Developing Mouse Embryo Ex-Utero from Stem cells: Beginning of a New Era in the Field of Embryology

The fusion of sperm with egg inside the female body followed by the development of embryo in the uterus was considered as the only approach for the emergence of new mammalian life until the development of in-vitro fertilization technique. The developing embryo needs the structural support from the extra-embryonic tissues; therefore the development of embryo inside the womb is the pre-requisite for the healthy growth of embryo. Further, the extra-embryonic tissues provide signals to the developing embryo, which is a highly complex process. The ex-utero development of embryo was thought imaginary until experimentally proved. Studies demonstrated the ex-utero growth of embryonic stem cells into the mouse embryos for 8.5 days leading to the development of distinct organs such as a beating heart, gut tube and the neural folds. The authors used bottles filled with liquids as a culture medium for cells, which rotate on wheels to add ventilation for the proper growth of embryo. In-vitro cultured stem cells have been exploited for developing the embryonic and extra-embryonic tissues but the development of an organized embryo from the stem cells remained unknown and these studies are the first of their types to explore the organs development from the ex-utero embryo. Earlier, placental stem cells and yolk stem cells had been used for the embryo development, but these studies provided evidences that embryos can even be developed from the routinely used naive pluripotent embryonic stem cells. However, the research in this field is still in its infancy and further research is warranted to understand the implication of this finding in the process of implantation and solving the health related challenges including infertility and birth defects. Further, the failure rate in the concerned experiments was high, just a small fractions of cells (50 of 10,000) developed the embryo like features and those too were not exactly identical to the natural embryo. Another major challenge of the concerned approach is the translation of these findings in humans. The findings of these studies open a completely new dimension in the field of embryology which can be highly beneficial to solve the complex puzzles of embryology. Since it is difficult to observe the embryological changes inside the uterus in real time manner, ex-utero development of embryo provides an edge over the conventional embryo development. It can be beneficial for better understanding the genetic control of the cellular differentiation and the effect of surrounding environment on the embryonic growth. (Tarazi et al. Cell (2022) 185: 3290-3306 & Amadei et al. Nature (2022): 1-3).

Artificial Intelligence: A new horizon in early diagnosis and management of Colorectal Carcinoma

Colorectal carcinoma (CRC) is one of the most prevailing malignancies, affecting over 1.9 million individuals globally. In order to augment the patient's survival rate, accurate early diagnosis, comprehensive evaluation of intervention response, and detailed prediction of prognoses are of pressing priority. In recent years, artificial intelligence has demonstrated remarkable applicability in the context of CRC, rendering novel auxiliary approaches in clinical settings to categorize high-risk patients, opting for precise and personally tailored treatment strategies as well as anticipation of prognoses. This is attributed to the surge ofomics and clinical data, and research in machine learning. To improve the existing technology, artificial intelligence, a subfield of computer sciences, integrates machine learning and neural networks, which successfully offer numerous AI-assisted systems that are available for individualized and novel treatment strategies in the management of CRC. (https://doi.org/10.3748/wjg.v23.i28.5086)

Screening is envisioned to effectively reduce disease incidence and fatalities, facilitate early detection and therapy, and thus improve patient prognosis. AI-assisted tumour screening technologies with prediction models have emerged in recent years with the goal of enhancing the reliability and reducing the expense of CRC screening. AI-driven model's finding proved an inverse correlation between ADR and fatal CRCs i.e., 1% escalation in ADR is assisted with a 5% reduction in fatal CRCs. Cell-free DNA from the blood is used in cfDNA testing, which serves as a substitute to stool-based assessment. However, due to the slender amount of cfDNA acquired from the tumour tissue in primary stage, early diagnosis utilizing tumour-derived mutations in cfDNA has proven difficult. Using an artificial intelligence-driven technique based on machine learning (ML) to find signals in cfDNA that are possibly representative of both tumour and immune contributions could be a possible avenue for cancer screening Biomarker and blood-based screening for early-stage tumours is aided by platforms like CellMax (CMx®) and ColonFlag®generate a risk score based on individual's parameters. Polyps are the benign outgrowths in colon lining which might progress towards cancer. Traditional colonoscopy detects polyps of size <10 mm, thus increases the chance for miss rate of polyp detection for the flat/small ones. At present, virtual colonoscopy by computer aided detection and diagnosis systems (CADx/e) assisted with AI-algorithms enables real-time detection and accurate localization of premalignant lesions. Based on PET-CT scans, mitotic count, sex, and non-gastric placement, AI-based predictive models offer time prediction of tumour recurrence. SVM model-based toxicity prediction of Irinotecan (CPT-11) successfully served as a viable reference for clinical physician in decision-making. Interestingly, nowadays AI-integrated NMR-QSAR based model and IC50 detection systems significantly contribute to the drug development for novel targets of CRC. In recent years, there has been considerable progress in robotic-assisted surgery, has developed with numerous benefits including smaller incision, minimal scarring, shortened hospital stay and reduced risk

of surgical-site infections. (https://doi.org/10.4253/wjge.v10.i10.239, https://doi.org/10.1038/s41598-018-21758-3)

Artificial intelligence is undeniably the prospect of an emerging scientific era, but it is still in its ingress-stage for mainstream use. Several studies on their application are gradually heading in the right way. Up to the present, it is clear that the adoption of deep learning tools will significantly improve the methods of acquiring information, diagnosing, and treating CRC. Current hurdles in AI-driven CRC management include lack of generalizability, poor interpretability, ethical issues, and privacy protection when managing clinical data. These can be addressed by enhancing information dependability, medical ethics guidelines, and efficient data optimization. Ultimately, artificial intelligence shows considerable potential in clinical and therapeutic management of CRC, which could lead to holistic and individualized therapy for the patients with CRC. (Huang et.al Cancer Letters (2020) 471: 61-71 & Qiu et.al Current Oncology (2022) 29: 1773-1795)

Lumipulse Test: Diagnostic test for early detection of amyloid plaques associated with Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative cause of cognition deficits and responsible for significant morbidity and mortality. Despite decades of laboratory and clinical research, none of the available treatments are able to provide a cure, but merely alleviate the AD related symptoms This may be due to the pathological features of AD which includes extracellular deposits of ?-amyloid (A?) plaques, intracellular neurofibrillary tangles (NFTs), as well as subsequent neuronal and synaptic loss, which begin to appear several years prior to memory loss and the damage is already irreversible and extensive at the time of clinical diagnosis. For these reasons, there is an immediate need of diagnostic tools to support the clinical diagnosis of AD. Despite the fact that several clinical studies have demonstrated the diagnostic performance of various biomarkers, such as Cerebrospinal fluid (CSF) related biomarkers evaluated by ELISA or Luminex technology. However, there is a significant discrepancy in absolute values whether employing the same ELISA variant or with laboratory variability. There is an unmet need for a reliable and safe test that can accurately identify patients with amyloid plaques consistent with Alzheimer's disease. The USFDA has permitted the marketing of first In vitro diagnostic test "The Lumipulse Test" for early detection of amyloid plaques associated with Alzheimer's disease. This test was considered as breakthrough device for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases conditions. The FDA evaluated the safety and effectiveness of this test in a clinical study of 292 CSF samples from the Alzheimer's disease Neuroimaging Initiative sample bank. The samples were tested by the Lumipulse G ?-amyloid Ratio (1-42/1-40) and compared with amyloid PET scan results. In this clinical study, 97% of individuals with Lumipulse G ?-amyloid Ratio (1-42/1-40) positive results had the presence of amyloid plaques by PET scan and 84% of individuals with negative results had a negative amyloid PET scan. FDA permitted marketing of the Lumipulse G ß-Amyloid Ratio (1-42/1-40) to Fujirebio Diagnostics, Inc. (Blennow et al. Journal of internal medicine. (2018) 284(6): 643-663), https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-new-test-improve-diagnosis-alzheimers-disease & Thomas et al. Alzheimers Dement (Amst). (2021) 13(1): e12238)

Adoptive cell therapy (ACT): promising immunotherapy for colorectal cancer

Colorectal cancer (CRC) is one of the most lethal and prevalent malignancies in both developed and developing countries. Surgery and chemotherapy have long been used for cancer patients. However, the prognosis of CRC has never been satisfying, especially for patients with metastatic lesions. Adoptive cell therapy is a new approach which has successfully prolonged the overall survival of CRC patients. In adoptive cell therapy, the cells are used from a patient (autologous) or from a donor (allogenic) to improve the immunity. T Cells are isolated from the patient or donor, grown in large numbers in laboratory and returned to the patient to help the patient's immunity to fight against the cancer cells. Adoptive cell therapy has three methods; chimeric antigen receptor (CAR) insertion, tumor-infiltrating lymphocytes (TIL) & modification of T cell receptors (TCR).

Till September 2022 there were 25 clinical trials conducted based on CAR-T cells intervention. There were 4 and 16 clinical trials in phase 0 & phase 1 respectively. GCC19CART is a drug manufactured by the Innovative Cellular Therapeutics (Rockville, Maryland, USA) undergoing Phase 1 clinical trial for metastatic CRC. GCC19CART works by targeting the enzyme guanylate cyclase 2C (GCC) present on the surface of cancer cells. The most frequently studied targets in CAR-T cell therapy for CRC are CEA and NKG2DL, followed by EGFR and HER2. There are 18 clinical trials in Phase 1 & 2 each for TIL-based therapy for CRC. For TCR-T-based cell therapy, there are 2 clinical trials in Phase 1 study. Currently, there are no Phase 3 clinical trials evaluating adoptive cell therapy in CRC. Adoptive cell therapy is more complex than other types of immunotherapies and has been criticized for being too costly. There is also the issue of ACT toxicity when targeting the antigens present both on tumor as well as on normal cells. Those targets that are present in normal cells but overexpressed in tumor cells have led to severe toxicity in patients. A better target would be those that are present only in tumor cells but absent in normal cells. According to a systematic review, ACT appears to be well tolerated in patients in terms of overall survival and progression-free survival in comparison to currently available second and third-line treatments. (Juat et al. Oncologist (2022) 27(3): 210-219)