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Qatar Biomedical Research Institute
جامعة حمد بن خليفة
HAMAD BIN KHALIFA UNIVERSITY

Summer Research Program - Projects

Project # 1

Title: Role of the heat shock response on pathophysiology of insulin resistance and type 2 Diabetes

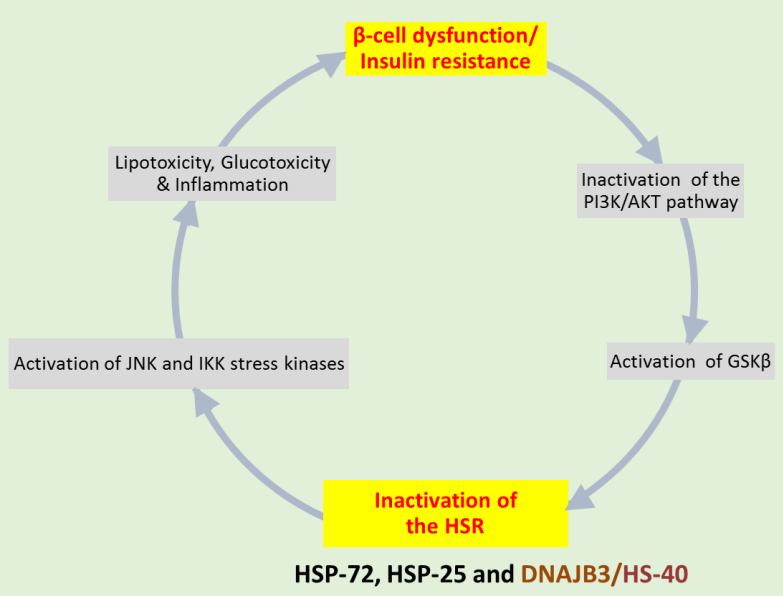
Description: The overall focus of our research is to understand the role of DNAJB3, a component of the heat shock response in the pathophysiology of obesity and diabetes. We recently described that obese and diabetic humans displayed impaired expression of DNAJB3 with a concomitant increase in various forms of metabolic stress that are known to contribute to diabetes through the development of insulin resistance (i.e., inflammatory response, oxidative stress, endoplasmic reticulum stress and activation of JNK-stress kinase). We are currently pursing our research activity to elucidate the direct role of DNAJB3 in glucose homeostasis and insulin signaling both in vitro and in vivo. More specifically, we will investigate the effect of DNAJB3 on:

- Glucose uptake
- Protein translocation
- Insulin signaling
- Protein-protein purification
- Inflammatory response/Luciferase assay
- Metabolic stress

We will use an array of modern techniques used in molecular and cellular biology such as transient and stable expression of the clone of interest in transfected cells, transfection of silencing RNA, luciferase assay, glucose uptake, insulin signaling and apoptosis, western blot, RT-PCR

Mentor: Dr. Mohammed Dehbi, Principal Investigator. Email: mdehbi@hbku.edu.qa

Heat shock response and type 2 diabetes: The vicious metabolic cycle



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Project # 2

Title: Effect of Glucagon-like peptide-1analog on modulating metabolic stress: Possible role of heat shock response

Description: Insulin resistance (IR) and b-cell failure are the two core metabolic defects that lead to type 2 diabetes (T2D). These defects occur as a consequence of chronic metabolic stress that includes chronic low-grade inflammation, imbalance in the redox system, persistent ER stress. Failure of the heat shock response (HSR) to mitigate these various forms of metabolic stress is an early event that precedes IR as manifested by impaired expression of heat shock proteins (Hsps). Developing strategies that mitigate metabolic stress or restore the HSR hold the promise to improve insulin sensitivity and prevent b-cell failure in individuals at high risk, thereby, preventing the epidemic spread of T2D.

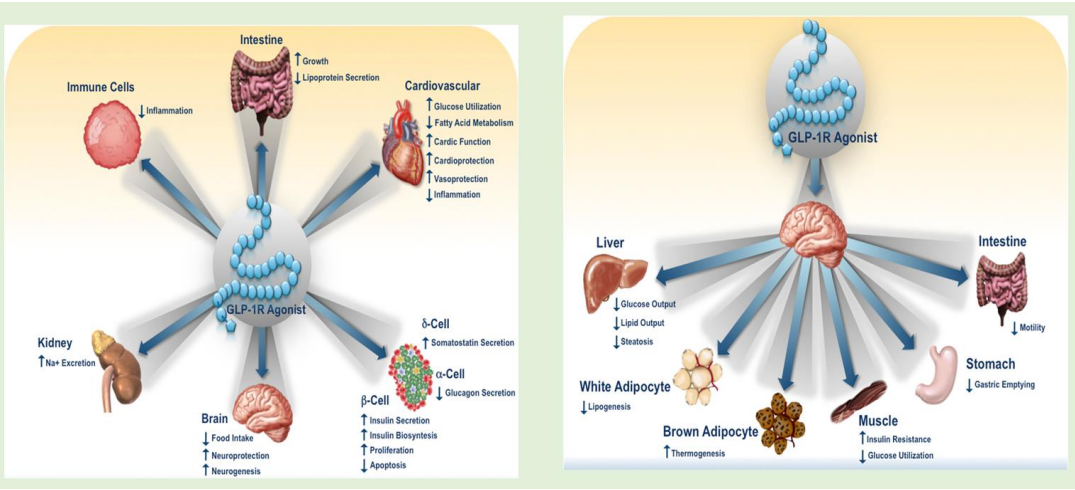
Although the current oral anti-diabetic drugs showed a clear beneficial effect to control and manage T2D, they have some undesirable side effects such as weight gain, digestive problem, CVD, risk of hypoglycemia & certain cancers, that may limit their use. In addition, they failed to show efficacy to preserve b-cell integrity and function. Recently, a new class of anti-diabetic drugs referred to as, Incretin hormones have become available and they showed efficacy with a higher therapeutic index. Incretin hormones are made by the gastrointestinal tract system and they consist of Glucagon-like peptide (GLP-1) and Gastric inhibitory polypeptide (GIP). They exert important actions that contribute to glucose homeostasis by stimulating insulin secretion by b-cell and improving its sensitivity at target tissues, reducing central satiety, promoting weight loss and mitigating metabolic stress. However, their effect on the heat shock response has never been investigated. In this investigation we will explore the in vitro effect of Exendin-4, a GLP-1 analog that mimics GLP-1 action on: 1) The expression of key components of the heat shock response (Hsp-40/DNAJB3, Hsp-25 and Hsp-72) in skeletal muscle, adipocyes, hepatocytes and pancretaic cells and 2- Investigate whether Exendin-4 effect is mediated by the activation of heat shock factor-1 “HSF-1”. The outcomes of this investigation will be related to glucose uptake and changes in the inflammation, oxidative stress and ER stress.

In this study, we will carry out a series of in vitro cell-based assays “western blot, transient gene transfer, luciferase activity, glucose uptake…”.

If successful, this will be the first demonstration that GLP-1 analogs exert a beneficial effect by modulating the HSR. It will also complement us in vivo study that we plan to conduct on Qatari patients.

Mentor: Dr. Mohammed Dehbi, Principal Investigator. Email: mdehbi@hbku.edu.qa

Direct or indirect effects of GLP-1 analogs



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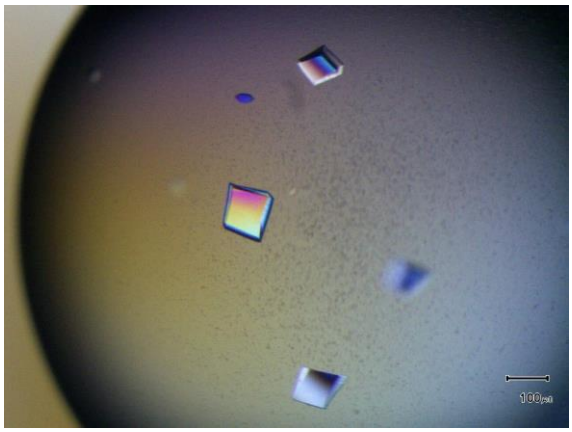
Project # 3

Title: Mechanisms of transcription factors involved in pluripotency and B cell development

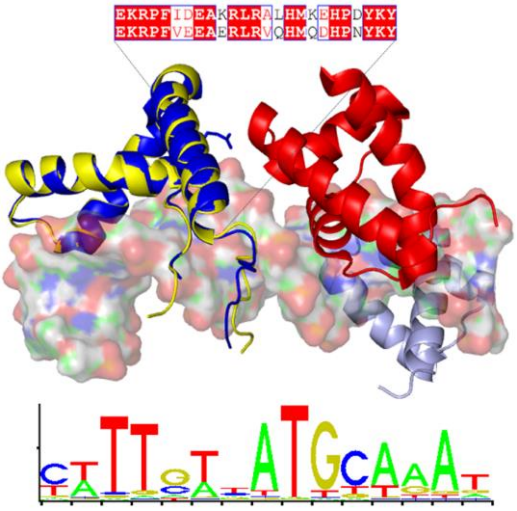
Description: Student will work with recombinant protein production (transcription factors) involved in stem cell pluripotency pathways as well as B cell development. The protein will be used for various protein-protein and protein-DNA interactions assays such as EMSA and ITC to find binding and thermodynamic parameters. Finally, protein crystallization and X-ray crystallography will also be used to find a high resolution three-dimensional structure.

Mentor: Dr. Prasanna R. Kolatkar, Senior Scientist. Email: pkolatkar@hbku.edu.qa

Brn2-DNA crystals OR crystals of a transcription factor-DNA complex



Using structural information to decipher mechanisms of Tf combinatorial binding



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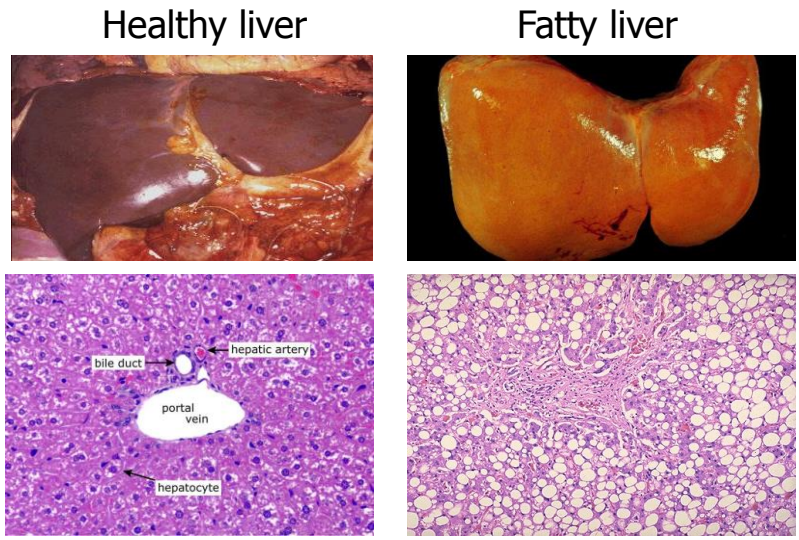
Project # 4

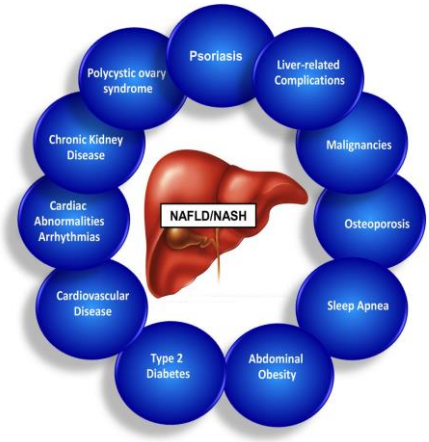
Title: How do GLP-1 agonists reverse the progression of non-alcoholic fatty liver disease?

Description: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases that increase the risk for cardiovascular disease. So far no treatment exists for NAFLD. Recently, Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to reverse the progression of NAFLD indirectly through an incretin effect that improves key parameters involved in NAFLD, but also directly affecting lipid metabolism of hepatocytes and inflammation in liver. However, the underlying mechanisms are not yet explained precisely. In this project we will use an in vitro model of NAFLD to investigate mechanisms behind the effect of GLP-1 agonists.

Mentor: Dr. Abdelilah Arredouani, Scientist. Email: aarredouani@hbku.edu.qa



Diseases associated with NAFLD



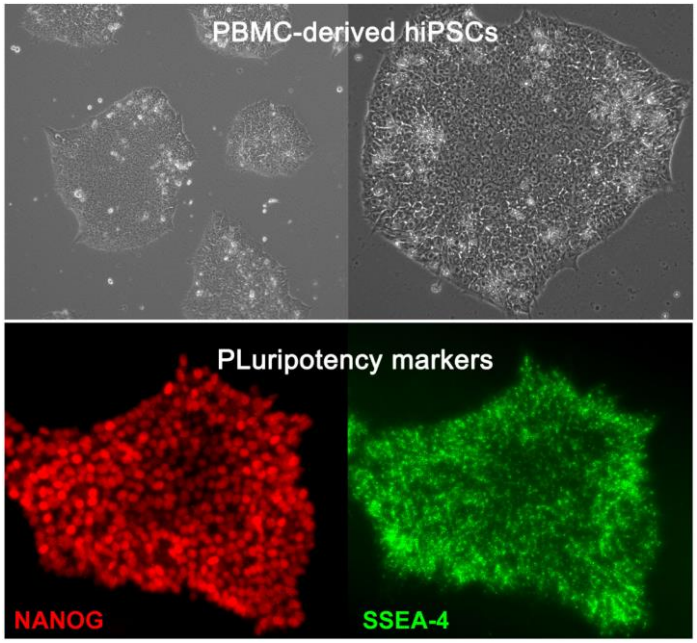
Project # 5

Title: Generation of multipotent pancreatic beta cell precursors from human pluripotent Stem cells

Description: Pancreatic progenitors co-expressing PDX1 and NKX6.1 are recognized as the only precursors of functional pancreatic beta cells. Recently, we have established a novel method for generation of PDX1+/ NKX6.1+ progenitors from human pluripotent stem cells (hPSCs) that could serve as a source of highly proliferative pancreatic progenitors facilitating scalable production of functional beta cells in vitro. This project is designed to provide participants with a solid understanding of the basic biology of hPSCs with a specific focus on pancreatic lineage differentiation. It will equip participants with hands-on experience in the following areas:

- Culture, expansion, and maintain hESCs/hiPSCs using feeder-free system.
- Differentiation of hPSCs into definitive endoderm (SOX17+/FOXA2+ cells).
- Differentiation of hPSCs into pancreatic beta cell precursors (PDX1+/ NKX6.1+ cells).
- Examine the pluripotency and differentiation markers in undifferentiated and differentiated hPSCs using different techniques.

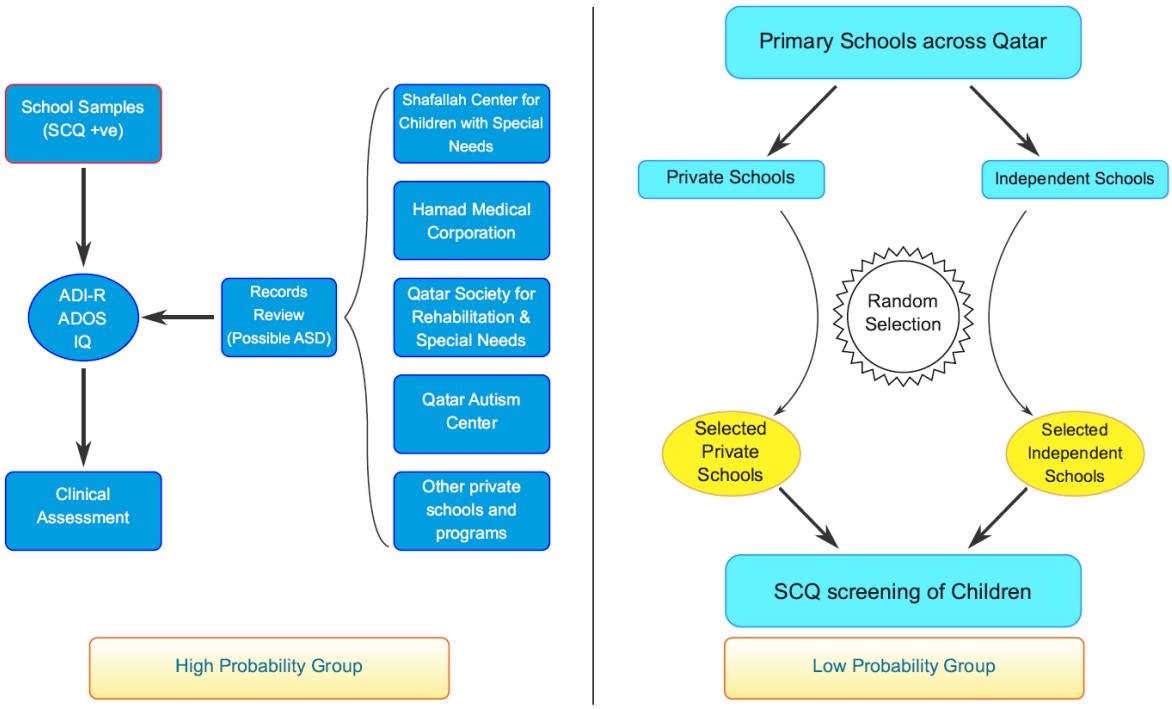
Mentor: Dr. Essam M. Abdelalim, Scientist. Email: emohamed@hbku.edu.qa



Project # 6

Title: Prevalence of Autism Spectrum Disorder in Qatar

Description: The purpose of the training is to understand the prevalence of Autism spectrum disorder in Qatar by learning how to apply the screening and diagnostic tools in Autism. Also how to recruit patients for the Autism research project. Training also includes taking medical history, demographic data and other related issues. The recruitment usually takes place in Rumaila hospital and includes taking full family history, child developmental milestone, and any other related information.
In addition, training includes the use of screening tools like the Social Communication Questionnaires (SCQ) and diagnostic tools like Autism Observation Schedule (ADOS-2) to diagnose children affected with this disorder.



Mentor: Dr. Fouad A Wahab Al Shaban, Senior Scientist. Email: falshaban@hbku.edu.qa

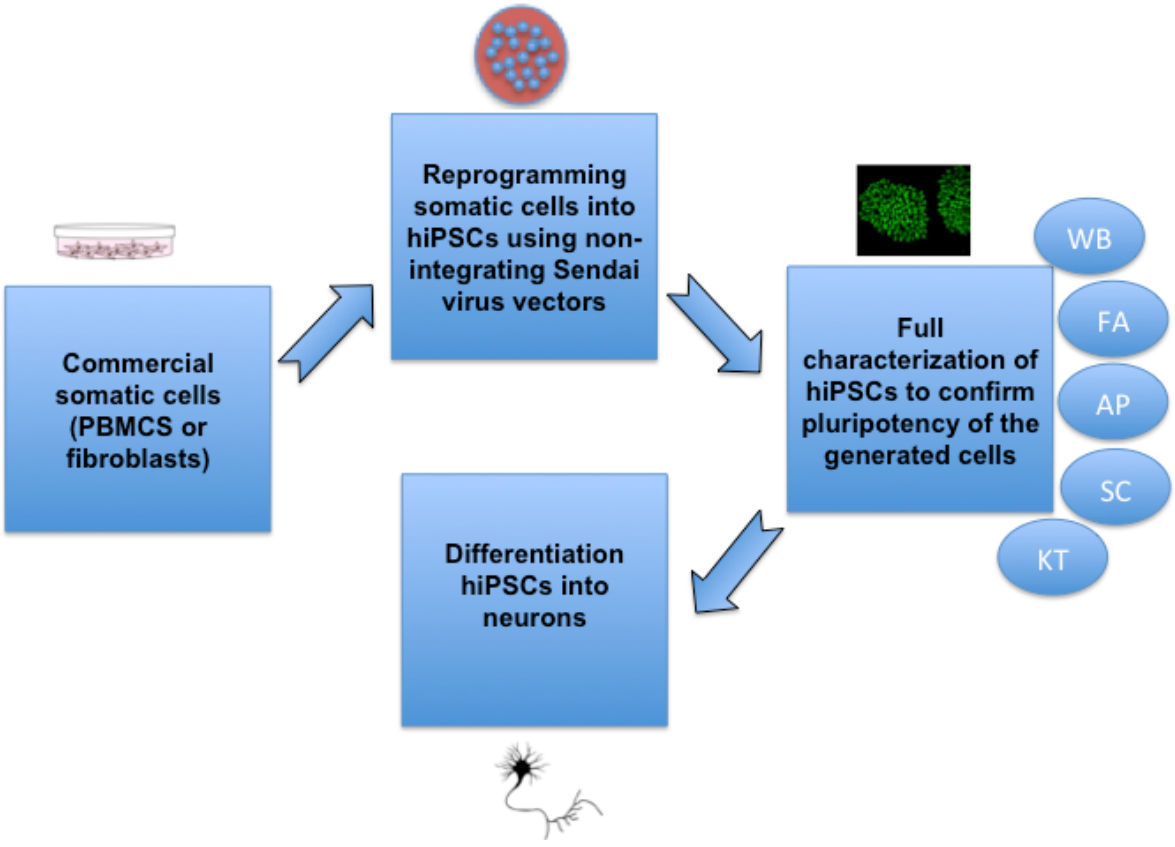
Note: Please note that there is no bench work involved

Project # 7

Title: Detailed characterization, and differentiation of human induced pluripotent stem cells into neuronal lineage.

Description: Induced pluripotent stem cells (iPSCs) is very promising tool to understand cellular and molecular events related to a disease pathogenesis. iPSCs have a unique capacity to differentiate into different cell lineage that resembles the developmental stages of a specific type of tissue. In this project we will differentiate hiPSCs into neuroprogenitors and neuroblasts. We will also study the effect of oxidative stress on the iPSCs and the differentiated neurons and how stress response program may play a role regulating stem cell fate. This will help to develop a reliable stem cell based model to study the pathogenesis neurological disorders.

Mentor: Dr. Mohamed M. Emara, Scientist. Email: memara@hbku.edu.qa



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Project # 8

Title: Identifying a role for glutamatergic receptors in hIPSC derived-neurones

Description: In the mammalian forebrain neuronal and synaptic plasticity of glutamatergic neurones is necessary for the processes involved in learning and memory formation. Perturbation or antagonism of glutamatergic receptor activity feeds forward morphological cell changes and or cognitive impairment in mammals. However due to ethical and safety considerations, using human tissue is impracticable. Human induced pluripotent cells (hIPSC) can be differentiated into mature glutamatergic neurones for study purposes. The aim of this project is to examine how known agonists of glutamatergic neurones affect cell structure and neuronal plasticity of hIPSC-neurones.

The candidate will characterise glutamatergic receptors in hIPSC-neurones, in the process learning the techniques of molecular, cell biology and biochemistry.

Mentor: Dr. Tariq Ahmed, Scientist. Email: taahmed@hbku.edu.qa

Project # 9

Title: Selection and characterization of Nanobodies for Parkinson disease

Description: In order to develop new therapeutic and diagnostic tools for Parkinson disease (PD), our project focus on the development of new antibody fragment against the most important proteins involvante in the PD. Single domain antibody derived from heavy chain only antibodies from camel (named also Nanobody) is a promising tool for PD therapy and diagnostic. They are much smaller and more stable than conventional antibodies. To select Nanobodies, libraries contains the whole repertoire gene that code for Nanobodies are available. These libraries will be selected by phage display technology to select specific Nanobodies against clef target in Parkinson disease. Selected Nanobodies will be purified and characterized for their affinity and specificity against their targets.

Mentor: Dr. Issam Hmila, Post-Doctoral Researcher. Email: ihmila@hbku.edu.qa

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Project # 10

Title: Engineering antibodies for diagnostic and therapeutic approaches in neurodegenerative disease

Description: Common neurodegenerative diseases such as PD, Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) are characterized by progressive deposition of α-synuclein (α-syn) protein within inclusions referred to as Lewy bodies and glial cytoplasmic inclusions respectively. Amongst the various approaches attempting to tackle the pathological features of synucleinopathies, immunotherapy holds much promise. α-Syn antibodies could potentially block processes leading to the pathogenesis of such neurodegenerative diseases. The limitation of such antibodies is their inefficiency in crossing the Blood-Brain Barrier. The aim of our project focuses on using a fusion protein engineered to include the FAb region of an existing α-Syn antibody.
This single-chain-fragment-variable is designed to have increased BBB penetration by virtue of its smaller size and its conjugation with a carrier. It is envisaged that with enhanced penetration there will be superior brain targeting results compared to conventional α-syn antibodies.

Mentor: Dr. Vijay Gupta, Post-Doctoral Researcher. Email: vgupta@hbku.edu.qa

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Project # 11

Title: Identifying protein conformations relevant to neurological disorders

Description: Synucleopathies are a group of neurological disorders that are characterized by abnormal aggregation of alpha synuclein protein in the nervous system. New and improved diagnostic tools and therapeutic strategies are crucial for early detection and effective management of these disorders including Parkinson's disorder, Dementia with Lewy Bodies and Multiple System Atrophy.
Dr. El-Agnaf's laboratory works on developing diagnostic biomarkers, immunoassays and identifying novel therapeutic targets for synucleopathies. The project proposed herein would be aimed at identifying synuclein conformations that are specific to neurological disorders using antibodies that detect specific forms of the protein.

Mentor: Dr. Indulekha Poovarangil Sudhakaran, Post-Doctoral Researcher. Email: isudhakaran@hbku.edu.qa

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Project # 12

Title: Assessing alpha synuclein neurotoxicity and its correlation to alpha synuclein S129 phosphorylation

Description: Parkinson's disease is a neurodegenerative disorder that is characterized by neuronal inclusions known as Lewy bodies with phosphorylated α-syn at S129 being the major component. Identifying the toxic species of α-syn and understanding the seeding effect of these forms on the aggregation of the protein allow us to understand α-syn induced toxicity implicated in neurodegenerative diseases such as Parkinson's disease. Moreover, studying the impact of phosphorylation on α-syn toxicity allow us to identify whether α-syn phosphorylation promotes or inhibits toxicity of the protein.

Mentor: Dr. Simona Ghanem, Post-Doctoral Researcher. Email: sghanem@hbku.edu.qa

Project # 13

Title: Evaluation of apoptotic and necrotic cell death using genetically encoded molecular platforms

Description: Escape from apoptosis is one among the critical hallmarks of cancer. A broad spectrum of anti-cancer therapeutics is designed to induce cell death through apoptosis. Majority of the promising cytotoxic agents are not favorable to use as anti-cancer agents as they include necrotic death and increase the therapy associated complications. Hence the differentiation of cell death mechanism is an essential step in the cancer therapeutic development.

The project involves the generation of stable cell lines expressing SCAT3 and mitoDSred probes. SCAT3 is a FRET-based genetic tool to evaluate the apoptotic cell death. The cells which are undergoing apoptotic cell death will result in an increase in FRET ratio. The necrotic cell death features with the leakage of cell contents. SCAT3 is a cytoplasmic probe and the cytosol the necrotic cell death can be identified with a probe loss. MitoDS red is a probe that imparts a red colour to the mitochondria. The necrotic cells can be enumerated using the red fluorescence retained in the mitochondria.

Mentor: Dr. Eyad Elkord, Principal Investigator. Email: eelkord@hbku.edu.qa

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Project # 14

Title: Investigation of methylation profile of TIGIT, CD112 and CD155 genes in CRC tumor microenvironment

Description: Modifications in the methylation patterns of DNA is considered to be an early event in the development of cancer. Aberrant methylation profiles are associated with clinical and histopathological features in cancer stage and differentiation. In mammalian cells DNA can be modified by the methylation of cytosine residue in CpG dinucleotides. Immune checkpoints (IC) are molecules participating in the inhibitory pathways in the immune system and play pivotal roles in the immune evasion of tumor cells. We found that multiple IC are upregulated in the tumor microenvironment (TME) of colorectal caner (CRC) patients.

In this current project, we are aiming to investigate the underlying mechanisms behind the upregulation of TIGIT and its ligands, CD112 and CD155 in the TME.

Mentor: Dr. Eyad Elkord, Principal Investigator. Email: eelkord@hbku.edu.qa

Project # 15

Title: Expression of immune checkpoints in peripheral blood from colorectal cancer patients

Description: Immune checkpoints (IC) negatively regulate T cell-mediated immune responses. High IC expression is involved in inhibiting anti-tumor immunity, associated with poor prognosis and cancer progression. In this study, we are investigating the expression of IC in the TME and peripheral blood of colorectal cancer(CRC) patients and the epigenetic modifications in both DNA and histone that are involved in the modulation of multiple IC genes.

In the current stage of the project, we will use cryopreserved peripheral blood mononuclear cells (PBMC) from CRC patients to investigate IC expression by multi-color flow cytometery and will perform RT-PCR to investigate IC gene expression.

Mentor: Dr. Eyad Elkord, Principal Investigator. Email: eelkord@hbku.edu.qa

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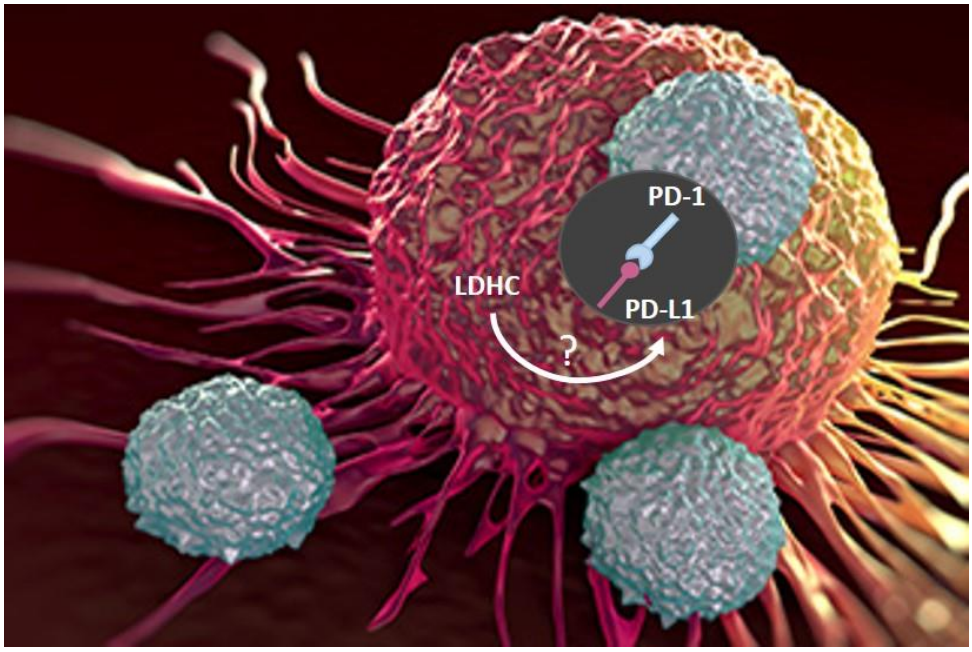
Project # 16

Title: Cancer lactate metabolism and anti-tumor immune evasion in breast cancer

Description: One of the challenges in immunotherapy is that even though the immune system can recognize tumor-associated antigens, the activity of the immune cells is often inhibited by the PD-1/PD-L1 inhibitory pathway. It has been shown that lactate, a hallmark of cancer metabolism, can impair anti-tumor activity by upregulating the PD-L1 ligand on tumor cells and reducing the cytokine production of cytotoxic T lymphocytes. We will investigate whether the cancer testis antigen lactate dehydrogenase C (LDHC) can alter PD-L1 expression on breast cancer cells through its role in pyruvate-lactate conversion, thereby protecting the tumor cells from elimination by the immune system.

Mentor: Dr. Julie Decock, Scientist. Email: jdecock@hbku.edu.qa

Hypothetical link between LDHC-mediated lactate metabolism and anti-tumor immune response inhibition through the PD-1/PD-L1 pathway



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Project # 17

Title: Let's flow! - Isolation & analysis of white blood cells by multicolor flow cytometry & imaging flow

Description: White blood cells are essential in mammalian immune response and therefore play major roles in many diseases, such as cancer, diabetes, autoimmune diseases and many more. In this project, we apply a panel of common immunological laboratory methods together with high-end multicolor flow cytometry, cell sorting and imaging flow to isolate and characterize different populations of white blood cells from fresh and frozen samples. The project will focus on current immunology methodology such as cell isolation and culture techniques, fluorescence staining and fixation protocols, live/dead staining and apoptosis assays, phenotyping, functional assays, etc. and discuss the obtained results in the context of the exciting field of cancer immunology. An exceptional array of cutting-edge technology, lab-equipment and expertise are available to support this project at highest level of quality, supervisory skills and determination.

Mentor/s: Dr. Gerald Pfister, Manager Flow Cytometry Core. Email:gpfister@hbku.edu.qa
Dr. Eyad Elkord, Principal Investigator. Email: eelkord@hbku.edu.qa

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Project # 18

Title: Mechanisms of breast cancer escape from Natural Killer (NK)-mediated anti-tumor immunity

Description: Natural Killer (NK) cells are lymphocytes of the innate immune system that play an important role in preventing and controlling tumor growth and metastasis. NK cells induce the elimination of tumor cells either by directly killing cancer cells or by secreting cytokines, which participate in cancer elimination by several mechanisms including activation of the adaptive immune system. During tumor development and progression, cancer cells develop mechanisms to escape NK surveillance. However, these mechanisms are still unclear.
Our aim is to study NK cell immune surveillance and immune escape in breast cancer which is the most common cancer and second leading cause of death among women in Qatar and worldwide. Understanding these mechanisms may lead to the development of new NK-based approaches to prevent and/or treat breast cancer.

Mentor: Dr. Manale Doldur, Post Doc Researcher. Email: mdoldur@hbku.edu.qa