

PMDA's activities related to qualification of safety biomarkers for drug development

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Pharmaceuticals and Medical
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The views and opinions expressed in the following PowerPoint slides are those of the individual presenter

Outline

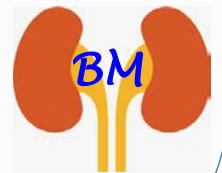
1. Perspective on potential biomarkers for immune-related pregnancy risk



1) Biomarker candidates

2) Drugs whose mechanism of action of drug efficacy may be common to the development of immune related pregnancy risk

2. Consultation on PGx/BM: Biomarker for nephrotoxicity



This section of presentation will be done in connection with the speaker's activity of the research group of the Japan Agency for Medical Research and Development (AMED) for 'Research on safety of vaccines and immunotherapeutics'. The aim of the research group is the establishment of internationally harmonized nonclinical safety guidelines (e.g., ICH, WHO). So far, there are only limited descriptions about biomarkers in those guidelines.



ICH-S8 wordings

'Immunophenotyping of leukocyte populations, a non-functional assay, can be conducted to identify the specific cell populations affected and might provide useful clinical biomarkers.'

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FDA approved drug report. **Neulasta (pegfilgrastim)**

Granulocyte colony-stimulating factor (G-CSF) receptor agonists

Pregnancy Category C

Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant **rabbits** received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryoletality (post-implantation losses) and spontaneous abortions occurred.

Immunosuppressive drug

Published by
Ministry of Health, Labour and Welfare



Translated by
Pharmaceuticals and Medical Devices Agency



This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Revision of Precautions

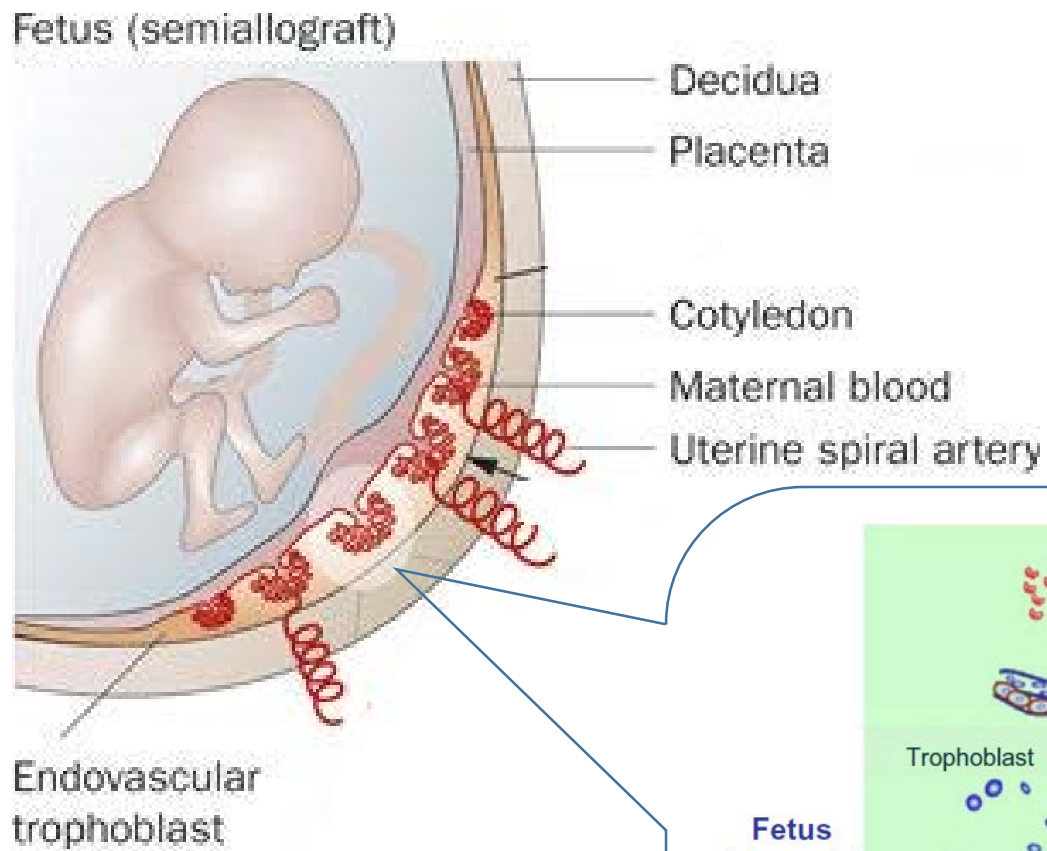
Taclorimus hydrate (oral and injectable dosage forms)

July 10, 2018

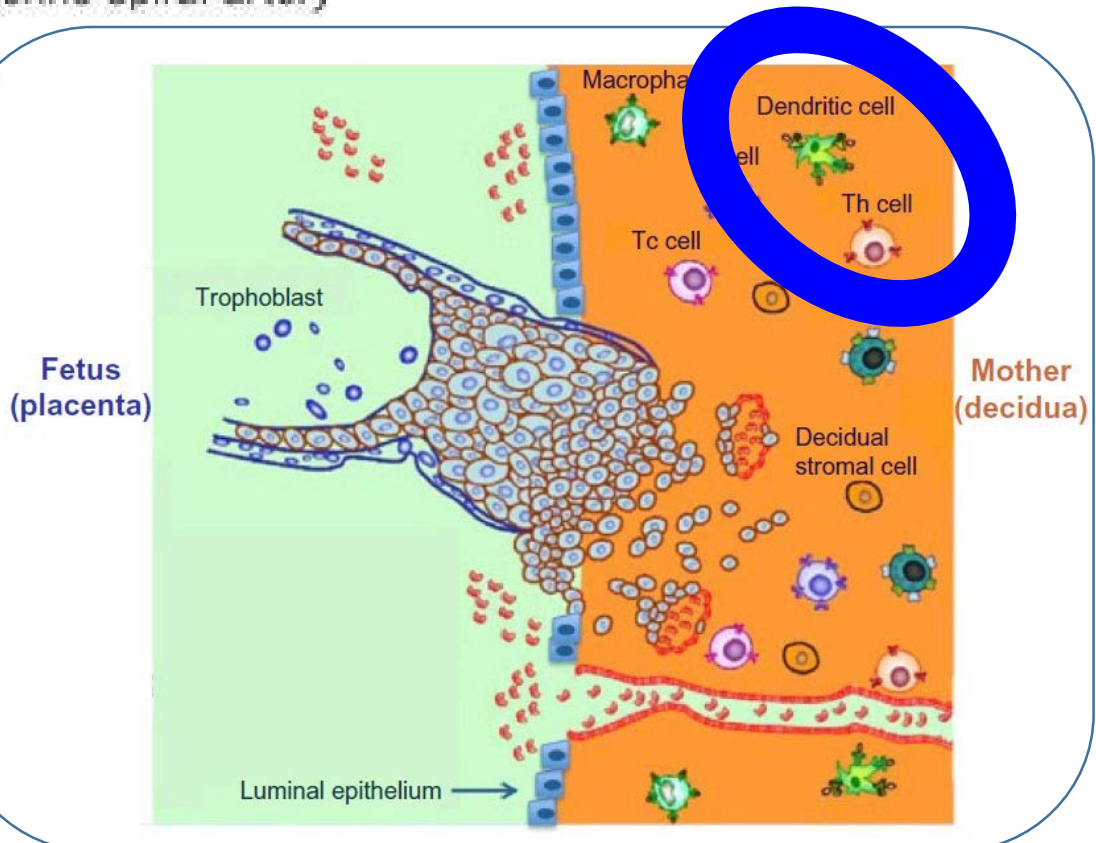
Pregnant women etc.:

Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks (Premature birth and influence on the infants [low birth weight, congenital anomalies, hyperkalaemia, renal impairment] have been reported in women who received this drug during pregnancy) .

Maternal tolerance of the fetus

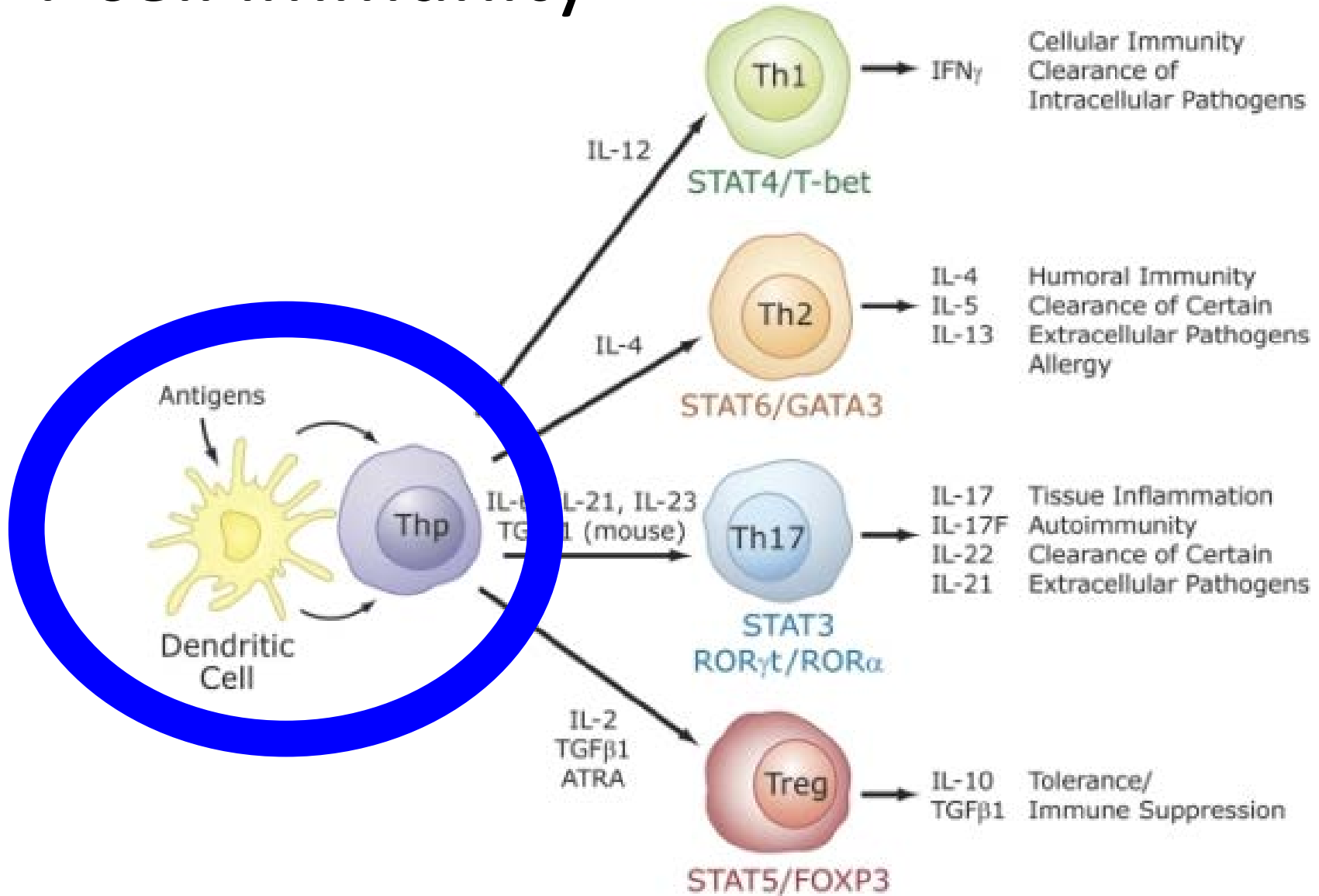


Tower C et al. *Nat Rev Rheumatol*, vol.7, p.124-82, 2011



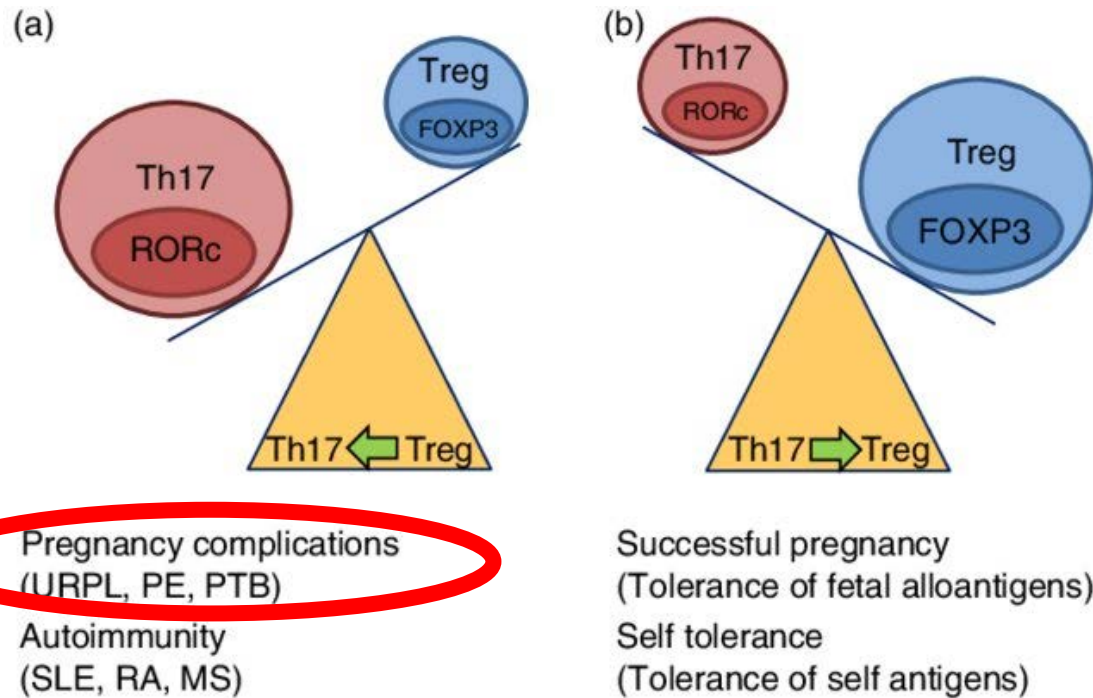
Morelli S, et al, *Dovepress*, vol. 2015:6 , p.171—189, 2015

T cell immunity



Abnormal maternal immunity and pregnancy risk

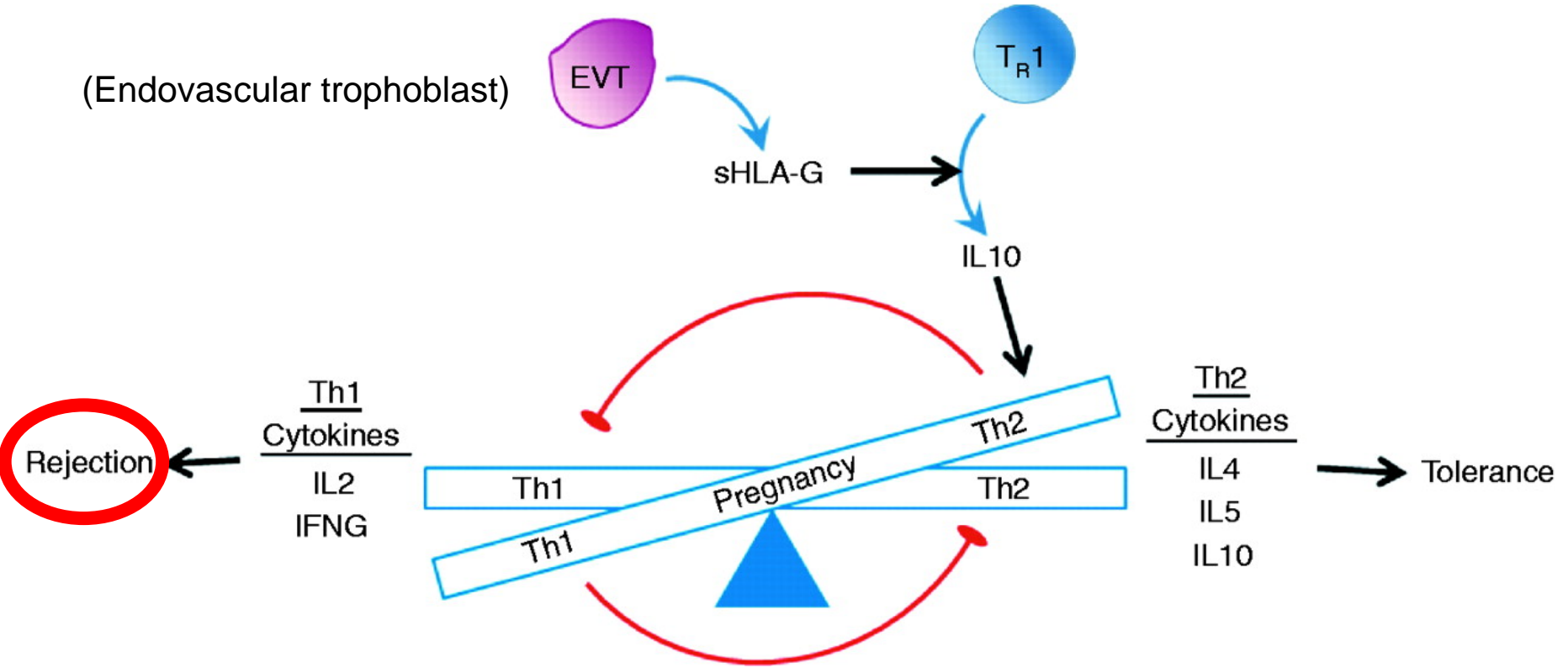
1. Th17/Treg balance



RPL(recurrent pregnancy loss), PE (Preeclampsia)

Abnormal maternal immunity and pregnancy risk

2. Th1/Th2 balance



Research articles that suggest the feasibility of the biomarkers

- *Hum Reprod*, vol.11, p.2964-2971, 2011

An imbalance in interleukin-17-producing T and Foxp31 regulatory T cells in women with idiopathic recurrent pregnancy loss

Lee SK¹, Kim JY¹, Hur SE¹, Kim CJ¹, Na BJ¹,

Lee M, Gilman-Sachs A², Kwak-Kim J²

- *Am J Reproductive Immunology*, vol.70, p.398-411, 2013.

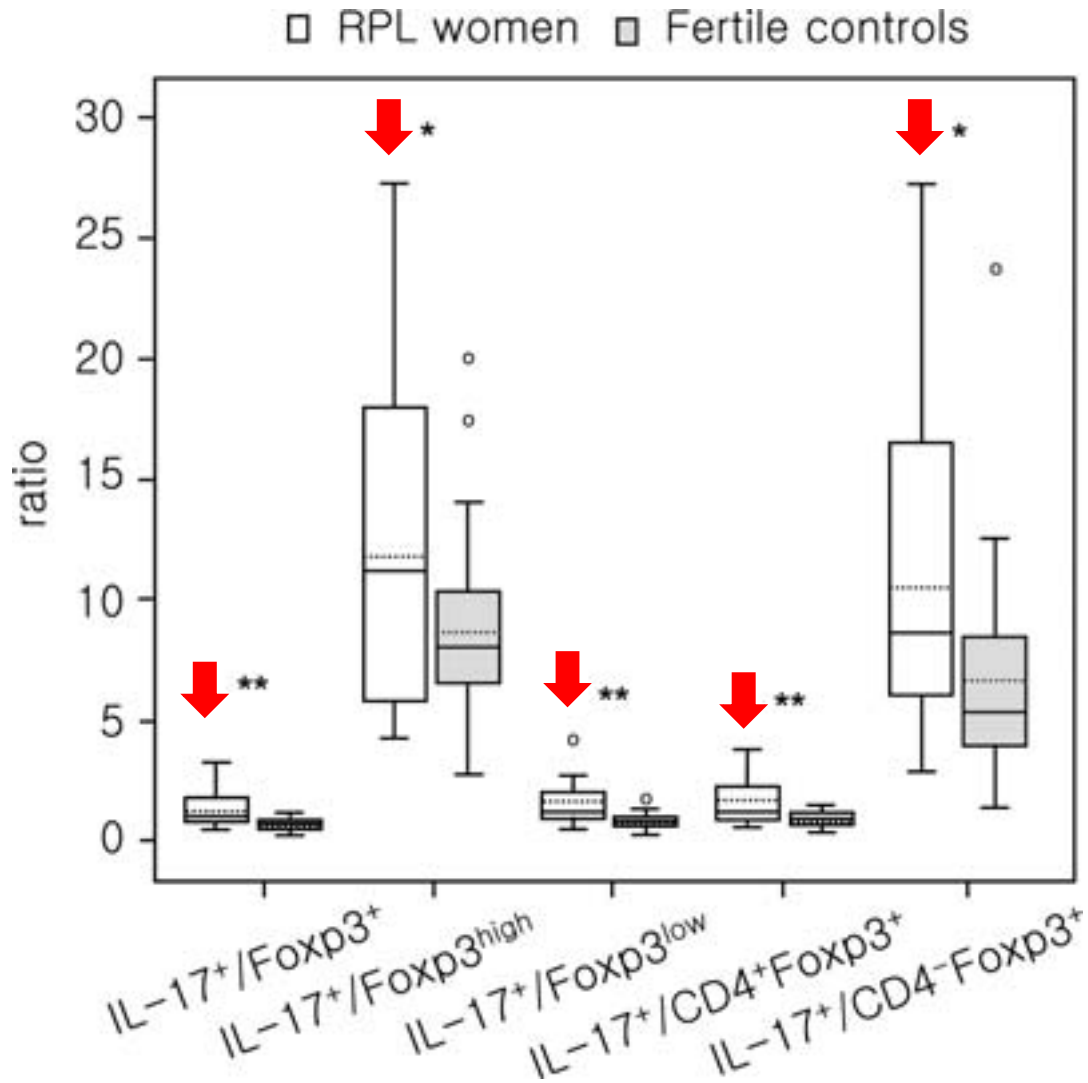
Determination of clinical cellular immune markers in women with recurrent pregnancy loss

Lee SK¹, Na BJ¹, Kim JY¹, Hur SE¹, Lee M¹, Gilman-Sachs A², Kwak-Kim J²

1. Konyang University, Korea
2. The Chicago Medical School at Rosalind Franklin University of Medicine

Th17/Treg cell ratio

between RPL women and fertile controls

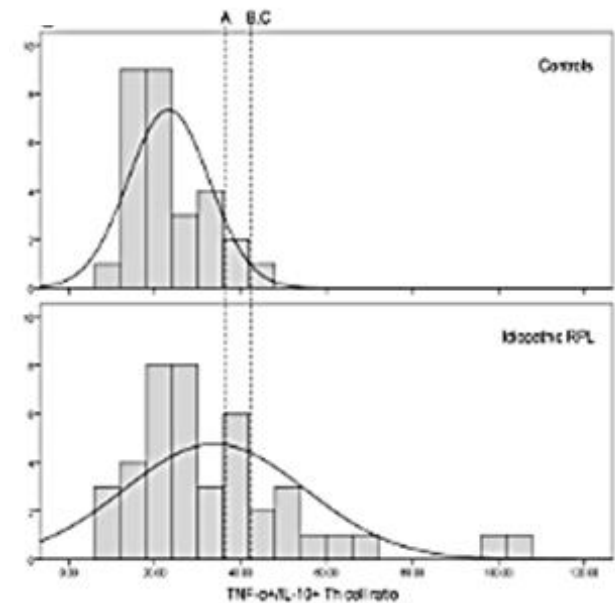
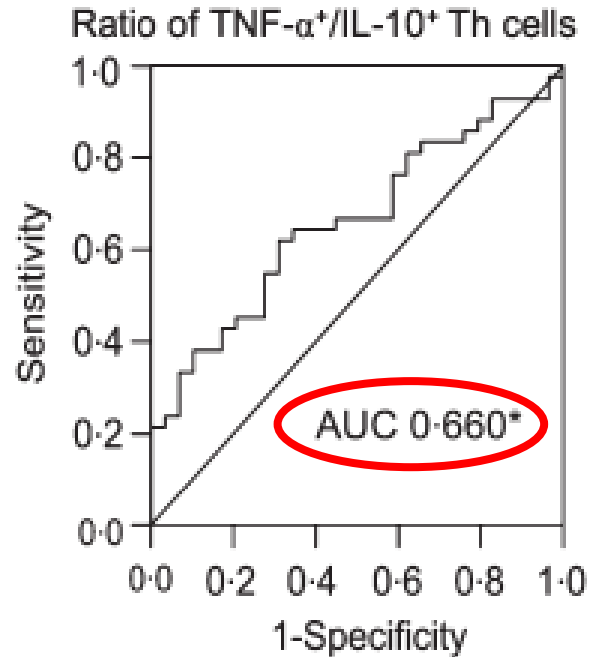
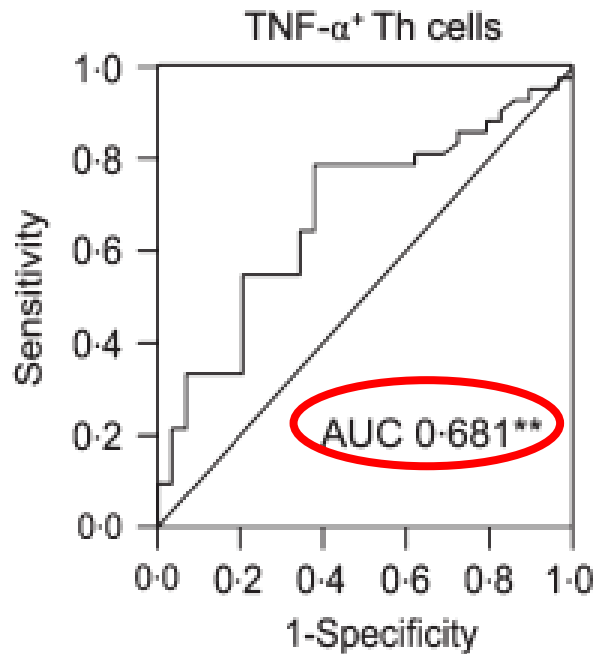


(RPL; Recurrent Pregnant Loss)

~ Th1/Th2 ratio

Area under the ROC curve of TNF- α ⁺ Th cell and TNF- α ⁺/IL-10 Th cells between (idiopathic) RPL and fertile controls

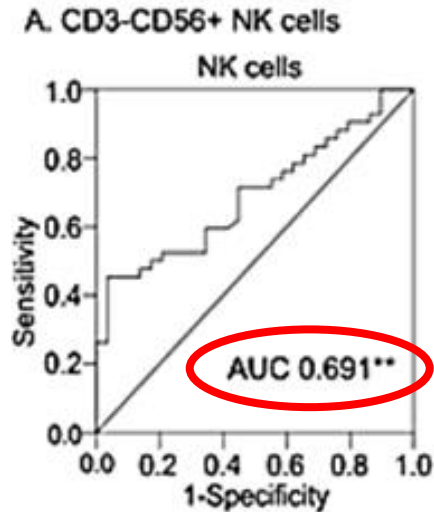
TNF- α production and a ratio of TNF- α ⁺/IL-10⁺ in CD3⁺CD4⁺ T lymphocytes.



* P<0.05

** P<0.001

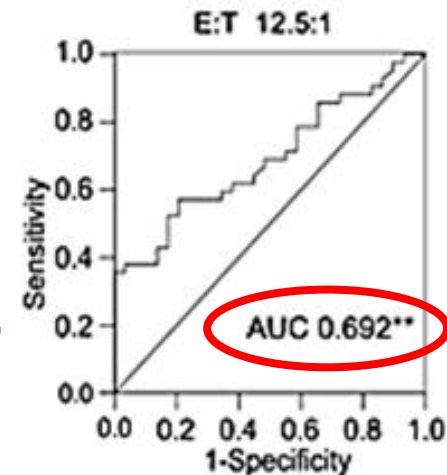
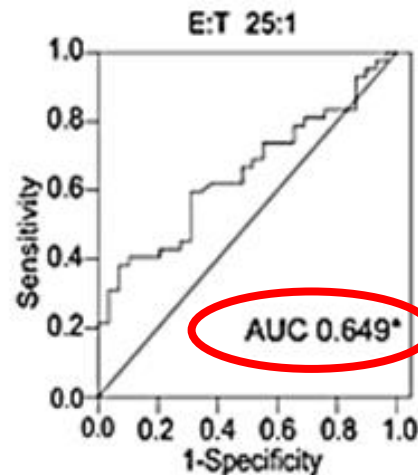
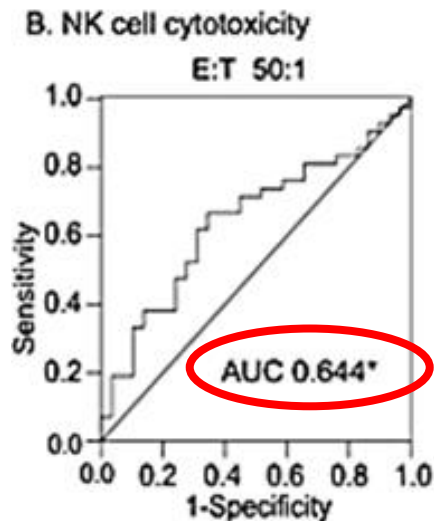
Area under the ROC curve analysis of CD3-CD56+ NK cells and NK cell cytotoxicity between (idiopathic) RPL and fertile controls



Lee SK, et al. *Am J Reproductive Immunology*, 2013

* $P < 0.05$

** $P < 0.001$



Outline

1. Perspective on potential biomarkers for immune-related pregnancy risk

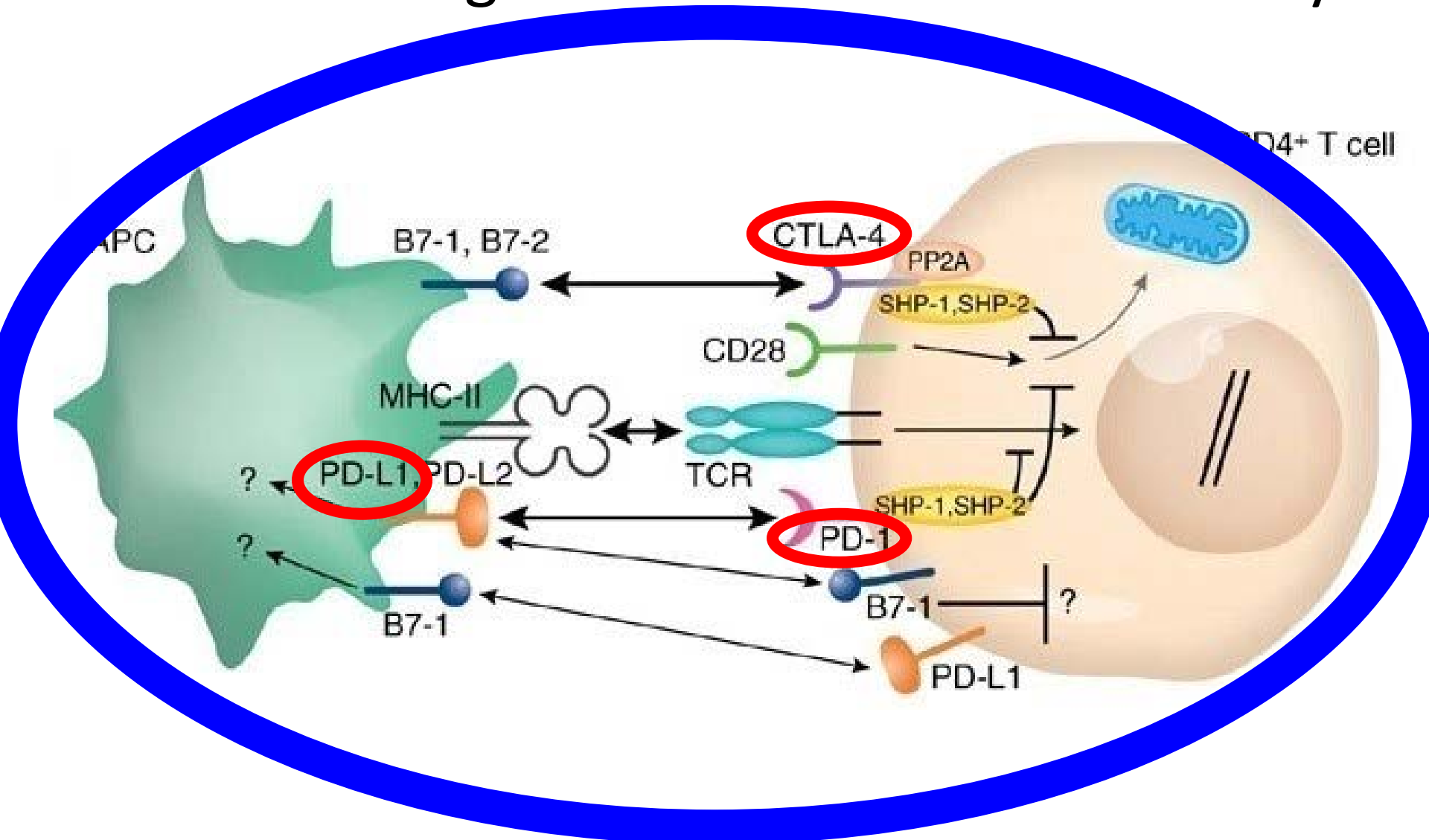
1) Biomarker candidates

2) Drugs whose mechanism of action of drug efficacy may be common to the development of immune related pregnancy risk

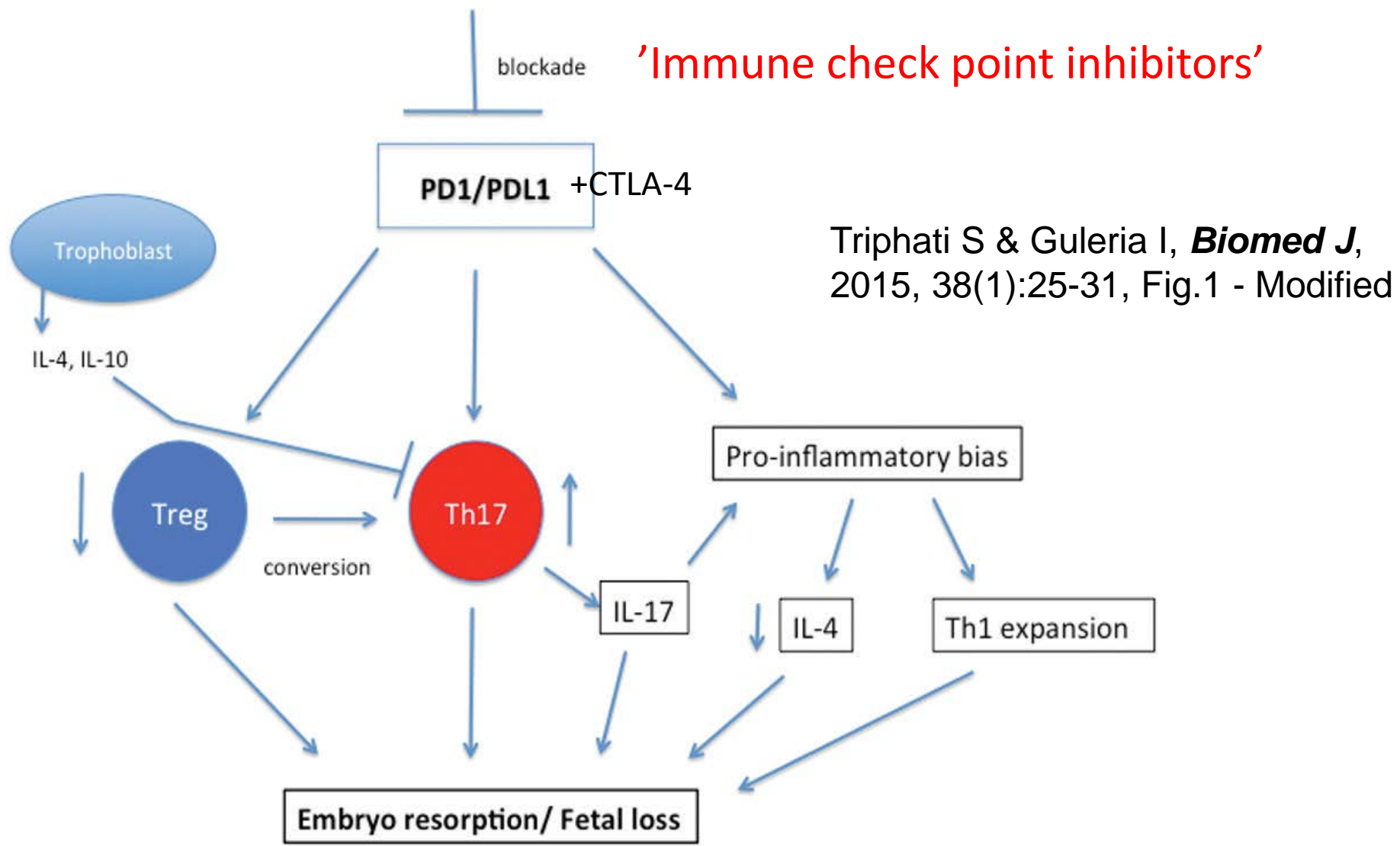
2. Consultation on PGx/BM: Biomarker for nephroto



PD-1/PD-L1 and CTLA-4 binding have similar negative effects on T-cell activity



Blockade of PD1/PDL1 (+CTLA-4) pathway may result in a decrease in the efficiency of Tregs and an increase in inflammatory Th17 cells leading to loss of tolerance at the feto-maternal interface



Tripathi S & Guleria I, *Biomed J*, 2015, 38(1):25-31, Fig.1 - Modified

Opdivo (nivolumab)

metastatic small cell lung cancer (SCLC)

Embryofetal Toxicity

In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO.

PD-L1 inhibition

20 July 2017

EMA/153102/2018

Committee for Medicinal Products for Human Use (CHMP)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report urothelial carcinoma, non small cell lung cancer (NSCLC)

Tecentriq (atezolizumab)

Reproduction Toxicity

In female Cynomolgus monkeys, menstrual cycles were monitored by daily vaginal swabs. An effect was observed on menstrual cycles at 50 mg/kg, with an irregular cycle pattern during the dosing phase with disturbed cycles especially between Weeks 8 and 14. This finding correlated with an absence of fresh corpora lutea in the ovaries (lack of cycling activity) at the time of the terminal phase necropsy.

PMDA Review Report

Yervoy (Ipilimumab)

approval; June 3, 2015

malignant melanoma

Reproductive and developmental toxicity study

Premature births, decreased birth weight, • • were observed.

post-marketing

The outcomes of their pregnancy were unknown in 7 patients, induced abortion in 4 patients, and death of a patient, delivery of a normal newborn, and a newborn with abnormal respiratory symptoms in 1 patient each.

PMDA's view:

The applicant should prepare appropriate information materials to ensure that patients or their family members are informed of the risks of ipilimumab including teratogenicity and abortion and that patients well understand the potential risks of ipilimumab before starting treatment.

1. Perspective on potential biomarkers for immune-related pregnancy risk

Conclusion



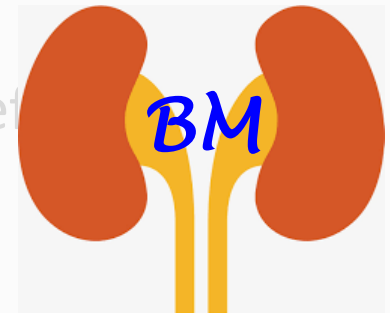
- There is a scientific background suggesting that molecules in the immunological pathways at the feto-maternal interface could be the biomarkers for some pregnancy complications, e.g., spontaneous abortion, preterm or preeclampsia. Recent research paper have raised out Th17/Treg ratio, Th1/Th2 ratio, or NK cell activity in maternal peripheral blood as the potential biomarkers.
- Drugs reported to have pregnancy risks are common in that they act on Th17/Treg in the immunological pathway. These may strengthen the likelihood of the above indices as the biomarkers together with their future reflection on related guidelines.

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2. Consultation on PGx/BM: Biomarker for nephrotoxicity

Publication of records of Consultation on Pharmacogenomics/Biomarkers on PMDA's website



- Reviews and Related Services
- Outline
- Consultations
- Reviews
- GLP / GCP / GPSP Compliance Assessments
- GMP / QMS / GCTP Inspections
- Assessments to Registered Certification Bodies
- Regulatory Information
- Public comments

Record of Consultations on Pharmacogenomics / Biomarkers

PMDA publishes on its website the results of the Consultation on Pharmacogenomics/Biomarkers held with the Predictive Safety Testing Consortium (PSTC) because PSTC requested the information addressed at the consultation to be made publicly available.

The contents and results of consultations conducted by PMDA are not subject to public disclosure, in principle. However, PMDA has decided to disclose the record of the consultation in the original Japanese as well as in English translation*, considering that such disclosure will not benefit certain companies or products alone but will help future drug development as a whole.

The conclusion shown in the record reflects the current PMDA's thoughts based on the submitted documents and scientific knowledge available at the time of the consultation. Please note, therefore, that the appropriateness of such conclusion may change as additional knowledge is accumulated and science advances.

*In the event of inconsistency between the Japanese original and the translation, the former shall prevail.

- [Record of the Consultation on Pharmacogenomics/Biomarkers for Drug-induced Kidney Injury Biomarkers](#)
- [Record of the Consultation on Pharmacogenomics/Biomarkers \(March 28, 2018/No. P-BM4\)](#)

This English version of the record of the consultation has been published by PMDA. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

(Attachment 1)

Record of the Consultation on Pharmacogenomics/Biomarkers

November 2, 2018
Pharmaceuticals and Medical Devices Agency

Concerning the following consultation on Pharmacogenomics/Biomarkers requested, the background of the consultation submitted by applicant (hereinafter referred to as the "applicant") and the summary of an evaluation by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "PMDA") are as described herein.

It should be noted that decisions in this document were made on the scientific level at the time of face-to-face consultation based on the data submitted by the applicant. Interpretation for the validity of the decisions may vary based on possible new findings and scientific advances, etc.

Date/No. of reception: March 28, 2018/No. P-BM4

Biomarkers consulted: Urinary clusterin, urinary cystatin C, urinary kidney injury molecule-1 (KIM-1), urinary *N*-Acetyl-*beta*-*D*-Glucosaminidase (NAG), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary osteopontin, urinary total protein, and urinary albumin

Consultation category: Additional consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)

Consultation applicant: Critical Path Institute's Predictive Safety Testing Consortium (PSTC)

Department in charge (Section): Omics Working Group

Consultation on PGx/BM:

Biomarker for nephrotoxicity

Date of reception; March 28, 2018

Biomarkers consulted;

Clusterin, Cystatin C, Kim-1, NAG, Lipocalin2 (NGAL),
Osteopontin, Total Urinary Protein, Albumin

Background;

- The applicant' objective is to obtain the qualification of Novel nephrotoxicity BMs.
- In the previous consultation
 - ▣ 7 novel BMs for detecting drug-induced nephrotoxicity in non-clinical studies were qualified
 - ▣ The early stage clinical application of Novel BMs was discussed
- Objectives in this consultation
 - ▣ To discuss the plan for qualification of 8 Novel BMs which are considered to be applicable for prediction of renal injury in early clinical studies
 - ▣ To confirm the PMDA's opinion on the bridging strategy intended to evaluate the ethnic differences based on the planned clinical studies in Japanese .

Consultation item 1

Appropriateness to use the results of Confirmatory Phase clinical studies in non-Japanese subjects (Cisplatin Study and Aminoglycoside Study) and a Learning Phase clinical study [PSTC-initiated study in healthy subjects and a clinical study in mesothelioma patients] as base data for the bridging study of Novel BMs in Japanese subjects.

PMDA opinions

- PSTC's strategy is acceptable.

Potential issues;

- It is important to make **the background characteristics of subjects in renal toxic drug treatment and non-renal toxic drug treatment groups in the bridging studies in Japanese subjects** as similar as possible to those in **the foreign clinical studies in the confirmatory phase** so that ethnic differences in the Novel BMs for drug-induced renal disorder can be properly assessed.

Consultation item 2

Appropriateness to determine that the analytical method using the 8 Novel BMs have been validated based on the concept of "fit-for-purpose" for uses in the Bridging Studies to be conducted in Japanese subjects.

PMDA opinions

- No particular objection to use of the analytical methods for the 8 Novel BMs used in non-Japanese clinical studies in the Bridging Study.

Potential issues;

- Urinary clusterin does not demonstrate long-term stability, and therefore, **a duration validated for stability** should be identified before the start of the Bridging Study.
- Applicant should **consider an additional analysis** without exclusion of samples **with blood contamination** that may interfere with the analysis **in case there are too many samples** invalidated due to blood contamination.

Consultation item 3

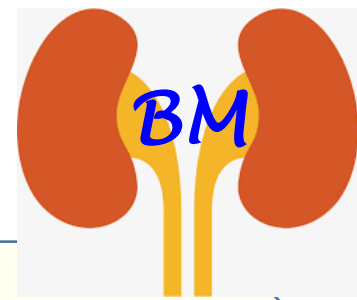
Acceptability of the bridging strategy intended to evaluate the ethnic differences based on the results of the clinical studies conducted in non-Japanese subjects compared on a step-by-step basis, first with data in Japanese healthy subjects, and then with the data in Japanese subjects with renal impairment so as to verify the qualification of the 8 Novel BMs in Japanese subjects.

PMDA opinions

- The applicant should **set out a criteria to demonstrate "similarities" or "the absence of problematic difference"** compared to the results of study in non-Japanese healthy subjects
- In principle, it is appropriate to **examine acceptable specificity and define criteria for the evaluation based on confidence intervals**
- However, PMDA understands that it is necessary **to take feasibility into account** when setting the criteria for similarity and the sample size.

Overall PMDA comment on development of Novel BMs

- While the clinical usefulness of the Novel BMs and the proposed appropriateness of their usage are unknown at this point, **to investigate whether or not the Novel BMs can be used in various regions and ethnic groups would be important for developing drugs utilizing the Novel BMs and clinically adopting them in multiple countries and regions.**
- PMDA expects the applicant to actively perform **an examination aimed at the implementation of the bridging studies of the Novel BMs in Japanese subjects** and recommends holding another consultation on pharmacogenomics/biomarkers to discuss the qualification of the Novel BMs in a timely manner when **the results of the clinical studies, which are ongoing or will be conducted to evaluate the Novel BMs,** are obtained.



Conclusion

- PMDA has started to publish the record of consultation on Novel safety BMs development on its website when it is anticipated to promote wide use of safety BMs in future drug development or further development on safety biomarkers by publishing the record.
- Executive summaries of results of the consultation on BMs for nephrotoxicity this time are as follows:
 - Evaluation of ethnic difference is important for the clinical use of the Novel BMs.
 - Utilization of results from overseas trials in biomarker **qualification is discussed** empirically in review process of pharmaceuticals (**e.g., approved by bridging strategy**).
 - It's expected that further discussions will be made as soon as new data are obtained.

Acknowledgement

(PMDA members)



Akihiro Ishiguro

Yasuto Otsubo

Taiki Sato



<http://www.pmda.go.jp/>