

1 **IFPA Meeting 2018 Workshop Report II: Abnormally invasive placenta; inflammation and**  
2 **infection; preeclampsia; gestational trophoblastic disease and drug delivery**

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46 **Abstract**

47 Workshops are an important part of the IFPA annual meeting as they allow for discussion of  
48 specialized topics. At IFPA meeting 2018 there were nine themed workshops, five of which are  
49 summarized in this report. These workshops discussed new perspectives and knowledge in the  
50 following areas of research: 1) preeclampsia; 2) abnormally invasive placenta; 3) placental  
51 infection; 4) gestational trophoblastic disease; 4) drug delivery to treat placental dysfunction.

52

53 **1 Preeclampsia and the placenta: what's new?**

54 **Chairs:** Christopher Redman and Mitsutoshi Iwashita

55 **Speakers:** Larry Chamley, Stephen Charnock-Jones, Akitoshi Nakashima, Manu Vatish

56 *1.1 Outline*

57 Preeclampsia is caused by the presence of the placenta although maternal factors are critical  
58 for development of the maternal syndrome. In this workshop four speakers described new  
59 developments which enlarge the bigger picture of this complex disorder.

60 *1.2 Summary*

61 **Larry Chamley** reminded us that, of the maternal factors that induce pre-eclampsia,  
62 antiphospholipid autoantibodies are one of the most powerful, increasing a woman's risk nearly  
63 tenfold. He summarised how they adversely affect syncytiotrophoblast to contribute to the  
64 pathology of the disease. The autoantibodies are transported from maternal blood into the  
65 syncytiotrophoblast where they interact with mitochondria and activate the cell death  
66 machinery. Rather than inducing cell death, antiphospholipid antibodies induce endoplasmic  
67 reticulum stress and the production of extracellular vesicles (EVs) that contain increased  
68 amounts of "danger signals", including mitochondrial DNA. These dangerous EVs cause the  
69 activation of maternal endothelial cells - a hallmark of preeclampsia.

70 **Akitoshi Nakashima** described the importance of placenta-specific autophagy in his mouse  
71 model of pre-eclampsia. If this autophagy is inhibited it elicits failure of invasion and vascular  
72 remodeling, resulting in poor placentation. Then chronic hypoxia of these poorly structured

73 placentas induces downregulation of transcription factor EB (TFEB), a master regulator of  
74 autophagy, in trophoblasts. Increased aggregation of protein ensues, associated with the  
75 impaired placentation. Observations in human tissue were consistent with this model.

76 **Stephen Charnock-Jones** and his colleagues set out to investigate why the risk of perinatal and  
77 infant death is greater in male fetuses exposed to placental dysfunction. They applied several “-  
78 omic” technologies to placenta and maternal serum of affected and unaffected pregnancies.  
79 They searched for differences in placental function associated with fetal sex, using data and  
80 biological samples from the Cambridge Pregnancy Outcome Prediction (POP) study. They found  
81 that spermine synthase (*SMS*) mRNA and protein are more abundant in the female than in the  
82 male placenta. *SMS* is an X-chromosome gene and its promotor methylation profile is similar to  
83 other genes that escape X-inactivation (XCI). However the escape is restricted to the placenta.  
84 *SMS* was reduced in male primary trophoblast cells, which were more sensitive to polyamine  
85 depletion. The spermine metabolite N1,N12-diacetylspermine (DiAcSpm) was found to be  
86 higher in the female placenta and sera of women carrying a female fetus. They made the  
87 surprising observation that higher DiAcSpm in maternal serum increased the risk of  
88 preeclampsia but reduced the risk of fetal growth restriction (FGR). This intriguing finding is the  
89 first to identify a maternal biomarker with opposite associations with preeclampsia and FGR. It  
90 is also the first evidence that implicates polyamine metabolism in sex-related differences in  
91 human pregnancy complications.

92 **Manu Vatish** described -omic investigations of syncytiotrophoblast extracellular vesicles that  
93 circulate in maternal blood. They were prepared by dual lobe placental perfusion. This is the  
94 most physiological *ex vivo* technique for isolating extracellular vesicles to enable separation into

95 microvesicles and exosomes. Samples from normal and preeclampsia placentae were subjected  
96 to comprehensive proteomics and deep sequencing analysis. Their bioinformatics analysis  
97 showed that there are specific differences between microvesicles and exosomes, in the  
98 diseased and normal state. Vatish and colleagues validated these changes and reveal a number  
99 of novel and promising biomarkers of pre-eclampsia that can be measured in the maternal  
100 circulation. This strengthens the concept that pre-eclampsia is secondary specifically to  
101 syncytiotrophoblast factors that are shed into the maternal circulation.

### 102 *1.3 Conclusions*

103 All four speakers presented novel methods and results from very different points of view. They  
104 included (1) the role of trophoblast autophagy of syncytiotrophoblast in early pregnancy; (2)  
105 the effect of syncytiotrophoblast damage secondary to antiphospholipid autoantibodies that  
106 generates release of syncytiotrophoblast extracellular microvesicles bearing danger molecules;  
107 (3) sex specific differences in polyamine metabolism in placentas; and differences in circulating  
108 polyamine metabolites that have opposite associations with pre-eclampsia and fetal growth  
109 restriction; (4) the application of dual lobe placental perfusion and -omics techniques to  
110 demonstrate the range and heterogeneity of potential signals released from  
111 syncytiotrophoblast; new potential disease biomarkers were discovered in this way for further  
112 testing and validation.

113

114 **2 Abnormally invasive placenta (AIP): an international perspective**

115 **Chairs:** Sally Collins and Kiyotake Ichizuka

116 **Speakers:** Sally Collins, Nick Illsley, Abdulla Al Khan, Kenji Tanimura

117 *2.1 Outline*

118 The aim of the workshop was to present and discuss recent advances in diagnosis and  
119 management of abnormally invasive placenta. The workshop was fully interactive with  
120 questions posed by both the speakers and the audience. These were answered via smartphone  
121 with the results displayed real time throughout.

122 *2.2 Summary*

123 **Sally Collins** introduced the International Society for AIP (<http://www.is-aip.org>). The IS-AIP  
124 evolved from the European Working Group on AIP (EW-AIP) and currently consists of 42  
125 Obstetricians, Gynecologists, Pathologists, Anesthesiologists and Basic-Science Researchers  
126 from 13 European countries. The aim of the group is to promote excellence in all aspects of  
127 healthcare relating to AIP including research (clinical, epidemiological and 'wet lab'),  
128 diagnosis/management, and education. It has published ultrasound markers for AIP (*Collins et*  
129 *al., Ultrasound Obstet Gynecol, 47(3): 271-5, 2016*) and is in the process of producing an  
130 evidence-based guide for intrapartum management. The IS-AIP welcomes new members from  
131 around the world.

132 **Kenji Tanimura** discussed prenatal diagnosis of AIP in women with placenta previa. Abnormally  
133 invasive placenta is a life-threatening obstetrical condition, and placenta previa (PP) is one of

134 the most significant risk factors for AIP. Prenatal diagnosis of AIP helps to minimize clinical  
135 complications by enabling obstetricians to plan for resources required during delivery. At Kobe  
136 University, pregnant women with PP who are suspected of having AIP receive preoperative  
137 internal iliac artery occlusion balloon catheter placement for reducing intraoperative blood loss.  
138 Their novel Placenta Previa with Adherent Placenta (PPAP) scoring system for predicting AIP in  
139 women with PP was also introduced. The PPAP score is composed of 1) past history of previous  
140 uterine surgery; and 2) imaging findings of ultrasonography and MRI (*Tanimura et al, Placenta*  
141 *64, 27-33, 2018*). Tanimura and colleagues have found that PPAP score may be useful for  
142 predicting AIP complicated by PP.

143 Through video recordings, **Abdulla Al Khan** demonstrated surgical techniques and methods  
144 used to manage abnormally invasive placentation at delivery. Hemorrhage is the leading cause  
145 of maternal morbidity and mortality in the setting of women with AIP. The objective of the  
146 presentation was to provide surgeons involved in the care of these complex patients a  
147 systematic surgical approach in order to decrease morbidity.

148 Current knowledge regarding the pathology of AIP was presented by **Nick Illsley**. Many women  
149 who have both placenta previa and uterine damage (e.g. Cesarean section) – primary risk  
150 factors for AIP – do not progress to AIP. Thus, other factors, perhaps cellular or molecular, may  
151 be involved. Illsley and colleagues examined the status of trophoblast cells on the epithelial-  
152 mesenchymal transition spectrum and showed that while cytotrophoblasts were converted to a  
153 metastable, mesenchymal form of extravillous trophoblast (EVT) in the first trimester, third  
154 trimester EVT regressed to a less invasive, more epithelial phenotype. EVT isolated from AIP  
155 pregnancies were found to be intermediate between the first and third trimester EVT, implying

156 a more invasive, mesenchymal endpoint than normal third trimester EVT, consistent with an  
157 over-invasive phenotype. They postulated that an abnormal or deficient decidua/myometrium  
158 is responsible for the impaired regression seen in AIP. Future directions involve identifying  
159 endometrial factors predisposing to AIP with the intent of therapeutic modification to reduce  
160 the risk of AIP.

### 161 *2.3 Conclusions*

162 A lively debate ensued regarding all of the issues covered. With regards to imaging, the opinion  
163 was that no single sign has been demonstrated to be diagnostic. Novel scoring systems, such as  
164 the one presented, may assist with this. A discussion regarding the possible option of  
165 conservative management followed the talk on surgical techniques. Although there was  
166 disagreement on the utility of this strategy, all were in agreement that the management  
167 offered should be an individualized decision taken on a case by case basis. Novel strategies for  
168 investigating AIP at a cellular level were also extensively discussed.

169

170 **3 Impact of infection on placental biology**

171 **Chairs:** Gendie Lash and Shigeru Saito

172 **Speakers:** Thaddeus Golos, Solene Grayo, Gendie Lash, Shigeru Saito, Kenji Tanimura, Bryce

173 Wolfe

174 *3.1 Outline*

175 The establishment of a successful pregnancy involves invasion of the maternal uterine tissues  
176 by fetal extravillous trophoblast cells (EVT) and remodeling of the uterine spiral arteries. Both  
177 of these processes are tightly regulated by a range of cell types, most notably the uterine  
178 natural killer cells (uNK) and uterine macrophages, which play important 'non-immune' roles in  
179 establishment of pregnancy. But what happens when the pregnancy is compromised by an  
180 infectious agent? Do the immune cells become repurposed so that they are no longer able to  
181 perform their tissue remodeling roles? Does the immunosuppressed environment of the fetal-  
182 maternal interface allow for a greater degree of viral/bacterial infection? Upon infection is  
183 placental function compromised? This workshop explored some of these questions using  
184 emerging knowledge from studies on viral (Zika, CMV) and bacterial (Listeria) infection during  
185 pregnancy.

186 *3.2 Summary*

187 **Gendie Lash** reviewed non-immune roles of decidual immune cells in early pregnancy. In early  
188 pregnancy 30% of the decidual stromal cells are leucocytes, predominantly uterine natural killer  
189 (uNK) cells (70%), macrophages (25%) and T cells (5%). These different cell types play essential

190 roles not only in establishment of tolerance to the semi-allogeneic fetus but also in regulation  
191 of EVT invasion and, in particular, remodeling of the uterine spiral arteries. Evidence for the  
192 different roles uNK cells and macrophages play was presented and several discussion points  
193 raised. In particular, why does spiral artery remodeling fail in some pregnancies, and are  
194 bacterial or viral infections a cause of this by altering the phenotype of decidual immune cells  
195 so that they can no longer perform their non-immune functions?

196 **Solene Grayo** posed the question: what can we learn from each congenital pathogen that can  
197 be applied to others? During pregnancy, the syncytiotrophoblast is an efficient physical and  
198 chemical antimicrobial barrier. Thus, most pathogens affecting the mother do not cause  
199 congenital fetal infection. Nevertheless, a few predominantly intracellular microbes (e.g.  
200 *Listeria monocytogenes*) are able to bypass these intrinsic defenses and invade the syncytium  
201 by using specific virulence determinants, such as internalins for *L. monocytogenes* (internalin-  
202 mediated invasion). Moreover, directly in contact with maternal cells in the uterus, EVT  
203 represent a possible pathway into the placenta and are targeted by microbes to facilitate  
204 vertical transmission (*Toxoplasma gondii*, *L. monocytogenes*, HCMV). The invasion of maternal  
205 immune cells, prior to EVT invasion of the uterus, is also described. Microorganisms (viruses,  
206 parasites and bacteria) use various ways to breach the placental barrier. Nevertheless, evidence  
207 that multiple congenital pathogens share common strategies is emerging, allowing to better  
208 predict the potential of new “TORCH” pathogens, such as Zika virus (ZIKV).

209 **Kenji Tanimura** discussed pathological mechanisms of placental cytomegalovirus (CMV)  
210 infection, and their identification of biomarkers for predicting congenital CMV infection. Human  
211 CMV is one of the most common causes of mother-to-child infection worldwide. Congenital

212 CMV infection can lead to neonatal death and major neurological sequelae in surviving infants.  
213 Recent studies demonstrate that not only direct effects of CMV on the fetus but also indirect  
214 effects of CMV by placental infection may cause adverse pregnancy outcomes. The detection of  
215 CMV-DNA in maternal uterine cervical secretions is a predictive biomarker for congenital  
216 infection in high-risk pregnant women, whereas maternal universal screening based on CMV  
217 IgG, IgM or IgG avidity index overlooks a number of newborns with congenital-infection in low-  
218 risk pregnant women. He also reported that threatened premature delivery was associated  
219 with the occurrence of congenital infection from non-primary infection.

220 **Thaddeus Golos** reported that although frank birth defects are uncommon with experimental  
221 infection of pregnant nonhuman primates (NHP) with Zika virus (ZIKV), early pregnancy  
222 infection is associated with a significant increase in adverse pregnancy outcomes, including  
223 miscarriage, preterm labor, stillbirth, and postnatal respiratory distress. These adverse  
224 outcomes are associated with placental and decidual vascular pathology and placental infarcts.  
225 Altered placental and decidual macrophage phenotypes and prevalence have been noted with  
226 infection. The reported tropism of ZIKV for Hofbauer cells suggests that this may be one  
227 pathway by which ZIKV causes placental insufficiency associated with adverse outcomes.

228 **Bryce Wolfe** presented their work in collaboration with Dr Leticia Reyes on oral pathogens and  
229 placental dysfunction. *Porphyromonas gingivalis* (Pg) is a periodontal pathogen implicated in  
230 pregnancy complications involving defective placentation. Pg strains that reduce trophoblast  
231 invasion and spiral artery remodeling disrupt activin signaling in the decidual stroma. Studies in  
232 rodents and humans suggest that activin promotes decidualization and trophoblast invasion,  
233 therefore this may be a novel mechanism whereby bacteria can impair placentation. In addition

234 to affecting stromal cell signaling and trophoblast function, they found that *in vivo* infection of  
235 macaque decidua and rat mesometria altered the activation state or proportion of uNK cells,  
236 respectively, without inflammation. These data suggest that Pg in the decidual stroma disrupts  
237 pathways important for cell differentiation and proliferation, and impacts non-immune  
238 functions of immune cells.

239 Intra-amniotic infection in extremely preterm birth was discussed by **Shigeru Saito**. Intra-  
240 amniotic infection is a major cause of preterm birth (PTB). Saito and colleagues established a  
241 new PCR method by which all the species of bacteria, Mycoplasma, Ureaplasma and fungi are  
242 detectable. As a result, PTB was classified into intra-amniotic infected PTB, sterile – inflamed  
243 PTB, and sterile–non-inflamed PTB. Antibiotics therapy was effective to prolong the gestational  
244 period in infected PTB, but did not prolong the gestational period in non-infected cases. 17 $\alpha$ -  
245 hydroxyprogesterone caproate could prolong the gestation in limited PTB cases with sterile-  
246 mild intra-amniotic inflammation.

### 247 *3.3 Conclusion*

248 This workshop provided insights into how different infectious agents affect placental biology,  
249 and therefore adversely affect pregnancy outcomes. Several common themes are starting to  
250 emerge regarding the impact of different infectious agents on the establishment of pregnancy;  
251 in particular, effects on EVT invasion, altered decidual leukocyte phenotypes and aberrant spiral  
252 artery remodeling. Discussion also centered around the best models to investigate some of the  
253 questions posed by the speakers, although no consensus was reached. In addition, it was noted  
254 that timing of infection during pregnancy may be critical for impacting pregnancy outcome.

255 Further research is required to address these questions, but it is evident that based on timing  
256 and type of infection, different treatment strategies will need to be developed.

257

258

## 259 **4 Gestational trophoblastic disease (GTD)**

260 **Chairs:** Kazuhiko Ino and Eiko Yamamoto

261 **Speakers:** Hiroshi Fujiwara, Kaoru Niimi, Hirokazu Usui, Eiko Yamamoto

### 262 *4.1 Outline*

263 Gestational trophoblastic disease (GTD) is a group of diseases characterized by abnormal  
264 cellular proliferation of atypical trophoblasts, including hydatidiform mole, invasive mole,  
265 choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelial trophoblastic tumor  
266 (ETT). Hydatidiform mole is an abnormal pregnancy caused by genetic fertilization disorders,  
267 which have higher potential to develop to gestational trophoblastic neoplasia (GTN) than  
268 normal trophoblasts. However, the involvement of the genetic origin of trophoblastic cells in  
269 the characteristics of GTN remains unclear. PSTT and ETT are rare tumors occurring from  
270 extravillous trophoblasts and have poor prognosis in metastatic cases because of low sensitivity  
271 to chemotherapy. Approximately 15% of choriocarcinomas become chemo-resistant and the  
272 factors for developing malignant potential of trophoblasts should be identified. In this  
273 workshop, novel therapeutic strategies for GTN in terms of management, diagnosis and  
274 treatment were discussed.

### 275 *4.2 Summary*

276 **Eiko Yamamoto** gave an overview of clinical features of gestational trophoblastic diseases in  
277 Japan. The registration data of gestational trophoblastic diseases in 1974-2015 showed that the  
278 incidence of hydatidiform mole was 1-3 per 1,000 live births in Japan. The incidence (per

279 100,000 live births) of invasive mole, choriocarcinoma and PSTT were 10-20, 1.9-5.5 and 0.1-  
280 0.9, respectively, in 1992-2015. The cure rate of choriocarcinoma was improved from 42% in  
281 the 1960s to 89.7% in the 2000s, and between these decades the proportion of hydatidiform  
282 mole in antecedent pregnancies of choriocarcinoma decreased from 40% to 24%. These results  
283 suggest that the registration system may be effective to improve the outcome of  
284 choriocarcinoma.

285 The cytogenetic classification of hydatidiform moles can be determined by DNA polymorphism  
286 analysis. **Hirokazu Usui** discussed how they have further applied this method to gestational  
287 trophoblastic disease. Using this approach, Usui and colleagues clarified the mitochondria origin  
288 of androgenetic complete hydatidiform mole. Second, they attempted to predict the efficacy of  
289 methotrexate to treat low-risk gestational trophoblastic neoplasia using  
290 methylenetetrahydrofolate reductase (MTHFR) polymorphisms. The MTHFR 677TT genotype in  
291 molar tissue might be a predictive marker of the failure of methotrexate. Finally, they showed  
292 the existence of the gestational components of cell-free DNA in choriocarcinoma patients'  
293 plasma, which may be a more sensitive marker of choriocarcinoma than serum hCG.

294 **Kaoru Niimi** presented evidence that glycosyltransferases regulate the malignant potential of  
295 trophoblasts. Core 2  $\beta$ 1, 6-N acetylglucosaminyl transferase (C2GnT) catalyzes Core 2 structure  
296 on serine-linked oligosaccharides of human chorionic gonadotropin (hCG) and produces  
297 hyperglycosylated hCG. C2GnT was highly expressed in choriocarcinoma cells. Suppression of  
298 C2GnT reduced cell migration and invasive potential, and adhesion to HUVEC cells. Natural  
299 killer (NK) cells killed C2GnT knockout cells more efficiently than control cells. These findings  
300 suggest that choriocarcinoma cells may acquire a highly malignant potential by expressing

301 C2GnT, and escape from the innate immune system by C2GnT-mediated glycosylation of MHC  
302 class I chain-related molecule A (MICA).

303 **Hiroshi Fujiwara** discussed the applicability of laeverin as a marker of PSTT. Fujiwara and  
304 colleagues produced monoclonal antibodies that react with human EVT and found a novel  
305 membrane-bound peptidase, named “laeverin”, which is specifically expressed on EVT. Using  
306 anti-laeverin antibodies, they observed that laeverin was also expressed on PSTT that is  
307 considered to be derived from EVT at the implantation site. Since the expression of laeverin  
308 was specific to EVT-lineage cells, we propose that laeverin is a new marker of PSTT.

#### 309 *4.3 Conclusion*

310 The aim of this workshop was to discuss how to cure 100% of GTDs. The registration system of  
311 GTDs is effective for decreasing choriocarcinoma that occurs after hydatidiform mole as well as  
312 understanding the features of GTDs. Cytogenetic analysis of molar tissue or patient’s blood may  
313 be used to predict the effectiveness of the treatment for post-molar gestational trophoblastic  
314 neoplasia (GTN) and choriocarcinoma. GnT-IVa and C2GnT are new biomarkers of  
315 choriocarcinoma, especially for early diagnosis and poor prognosis of choriocarcinoma.  
316 Preventing escape from NK cell attack by suppressing C2GnT, may be a novel strategy for  
317 treatment of choriocarcinoma. In terms of PSTT, laeverin may contribute to the correct  
318 diagnosis of PSTT and a new treatment may be found using anti-laeverin antibody.

319

320 **5 Drug delivery in pregnancy: overcoming problems and developing new technologies**

321 **Chairs:** Lynda Harris and Masatoshi Tomi

322 **Speakers:** Natalie Hannan, Lynda Harris, Sampada Kallol (presented on behalf of Christiane

323 Albrecht), Takeshi Nagamatsu, Masataka Nomoto, Masatoshi Tomi

324 *5.1 Outline*

325 The aim of this workshop was to raise awareness of the technical problems and barriers  
326 associated with drug delivery in pregnancy, and to discuss current advances in the field. The  
327 workshop was designed for delegates who are considering undertaking drug delivery-based  
328 research projects, and those who wish to troubleshoot current strategies.

329 *5.2 Summary*

330 **Lynda Harris** opened the workshop by giving an overview of methods for targeted drug delivery  
331 in pregnancy. To mitigate the risks associated with systemic administration of drugs in  
332 pregnancy, novel strategies are being developed that allow targeted delivery of payloads  
333 specifically to uterine and/or placental tissues, limiting transfer to the fetus. This is achieved by  
334 encapsulating drugs inside biocompatible nanoparticles and decorating their surface with  
335 targeting moieties such as peptides or antibodies. Targeted delivery offers enhanced drug  
336 efficacy, improved pharmacokinetics and reduced off target side effects. Dr Harris discussed the  
337 advantages and disadvantages of targeted delivery systems and reviewed current targeted  
338 approaches for inhibition of pre-term labour, enhancement of placental function and uterine  
339 blood flow, and improved gene delivery.

340 **Sampada Kallol** introduced transport studies in human primary trophoblast cells. Investigations  
341 of placental drug and nutrient transporters revealed major differences in transporter  
342 expression and activity depending on the differentiation state of the trophoblast cells. The  
343 directionality of selected substrates (e.g. cholesterol) was further explored on confluent human  
344 primary trophoblast monolayers using Matrigel-coated Transwell® inserts. The results  
345 demonstrated a predominant apically (maternally) orientated cholesterol efflux, consistent  
346 with the localization of the cholesterol transporter ABCA1. These findings underline that human  
347 primary trophoblasts represent a highly physiological and suitable model for transport studies  
348 in term placenta.

349 **Masatoshi Tomi** discussed the physiological and pharmacological roles of organic anion  
350 transporter 4 (OAT4) in the placenta. Human OAT4 is localized at the basal plasma membrane  
351 of placental syncytiotrophoblasts. Because orthologs of human OAT4 are found in primates, but  
352 not in rodents, OAT4 is speculated to have some unique roles that cannot be clarified in  
353 rodents. Tomi and colleagues uncovered the role of placental OAT4 in estriol biosynthesis,  
354 which is unique to human and higher primates. Placental OAT4 mediates the uptake of 16 $\alpha$ -OH  
355 DHEAS –an estriol precursor. Additionally, OAT4 mediates the transport of angiotensin-II  
356 receptor blockers, which cause adverse pregnancy outcomes like oligohydramnios in humans.

357 **Takeshi Nagamatsu** introduced a drug delivery system to regulate placental transfer using  
358 nano-micelle technology. Medical application of nano-micelle technology is a promising  
359 strategy to concentrate drug distribution to target tissues. During pregnancy, drug selection is  
360 quite restricted due to concern for harmful effects on the fetus. Dr Nagamatsu discussed his  
361 current work using PEGylated-drug compounds, which spontaneously assemble into nano-

362 micellar structures, to enhance uteroplacental drug targeting. He discussed the potential  
363 challenges of regulating placental transfer using drug-incorporated nano-micelles and the  
364 future possibility of their clinical application for perinatal diseases.

365 **Masataka Nomoto** gave an update on the search for therapeutic agents for fetal growth  
366 restriction (FGR). FGR is associated with neonatal morbidity and mortality, yet no effective  
367 treatment has been established. Based on preeclampsia research, Dr. Nomoto proposed that  
368 drugs altering the function of extravillous trophoblasts are a treatment for FGR. Nomoto and  
369 colleagues screened drugs for the ability to alter trophoblast function, using drug repositioning  
370 strategies. The effects of a commercially available chemical library (about 1500 compounds) on  
371 BeWo cell proliferation, invasion, and placental growth factor production were investigated  
372 using cell culture-based assays. They identified multiple compounds that might regulate the  
373 function of trophoblasts. These drugs may be useful for elucidating the mechanism of diseases  
374 related to placental formation, such as FGR.

375 Finally, **Natalie Hannan** introduced esomeprazole as a novel therapeutic to treat preeclampsia.  
376 Preeclampsia is clinically characterized by new onset hypertension and either end organ  
377 damage or fetal growth restriction. There are currently no treatments for preeclampsia.  
378 Previously Hannan and colleagues discovered that the proton pump inhibitor, esomeprazole,  
379 can mitigate the pathophysiology of preeclampsia *in vitro*, *ex vivo* and *in vivo*. Together with  
380 clinical collaborators they assessed the potential of esomeprazole to treat preeclampsia in  
381 women with severe early onset (<34 weeks gestation) in a Phase II clinical trial. They observed  
382 that daily esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm  
383 preeclampsia, nor decrease circulating plasma soluble fms-like tyrosine kinase 1 levels. Higher

384 levels in the maternal circulation may be needed for clinical effect especially as a treatment to  
385 alleviate pathology in this cohort of very sick women. A prospective trial to assess the ability  
386 esomeprazole to prevent preeclampsia in high risk women is currently underway.

### 387 5.3 Conclusions

388 It is evident that whilst the placental barrier acts effectively to facilitate hormone biosynthesis,  
389 nutrient partitioning, and to prevent toxic substances entering the fetal circulation, it  
390 represents both an exciting therapeutic target and a logistical challenge in terms of drug  
391 delivery in pregnancy. Numerous targeted approaches are being developed for selective  
392 delivery of therapies to the placenta and uterus, which offer enhanced drug efficacy, improved  
393 pharmacokinetics and reduced side effects. In parallel, the search continues to identify  
394 appropriate compounds to treat placental dysfunction and/or maternal symptoms that are  
395 both safe and effective.

396

397