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Breakthroughs and challenges of modern developmental biology and reproductive medicine

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ABSTRACT In recent decades we have witnessed unprecedented progress in the field of the developmental biology of mammals. Building on 20th century discoveries, we have managed to increase our understanding of the molecular and cellular mechanisms governing early mammalian embryogenesis and link them to other biological questions, such as stem cells, regeneration, cancer, or tissue and organ formation. Consequently, it has also led to a creation of a completely new branch of reproductive medicine, i.e. assisted reproductive technology (ART). In this Special Issue of *The International Journal of Developmental Biology (Int. J. Dev. Biol.)* we wished to review state-of-the-art research regarding early mammalian development, from fertilization up to the implantation stage, and discuss its potential meaning for practical applications, including ART. As an introduction to the issue we present a compilation of short essays written by the most renowned scientists in the field, working both in basic and clinical research. The essays are dedicated to the greatest breakthroughs and challenges of 21st century developmental biology and reproductive medicine.

KEY WORDS: *embryo, fertilization, ART, developmental biology*

In recent decades we have witnessed unprecedented progress in the field of the developmental biology of mammals. Building on the 20th century discoveries of Tarkowski, McLaren, Austin, Chang, Yanagimachi and many others, we managed to increase our understanding of molecular and cellular mechanisms governing early mammalian embryogenesis and link them to other biological questions, such as stem cells, regeneration, cancer, or tissue and organ formation. This advancement has also led to a creation of a completely new branch of reproductive medicine: starting with the introduction of the *in vitro* fertilization protocol by Edwards and Steptoe, the assisted reproduction technology (ART) was born.

In the current issue of the International Journal of Developmental Biology we wished to review state-of-art research regarding early mammalian development, from fertilization up to implantation stage, and discuss its potential meaning for practical applications, including ART. Therefore, we thought that there is no better way to introduce readers to the issue, than to put together a number of short essays written by the most renowned scientist in the field, working both in basic and clinical research. The essays are dedicated to the greatest breakthroughs and challenges of the 21st century developmental biology and reproductive medicine.

The common theme in the essays is appreciation for novel techniques (genetic and 'omic analyses, genetic modification tools, imaging systems, optimization of embryo culture conditions) permitting to deepen and extend the research and improve clinical outcomes. A strong need for interdisciplinary research, combining expertise of biologists, clinicians, physicists, biostatisticians and computational scientists, as well as moving towards non-canonical mammalian models, is yet another motif that emerges in all the essays. And everybody agrees that there are plenty of exciting discoveries in developmental biology and reproductive medicine waiting ahead.

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The 20th century, exactly 40 years ago, saw the realisation of the first birth achieved by extracorporeal fertilisation – for which the Nobel Prize in Physiology or Medicine was awarded in 2010 (re-

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viewed in Fishel, 2018). The end of the 20th century therefore saw enormous progress in human reproduction and developmental biology as a consequence of scientific research and clinical application that has far-reaching implications for the 21st century.

Successful human conception is known to be relatively inefficient, due to a large extent of aneuploidy in embryos, which was known to be prevalent since the early 1980's (Angell *et al.*, 1983). Hence the development of genetic tests to detect aneuploidy became a clinical imperative. Once embryos could be successfully biopsied, it was realised that biopsied cells could reveal the sex and then single gene mutations for clinical use.

The first involvement of genetic screening of embryos some 30 years ago was sexing for a monogenic condition. During the 21st century we have seen the introduction of Next Generation Sequencing (NGS), further developments of this technology for aneuploidy screening, monogenic diagnosis of embryos for hundreds of conditions, pre-conception carrier screening and only recently the prospect of screening human embryos for polygenic conditions has become reality (Lello *et al.*, 2018; www.genomicprediction.com). The combination of embryology technologies and genetics has seen the introduction of 'pronuclear transfer' for mtDNA cytopathies, and the so-called three-parent DNA children (Zhang *et al.*, 2016). DNA detection for embryo assessment still requires an invasive cell removal, but more recently non-invasive and high-throughput assays have been developed (Liu *et al.*, 2017). CRISPR-Cas9 research has been reported successfully to eliminate a whole chromosome raising the prospect of this technology being used for the correction of genetic and chromosome anomalies in embryos rather than their disposal (Zuo *et al.*, 2017).

The 21st century has seen the introduction of 'embryoscopy' into clinical IVF practice – the use of closed incubation systems with integrated microscopy for time-lapse imaging. This not only opened a window on cleavage anomalies that hitherto were unrecognised, but also permitted the use of morphokinetic algorithms for objective embryo selection. Although yet to be adopted completely, it is likely to be heralded as breakthrough technology for understanding human preimplantation embryo *in vitro* cleavage, and embryo selection for clinical IVF (Campbell and Fishel, 2016; Pribenszky *et al.*, 2017; Fishel *et al.*, 2018). Increasingly we shall see these technical advances in time-lapse imaging, genetic, epigenetic and chromosomal analyses of whole human embryos, and also the advent of 'artificial embryos' greatly improve our understanding of early human embryogenesis at the cell interactive and single, subcellular levels (Carbone *et al.*, 2015; Deglincerti *et al.*, 2016; Shahbazi *et al.*, 2016).

The introduction of vitrification for successful egg freezing has created opportunities for a whole group of patients; particularly for fertility preservation for cancer patients and those with benign disease. It also opens the opportunity for mothers of girls with galactosaemia to preserve eggs for their daughters, as well as empowering all women to preserve fertility for personal, non-medical reasons. Further still, the advent of success ovarian tissue cryopreservation and transplantation may not only provide for fertility preservation, it may become an important health opportunity for naturally postponing the menopause in the aging population (Donnez and Dolmans, 2017; Amorim *et al.,* 2018).

Perhaps amongst the most intriguing advances of this century is the development of 'artificial gametes', developed from progenitor somatic cells. Live births have already been achieved in animals from a variety of antecedent cells, but in humans, apart from the social and ethical implications the safety and efficacy of such cells remains to be established (reviewed in Hendriks *et al.*, 2015).

Finally, with all the remarkable developments of the 21st century, many of which will undoubtedly continue to bring improvements to human health and a deeper understanding of human conception and developmental biology, possible one of the most remarkable changes has been the use of these technologies for the first time in human history to redefine family life and human procreation (Imrie *et al.*, 2018).

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Embryonic development; what it achieves, and the accuracy with which it is accomplished, is astonishing. Understanding development not only explains how embryos form and tissues are sculpted, but is the benchmark against which we can determine what goes wrong in pathological conditions, such as congenital malformations or cancer. Understanding development underpins any endeavor to repair or replace damaged tissues.

An overarching goal of developmental biology is to glean an understanding of how cells collectively, reproducibly and robustly make embryos (or tissues) of the correct size, and within the correct time-frame. One fundamental behavior that has recently been increasingly appreciated is that cells usually make their individual fate decisions asynchronously within the populations they comprise. We seek to understand how signaling and gene activities interface to define cell states and identities, and how acquisition of an identity is coordinated with cellular organization in emergent tissues.

Rather than looking at a single gene, gene family or signaling pathway of interest, in diverse contexts, an approach prevalent in the late 20th century, there has been a shift to tissue-focused investigations. As we near the end of the first quarter of the 21st century, our qualitative descriptions of old are being replaced by quantitative and dynamic understandings. Moving forward we will traverse scales; from elucidating molecular circuits and determining how they impact cellular states, to cells and understanding how their behaviors impact tissue-level architectures.

From the experimental embryology of the 19th, and molecular embryology of the late 20th century, comes the advent of organoid biology, and the ability to generate size-appropriate synthetic embryo-like structures *in vitro* through the reconstitution of, oftentimes, embryo-derived stem cells. These approaches have some way to go, but one can expect their efficiency to improve, which coupled with their scalability, makes the prospect of synthetic mammalian

embryos something to anticipate and consider.

Over the past decade a suite of technical innovations has propelled what we can do experimentally. Our methodological toolkit encompasses improvements in the *ex utero* culture of embryos (or tissues); with better efficiencies and for longer periods of time. This is coupled with the ever-evolving ability to image molecules in cells, and cells in embryos; at increasing temporal, spatial and spectral resolutions. These approaches are complemented by the recent feasibility of precision genomic perturbations, as well as the increasing application of 'omics approaches at the level of single cells. There is an increasing cognizance of the importance of mechanics; the acquisition of biophysical measurements, and consequences of perturbations.

A key challenge moving forward will be to formulate the right questions to ask, and the best system to frame them in. Studies will increasingly be run in parallel in embryos and in synthetic *in vitro* systems, some of them reductionist. In classical mammalian models such as the mouse, and by extension in human, as well as taking in details from non-classical models. The future is collaborative; an unbiased informed and holistic understanding of embryonic development will only arise through the integration of multiple types of data, by individuals having diverse expertise and perspectives.

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The notion that development is a one-way process, during which cells inevitably lose their developmental potential, was successfully contested in the middle of the last century by John Gurdon, who demonstrated that a differentiated, somatic nucleus could be re-programmed by the cytoplasm of the egg and could drive the embryonic development, regaining the ability to give rise to the various cell types (Gurdon, 1962). At the beginning of 21st century, Kazutoshi Takahashi and Shinya Yamanaka followed Gurdon's pioneering work and demonstrated that mouse fibroblasts can be reprogrammed into the pluripotent cell type - induced pluripotent stem cells (iPS cells), using a combination of only four transcription factors (Takahashi and Yamanaka, 2006). Subsequent generation of human iPS cells (Takahashi *et al.,* 2007) opened entirely new avenues for regenerative medicine and patient-specific therapies. For their discoveries, Gurdon and Yamanaka were awarded the 2012 Nobel Prize in Physiology or Medicine.

Somatic cell reprogramming and iPS technology represent a huge step forward towards the generation of patient-specific cell lines - and potentially whole organs - for replacement therapies. However, to assure safety and reproducibility of the regenerative medicine techniques, the detailed knowledge and understanding of the normal development processes is of the utmost importance. To create complex structures, like a heart or a liver, we need a detailed 4D roadmap that explains how the cells that constitute given tissue or organ specify and position themselves in their appropriate place, how the functional connections are established between different cell types and cell lineages, and finally how the cells deposit and interact with extracellular matrix components. Formation of an adult organism from a fertilized zygote is a journey with many critical steps and potential roadblocks. Developmental biology provides tools and intellectual paradigm to facilitate understanding of the processes that govern lineage and organ formation. In that sense, developmental biology is still the science of the future.

Looking for stereotypical behavior in flexible, self-organising environment is a very challenging task. Quantification of a variable cell dynamics (cell origin, physical properties, division rate, migration speed and directionality, description of cell dynamic neighborhood, etc.) across different tissues and cell lineages within the developing organism is an important step towards creation of the "digital map" of the lineage and organ development. This needs to be combined with the further understanding of how physical interactions between different parts of the embryo/organs can shape developmental processes. Importantly, combining and comparing digitalized information from multiple embryos/foetuses per stage/developmental process/developmental period is necessary to account for the high embryo-to-embryo variability - an intrinsic feature of self-organising systems with high plasticity. Data from multiple embryos can then be averaged and used to create a very detailed map of the predicted cell behavior within specific developmental periods. This in turn, can be used to create much more accurate models of developmental processes, as was recently demonstrated by Philipp J. Keller's lab (McDole *et al.,* 2018). Similar "digital organism" maps would be created for mutant embryos, where the function of the gene (or sets of genes) was perturbed in order to understand the origin of pathological processes.

Construction of new models that incorporate both biochemical and physical interaction between different cell lines, organs or embryo components is necessary to further our understanding of the developmental processes. This might not be possible without forging the successful collaborations between developmental biologists, computational scientists, physicists, statisticians, modelers etc. Formation of such intra-disciplinary teams may be an absolute necessity for the developmental biology of the 21st century.

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[#]The essay was prepared in collaboration with D. Cimadomo and FM. Ubaldi (Clinica Valle Giulia, g.en.e.r.a. centers for reproductive medicine, Rome, Italy), and S. Alfano and E Alviggi (Clinica Ruesch, g.en.e.r.a. centers for reproductive medicine, Naples, Italy).

IVF is among the fastest developing fields of medicine. Thanks to the pioneering work of Steptoe and Edwards and the courage of their first patients (Edwards, 1981), nowadays millions of infertile couples worldwide might benefit from assisted reproduction technologies. An intensive research activity in this field keeps

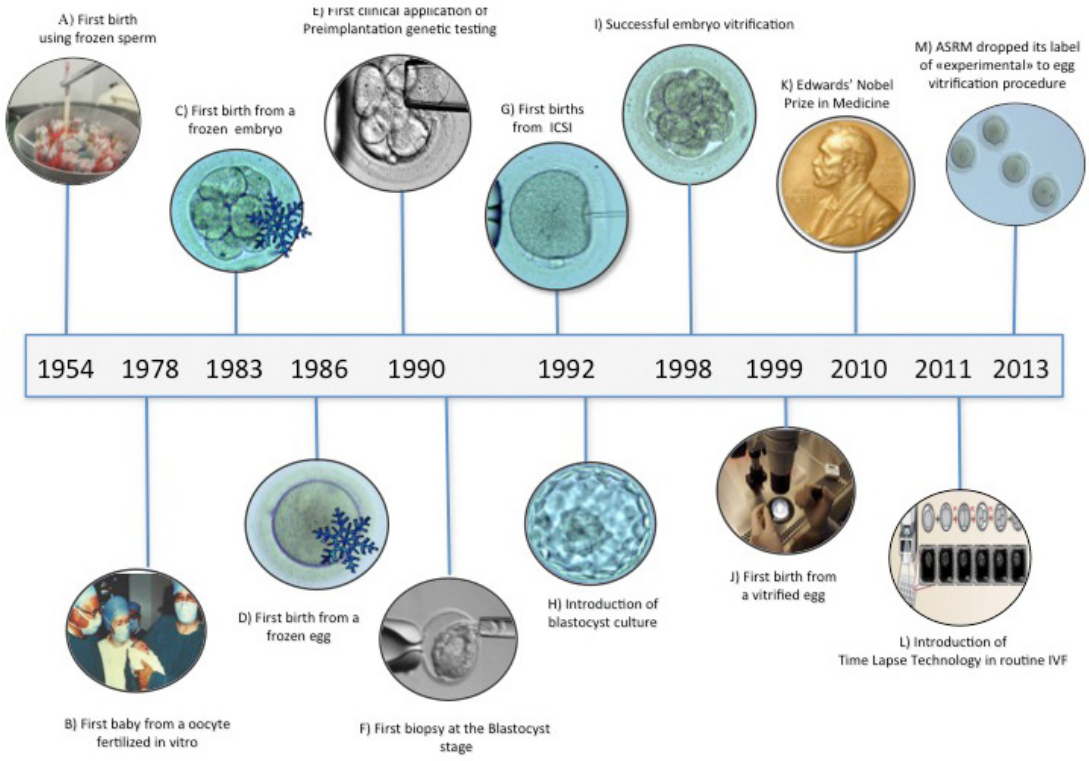

Fig. 1. Timeline of the main achievements of assisted reproductive technology (ART) since its introduction. (A) *Bunge et al., 1954;* **(B)** *Edwards, 1981;* **(C)** *Trounson and Mohr, 1983;* **(D)** *Chen, 1986;* **(E)** *Handyside et al., 1990;* **(F)** *Dokras et al., 1990;* **(G)** *Palermo et al., 1992;* **(H)** *Menezo et al., 1992;* **(I)** *Mukaida et al., 1998;* **(J)** *Kuleshova et al., 1999;* **(L)** *Meseguer et al., 2011;* **(M)** *Practice Committees of American Society for Reproductive Medicine (ASRM); Society for Assisted Reproductive Technology, 2013.*

modifying the present and shaping the future approaches and strategies (Fig. 1).

The introduction of cryopreservation represented a game-changer in IVF. Even if slow-freezing led to substantial improvements, vitrification is a real milestone, which allowed embryologists worldwide to boost oocyte/embryo cryo-survival rates (Rienzi *et al.*, 2017). The optimization and the widespread application of cryopreservation in IVF largely increased also clinical possibilities including: i) the systematic application of an elective single-embryo-transfer policy (Pandian *et al.*, 2013); ii) the possibility to perform blastocyst biopsy and complex time-consuming genetic testing (PGT) (Scott *et al.*, 2013; Chen *et al.*, 2015; Dahdouh *et al.*, 2015); iii) the application of cycle segmentation and freeze-all policy (Devroey *et al.*, 2011; Evans *et al.*, 2014); iv) and the possibility to perform fertility preservation via egg banking for women wishing to postpone their desire of motherhood for either medical (e.g. cancer, endometriosis) or social issues (Cobo *et al.*, 2016; Gunnala and Schattman, 2017).

Several invasive and non-invasive strategies have also recently been proposed to improve embryo selection and encourage SET also in advanced maternal age patients (Gardner *et al.*, 2015), thereby decreasing the risk for multiple pregnancies and their related obstetrical and perinatal consequences (Forman *et al.*, 2013; 2014). The goal of embryo selection is indeed to recognize the most competent embryo(s) within a cohort produced by a couple during IVF, namely the one(s) with the highest chance of resulting in the birth of a healthy child. Recently, time-lapse microscopy and single step culture media suitable for embryos up to blastocyst stage converged into the creation of incubators guaranteeing undisturbed *in vitro* culture. Such technology enhanced the conventional morphological assessments by involving the detection of several dynamic phenomena and criteria that could be useful to select/deselect the embryo(s) to transfer without the need to extract the embryos from the incubator during observations. Nevertheless, to date, it mainly represents an ideal incubation system rather than a tool to conduct embryo selection (Kaser and Racowsky, 2014). The most promising data to predict embryo implantation potential has been derived from the advances in genetic testing (Chen *et al.*, 2015; Dahdouh *et al.*, 2015). This strategy, that combines blastocyst culture, trophectoderm biopsy and vitrification needs a high-standard laboratory and highly-trained embryologists and even though has an incredible potential, is still very expensive and not accessible to all.

Many scientists have focused their research upon the biology of human preimplantation embryos and the definition of the blastocyst-endometrial dialogue, aiming at unveiling its dynamics and some putative biomarkers of competence via '-omic' approaches (genomics, transcriptomics, proteomics etc. (Gardner *et al.*, 2015; Gardner and Balaban, 2016)) applied to the investigation of non-invasive sources of oocyte/embryonic biological material (cumulus cells, follicular fluids, spent culture media, etc). Interesting perspectives may indeed derive from ground-breaking studies conducted in this field, especially through multidisciplinary approaches (e.g. stem cell research, microfluidics, automation) (Meseguer *et al.*, 2012; Woods and Tilly, 2015; Horan and Williams, 2017; Silvestris *et al.*, 2018).

The success of IVF must be grounded on cumulative-live-birth-

rate per intention-to-treat (Maheshwari *et al.*, 2015) and, via encompassing gynecological, embryological, psychological, genetic and social aspects, envision a personalized treatment for each couple. The future in IVF is yet to come with unpredictable avant-gardes.

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Remarkable progress has been made in understanding mammalian preimplantation development and reproduction. Many basic studies performed in laboratory animals, predominantly mice, have been translated to other mammalian species, including humans. The development of novel experimental techniques to study single cells over the last decade has provided the opportunities for direct comparison between various mammalian species at the molecular and cellular levels. As expected, there are many evolutionarily conserved molecular players and mechanisms, but we have also begun to recognize the differences between mammalian species. As a mouse developmental biologist, I have been fascinated (with a slight disappointment ...) to learn the developmental differences between mice and other mammals.

On the other hand, interestingly, all mammalian preimplantation development follows a remarkably similar process: early cleavages, compaction, formation of a morula and then a blastocyst. This common process appears to be the base of plasticity and tolerance against experimental insults in mammalian development. The self-organizing ability from compaction to blastocyst formation, driven by the biophysical properties of individual cells, has to be tightly linked with the regulation of gene expression to control lineage specification. We are still far from a full understanding of the molecular mechanisms behind them.

Looking forward, what will be the essential breakthroughs and challenges in the 21st century? To be honest, who knows. Who could have envisioned smartphones, iPSCs and other current inventions 30 years ago? However, since I accepted the editor's invitation, I would like to raise three of them for the next 10-30 years. 1. Understanding development --- molecular and cellular bases of totipotency: I expect that the essence of totipotency, the process of how an egg develops into an organism will be revealed. We might be able to recreate totipotency solely from *in vitro* cultured cells. 2. Innovation in Assisted Reproductive Technology (humans and livestock) --- selection of good embryos and improving the embryo quality. Currently, morphogeometric and morphokinetic analyses are used to assess the quality of an embryo that potentially implants and develops to term. But what is "the quality"? These experience-based selections should be interpreted at the molecular and cellular levels. This knowledge will help improving not only the selection but developing strategies to increase the quality. 3. Understanding mammalian evolution in placentation and polyembryony. It is interesting to recognize differences in early development and reproduction in mammalian species. Particularly, I am fascinated by variations in placentation and unique polyembryony in nine-banded armadillo. I expect that non-traditional lab animal studies will bring new prospects in the field of development and reproduction.

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