



# New roles for IL-11 and LIF in endometrial remodelling

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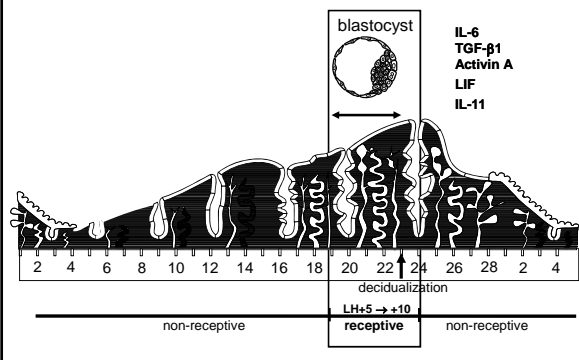
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## Endometrial remodelling in preparation for implantation



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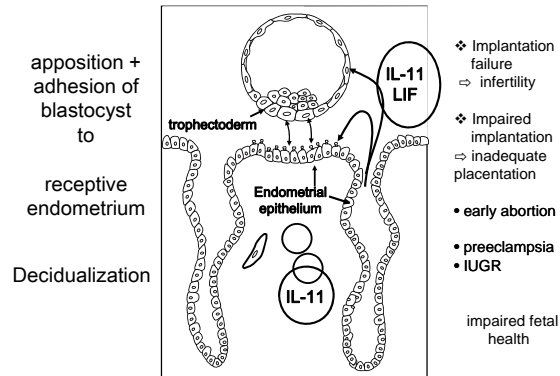
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## Embryo implantation



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## LIF and IL-11

### *In mice*

- Both critical for implantation
- LIF<sup>-/-</sup> mouse infertile due to implantation failure (*Steward et al, Nature, 1992*)
- IL-11R $\alpha$ <sup>-/-</sup> mouse is infertile due to defective decidualization (*Robb et al, Nature Med, 1998*)
- Endometrial expression tightly regulated temporally and spatially

### *In humans*

- Appropriately expressed in endometrium BUT some differences in cellular location vs mice

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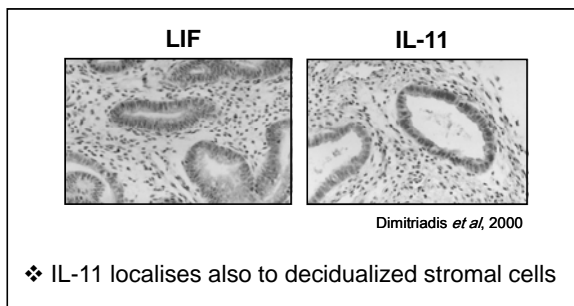
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## LIF and IL-11 in epithelium during 'window of implantation' in humans



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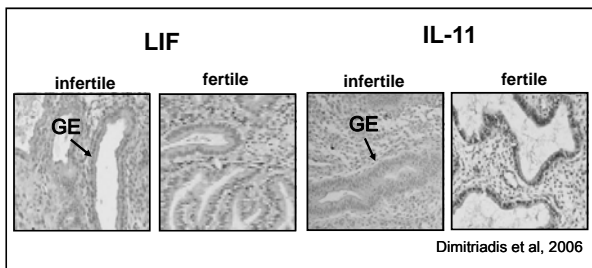
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## LIF and IL-11 are reduced in GE of women with infertility and endometriosis



❖ During the 'window of receptivity'

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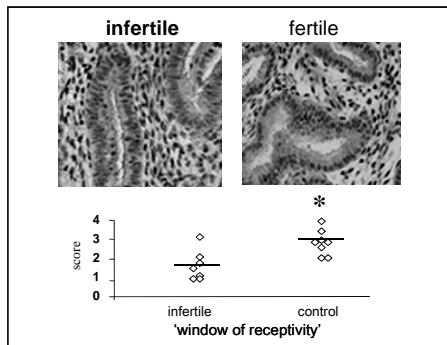
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**IL-11 is reduced in endometrial GE in women with primary infertility**



Dimitriadis et al, 2007

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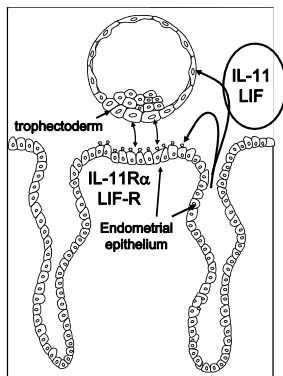
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**trophoblast- epithelial interactions**

apposition + adhesion of blastocyst to

receptive endometrium



IL-11 & LIF present in uterine fluid during the receptive phase

Makkar, JCEM, 2006

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**IL-11 and LIF roles in infertility in women**

*Do IL-11 and LIF regulate human endometrial epithelial cell adhesion?*

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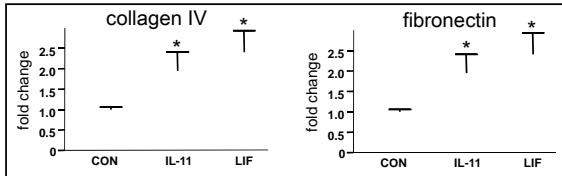
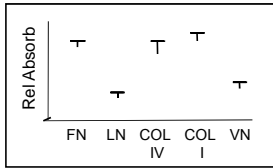
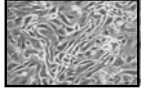
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**IL-11 and LIF increase adhesion of primary HEEC to fibronectin and collagen**




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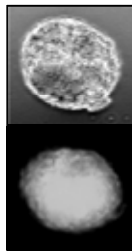
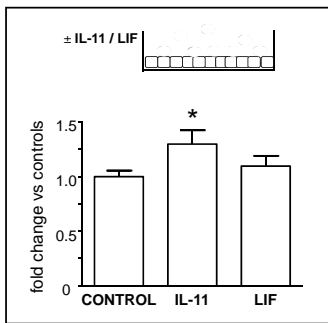
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**IL-11 increases adhesive capacity of HEEC for primary trophoblast cells**



*Shimomura et al Mol HR, 2006*

*Dimitriadis et al, Endo, 2009*

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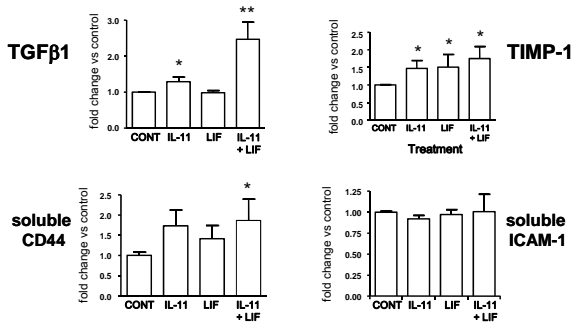
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**IL-11 and LIF regulated ECM and adhesion molecule secretion in primary HEEC**




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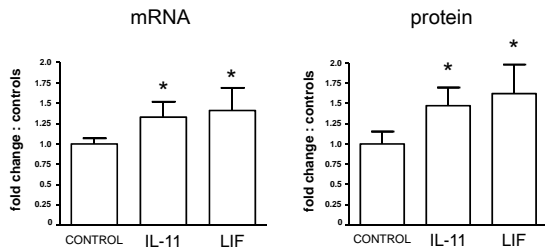
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### IL-11 and LIF stimulate integrin $\alpha 2$ in HEEC



integrin  $\alpha 2$  binds to collagen IV / laminin

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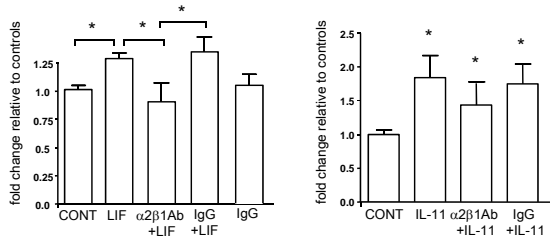
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### LIF stimulates adhesion of HEEC to collagen IV is via integrin $\alpha 2\beta 1$



❖ Col IV and IT $\alpha 2\beta 1$  are present in EEC in secretory phase

*Dimitriadis et al. Endo, 2009*

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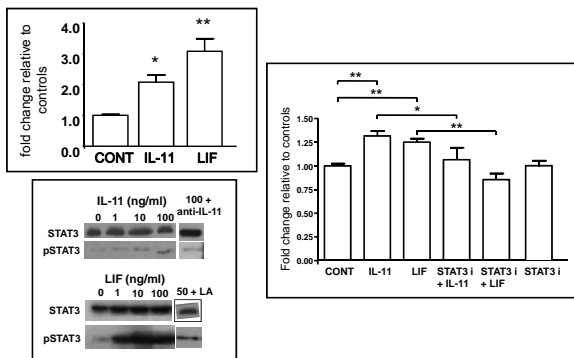
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### IL-11 and LIF stimulate adhesion of primary HEEC to fibronectin via pSTAT3




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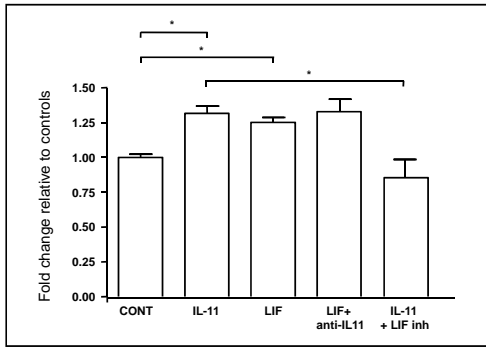
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### HEEC binding to fibronectin : LIF compensates for IL -11




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### SUMMARY 1

- IL-11 and LIF
- ❖ increase HEEC adhesion to FN and collagen IV
- ❖ regulate ECM and adhesion molecule protein secretion
- ❖ increase binding to FN via STAT3 phosphorylation
- LIF
- ❖ Compensates for IL-11 in binding to FN in EEC
- ❖ but not IL-11 stimulates adhesion of HEEC to col IV via integrin  $\alpha 2\beta 1$

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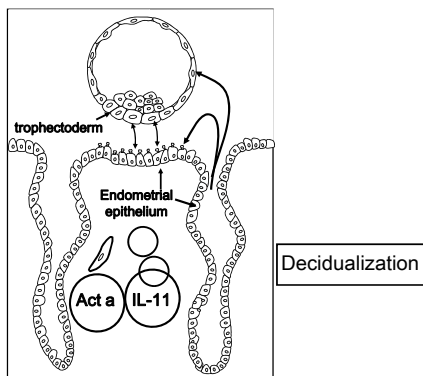
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### Decidualization




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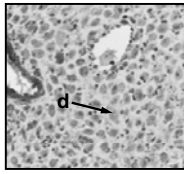
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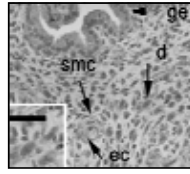
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## Interactions during decidualization



Jones et al, 2000,02



Dimitriadis et al, 2000,02

- ❖ IL-11 & Activin a progress P-induced decidualization
- ❖ Do IL-11 & Activin A interact to promote decidualization?

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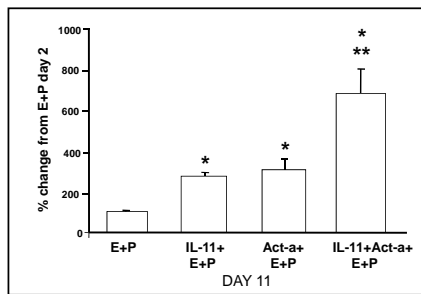
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## IL-11 and Activin A synergise to enhance decidualization




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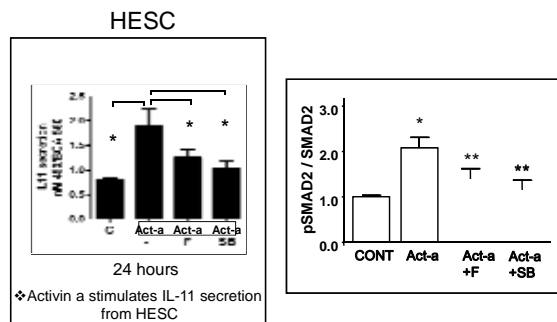
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## IL-11 and Activin A synergise to enhance decidualization



▪ Bioactivity regulated via its BP, follistatin; SB is an activin type II receptor inhibitor

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## SUMMARY 2

- ❖ Activin a and IL-11 synergise to progress decidualization
- ❖ Activin a stimulates IL-11 secretion via pSMAD2

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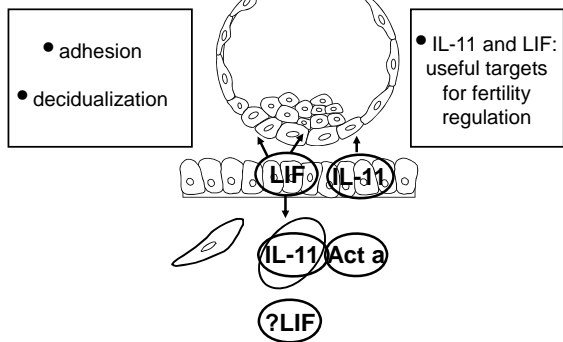
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## Critical mediators of human implantation



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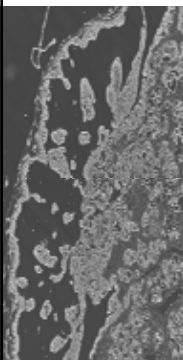
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## Acknowledgements



Melinda Marwood  
Kathryn Visser  
Joanne Yap

Lois Salamonsen  
Jin Zhang  
Ellen Menkhorst  
Jun Gu  
Craig Harrison

Jianguo Zhang  
Nick Nicola

Rob Sherwin  
Andrew Sharkey

Gabor Kovacs  
Martin Stafford-Bell  
Bev Vollenhoven  
Gareth Evans

*Funding : NHMRC (Australia)  
CONRAD/CICCR (USA)*

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### **Conclusions - Implications**

- ❖ Locally produced cytokines regulate adhesion-related molecules at the human endometrial epithelium during implantation: important for the attachment of movement of trophoblast through the endometrium until they tap into the maternal blood supply
  
- ❖ Inadequate implantation / placentation results in infertility, early miscarriage, pre-eclampsia

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## Leukaemia inhibitor factor (LIF) and Interleukin-11 (IL)-11



- secreted IL-6 type cytokines
- bind the IL-11R $\alpha$  or LIFR $\alpha$ :
- and bind the common transducing element, gp130
- phosphorylation of JAK/STAT pathway
- redundancy
- Numerous roles and including:  
*embryo implantation and tumorigenesis*

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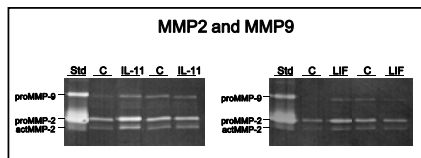
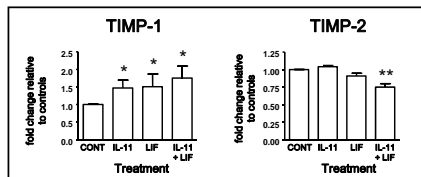
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## IL-11 and LIF regulate TIMP secretion from HEEC




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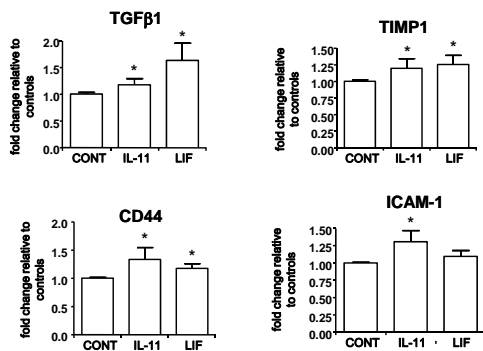
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## IL-11 and LIF regulated ECM and adhesion molecule mRNA expression in primary HEEC



*Dimitriadis et al, Endo, 2009*

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