1. Project #1

Project title: Epigenetic control in human cancer

Supervision: Dr. Tokameh Mahmoudi; Prof. Dr. Riccardo Fodde and Prof. Dr. Peter Verrijzer
Department of Biochemistry, Erasmus MC

Keywords: Chromatin; Oral Cancer; Liver Cancer; Epigenetics Organoids; (Stem) Cell Differentiation; SWI/SNF; Polycomb; NURD

Project Summary:

One of the major surprises that came out of the cancer genome sequencing studies was the preponderance of mutations in ATP-dependent chromatin remodelers, which were associated with a broad spectrum of cancer types. Although these findings suggest a crucial role for remodelers in human cancer, the underlying molecular mechanisms remain enigmatic. Our previous work in Malignant Rhabdoid Tumors and in oral cancer suggested that subunit-dependent gene-selection is a major cause of the association between the loss of specific remodeler subunits and particular types of cancer. Our results emphasize that gene control involves a dynamic equilibrium between opposing chromatin modulating enzymes rather than a static chromatin state. Disturbances in this balance can initiate a cascade of chromatin reprogramming events that drives oncogenesis. Such an intertwined system of epigenetic regulation suggests therapeutic strategies aimed at restoring the balance between antagonistic activities. The main goal of this proposal is to elucidate the cooperative and antagonistic interplay between the NURD, Polycomb and SWI/SNF chromatin modulating enzymes during the onset and malignant progression of oral and liver cancer. We will use an integrated combination of tumor analysis, whole genome epigenetic and gene expression analysis, 3D organoid cultures and CRISPR/CAS9 genome editing technologies. We anticipate that our results will not only identify the relevant tumor suppression pathways, but also provide general insights in the roll of epigenetic balance in (cancer) stem cell differentiation.

Main methodology and techniques:

3D organoid cultures of normal and cancerous cells - liver and oral
Next generation sequencing analysis of chromatin and gene expression (ChIP-seq and RNA-seq)
Proteomics
High resolution imaging
CRISPR/CAS9 genome editing

2. Project #2

Project title: X inactivation and reactivation in human induced Pluripotent Stem (iPS) cells

Supervision: Dr. Mehrnaz Ghazvini; Prof. Dr. Joost Gribnau; Dr. Tokameh Mahmoudi
Department of Reproduction and Development, and iPS core facility, Erasmus MC

Keywords: induced pluripotent stem (iPS) cells ; X inactivation; cancer; epigenetics; CRSPR Cas9 gene editing

Project Summary:

All biological differences between women and men originate from the sex chromosomes. Some 160 million years ago, the X and Y chromosomes were very similar, but since then the Y chromosome has lost most of its genes, whereas the present X chromosome contains more than 1000 genes. Hence, the dosage of X-encoded genes needs to be equalized between female (XX) and male (XY) cells. This is achieved by random inactivation of one of the X chromosomes in female embryonic cells. X chromosome inactivation (XCI) is directed by a multitude of epigenetic processes and has been instrumental as a model system to provide new insights in gene regulation. Our work and that of others revealed a close link between loss of pluripotency and initiation of XCI. These studies were performed in mouse embryonic stem (ES) cells representing a powerful model system to study XCI. In contrast to female mouse ES and induced pluripotent stem (iPS) cells that retain two active X chromosome prior to differentiation, most female human ES and iPS cells retain one inactive X chromosome. In culture this inactive state is gradually lost, but unfortunately is not reinstalled upon differentiation. Therefore human female iPS cells are less suited to study human disease, perform drug screens or as a source for regenerative medicine. Proper understanding of the human XCI process is crucial to address this problem and facilitate robust reactivation of the inactive X as well as robust XCI upon cell differentiation. For this project we would like to increase our understanding of human XCI, by translating our findings observed in mouse to human.

Main methodology and techniques:

We will use human iPS cells as a model system to study XCI, and apply the Crispr/Cas9 targeting technology to remove genes with a known and putative role in XCI and study the effect on XCI and cell differentiation. The post-doctoral fellow will work in well-equipped laboratories with expertise in X inactivation (Gribnau) and iPS and stem cell (Ghazvini) research. Prof. Gribnau is an expert in sex chromosome biology and epigenetics, focusing on different aspects of the X inactivation process, to identify and characterize mechanisms in gene regulation. Dr. Ghazvini is the director of the Erasmus MC iPS core facility and an expert on embryonic stem cell and iPS cell research.

3. Project #3

Project title: Assessing in vitro responsiveness of patient-derived human colorectal cancer organoids to in vivo patient response to drugs: a proof of concept

Supervision: Dr. Robert Vries, Hubrecht Organoid Technology (HUB), Dr. Tokameh Mahmoudi, PhD, Department of Biochemistry Erasmus MC

Keywords: colorectal cancer (CRC); LGR5 stem cells; organoid-tumoroid technology platform, lentiviral transduction and gene editing

Project Summary:

The stem cell based organoid / tumoroid technology for the first time allows the culturing and expansion of a patient's own organoids in vitro in order to test and select the most effective and least toxic drug combination for the specific patient. Organoids display all the characteristics of differentiated primary cell types within the organ, thereby representing an in vitro platform for preclinical drug discovery and validation and a tool for precision personalized medicine.

Colorectal cancer (CRC) is one of the top five most common cancer types in the world. In The Netherlands while the majority of patients present with stage I-III disease with a fraction displaying distant metastases, eventually, approximately half will develop distant metastases, a small subset of which, who harbour metastasis usually in the liver undergo surgical resection of metastases either before or after downsizing of the tumor by chemotherapy with the intent to cure the disease. Colorectal Cancer patient tumoroids have been examined as a platform to determine predictive susceptibility to different chemotherapeutic compounds (van de Wetering et al, Cell, 2015), where based on the genetic profile of the tumor it would be impossible to predict responsiveness to specific drugs. Thus, stem cell-derived organoids present a potentially game changing strategy to improve preclinical testing and pharmacological compound validation while additionally addressing inter-individual variability of drug response (personalized medicine). This observational clinical study will assess the discriminative performance of metastatic CRC tumor organoids for therapy response prediction. Patient tumoroids will be seeded from biopsies or resections of metastatic CRC patients. The tumoroid culture will be treated in parallel with the same standard of care therapy in vitro. In vivo patient response to therapy (clinical parameters) will then be compared with in vitro tumoroid response to therapy. This is an ongoing project, which the successful candidate (preferable MD-PhD) will join in order to acquire training in performing organoid-tumoroid cultures, clinical trials and molecular analysis.

Main methodology and techniques:

3D organoid and tumoroid cultures
Next generation sequencing analysis of chromatin and gene expression (ChIP-seq and RNA-seq)
High resolution imaging (OIC-confocal, fluorescence microscopy)
Flow Cytometry Activated Cell Sorting
Drug screening

4. Project #4

Project title: Organoids as diagnostic platform in Cystic Fibrosis

Supervision: Dr. Robert Vries, Hubrecht Organoid Technology (HUB), Dr. Tokameh Mahmoudi, PhD, Department of Biochemistry Erasmus MC

Keywords: Cystic Fibrosis; Orkambi; LGR5 stem cells; organoid-tumoroid technology platform, lentiviral transduction and CRSPR-Cas-9 gene editing; clinical trial

Project Summary:

The stem cell based organoid / tumoroid technology for the first time allows the culturing and expansion of a patient's own organoids in vitro in order to test and select the most effective and least toxic drug combination for the specific patient. Organoids display all the characteristics of differentiated primary cell types within the organ, thereby representing an in vitro platform for preclinical drug discovery and validation and a tool for precision personalized medicine.

Cystic Fibrosis (CF) is the most common life shortening, hereditary disease in the Caucasian population. CF is a monogenetic disease caused by defects in the Cystic Fibrosis Transmembrane Regulator (CFTR) protein, which regulates the fluid flow within cells and effects the components of sweat, digestive fluids and mucus. Current therapies for CF are mainly directed at treating the symptoms of the disease, focusing on preventing and reducing bacterial infection and inflammation and normalizing nutrient digestion and physical growth. However, the underlying cause of the disease, which is a defectively functioning CFTR protein is not addressed, resulting in death of the patient, usually by their mid-30's. Recently, high-throughput screening of chemical libraries has identified compounds that enhance the CFTR channel gating or that partially correct defects in folding of the protein and were shown to have the potential to treat the underlying cause of CF. However, not all patients respond to the drugs (which are very expensive), and therefore identifications and stratification of the responsive patients would be essential to justify the enormous costs of treatment. Recently this platform has been used as a predictive tool to screen Cystic Fibrosis patient organoids for responsiveness to specific drugs (Dekkers et al., 2013 Nature Medicine; Schwank G et al., Cell Stem Cell). In this proof-of-concept clinical study we aim to validate the CF organoid model system as a diagnostic tool to predict treatment outcome in patients with CF, by analyzing and comparing in vitro organoid response with in vivo clinical response to CF drug treatment. This is an ongoing observational clinical study, which the successful candidate post-doc (preferable MD-PhD) will join.

Main methodology and techniques:

3D colorectal organoid cultures

Next generation sequencing analysis of chromatin and gene expression (ChIP-seq and RNA-seq)

High resolution imaging (OIC-confocal, fluorescence microscopy)

Flow Cytometry Activated Cell Sorting

Drug screening

5. Project #5

Project title: Liver organoid-tumoroid platform in study of HBV infection, replication and tumorigenesis

Supervision: Dr. Robert Vries, Hubrecht Organoid Technology (HUB), Dr. Tokameh Mahmoudi, PhD, Department of Biochemistry Erasmus MC

Keywords: Liver organoid-tumoroid technology; HBV infection; lentiviral transduction and CRSPR-Cas-9 gene editing

Project Summary:

Persistent Hepatitis B virus (HBV) infection remains the leading cause of liver cirrhosis and hepatocellular carcinoma world-wide. However, identification and study of the molecular events that occur as consequence of HBV infection and which mediate onset of hepatocellular carcinoma have been greatly hindered because of the lack of a relevant primary untransformed model system. The stem cell based liver organoid / tumoroid technology for the first time allows the culturing, expansion, banking, differentiation of hepatocytes from healthy donors or infected patients at various stages of disease (Huch M et al., 2015). We apply the human liver organoid technology to the study of HBV infection and HBV-induced tumorigenesis. We have generated HBV infected patient and healthy liver organoid culture lines seeded from surgically explanted tissue. Human liver organoids are infected with both recombinant virus as well as HBV infected patient serum and determinants of infection and viral replication are examined. We will also examine the role of various pathways implicated in liver cancer such as Wnt-beta-catenin (Li VS et al Cell 2012), p53 and Ras in the organoid model. Transgenic liver organoid lines including those that exogenously express the HBV receptor NTCP or the viral gene HBX, E and core Antigens are also generated and molecular determinants of infection and oncogenesis are investigated using these tools.

Main methodology and techniques:

3D liver organoid cultures from healthy donor, HBV infected and hepatocellular carcinoma patients

Next generation sequencing analysis of chromatin and gene expression (ChIP-seq and RNA-seq)

High resolution imaging (OIC-confocal, fluorescence microscopy)

Flow Cytometry Activated Cell Sorting

Lentiviral transduction and gene editing

بسمه تعالی

"فراخوان پذیرش دانشجوی پسادکترای پژوهشی در زمینه فناوری ارگانوئید"

مادهٔ ۱ – تعریف:
دوره پسادکترای پژوهشی دوره‌ای است که برای تربیت پژوهشگران حرفه‌ای در مراکز تحقیقاتی تابعه دانشگاه اجرا می‌شود.

مادهٔ ۲ – هدف:
هدف از برگزاری این دوره حفظ و حمایت از پژوهشگران مستعد و جوان در راستای ارتقاء سطح تحقیقات پایه و کاربردی در مراکز تحقیقاتی علوم پزشکی کشور می‌باشد.

مادهٔ ۳ – شرایط ورود به دوره:

۱. برخورداری داوطلب از صلاحیت‌های عمومی و قانونی جمهوری اسلامی ایران.
۲. برخورداری داوطلب از صلاحیت‌های اختصاصی علمی که از سوی اساتید دانشگاه اراسموس ام سی هلند (Erasmus MC) در نظر گرفته می‌شود.
۳. داوطلب این دوره می‌بایست واجد مدرک دکترای تخصصی (PhD) یا MD-PhD باشد (که حداکثر دو سال از تاریخ اخذ مدرک وی گذشته باشد) و یا دانشجوی ترم آخر مقطع دکتری تخصصی (PhD) (که حداکثر تا بهمن ماه ۱۳۹۷ فارغ‌التحصیل شود) باشد.

تبصره ۱: داوطلب این دوره می‌بایست دروس ارائه شده در مدت زمان تحصیل خود را با اخذ درجه عالی (تئوری و عملی) گذرانده باشد.

تبصره ۲: رشته‌های اولویت‌دار مورد پذیرش در دوره مذکور شامل علوم سلولی کاربردی، بیولوژی سلولی و ملکولی، بیولوژی تکوین، ویروس شناسی و مهندسی بافت می‌باشند. شایان ذکر است داوطلبان بهتر است واجد اطلاعات زمینه‌ای در حوزه بیوانفورماتیک نیز باشند.

۴. دارا بودن مهارت‌های نوشتاری و گفتاری لازم در زبان انگلیسی همراه با مدرک معتبر.
۵. در صورت پذیرفته شدن، داوطلب ملزم به ارائه تعهد محضری جهت گذراندن تعهدات نیروی انسانی می‌باشد.

مادهٔ ۴ – طول دوره:

۱. این دوره پسادکتری سه سال به طول خواهد انجامید که توسط دانشگاه اراسموس ام سی هلند و دانشگاه علوم پزشکی تهران به شرح ذیل طراحی گردیده است:
دو سال ابتدایی در دانشگاه اراسموس ام سی هلند (Erasmus MC) و شرکت فناوری ارگانوئید هوبرخت (Hub) طی خواهد شد و سپس یک سال در مرکز جامع سلول‌های بنیادی و پزشکی بازساختی واقع در دانشگاه علوم پزشکی تهران تکمیل خواهد گردید.

۲. نظارت بر حسن اجرا و هماهنگی های لازم با تائید اسـتاد راهنمای مربوطه بوده و شروع دوره از ابتدای دریافت تائیدیه دانشگاه مقصد جهت آغاز به کار داوطلب در آن دانشگاه خواهد بود.

۳. بدیهی است در پایان هر نیم سال تمدید دوره منوط به تأیید استاد راهنما می باشد.

۴. پایان دوره منوط به انتشار حداقل دو مقاله علمی معتبر با نمایه (PubMed, ISI web of science) می باشد.

ماده ۵ – موضوعات تحقیق:

۱. تولید ارگانوئیدها به عنوان ابزار تشخیصی برای بیماری سیستیک فیبروزیس (Organoids as diagnostic platform in Cystic Fibrosis)

۲. سنجش واکنش‌دهی برون‌تنی سلولهای ارگانوئید سرطان کولورکتال به میزان پاسخ‌دهی درون‌تنی بیماران به داروها
(*In vitro* responsiveness of patient-derived human colorectal cancer organoids to *in vivo* patient response to drugs)

۳. سازه ارگانوئید-تومروئید کبد برای مطالعه عفونت، تکثیر و تومورزایی ویروس هپاتیت B انسانی (Liver organoid-tumoroid platform in study of HBV infection, replication and tumorigenesis)

۴. غیرفعالسازی و بازفعالسازی کروموزوم X در سلول‌های بنیادی پرتوان القایی انسانی (X inactivation and reactivation in human iPS cells)

۵. کنترل اپی‌ژنتیکی سرطان در انسان (Epigenetic control in human cancer)

تبصره: توضیح کامل موضوعات فوق در فایل پیوست (فراخوان ارسال شده از سوی اساتید دانشگاه اراسموس ام سی) بیان شده است.

ماده ۶– مراحل پذیرش دانشجویان:

۱. متقاضیان شرکت در این دوره آموزشی می بایست فرم تقاضای خود را بعلاوه مدارک همراه از جمله آخرین رزومه (CV)، توصیه‌نامه دو استاد راهنمای پیشین متقاضی (Recommendation letter) و نامه علاقه‌مندی (Letter of interest) را حداکثر تا تاریخ ۳ آذر ۱۳۹۷ به ایمیل stemcell@sina.tums.ac.ir ارسال نمایند.

۲. پس از بررسی اولیه مدارک متقاضیان توسط اساتید راهنما در دانشگاه اراسموس ام سی، از ۱۰ متقاضی واجد صلاحیت برای مصاحبه حضوری با آن اساتید در تاریخ ۷ آذر ۱۳۹۷ دعوت به عمل خواهد آمد.

۳. سپس، صلاحیت های عمومی و حرفه‌ای افراد بر اساس اولویت اعلام شده از سوی اساتید راهنمای دانشگاه اراسموس ام سی هلند (Erasmus MC) مورد بررسی قرار خواهد گرفت و در نهایت اسامی ۵ نفر اولویت اول و ۵ نفر اولویت دوم برای موضوعات مشخص شده در ماده ۵ از سوی دانشگاه علوم پزشکی تهران اعلام خواهد شد.

۴. در مرحله بعد، اساتید راهنمای دانشگاه اراسموس ام سی هلند (Erasmus MC) فرایند پذیرش دانشجویان را در دانشگاه علوم پزشکی تهران به سرانجام خواهند رساند.

۵. در مرحله نهایی، نامه پذیرش دانشجو از دانشگاه اراسموس ام سی به همراه مدارک عمومی جهت دریافت ویزای کشور میزبان ارسال خواهد شد.

تبصره: فرایند دریافت ویزا می‌تواند تا ۳ ماه بطول بیانجامد و دانشگاه میزبان نقشی در تضمین صدور ویزا برای دانشجویان پذیرفته شده نخواهد داشت.