# *Regional Health Genomics & Biotechnology Newsletter*

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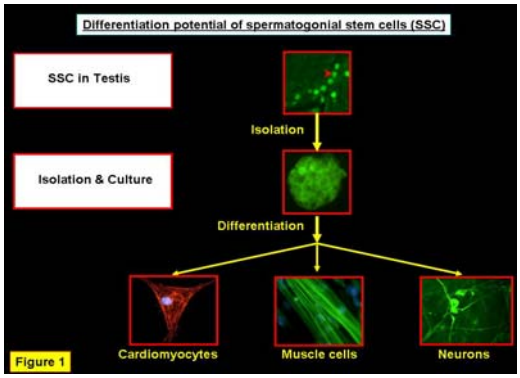
## Immature sperm cells made from human bone marrow

By S. Mostaan

Professor Karim Nayernia now at the North-east England Stem Cell Institute based at the Centre for Life in Newcastle upon Tyne and his colleagues say they have successfully made immature sperm cells from human bone marrow samples. If these can be grown into mature sperm, which they hope to do within three to five years, they may improve fertility treatments.

Lead researcher Professor Karim Nayernia, believes his investigations will mean he might one day be able to treat young men rendered infertile by chemotherapy. They are very excited about this discovery and believe that their next goal might lead to see if we can get the spermatagonial cells to progress
to mature sperm in the laboratory and this should take around three to five years of experiments.



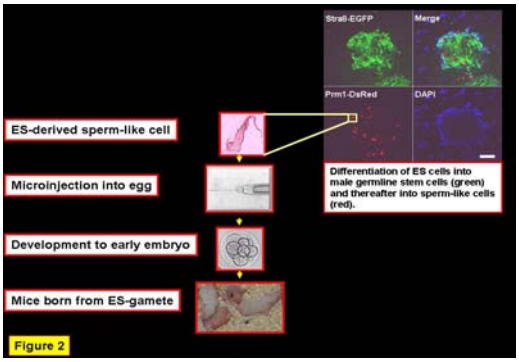

Professor Karim Nayernia says: in its most general sense, our research programme seeks to elucidate molecular mechanisms underlying development and differentiation of germline stem cells. Within this framework, we are exploring three general issues

1. Potential of embryonic and adult stem cells to differentiate to male germ cells
2. Potential of spermatogonial stem cells to differentiate to somatic stem cells.
3. Functional analysis of genes involved in germline stem cell proliferation and differentiation.
4. Elucidation the role of germline stem cell proteins in cancer

In exploring these issues we use a variety of research tools and experimental systems, including

generation of transgenic and knockout mice, *in vitro* gametogenesis system, *in vitro* differentiation systems and laboratory work employing cytological, molecular, cellular and embryological techniques. Recently, we have isolated spermatogonial stem cells from adult male mice. These cells are physiologically responsible for the continuous production of sperm cells. We then showed that these cells, when cultured in a test tube, can be brought into a condition that mimics that of embryonic stem cells. The cells form a cell mass (embryoid body), which can differentiate into various if not all cell types of the organism (Figure 1). These results may help to avoid the ethical and immunological problems that arise when embryonic stem cells are used in medical research. We have laid the basis for a future treatment of severe illnesses like cardiac insufficiency with the help of a body's own stem cells.

Using another approach, we developed a strategy for the establishment of spermatogonial stem cell lines from embryonic stem cells (ES). These cells are able to undergo meiosis, generate haploid male gametes *in vitro* and are functional, as shown by fertilization after intra-cytoplasmic injection into mouse oocytes (Figure 2). Molecular and cellular mechanisms underlying differentiation of ES to functional gametes should be elucidated in future research.




In the third approach, we show that bone marrow stem cells are able to trans-differentiate into male germ cells. BMS cell-derived germ cells expressed the known molecular markers of primordial germ cells. Our ability to derive male germ cells from bone marrow stem cells provides novel aspects of germ cell development.

The findings to be published in Gamete Biology: Emerging Frontiers on Fertility and Contraceptive Development.

**Selected Publications:**

Guan K *, **Nayernia K***, Maier LS, Wagner S, Dressel R, Lee JH, Nolte J, Wolf F, Li M, Engel W, Hasenfuss G. Pluripotency of spermatogonial stem cells from adult mouse testis. Nature 440: 1199-1203 (2006) (* joint first authors).

**Nayernia K**, Nolte J, Michelmann HW, Lee JH, Rathsack K, Drusenheimer N, Schwandt I, Wulf G, Ehrmann I, Elliott DJ, Zechner U , Haaf T, Meinhardt A, and Engel W. In vitro Differentiated Embryonic Stem Cells Give Rise to Male Gametes That Can Generate Offspring Mice Developmental Cell 11 (2006).

**Nayernia K**, Lee JH, Drusenheimer N, Nolte J, Wulf G, Schwandt I, Müller Ch, Gromoll J, Engel W. Derivation of germ cells from bone marrow stem cells. Lab Investigation 86: 654-656 (2006).

Lee, J.H., Engel, W., **Nayernia, K**.: Stem Cell Protein Piwil2 Modulates Expression of Murine Spermatogonial Stem Cell Specific Genes. Molecular Reproduction and Development 73: 173-179 (2006).

Lee, J.H., Schütte, D., Wulf, G., Füzesi, L., Radzun, H.J., Schweyer, S., Engel, W., **Nayernia, K**. : Stem Cell Protein Piwil2 is Widely Expressed in Tumors and Inhibits Apoptosis through Activation of Stat3/Bcl-X(L) Pathway. Human Molecular Genetics 15: 201-211 (2006).

Putative human male germ cells from bone marrow stem cells. Drusenheimer N, Wulf G, Nolte J, Lee JH, Dev A, Dressel R, Gromoll J, Schmidtke J, Engel W and **Nayernia K**. Reproduction: Gamete Biology (in press).

## Correlation between the structural stability and aggregation propensity of proteins

**www.bioinfo.de/isb/2007/07/0023**

**Susan Idicula-Thomas and Petety V. Balaji* School of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai 400 076, India , In Silico Biology 7, 0023 (2007)**

As in other fields, biology will experience an increased use of systems mathematics and computer simulations. Many other fields of science and engineering have developed systems science and complicated mathematical simulations to a high level of sophistication. These capabilities influence our everyday life. The relationship between the conformational stability of folding intermediates and folding kinetics has been investigated by a variety of methods. Mutation studies have revealed that the stabilization of the rapidly collapsed intermediate is accompanied by a faster acquisition of the folded state. It has also been observed that mutations which increase the stabilization of secondary structural elements of a protein increase the rate of folding or decrease the rate of unfolding depending on whether they are formed before or after the rate-limiting transition state of folding. The rates of folding as well as unfolding are important in the case of protein aggregation since the aggregating intermediates can either be the ones formed during folding, as in the case of inclusion body formation in an over expression system, or the ones formed during unfolding in a mildly denaturing environment as in the case of amyloid fibril formation in physiological systems. Correlation between structural instability, as exemplified by backbone hydrogen bonds that are insufficiently shielded from water or by the presence of unstable helices, and amyloidogenic potential has been previously investigated. In this *in silico* study, the secondary and tertiary structures of proteins a) that form inclusion bodies on over expression in *Escherichia coli*, b) that form amyloid fibrils and c) that are soluble on over expression in *E. coli* are analyzed for certain features that are known to be associated with structural stability.

## CTGA: the database for genetic disorders in Arab populations

**http://www.cags.org.ae**

**Centre for Arab Genomic Studies, PO Box 22252, Dubai, United Arab Emirates**

The Arabs, comprising of 315 million individuals, are living in Regions encompassing Mesopotamia, Middle East, Arabian Gulf, North Africa and parts of East and West Africa.

The Arabs comprise a genetically heterogeneous group that resulted from the admixture of different populations throughout history. They share many common characteristics responsible for a considerable proportion of perinatal and neonatal mortalities.

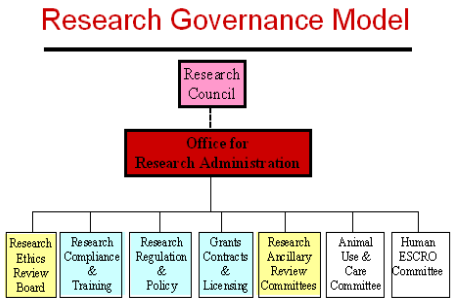
To this end, the Centre for Arab Genomic Studies (CAGS) launched a pilot project to construct the 'Catalogue of Transmission Geneticsin Arabs' (CTGA) database for genetic disorders in Arabs. Information in CTGA is drawn from published research and mined hospital records. The database offers web-based basic and advanced search approaches. In either case, the final search result is a detailed HTML record that includes text-, URL- and graphic-based fields. At present, CTGA hosts entries for 692 phenotypes and 235 related genes described in Arab individuals. Of these, 213 phenotypic descriptions and 22 related genes were observed in the Arab population of the United Arab Emirates (UAE). These results emphasize the role of CTGA as an essential tool to promote scientific research on genetic disorders in the region.

The priority of CTGA is to provide timely information on the occurrence of genetic disorders in Arab individuals.
It is anticipated that data from Arab countries other than the UAE will be exhaustively searched and incorporated in CTGA.

## The Harvard Medical School Dubai Center in a glimpse

**http://www.hmsdc.hms.harvard.edu**

The Harvard Medical School Dubai Center (HMSDC) Institute for Postgraduate Education and Research has been established to foster the professional development of physicians, nurses, research scientists, and allied health professionals in the Persian Gulf Region. Launched in 2004 through a joint effort by Harvard Medical International (HMI) and Dubai Healthcare City (DHCC), HMSDC is part of the Government of Dubai's mission to develop DHCC into a center of excellence for health care delivery, medical education, and research. HMSDC provides an unprecedented link between the Persian Gulf Region and the global medical community, and will help to bring the knowledge and expertise of world-class academic medical centers to bear on the area's most pressing health care challenges. Through a range of educational programs and specialty training, the HMSDC will address the need for professional development in the region and help create a cadre of leaders in academic medicine who will constitute the professional workforce and intellectual resources of DHCC, and ultimately the region. HMSDC will eventually have its home in a state-of-the-art facility that is expected to be completed by Fall of 2007. Initially, the building will include teaching space and case study rooms, an auditorium, and the Maktoum-Harvard Medical Library. When it is finished, this library will be the most advanced collection of clinical and professional development resources in the region, and will include a unique patient and family education center that will provide a close connection between HMSDC and the medical services



offered at Dubai Healthcare City. The creation of HMSDC is a monumental step into the future for the people of Dubai and the surrounding Persian Gulf Region. Whether striving to move discoveries from the laboratory to the bedside, promote active learning in clinical education, or develop the skills and knowledge to provide patient care of an international standard, the people who become part of the HMSDC and its programs will benefit from the expertise and experience of globally recognized faculty, the implementation of leading-edge facilities and technologies, and a commitment to excellence, continuous improvement, and community-building that is a hallmark of the Harvard Medical School mission.

**EDUCATION**

The development of Dubai into a center of excellence for health care delivery depends on the establishment of a sustainable education system to foster the development of the region's health care workforce. To this end, the Harvard Medical School Dubai Center was established to bring updated medical knowledge, high-impact training, and state-of-the-art professional development resources to the physicians, nurses, and allied health professionals of the region. Through Continuing Medical Education (CME) programs, HMSDC provides opportunities for health care professionals to enrich their clinical skills, expand their medical knowledge, and learn about important advances in the diagnosis, prevention, and treatment of disease. HMSDC collaborates with regional health authorities, local hospitals and universities, and medical societies and specialty groups to identify areas of need and interest, and develop customized programs that are relevant to practice. Each program is led by a multidisciplinary faculty drawn from preeminent academic medical centers around the world as well as local institutions. HMSDC works to ensure that each program maintains academic independence, and that course content is consistent with the principles of evidence-based medicine.

HMSDC's CME programs are developed for a wide range of participants:

Physicians, Faculty Members, Dentists, Nurses & Nurse Practitioners, Pharmacists, Allied Health Professionals, Research Scientists, Industry Representatives & Medical Students.

**HMSDC RESEARCH INITIATIVES**

Harvard Medical School Dubai Center (HMSDC) Institute for Postgraduate Education and Research at Dubai Healthcare City (DHCC) is in the process of establishing the Office for Research Administration (ORA) and the Research Council which will govern the conduct of clinical research at DHCC. The Office for Research Administration, under the governance of the Research Council, will oversee the implementation of all policies and procedures for research activities and serve as the central office for research support and training.

## ***Training/Continuing Education***

### Genetic and Treatment of Cancer

http://www.who.int/genomics/about/Cancer.pdf

The increasing evidence of genetic linkage to cancer onset and development makes it an important Part of research and public health which can no longer be over looked. According to the International Agency of Research for Cancer (IARC), a 50% increase in cancer rate within the next 20 years is expected. Causal factors fall usually in to two broad categories: environmental and genetic. Cancer cases may fall under one of three categories: inherited, familial and sporadic. Approximately 4% (1 to 20% , dependent of type) of cancer cases can be characterized as inherited cancers . A larger Percentage of cancers are familial, and involve mutations on multiple susceptibility genes that increase an individual's risk for cancer. Familial cancers appear to run in the family and Sporadic Cancer cases are those where an individual randomly develops cancer in the absence of any familial pattern. To prevent cancer a genetic testing facilities are available, they should be made more accessible to individuals, as many would benefit immensely from this information. The current most common treatment for cancer is surgery and chemotherapy but this method is known to have numerous adverse side effects. To improve the benefit to harm ratio of chemotherapy, the concept of pharmacogenetics must be recognized. Pharmacogenetics involves tailoring treatment to an individual's genetic characteristics to optimize drug response, and the last long term solution is gene therapy, a cure that provides a single treatment correction at the source of the problem. Concurrently, more resources need to be devoted to research in pharmacogenetics and gene therapy, where existing data shows that within these two fields lie promisingly the future treatments for cancer.

## MicroRNAs

**http://www.opengenomics.com/**

MicroRNAs (miRNAs) are an abundant class of small single-stranded non-coding RNAs (19-30 nucleotides long) that serve widespread functions in post-transcriptional gene silencing. Recently, research has demonstrated that miRNAs are crucial regulators of gene expression, affecting a wide variety of cellular functions including development, proliferation, differentiation, and apoptosis. To address your novel research questions related to miRNA expression, Some companies now offers the MicroRNA Profiling System, an 8 x 15K miRNA-specific microarray. This novel microarray features:

**Low Sample Input** – new probe design and direct labeling protocol require just 100ng of total RNA for reliable results

**Broad Dynamic Range** –miRNA profiling system spans greater than 4 logs for comprehensive miRNA expression profiling

**Precise miRNA Discrimination** – *in situ* synthesis process delivers probes capable of accurate single-nucleotide discrimination between similar size and sequence miRNAs.

In1993, R.C. Lee of Harvard University first described miRNA-mediated silencing in C. elegans, and since, these molecules have been more clearly defined as single-stranded RNA molecules, 19-25 nucleotides in length, that are generated from endogenous

hairpin transcripts. MicroRNAs (miRNAs) serve as guides in post-transcriptional gene silencing by complimentary base pairing with target mRNAs, resulting in mRNA cleavage or translational repression. As a result, miRNAs enable regulation of complex biological pathways such as those associated with developmental processes, haematopoietic cell differentiation, apoptosis, and cell proliferation. Interestingly, it now appears that miRNAs may actually form complex regulatory networks with target mRNAs, as a single miRNA may be responsible for the regulation of several different targets, or conversly, several miRNAs may cooperatively regulate a single mRNA target. To date, there have been approximately 4300 precursor miRNAs found in virtually all species animals, plants, and viruses of which ~475 are human miRNAs. Research suggests that as many as one-third of all human genes may be miRNA regulated, many of which are involved in cancer and other disease regulation.

Due to their involvement in gene regulation, miRNAs have received significant attention with respect to their role in cancer, disease, and stem cell differentiation. Traditional characterization of miRNA follows small RNA identification by cDNA cloning. Expression of miRNAs is typically confirmed by hybridization to a size-fractionated RNA sample, usually achieved by Nothern blot analysis. Alternative methods for miRNA detection and confirmation include reverse transcription PCR (RT-PCR), primer extension analysis, RNase protection assays, and microarray analysis. Typically, even when miRNAs are identified using these alternative methods, Northern blot analysis follows as it enables the confirmation of both the hairpin precursor (~70 nt) and mature miRNA (~22 nt) forms. Global gene expression profiling of miRNAs using microarrays provides high-throughput information on miRNA involvement in disease progression and developmental changes, while offering an alternative to some of the time- and labor-intensive techniques previously described.

Known Applications to date includes:

**Cancer Research**

Leukemia and Lymphoma Research, Lung Cancer Research, Brain and Nervous System Cancer Research, Breast Cancer Research, Prostate and Colon Cancer Research, p53 Research

**Disease Research (Non-Cancer)**

Neurodegenerative Disease Research, Fragile X Disease Research

**Other Applications or Research Areas**

Correlating miRNA Data with Copy Number Analysis, Stem Cell Research & Developmental Biology Research

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