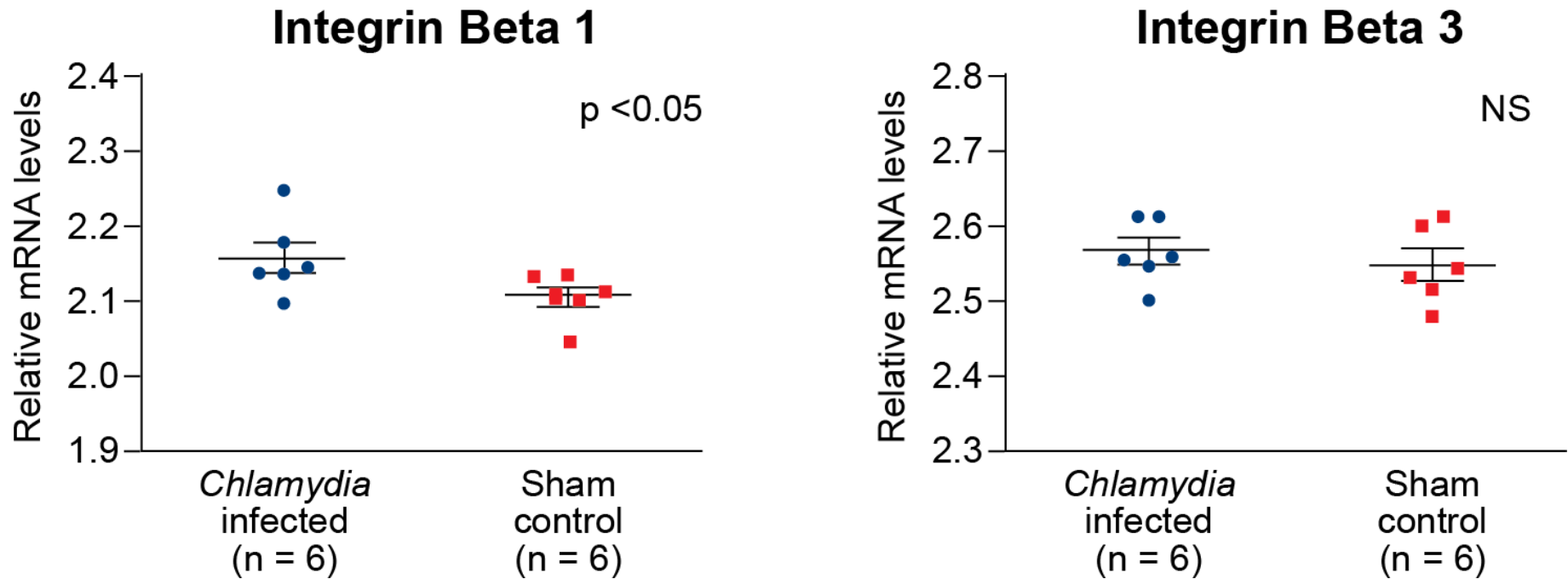
Murine model of tubal integrin expression following *C. trachomatis* infection



C57BL/6



Integrins and *C. trachomatis*



Integrin beta 1 is increased in mice with past exposure to chlamydial infection

Past exposure to genital *C. trachomatis* infection
leads to increased Fallopian tube integrin
expression resulting in a tubal microenvironment
predisposed to ectopic pregnancy

Why is this important?

- National Chlamydia Screening Program (NCSP) introduced in England, Sweden and USA

SIGN state that “in the absence of a complication rate of 10% or more in women with untreated chlamydial infection, there is no evidence that a screening program is cost effective with regard to reducing morbidity”

- Impact research into prophylactic and therapeutic vaccines against *C.trachomatis*

Understanding the natural history of infection, the host immune response and how these impact on subsequent pathology is crucial to rational vaccine design

Summary

- Pelvic infection is common
- Most of the published data focuses on the association between *C. trachomatis* infection and adverse reproductive outcome
- More studies are needed to determine the causative role of *C. trachomatis* in adverse reproductive outcomes
- The underlying mechanism linking *C. trachomatis* infection to ectopic pregnancy is due to subtle alterations in gene expression rather than gross fibrosis
- More research is required on the impact on reproductive outcome from pelvic infection due to non-STD pathogens

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