Vitamin D And Preeclampsia: Maternal Adverse Outcomes

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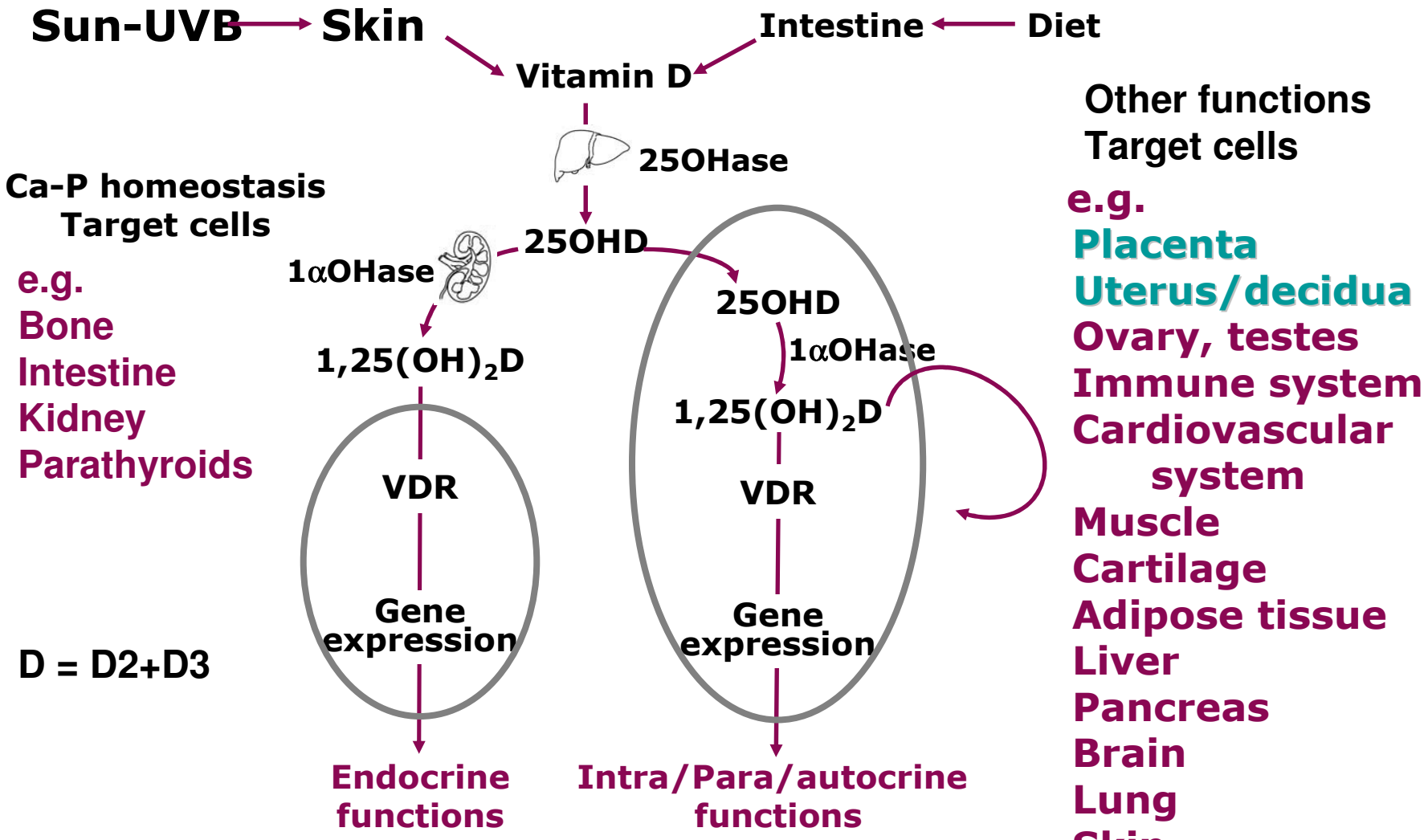
Objectives of Presentation

- Overview of preeclampsia & placentation
- Critical assessment of evidence linking vitamin D and preeclampsia
- Role of vitamin D in placenta
  - immunomodulation at maternal-fetal interface
  - regulation of placental hormonal function
- Knowledge gaps & research needs

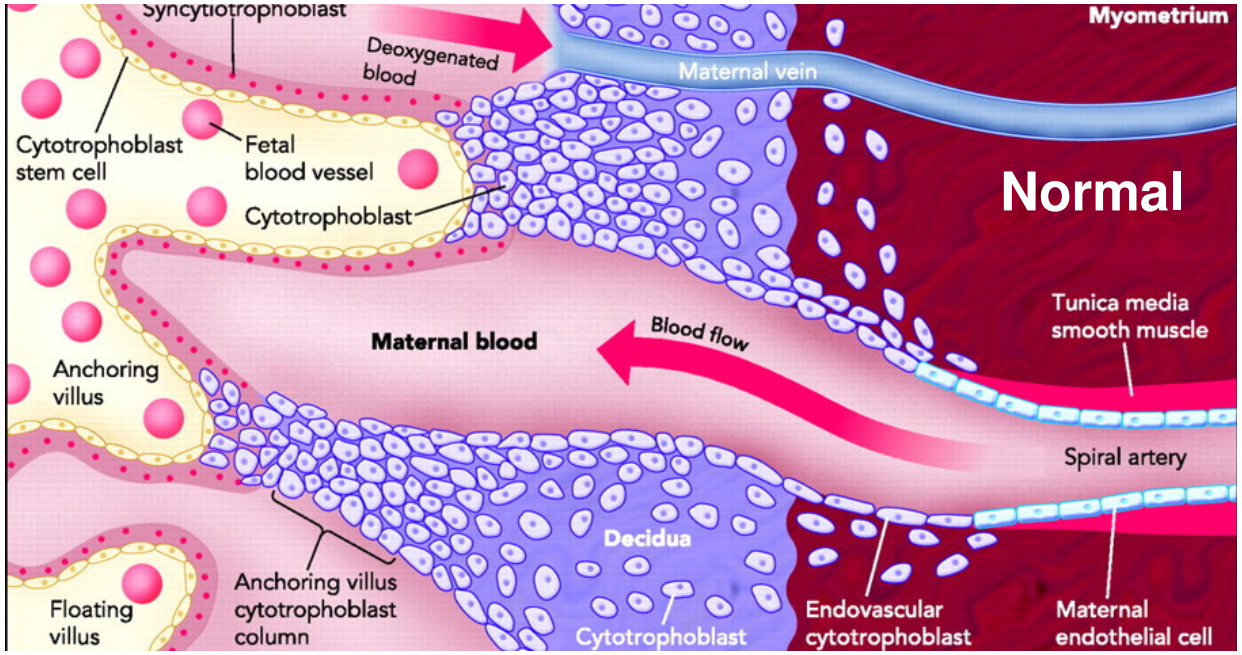
Functions of Vitamin D



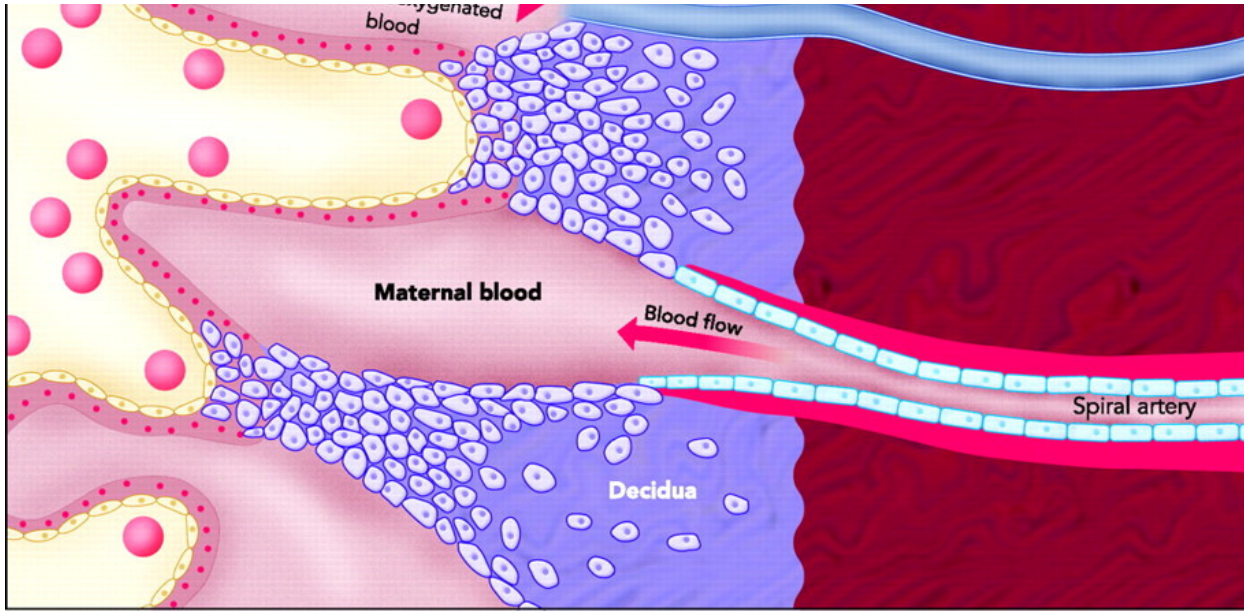
Preeclampsia (PE)

- Major cause maternal mortality & maternal/fetal morbidity
  - 50,000 maternal deaths/yr worldwide
- Characterized > 20 weeks by
  - Pregnancy induced hypertension
    - >140 mmHg systolic or >90 mmHg diastolic
  - Proteinuria
    - >300 mg 24 hr urine or >1+ dipstick
    - >0.3 protein to creatinine ratio
- Prevalence similar US & India
  - 5-8% US and 4-10% India
  - > in nulliparous or multiparous with new partner
  - > prior PE or family history of PE

Impaired Placentation in Preeclampsia

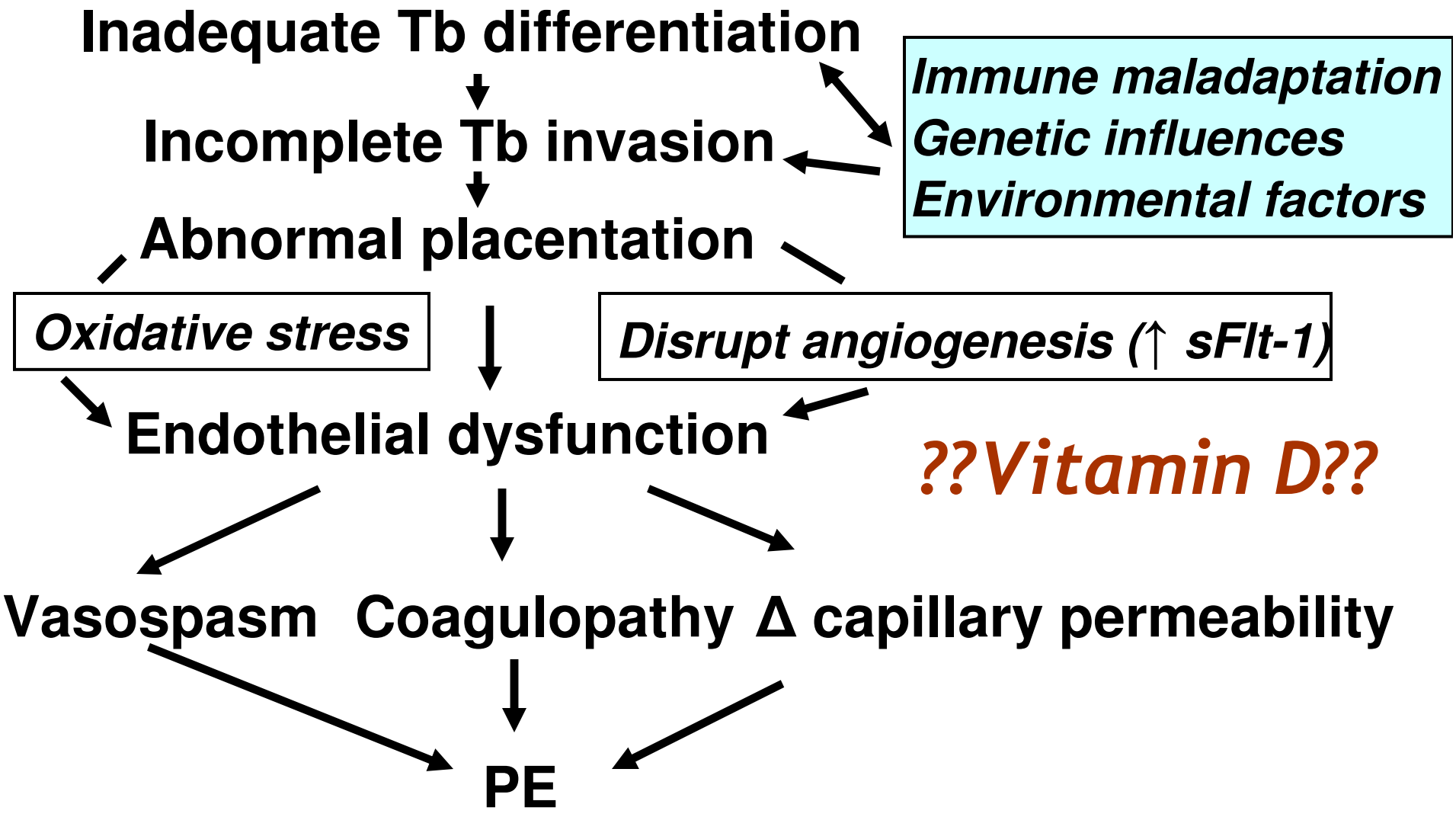


Incomplete trophoblast (Tb) invasion



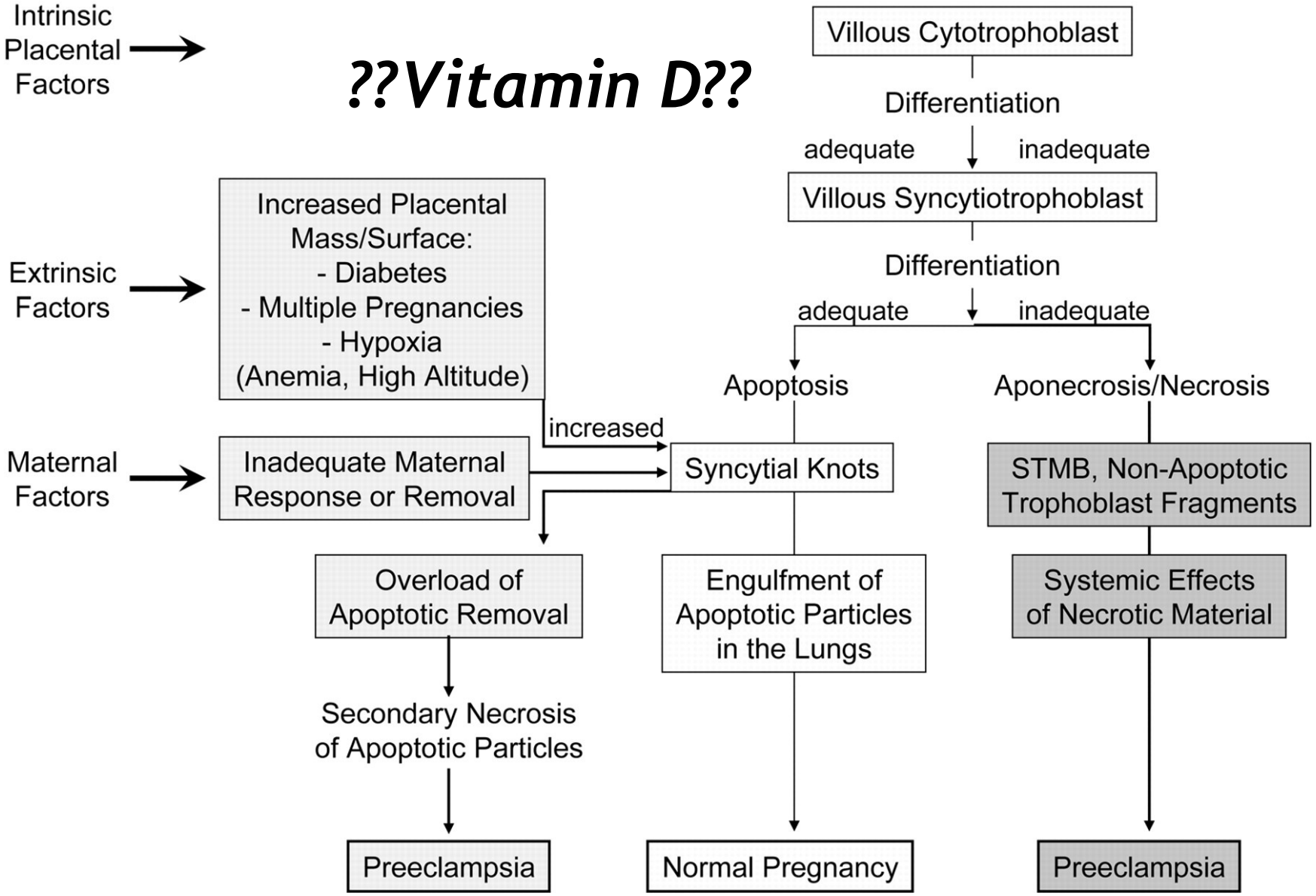
Wang, A. et al. Physiology 24: 147-158 2009;

Multifactorial Model of Preeclampsia



Adapted from Cheng M, Wang PE Expert Rev Mol Diag 2009;o:37-49 & Huppertz*B Hypertension 2008;51:970-5*

Multifactorial Model of Preeclampsia



American Heart Association Learn and Live

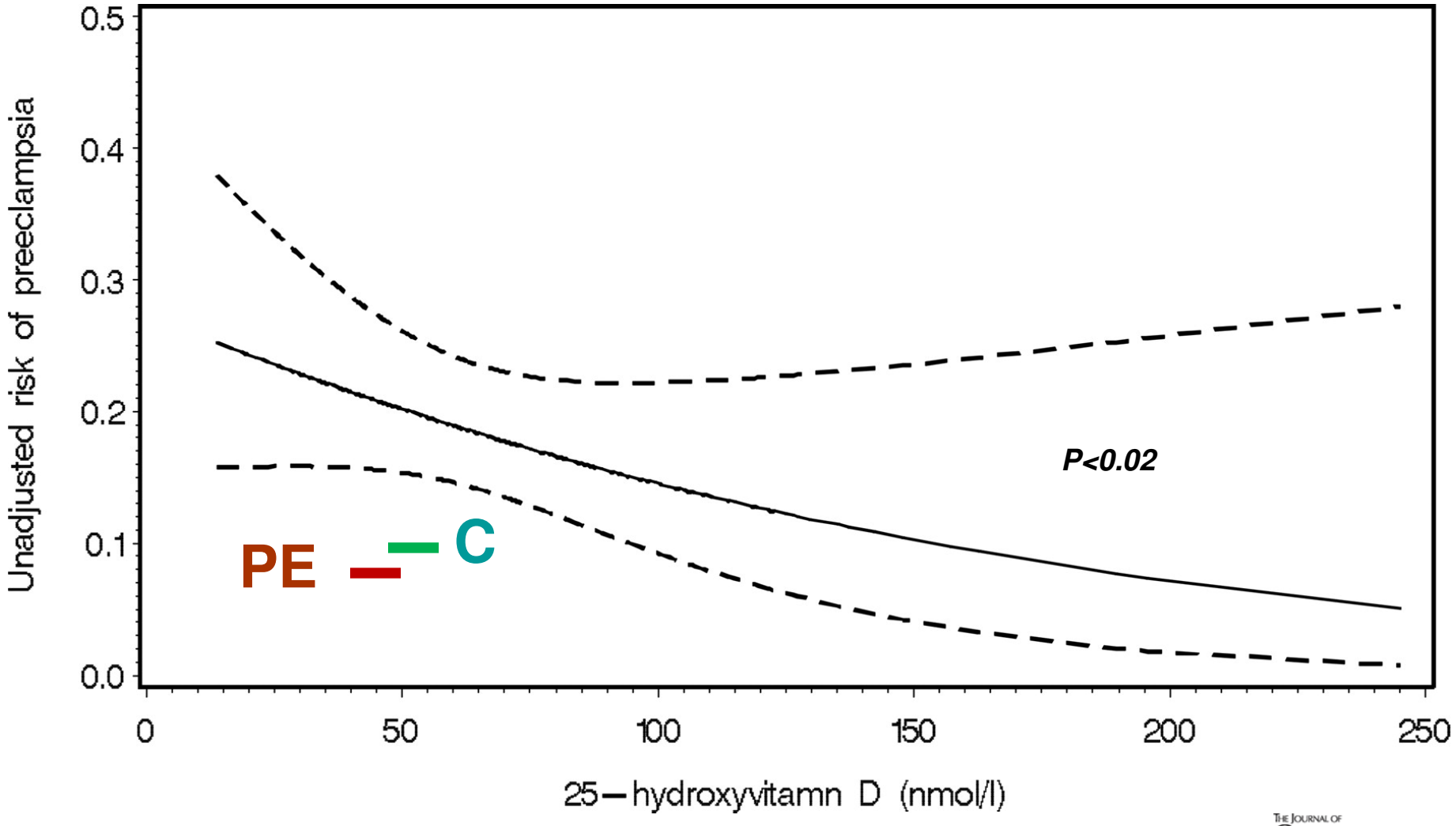
Huppertz, B. Hypertension 2008;51:970-975

Hypertension

Observational Studies on Vitamin D & PE or PIH

	PE	C		$1,25(OH)_2D$ pmol/L		25(OH)D nmol/L	
	----- n----			PE	C	PE	C
Prospective nested case control							
Halhali 2004 (MX)	10	40(160)	21 wk	77.5	72.5		
			28 wk	107.5	97.5		
			36 wk	137.5	132.5		
Bodner 2007(US; NP)	49(59)	216(220)	<22 wk			45.4*	53.1
			Term			54.7*	64.7
Case control							
Seely 1992 (US; 3rd)	12	24		172.1*	219.6	73.9	89.8
August 1992 (US; 2/3)	9	9		95*	165		
Frolich 1992 (DN;3rd)	53 (37%PIH)	20		96.5*	227.5	67.5	59
Lalau 1993 (FR; 2nd/3rd)	21(PIH/1PE)	25		215*	275		
Halhali 1995 (MX; 3rd)	26	26		106.5*	130.3		
Halhali 2000 (MX; Term)	24	24		117,5*	157.5		
Halhali 2007 (MX; 3rd)	26	26		107.5*	125		

Dose-Response Association Early Maternal 25OHD and Risk of PE



Bodnar et al. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 2007;92:3517-3592.

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Clinical Trials on Vitamin D and PE or PIH

Randomized Clinical Trial

		+Ca/vit D	*NS*
Marya et al. 1987		**200**	**200**
***Rohtak,* India**		**+ 375 mg Ca**	
Dietary Ca 500mg;		**1200 IU D**	
vit D 40 IU			
	PE	**12**	**18**
Blood Pressure (32 wk)			
	Systolic	**109.6***	**117.7**
	Diastolic	**70***	**66**

Non-randomized Clinical Trial

Ito et al. 1994

Kuramoto, Japan	**High Risk**	**PE**
	+ 312 mg Ca/d	**2/10**
	+ 312 mg Ca/d + 20 IU vit D/3 days	**3.7**

Assessed risk based on Angiotensin Sensitivity Test BUT differed between the 2 groups

Observational and Trial Evidence for Vitamin D and PE

- No double-blind placebo controlled RCT on vitamin D and incidence of PE
- 1 RCT (no placebo) found no effect on PE but a small ↓ in systolic and diastolic BP with Ca/vitamin D supplements
- Inconsistent association of $1,25(OH)_2D$ and PE
  - 29% lower $1,25(OH)_2D$ in PE in cross-sectional case studies
  - No association in prospective nested case control study
- Inconsistent association of 25(OH)D and PE
  - No association in 2 cross-sectional case studies
  - 15% lower in PE in prospective nested case control study

Vitamin D Metabolism in Placenta

- **Placental trophoblasts and decidua express 1α OHase**

Zehnder et al. Am J Pathol 2002;161:105-114.

Vitamin D Metabolism in Placenta

- **Placental trophoblasts and decidua express 1α OHase**
- **Placental specific methylation of 24OHase promoter may ↓ capacity of 1,25(OH)$_2$ D to induce 24OH-lase**

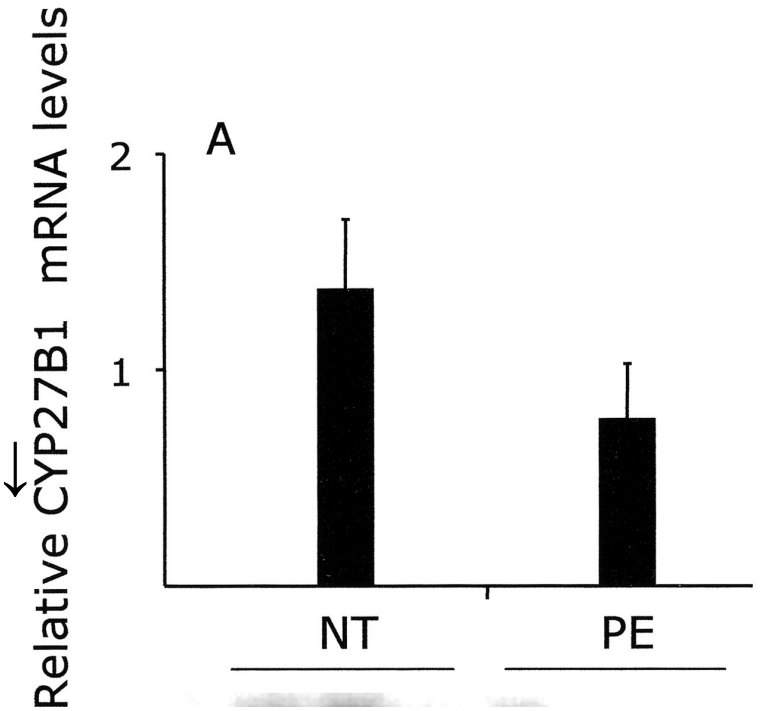
	% Methylation
24 OHase	
Placenta	*57*
Placental Fb	*3*
Decidual cells	*2*
Choriocarinoma	*80*
1αOHase	
Placenta	*5*
Choriocarcinoma	*87*
VDR	
Placenta	*<1*
Choriocarinoma	*87*

Novakovic et al. *J Biol Chem* 2009;284:14838-48.

Vitamin D Metabolism in PE Placenta

- **Conflicting reports on 1αOHase in PE placenta at term**
  - **Fischer and co-workers report ↑**

    (Clin Exp Obstet Gynecol 2007;34:80-4).
  - **Diaz and co-workers report ↓ in cultured syncytiotrophoblasts**



Diaz, L. et al. J Clin Endocrinol Metab 2002;87:3876-3882

- **Fischer and co-workers also report ↓ 24OHase**

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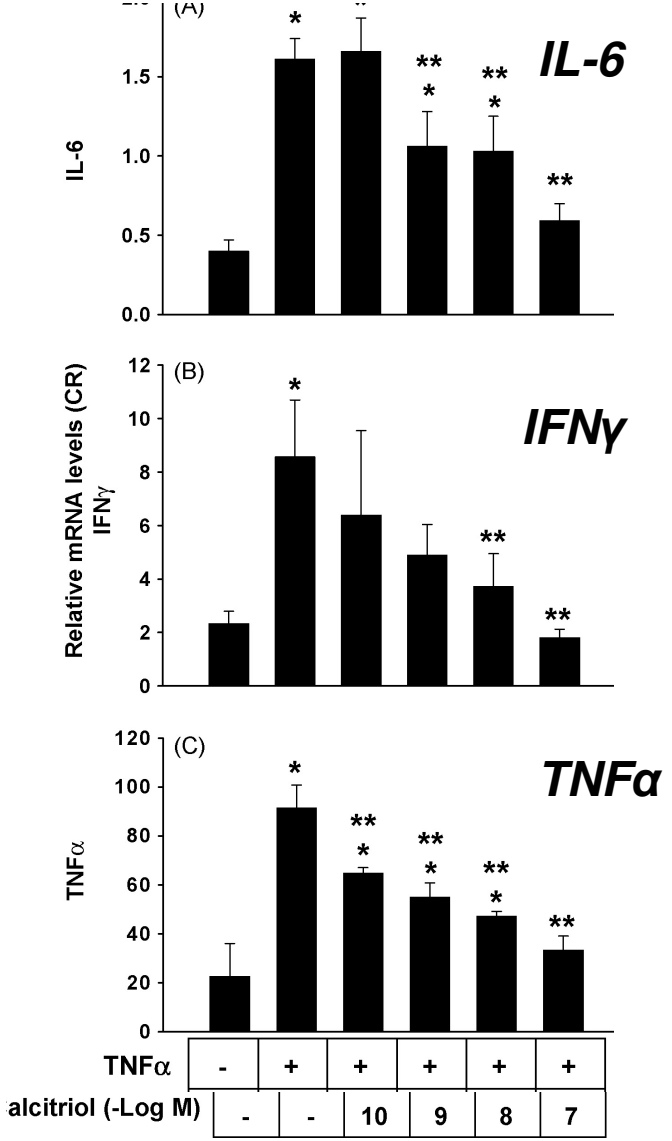
Vitamin D Function in Placenta & Decidua In Vitro

- **Immunomodulatory regulation of cytokines and cathelicidin (CAMP)**
  - **↓TNFα induction of placental IFNγ, IL6, TNFα**
  - **↓ decidual NK cell IL1, IL6, TNF & CSF2**
  - **↑ placental & decidual CAMP**



Diaz L et al. J Reprod Immunol 2009;81:17024.

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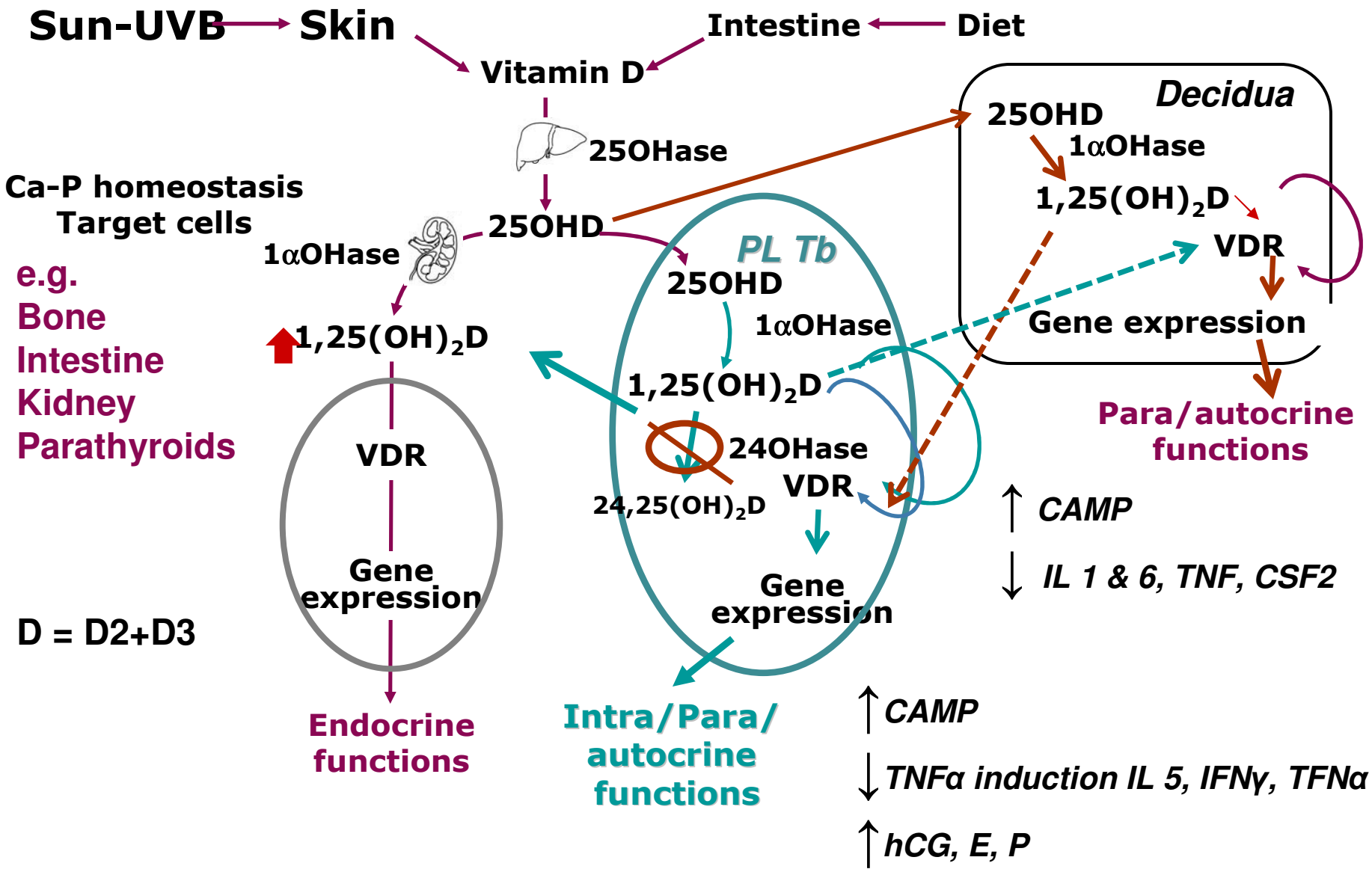
- **Immunomodulatory regulation of cytokines and cathelicidin antimicrobial peptide (CAMP)**
  - **↓ TNFα induction of placental IFNγ, IL6, TNFα**
  - **↓ decidual NK cell IL1, IL6, TNF & CSF2**
  - **↑ placental & decidual CAMP**

- **Regulation of placental hormonal function**
  - **↑ hPL mRNA & secretion (10-100 0nmol/L)**
  - **↑ hCG mRNA & secretion (0.1-10 nmol/L)**
  - **↑ E & P secretion 0.1-100 nmol/L)**

Functions of Vitamin D: Placenta



Vitamin D and PE
Gaps in Our Knowledge and Research Needs

- **Understand the regulation by vitamin D of normal placentation and abnormal placentation in PE**
  - **immunomodulatory role**
    - **Placenta**
    - **Decidua**
  - **regulation of placental hormonal function**

- **Need a double-blind placebo RCT on vitamin D and incidence of PE**

Acknowledgements

- **Jane Caty**
- **Sara Jones**