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IFPA meeting 2017 workshop report: Clinical placentology, 3D structure-based modeling of placental function, placental bed, and treating placental dysfunction☆

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ABSTRACT

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2017 there were four themed workshops, all of which are summarized in this report. These workshops discussed new knowledge and technological innovations in the following areas of research: 1) placental bed; 2) 3D structural modeling; 3) clinical placentology; 4) treatment of placental dysfunction.

1. Placental bed in the next generation

Chairs: John Aplin and Larry Chamley.

Speakers: John Aplin, Judith Bulmer, Graham Burton, Larry Chamley, Terry Morgan.

1.1. Outline

In this workshop, after Larry Chamley had set the scene, four established investigators introduced materials available to help

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familiarize researchers with the complexities of placental bed histology and pathology, with a strong emphasis on vascular function. Speakers posed questions they considered important for future research. The session was a true workshop, with questions and comments from the floor to all speakers stimulating intense discussion.

1.2. Summary

Graham Burton discussed placental bed resources available at the Cambridge Centre for Trophoblast Research. The Centre for Trophoblast Research holds two archival collections of placental histological material available for study. The Boyd collection comprises material from over 200 pregnancies collected in the 1960's and 1970's [1]. The most informative slides are the placenta-*in-situ* specimens, which range in gestational age from 6 to ~34 weeks. Runs of serial sections stained with different dyes are available for some of the earlier specimens. Representative sections of the larger slides have been scanned and can be viewed at http://www.trophoblast.cam.ac.uk/Resources/boyd-collection. The Dixon material was collected in the 1970's and comprises ~60 placenta-*in-situ* specimens from 8 to 16 weeks gestational age that are believed to have come from normal pregnancies. Unfortunately, there are no clinical data or blocks associated with either collection.

John Aplin shared a histology resource for normal and pathological term placental bed. He described a set of term placental bed specimens originally produced in Leuven by Robert Pijnenborg. They have been used for teaching at the Queen's University placenta workshops in Kingston, Ontario, and in the Manchester Master of Research in Reproduction and Pregnancy program. There are 15 tissues from normal or pathological pregnancies, each in a set of 4 serial sections stained with different markers. With respect to vascular features, there are examples of deep myometrial arteries that remain untransformed, spiral arteries that have undergone normal physiological conversion as well as profiles exhibiting a range of pathological features. The respective patterns of trophoblast invasion are well documented. The scanned slides are available for online study; Dr Aplin will supply details on request.

Judith Bulmer described first and second trimester placental beds in Newcastle. Uterine spiral artery remodeling is crucial for a successful pregnancy, but these arteries are not readily accessible. In Newcastle, a reliable technique was developed to biopsy the placental bed after termination of pregnancy using a transvaginal approach [2]. Over 500 placental bed biopsies ranging from 6 to 20 weeks gestational age have been collected. Collection of decidua and placenta from the same patients has allowed investigators to combine *in situ* immunohistochemical studies or laser capture and PCR with functional studies of decidua and trophoblast populations. There was discussion of the extent to which endothelial cells become displaced from spiral arteries during remodeling. Dr Bulmer agreed that residual endothelial cells remain during active remodeling and can later reform a continuous covering layer in remodelled vessels.

Terry Morgan presented uterine radial artery remodeling and the progressive disintegration of spiral artery plugs. Contrast-Enhanced Ultrasound has provided the sensitivity to detect low level intervillous space (IVS) perfusion as early as 6 weeks gestation with significantly more flow measured at 13 weeks. His group's histopathological review of the Boyd collection in Cambridge revealed loosely cohesive 'plugs' with capillary-sized channels filled with red blood cells at 7 weeks gestation and progressive disintegration of these plugs thereafter. Interestingly, the progressive loss of spiral artery plugs was not reflected in IVS blood flow data. Resistance did not appear to change from 7 to 12 weeks. Instead, myometrial radial artery remodeling was observed beginning at the end of the first trimester, which may be more closely related to the observed increase in early second trimester blood flow. Delegates discussed the phenotype of cells in the plugs, some of which are $CD56^{+}$.

1.3. Conclusions

Collections of placental beds/placentae *in situ* are available in the three centers included in this workshop (as well as the Carnegie collection, not discussed here). These samples provide invaluable information regarding human implantation and their ongoing examination continues to provide new insights as we reinterpret the histology in the light of information provided by new technologies. As many of these specimens are irreplaceable it is imperative that the collections are maintained and access to them assured. One of the aims of this very well-attended workshop was to inform and stimulate young investigators, and no one who attended could doubt that there are important unanswered questions in placental bed pathobiology.

2. 3D structure-based modeling of placental function

Chairs: Paul Brownbill, Igor Chernyavsky, Alys Clark, Oliver Jensen, Ed Johnstone, Lopa Leach, Rohan Lewis, Carolyn Salafia, Henning Schneider.

Speakers: Alys Clark, David Elad, Marcel Filoche, Rohan Lewis, Michelle Oyen, Gareth Nye.

2.1. Outline

The workshop comprised of three synergistic parts, each followed by interactive discussion: (i) placental imaging, accounting for state of the art three-dimensional microscopy; (ii) human placenta physiology relating to blood flow and oxygen transfer; (iii) advances in human placental mathematical modeling predicting transfer and blood flow based on placental structural morphology.

2.2. Summary

In the first section on "Structure", **Rohan Lewis** introduced multi-scale 3D imaging of placental villi as the basis for modeling and functional analysis. It was described how the three-dimensional structure of the placental villi and the complex spatial relationships of the cells they contain are central to placental function. Multi-scale imaging techniques including micro-CT, whole-mount confocal, light sheet and serial block-face scanning electron microscopy now allow three-dimensional imaging of whole placentas or regions of placenta down to the nm scale. There was an illustration of how these approaches can inform computational and molecular studies and advance our understanding of placental function. Discussion centered on pericyte associations with the endothelium; and potential future insight into the true meaning of syncytial knots, given the high-resolution imaging that is now possible at the microvillous surface.

In the second section on "Function", **David Elad** showed how the *ex vivo* human placental perfusion model could be used in a single (fetal) side perfusion adaptation to analyze resistance indices in the feto-placental chorionic plate vasculature with Doppler. The efficacy of material exchange in the human placenta depends on proper blood perfusion through the complex 3D branching network of the feto-placental vasculature. Accordingly, obstetrics monitoring guidelines have evolved based on clinical studies that explored correlations between umbilical Doppler indices and pregnancy outcome. However, the biophysical foundation is vague and only based on simplified lumped element models of electronic

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