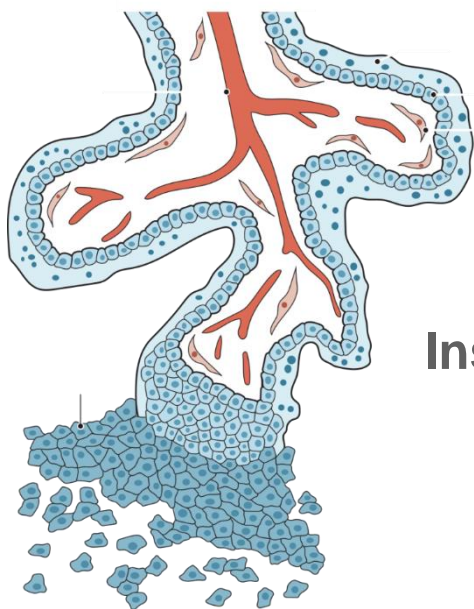


## IFITM proteins inhibit placental syncytiotrophoblast formation and promote fetal demise



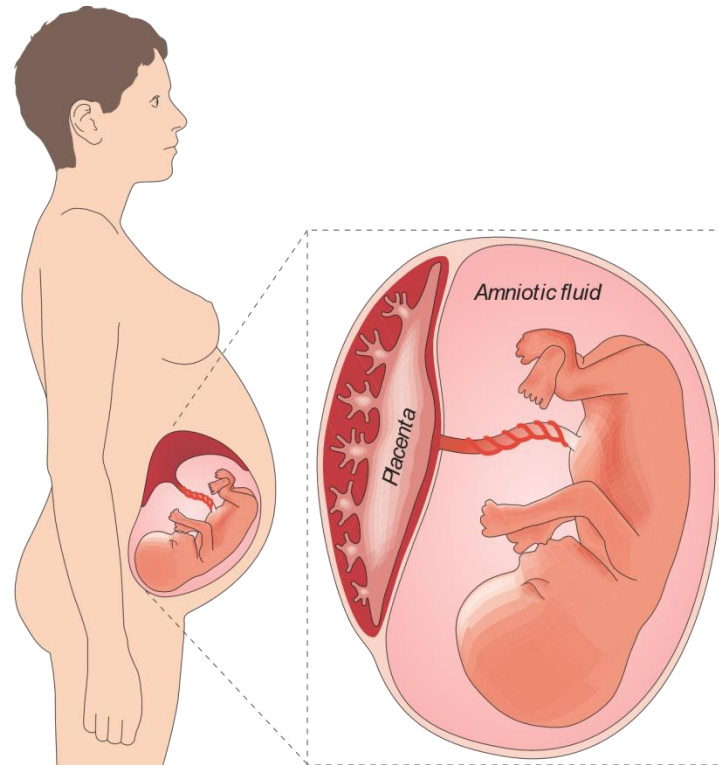
*Kellam & Weiss, Science (2019)*

*Julian Buchrieser*

Institut Pasteur, Paris - Virus and Immunity Unit

Olivier Schwartz

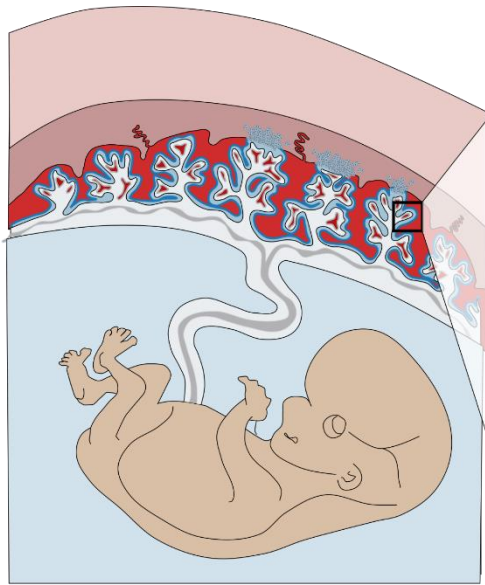
# The placenta



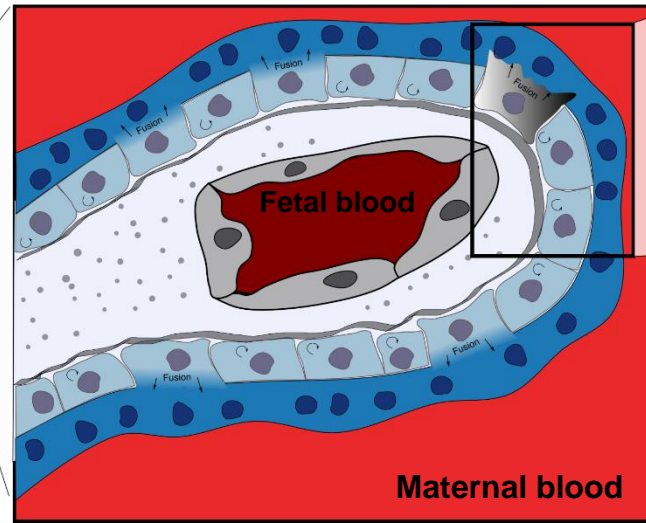
Adapted from Coyne 2018

- Nutrient exchange
- O<sub>2</sub>/CO<sub>2</sub> exchange
- Hormone production
- Pathogen protection
- Immune tolerance

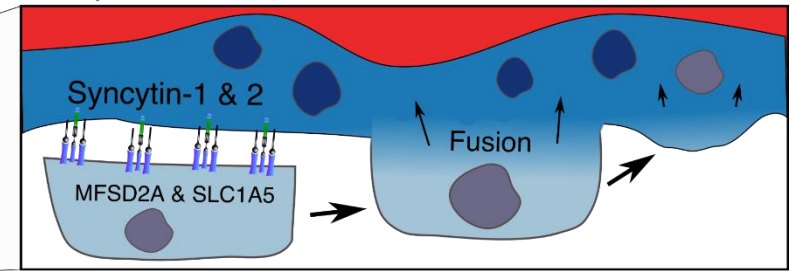
# Placental syncytiotrophoblast development



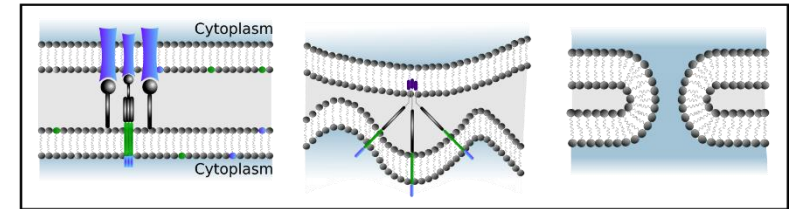
Adapted from Zeldovich et al. 2011



## Simplified Fusion mechanism



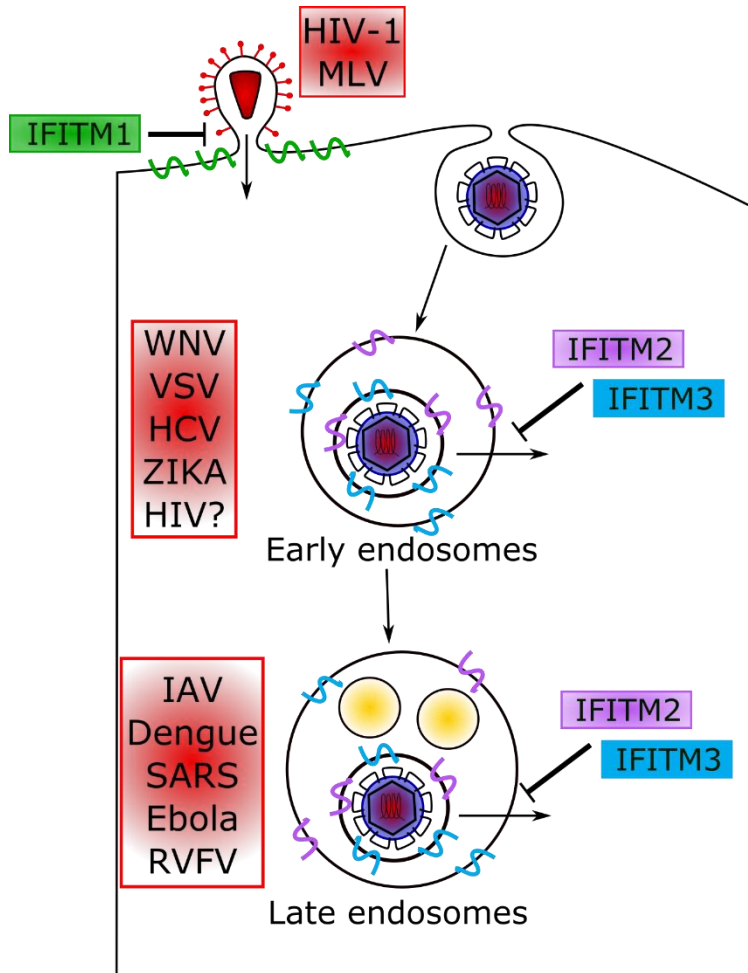
## Syncytin-2 (FRD) fusion mechanism:



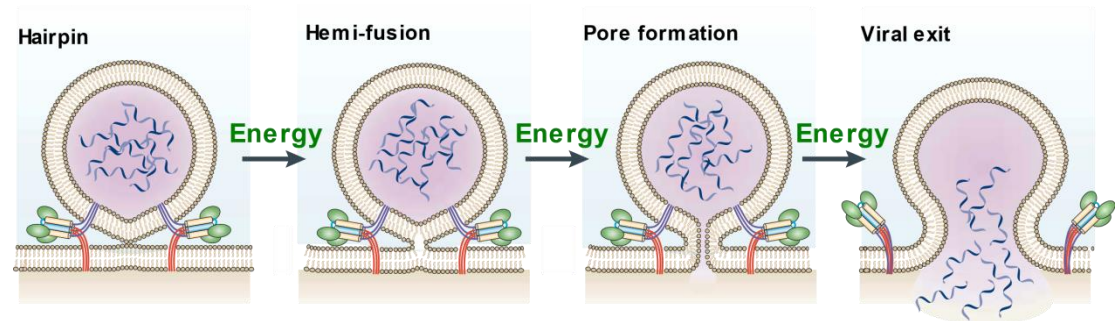
## Syncytin-1/2 (ERV-W/FRD):

- Endogenous retroviral envelope
- Type I fusion protein
- Integrated 40M & 20M years ago

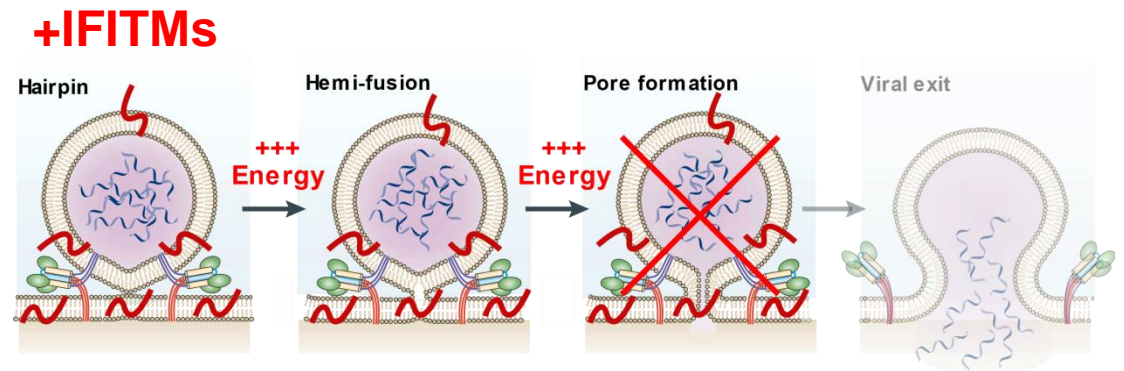
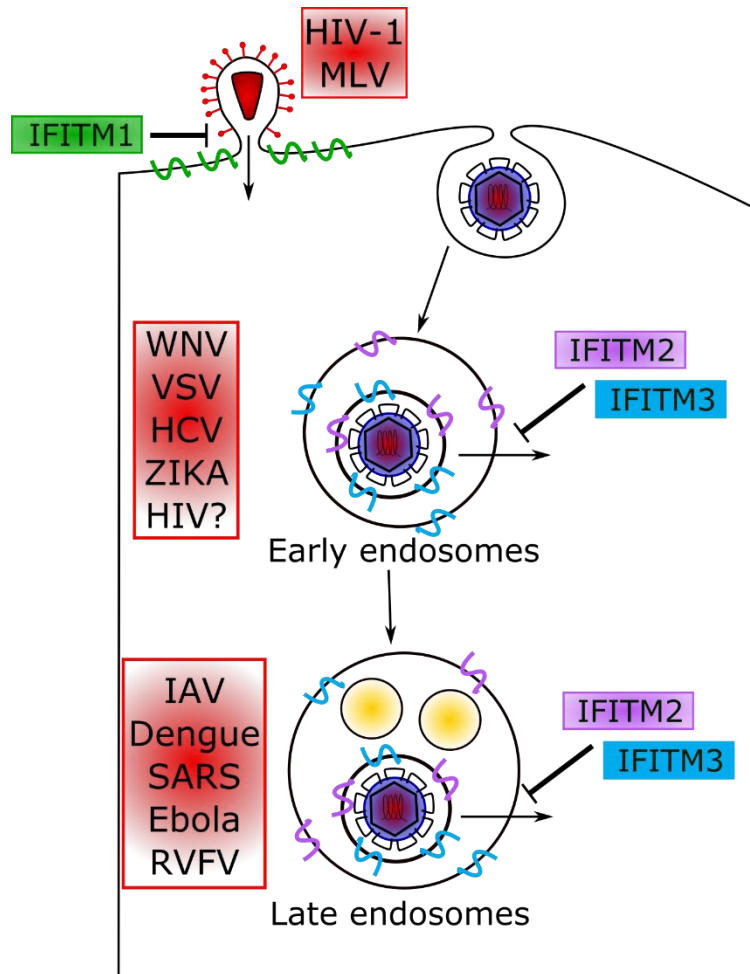
# Interferon-induced transmembrane proteins (IFITMs)



## No IFITMs



# Interferon-induced transmembrane proteins (IFITMs)



→ Increased membrane rigidity  
 → Hemi-fusion block

# IFNs & pregnancy complication

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

ANTIVIRAL IMMUNITY

## Type I interferons instigate fetal demise after Zika virus infection

Laura J. Yockey,<sup>1</sup> Kellie A. Jurado,<sup>1</sup> Nitin Arora,<sup>2</sup> Alon Millet,<sup>1</sup> Tasfia Rakib,<sup>1</sup> Kristin M. Milano,<sup>3</sup> Andrew K. Hastings,<sup>4</sup> Erol Fikrig,<sup>4,5</sup> Yong Kong,<sup>6</sup> Tamas L. Horvath,<sup>7</sup> Scott Weatherbee,<sup>8</sup> Harvey J. Kliman,<sup>3</sup> Carolyn B. Coyne,<sup>2,9</sup> Akiko Iwasaki<sup>1,5\*</sup>

## Trisomy 21 consistently activates the interferon response



Kelly D Sullivan<sup>1,2,3,4\*</sup>, Hannah C Lewis<sup>1,2</sup>, Amanda A Hill<sup>1,2</sup>, Ahwan Pandey<sup>1,2,3,4</sup>, Leisa P Jackson<sup>1,3,4</sup>, Joseph M Cabral<sup>1,3,4</sup>, Keith P Smith<sup>1</sup>, L Alexander Liggett<sup>1,5</sup>, Eliana B Gomez<sup>1,3,4</sup>, Matthew D Galbraith<sup>1,2,3,4</sup>, James DeGregori<sup>1,5,6,7,8,9</sup>, Joaquín M Espinosa<sup>1,2,3,4\*</sup>

## Review: Human trophoblast fusion and differentiation: Lessons from trisomy 21 placenta

G. Pidoux<sup>a,b,c</sup>, P. Gerbaud<sup>a,b,c</sup>, M. Cocquebert<sup>a,b,c</sup>, N. Segond<sup>a,b,c</sup>, J. Badet<sup>a,b,c</sup>, T. Fournier<sup>a,b,c</sup>, J. Guibourdenche<sup>a,b,c,d</sup>, D. Evain-Brion<sup>a,b,c,\*</sup>

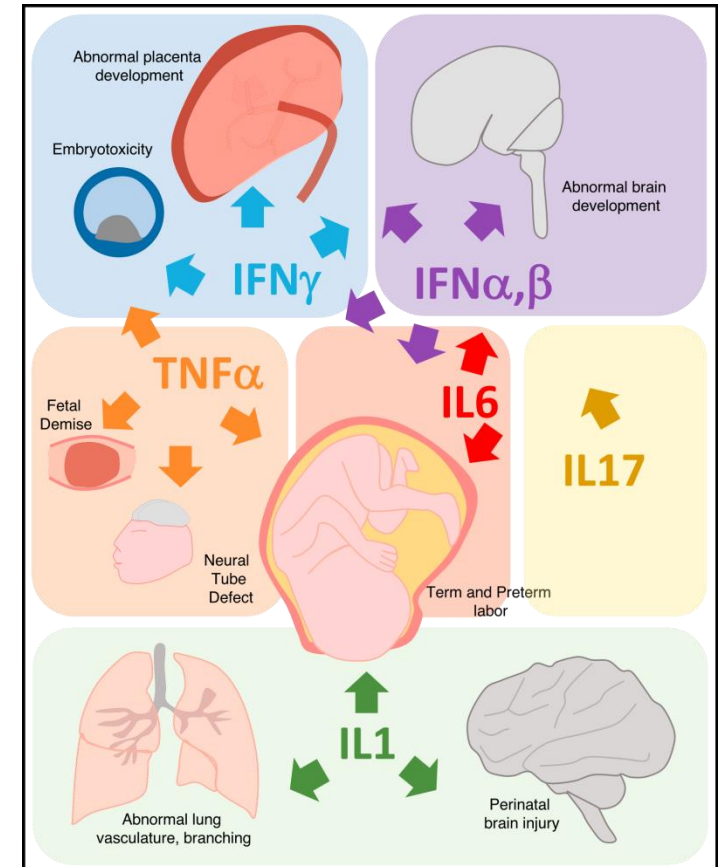
Placenta

## Interferon- $\alpha$ and Angiogenic Dysregulation in Pregnant Lupus Patients Who Develop Preeclampsia

Danieli Andrade,<sup>1</sup> Mimi Kim,<sup>2</sup> Luz P. Blanco,<sup>3</sup> S. Ananth Karumanchi,<sup>4</sup> Gloria C. Koo,<sup>1</sup> Patricia Redecha,<sup>1</sup> Kyriakos Kirou,<sup>1</sup> Angela M. Alvarez,<sup>5</sup> Melissa J. Mulla,<sup>6</sup> Mary K. Crow,<sup>1</sup> Vikki M. Abrahams,<sup>6</sup> Mariana J. Kaplan,<sup>3</sup> and Jane E. Salmon<sup>1</sup>

ARTHRITIS & RHEUMATOLOGY

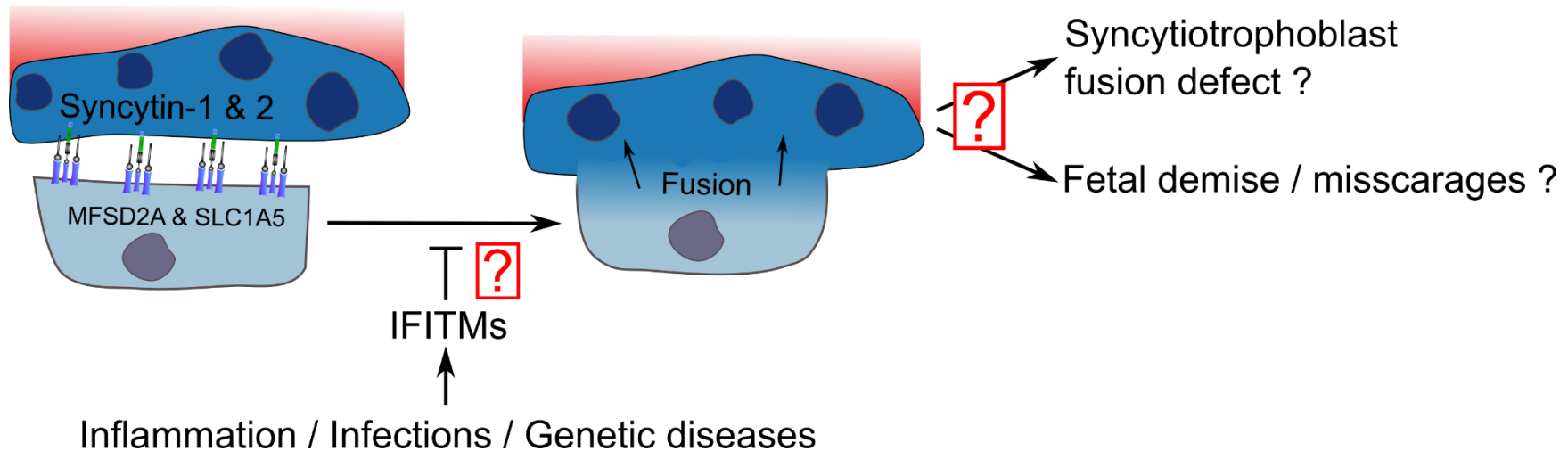
## Inflammation & pregnancy complications



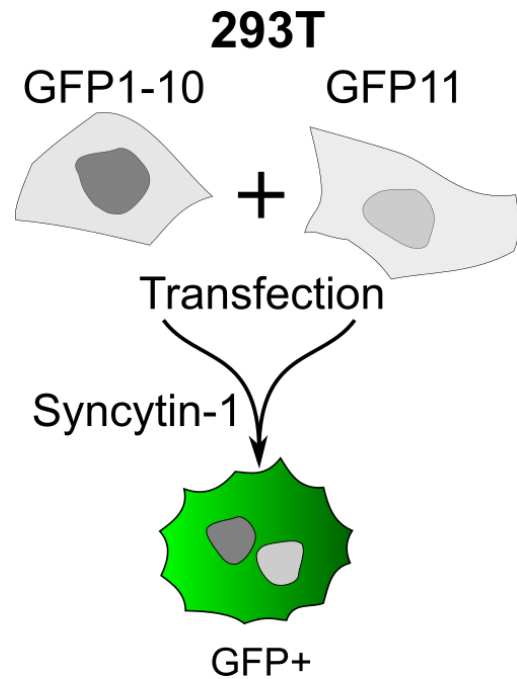
Adapted from Yockey et al. Immunity 2018

# Can IFITMs inhibit syncytiotrophoblast formation?

## Are IFITMs responsible for IFN mediated placental damage and fetal demise?

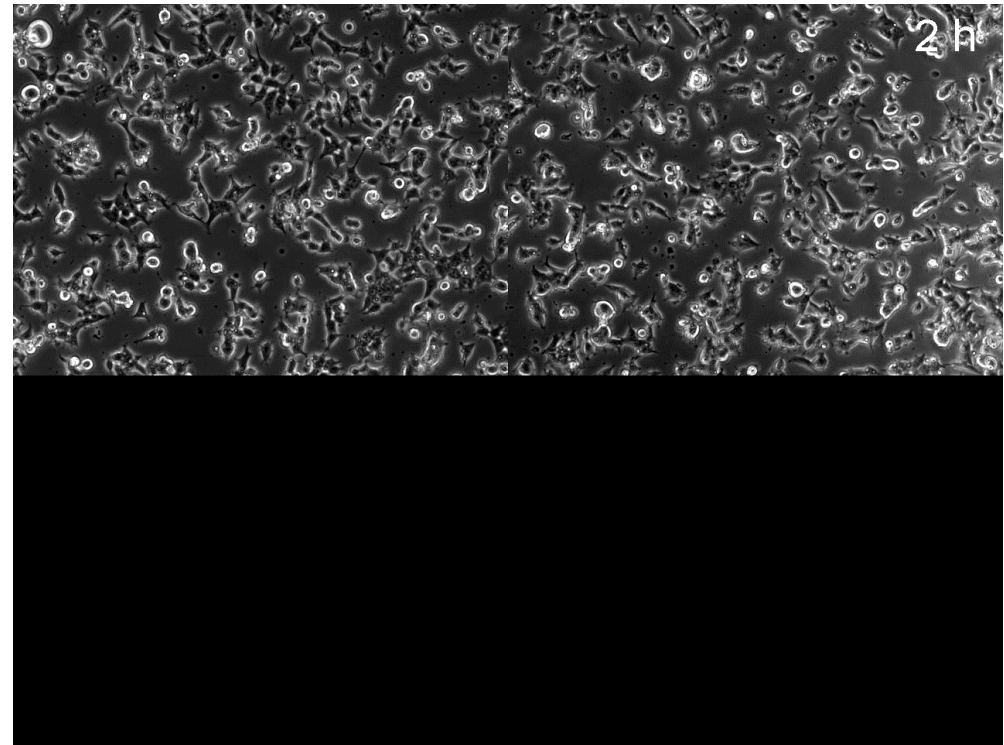


# Complementation System – GFP Split



Control

Syncytin-1

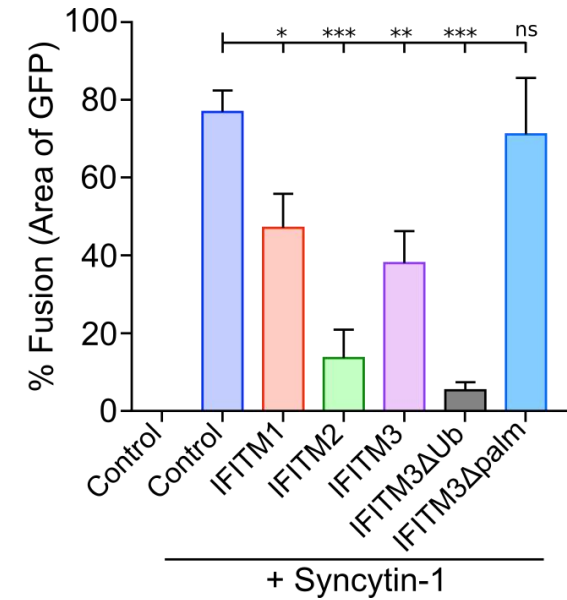
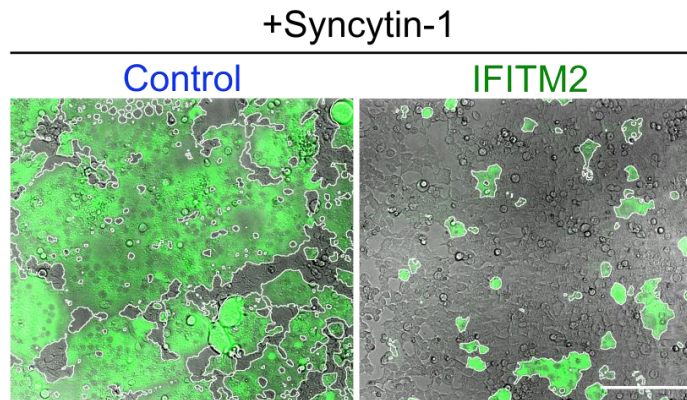
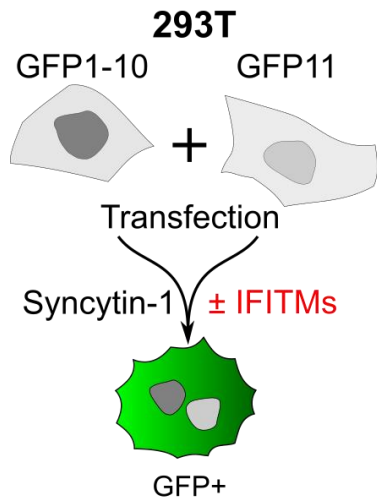


GFP = Syncytia

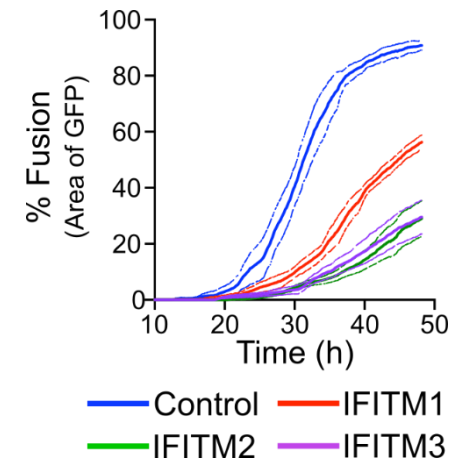
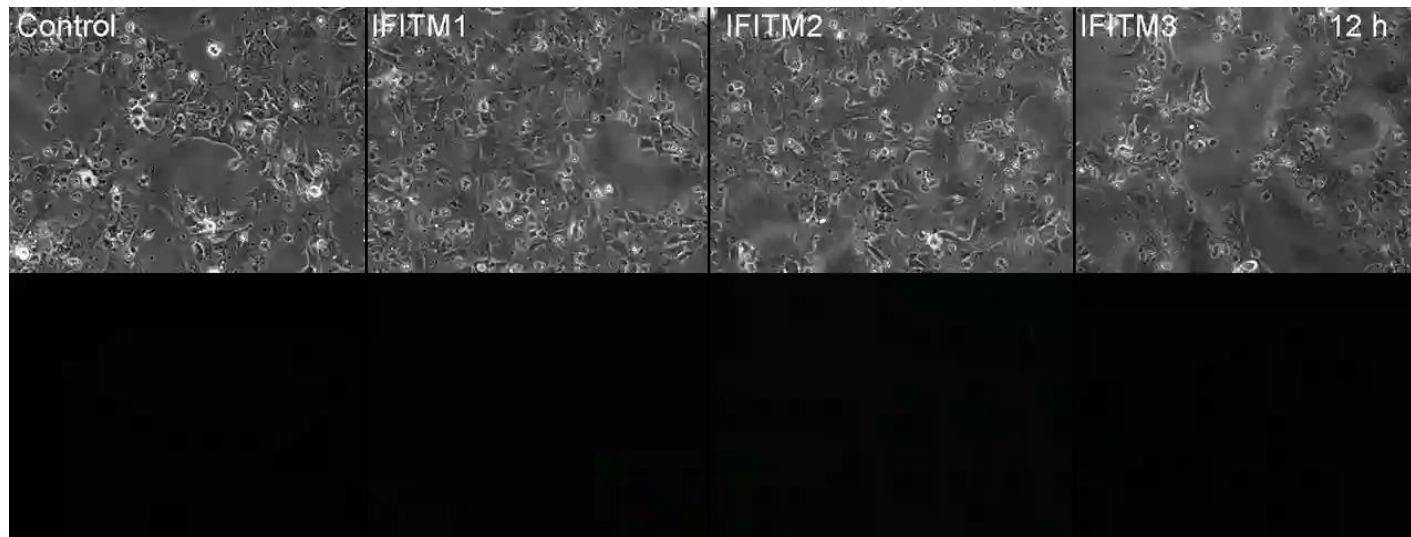
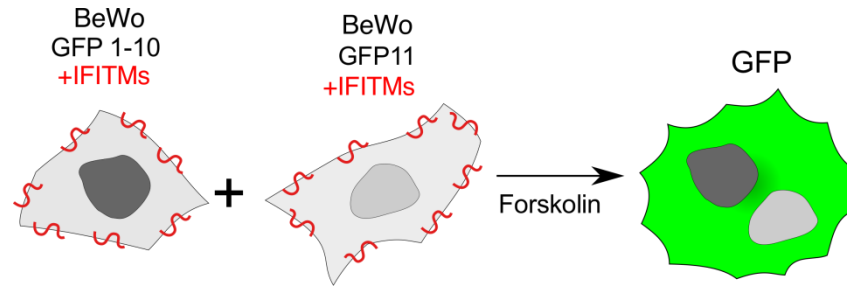




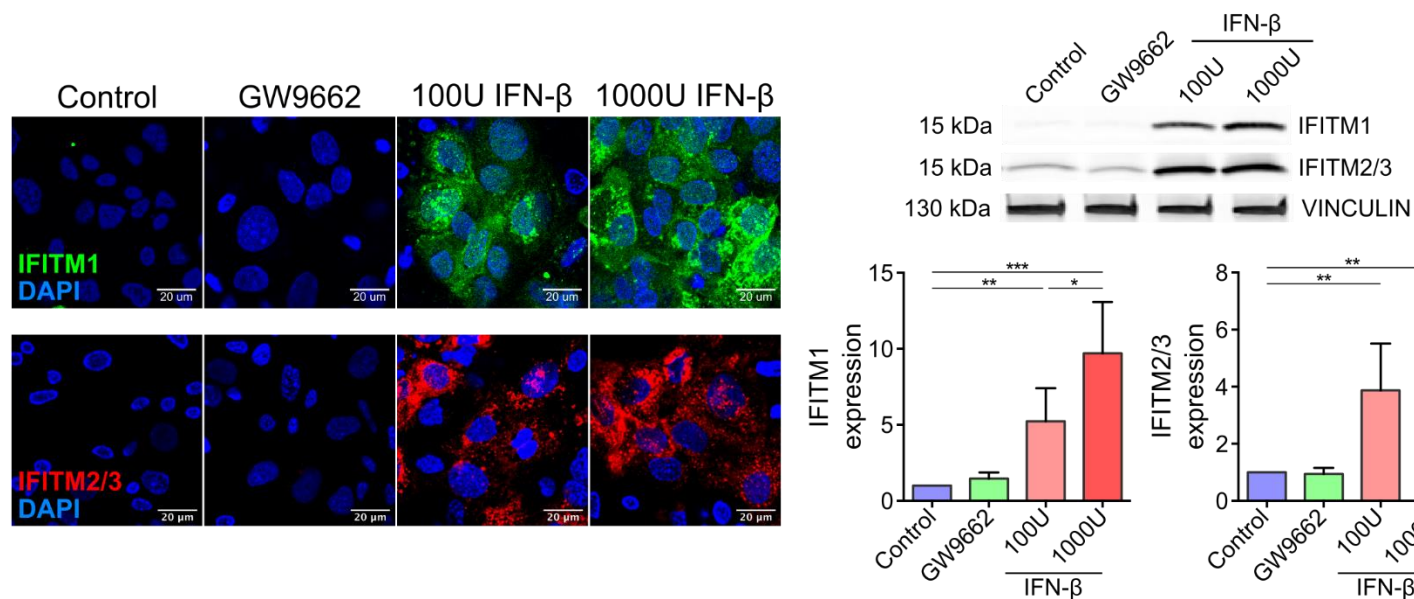
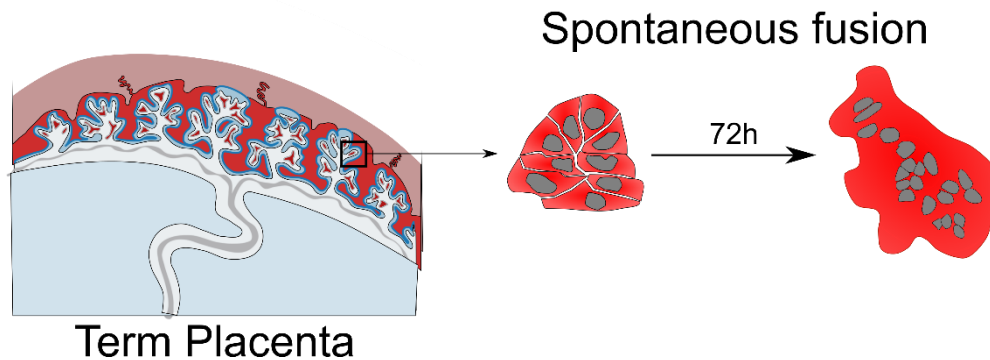
# IFITMs inhibit Syncytin mediated cell fusion



# IFITMs inhibit Syncytin mediated cell fusion

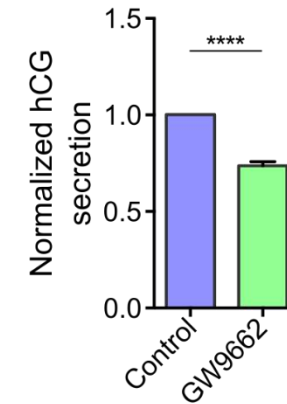
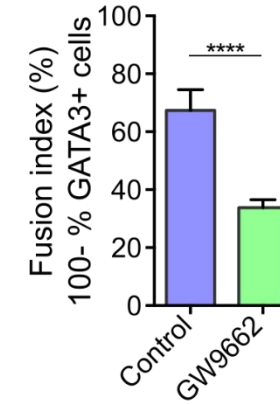
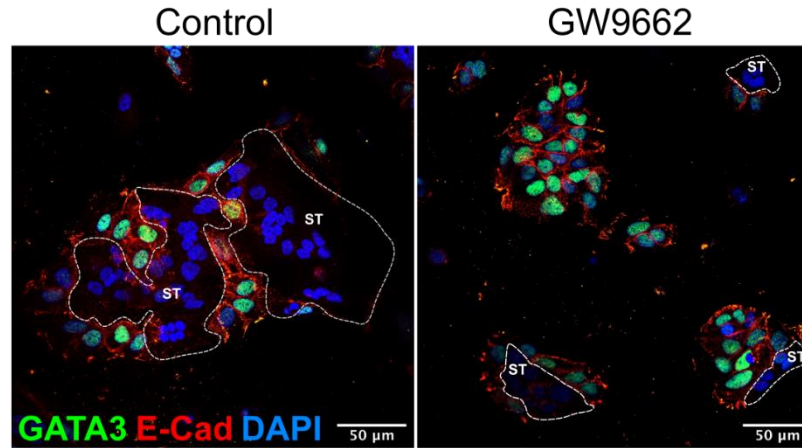
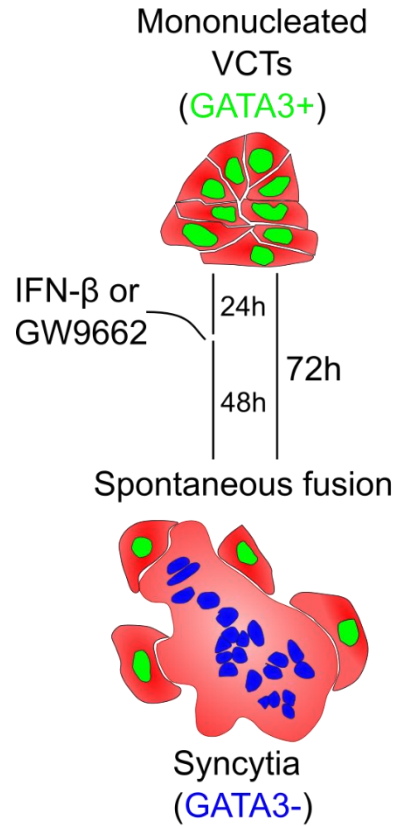


# IFN- $\beta$ upregulates IFITMs in primary human villous cytotrophoblasts (VCTs)



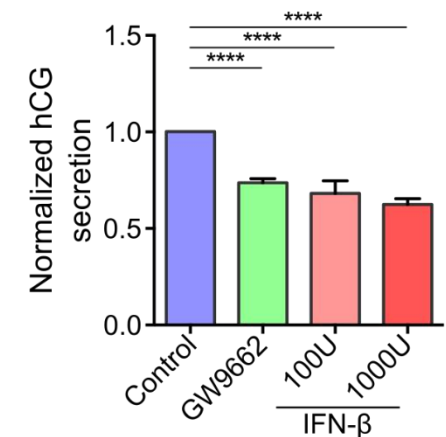
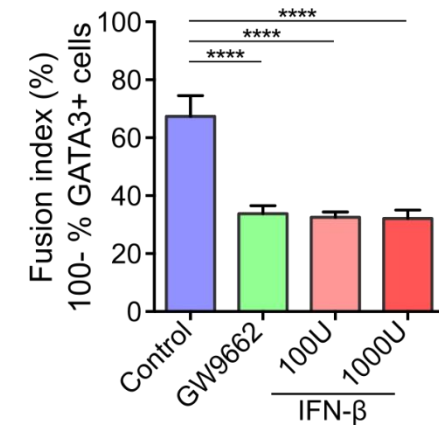
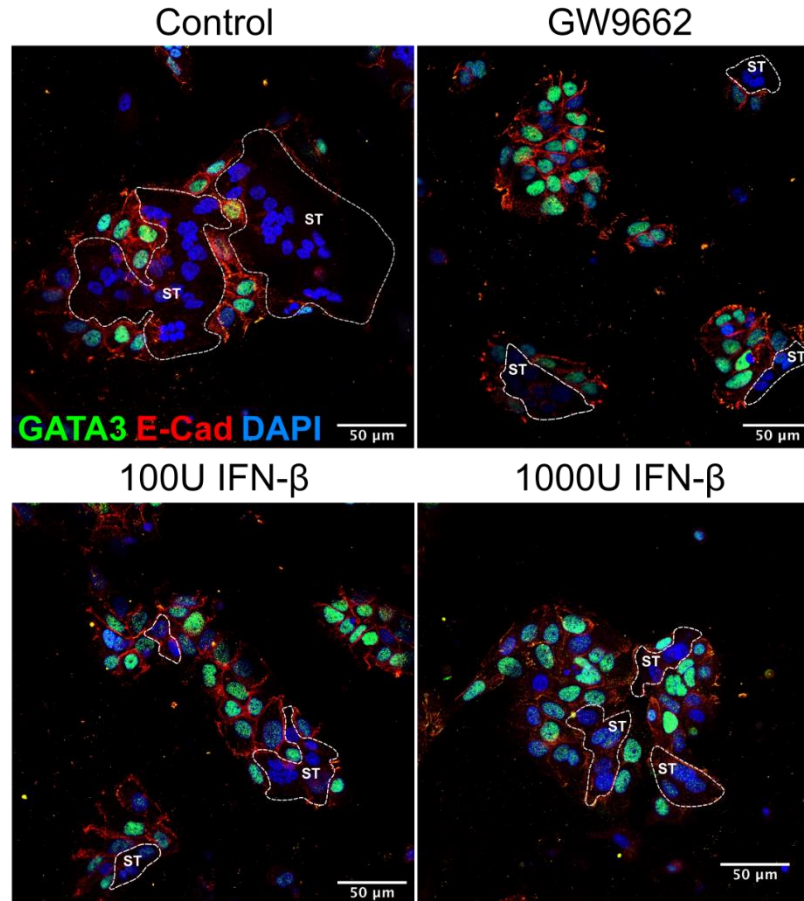
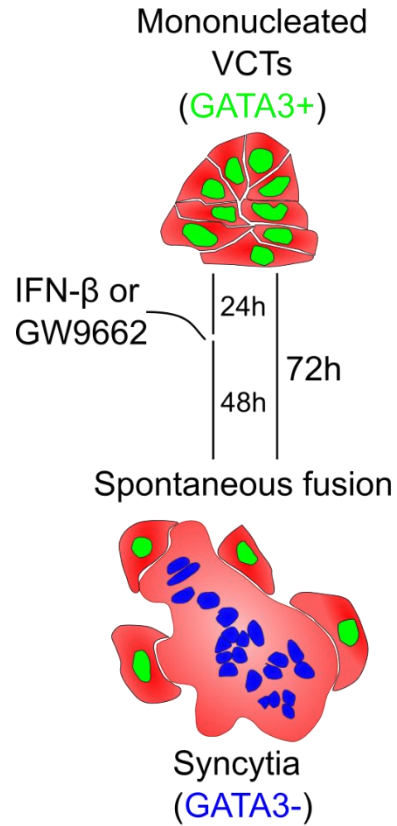
In collaboration with Séverine Degrelle & Thierry Fournier

# IFN- $\beta$ inhibits VCTs cell-cell fusion



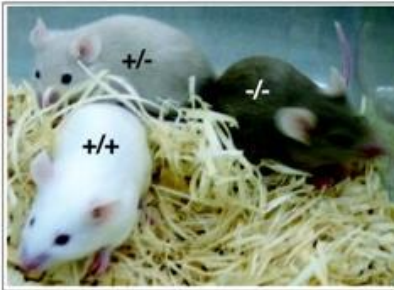
In collaboration with Séverine Degrelle & Thierry Fournier

# IFN- $\beta$ inhibits VCTs cell-cell fusion



In collaboration with Séverine Degrelle & Thierry Fournier

# Mouse model – *IfitmDel* mice

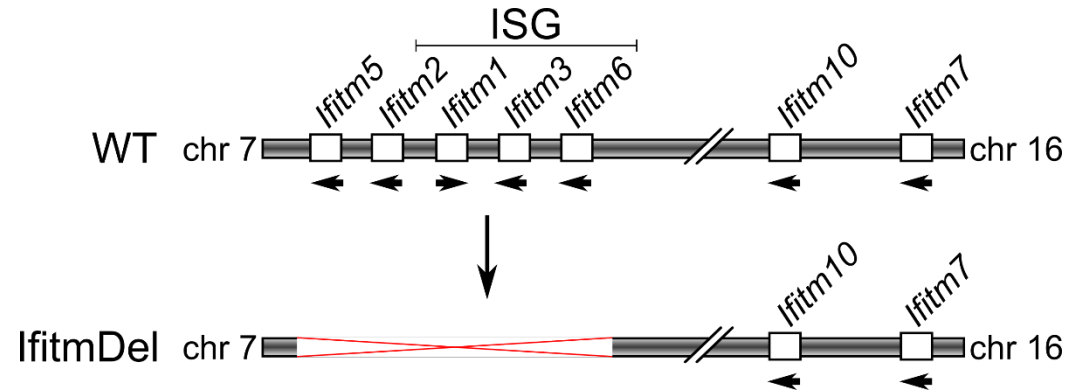


→ Viable & fertile

→ No overt differences in size or behaviour

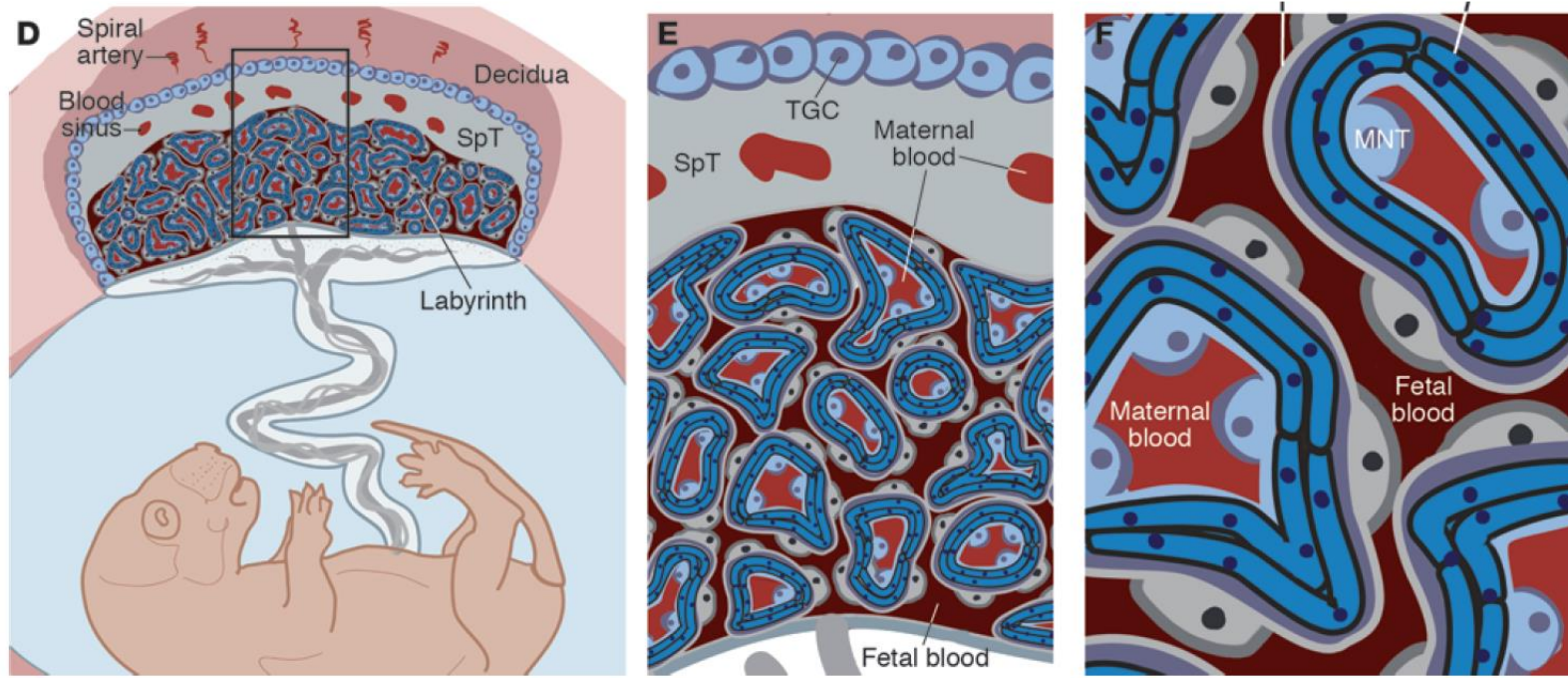
→ More susceptible to viral infections

→ Some metabolic disorders (get fat with age)



Lange et al. *Mol. Cell. Biol.* 2008

# Placental syncytiotrophoblast development



## Syncytin-A & -B:

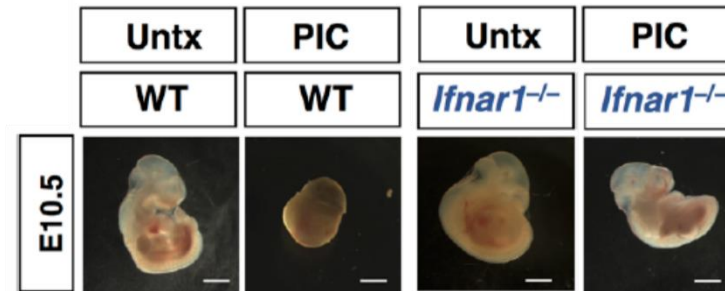
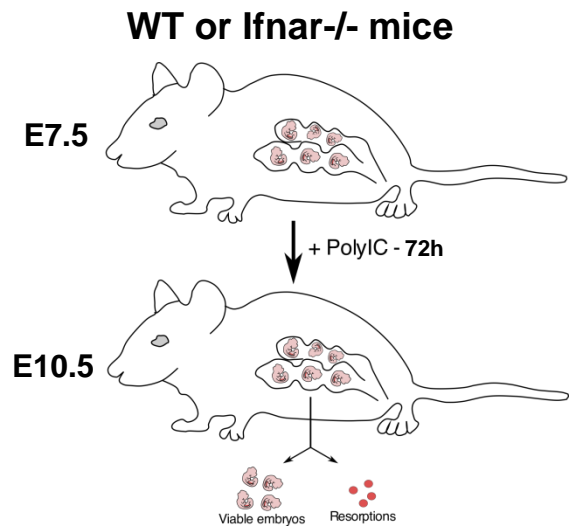
- Endogenous retroviral envelope
- Type I fusion protein
- Different integration event than humans



ANTIVIRAL IMMUNITY

# Type I interferons instigate fetal demise after Zika virus infection

Laura J. Yockey,<sup>1</sup> Kellie A. Jurado,<sup>1</sup> Nitin Arora,<sup>2</sup> Alon Millet,<sup>1</sup> Tasfia Rakib,<sup>1</sup> Kristin M. Milano,<sup>3</sup> Andrew K. Hastings,<sup>4</sup> Erol Fikrig,<sup>4,5</sup> Yong Kong,<sup>6</sup> Tamas L. Horvath,<sup>7</sup> Scott Weatherbee,<sup>8</sup> Harvey J. Kliman,<sup>3</sup> Carolyn B. Coyne,<sup>2,9</sup> Akiko Iwasaki<sup>1,3\*</sup>



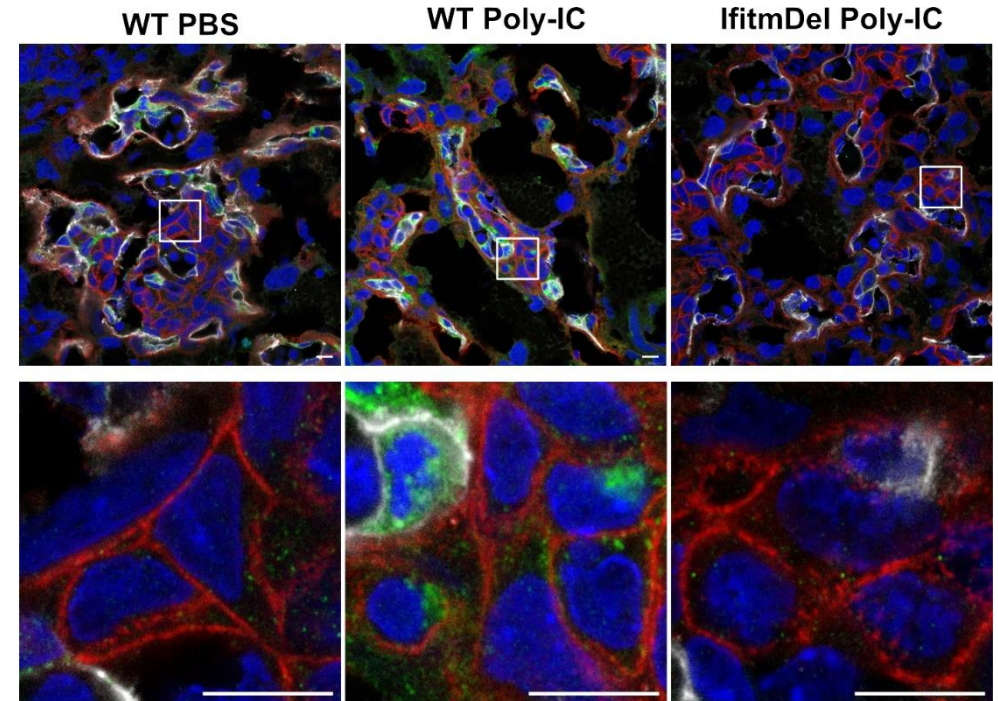
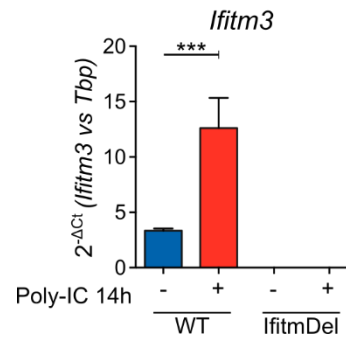
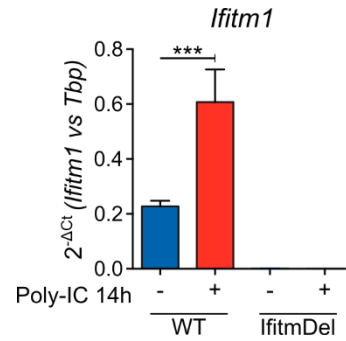
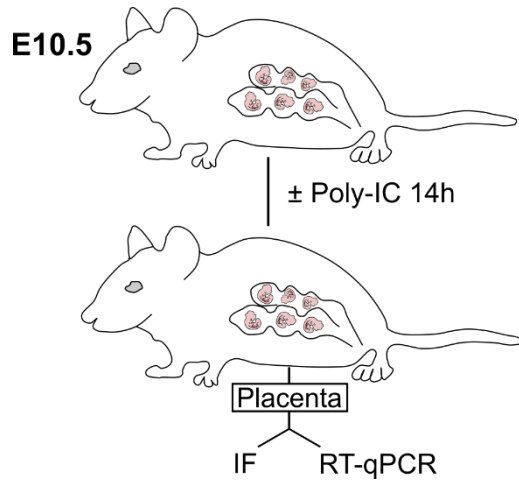
**PolyIC injection of pregnant dams leads to fetal resorption in an IFNAR dependent manner**



Yockey et al. *Science Immunol.* 2018



# Poly-IC induces IFN response in WT and *IfitmDel* mice

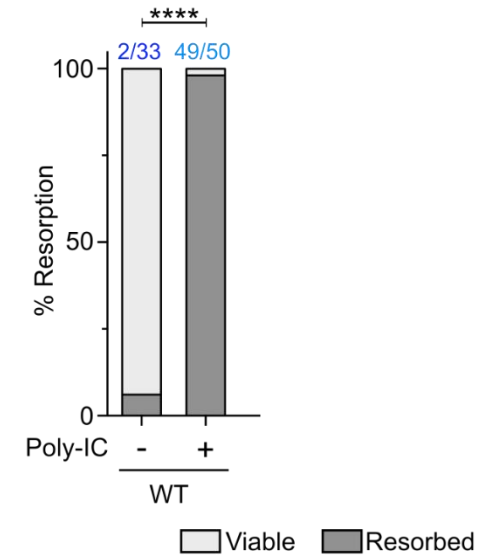
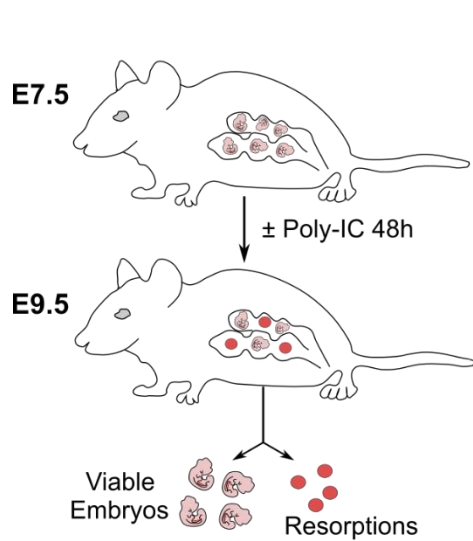


CD31 E-Cad  
Ifitm3 Hoechst



In collaboration with Thérèse Couderc, Olivier Disson & Marc Lecuit  
Caroline Manet & Xavier Montagutelli

# IFITMs are key mediators of IFN mediated fetal demise



*In collaboration with Thérèse Couderc, Olivier Disson & Marc Lecuit  
Caroline Manet & Xavier Montagutelli*



CEA



CHRU



CNRS



CPU



INRA



INRIA



INSERM



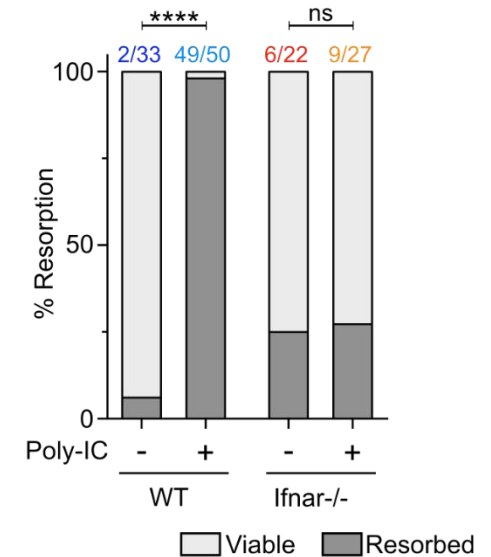
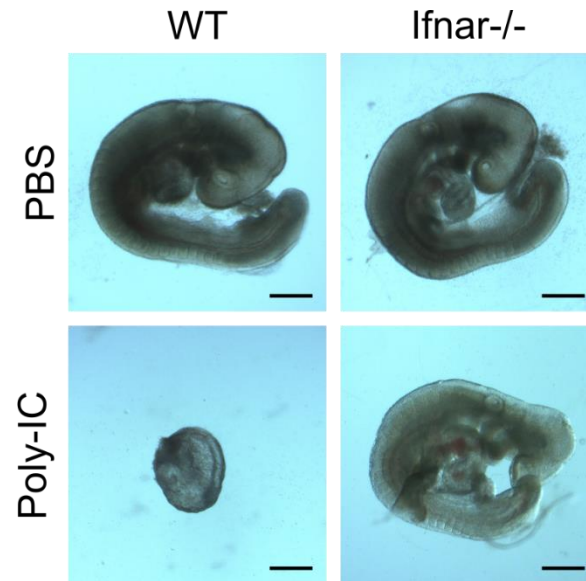
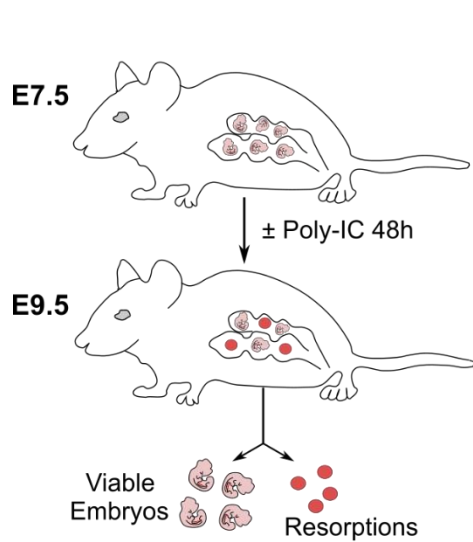
INSTITUT PASTEUR



IRD

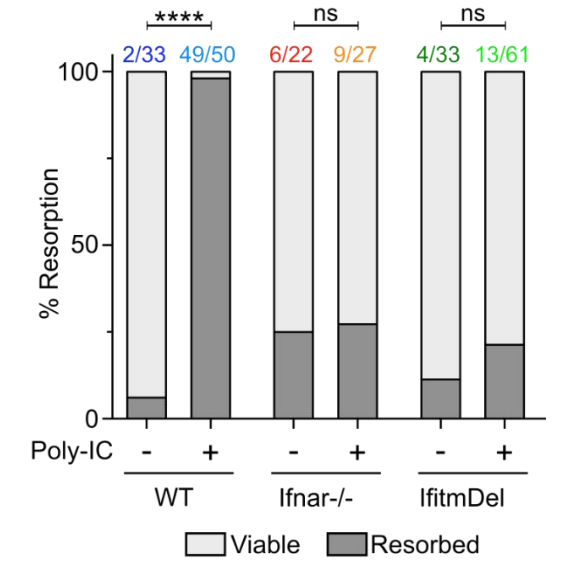
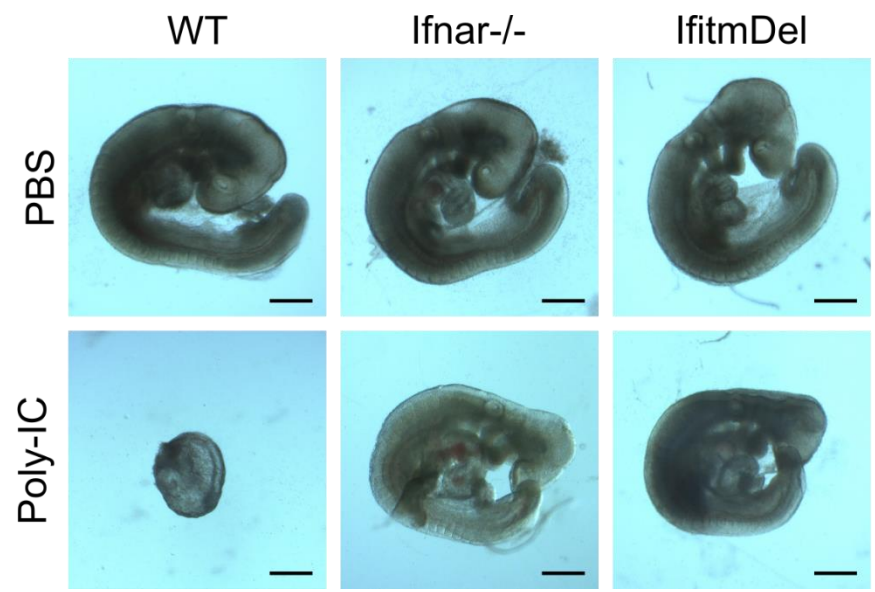
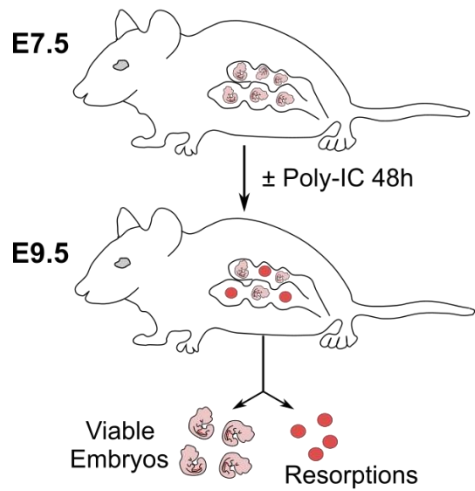


# IFITMs are key mediators of IFN mediated fetal demise



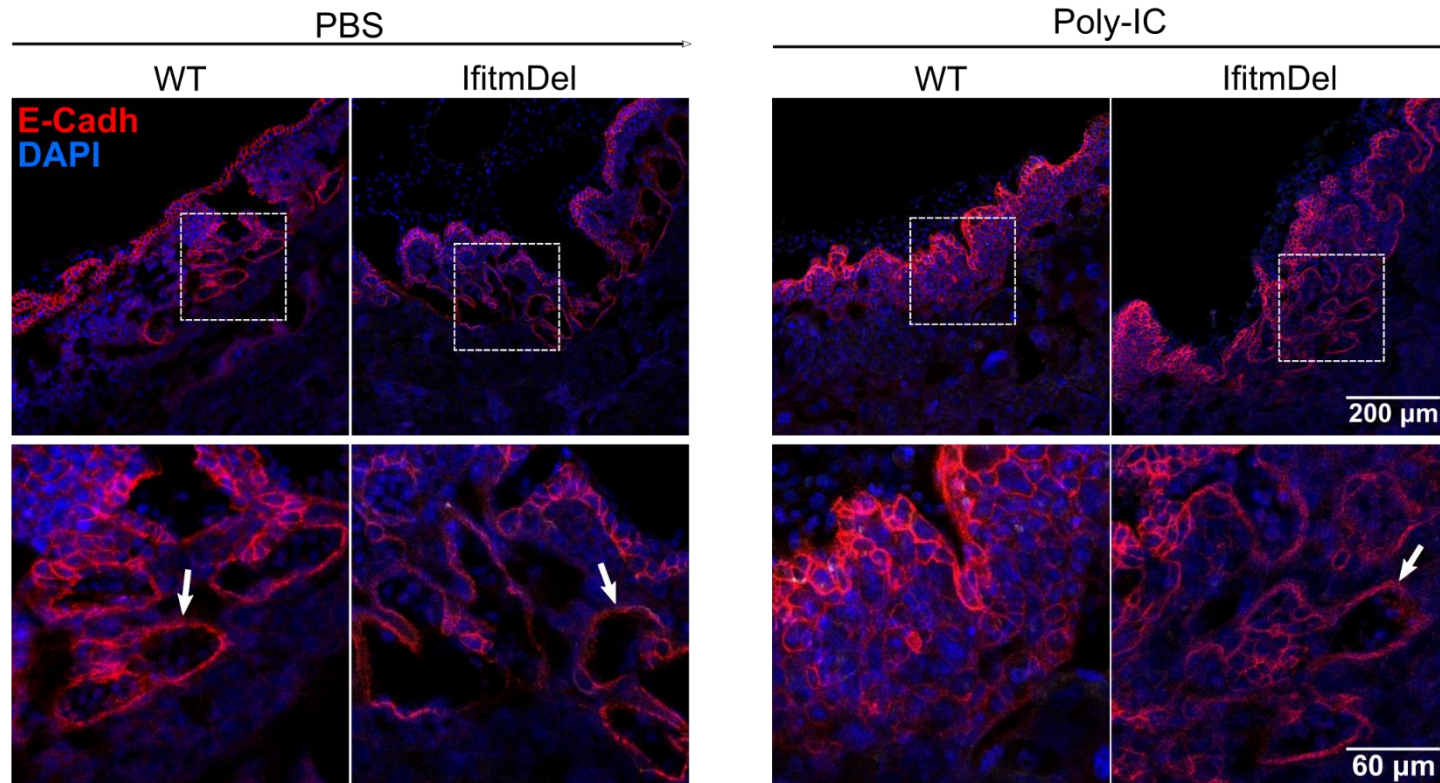
In collaboration with Thérèse Couderc, Olivier Disson & Marc Lecuit  
Caroline Manet & Xavier Montagutelli

# IFITMs are key mediators of IFN mediated fetal demise



*In collaboration with Thérèse Couderc, Olivier Disson & Marc Lecuit  
Caroline Manet & Xavier Montagutelli*

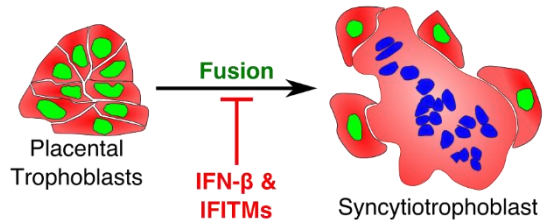
# Syncytiotrophoblast structure after PolyIC injection



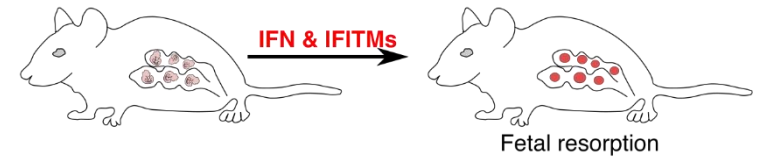
*In collaboration with Thérèse Couderc, Olivier Disson & Marc Lecuit  
Caroline Manet & Xavier Montagutelli*

# Conclusion & Perspectives

IFN and IFITMs inhibit trophoblast fusion

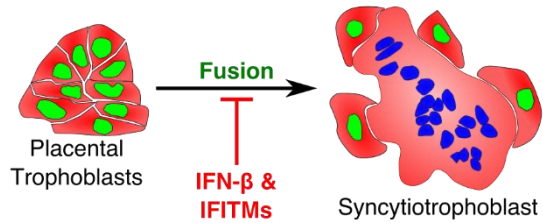


IFITMs are key factors of IFN mediated fetal demise

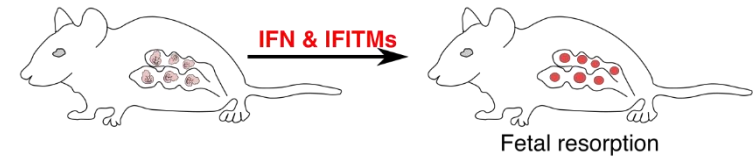


# Conclusion & Perspectives

## IFN and IFITMs inhibit trophoblast fusion



## IFITMs are key factors of IFN mediated fetal demise

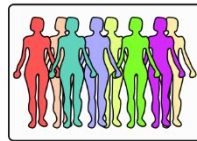


### Role of IFITMs in human IFN mediated placental complications?



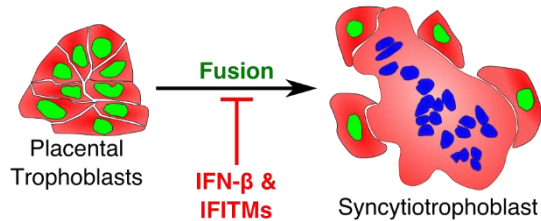
- Lupus?
- Trisomy 21?
- ZIKA?
- Listeria?
- etc.

### Human IFITM polymorphisms of placental disorders

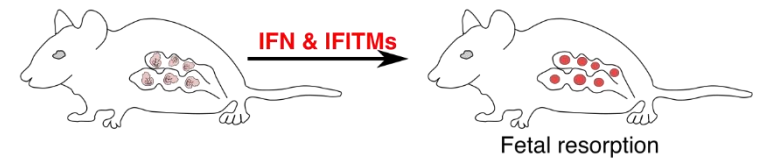


# Conclusion & Perspectives

## IFN and IFITMs inhibit trophoblast fusion



## IFITMs are key factors of IFN mediated fetal demise

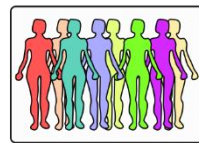


### Role of IFITMs in human IFN mediated placental complications?

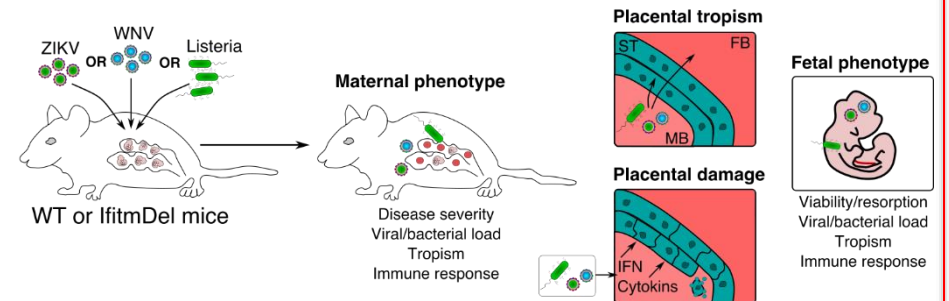


- Lupus?
- Trisomy 21?
- ZIKA?
- Listeria?
- etc.

### Human IFITM polymorphisms of placental disorders



### Role of IFITMs during congenital infections?





REPRODUCTION

Science  
AAAS

# IFITM proteins inhibit placental syncytiotrophoblast formation and promote fetal demise

Julian Buchrieser<sup>1,2\*</sup>†, Séverine A. Degrelle<sup>3,4,5\*</sup>, Thérèse Couderc<sup>6,7\*</sup>, Quentin Nevers<sup>1,2\*</sup>, Olivier Disson<sup>6,7</sup>, Caroline Manet<sup>8</sup>, Daniel A. Donahue<sup>1,2</sup>, Françoise Porrot<sup>1,2</sup>, Kenzo-Hugo Hillion<sup>9</sup>, Emeline Perthame<sup>9</sup>, Marlene V. Arroyo<sup>1,2,10</sup>, Sylvie Souquere<sup>11</sup>, Katinka Ruigrok<sup>12</sup>, Anne Dupressoir<sup>13,14</sup>, Thierry Heidmann<sup>13,14</sup>, Xavier Montagutelli<sup>8</sup>, Thierry Fournier<sup>3,4\*†</sup>, Marc Lecuit<sup>6,7,15\*†</sup>, Olivier Schwartz<sup>1,2,16\*†</sup>

2019

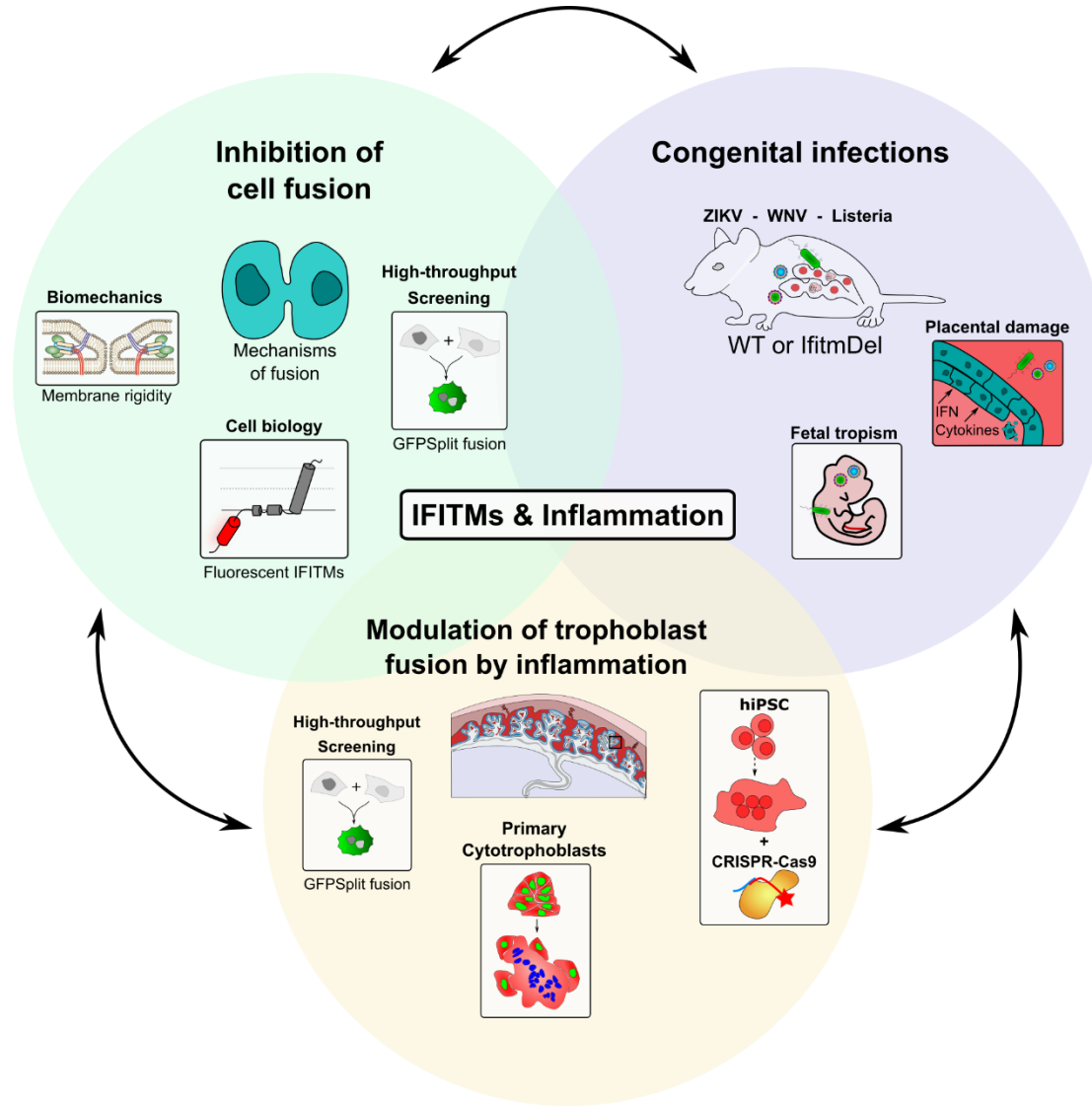
JBC  
JOURNAL OF  
BIOLOGICAL  
CHEMISTRY

## Interferon-Induced Transmembrane Proteins Inhibit Cell Fusion Mediated by Trophoblast Syncytins

Ashley Zani<sup>1,4</sup>, Lizhi Zhang<sup>1,4</sup>, Temet M. McMichael<sup>1,4</sup>, Adam D. Kenney<sup>1,4</sup>, Mahesh Chemudupati<sup>1,4</sup>, Jesse J. Kwiek<sup>2,4</sup>, Shan-Lu Liu<sup>3,4</sup>, and Jacob S. Yount<sup>1,4,\*</sup>

2019

# Perspectives



# Acknowledgments



## *Virus and Immunity Unit - IP*

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Blandine Monel  
Michael Rajah  
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Marlene Vreni Arroyo  
Cécile Meunier  
Mathieu Hubert

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**Thérèse Couderc**  
**Olivier Disson**

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**Thierry Fournier**

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