EMHGBN Newsletter

Vol. 1, Issue 8, May. 23, 2007

The germinating seed of Arab genomics

http://www.nature.com/naturegenetics

Mention Arab genetics and most people will immediately think of the origins and regional pre-eminence in thoroughbred horse racing in North Africa and the Arabian Peninsula. However, it is the diverse people across this geographical area who present one of the greatest opportunities for the application of medical genetics. In turn, the study of their constituent regional populations can form a new research resource from which their scientists can bring fresh insights to the world genomics community.

The 23 member states of the Arab League are bound by the aim of cooperation for the health of their peoples, who comprise over 323 million from Mauritania to Oman. Their economies grossed some $1.5 × 1012 in 2005, with significant economic growth. So there now exists the declared intent, the human capital and the financial potential for considerably greater investment in research and development across the entire region. In addition, some 30 million people worldwide can trace their ancestry to this region.

Editorials in Nature (441, 1027, 2006) and The Lancet (367, 959, 2006) earlier this year have reviewed the prospects for international funding of regional research and for the restructuring of medical education and practice in response to the three United Nations Arab Human Development Reports, respectively.

Close-kin marriage and large families are cultural factors in the Eastern Mediterranean region that have drawn the attention of geneticists; their implications increase as development progressively reduces the mortality resulting from poor childhood nutrition and infectious disease. Ahmad S. Teebi and Hatem I. El-Shanti (Lancet 367, 970–971, 2006) estimate the rates of consanguinity (marriages between second cousins or more closely related family members) at between 20% and 70% in the Middle East excluding Israel and Cyprus. They estimate that a first-cousin couple has a two-fold higher risk of a child with a major birth defect and also point out the utility of consanguineous pedigrees for homozygosity mapping of rare autosomal recessive disorders.

An "Eastern Mediterranean Variome Project" would Build upon the sense of common purpose inherent in these distinctive populations and provide an appreciation of their place in the history of the human population. The knowledge gained, could be immediately used to address urgent health needs. It would also offer an opportunity to promote education and knowledge drawing upon local examples, constructive engagement of global research efforts in human health from a position of strength, and opportunities to build sustainable post-petroleum economic activity based upon education and the improvement of human health.

INSIDE THIS ISSUE:

The germinating seed of Arab genomics	1
Muslim science must join the 21st century	2
Research Writing & Editing Workshop announcement	3
Gene variation linked to heart attacks	4
Change your Blood type?	5
New Link Between Down Syndrome And Alzheimer's	5
Training	6,7

it is the diverse people across this geographical area who present one of the greatest opportunities for the application of medical genetics

Muslim science must join the 21st

www.SciDev.net

Muslim countries contribute just 2.5 per cent of more than 11.5 million papers published worldwide each year

For decades, Muslim countries have struggled to understand the value of scientific and technological research. But a recent study by the Organization of the Islamic Conference (OIC) on the status of scientific research in its 57 member states sheds some light on the nature of the 'science deficit' in these countries.

Although the results show that many Muslim countries have a poor scientific output, they also indicate a growing realization among such countries that they must catch up with the rest of the world or lag behind economically, socially and politically.

Country	Number of publications (1995 - 2004)	Publications per million population (rank)	Publications growth rate**
Turkey	82,407	116.5 (4)	82.30%
Egypt	27,723	38.9 (8)	13%
Iran	19,114	28.0	123%
Saudi Arabia	17,472	72.62	-5.85%
Malaysia	10,674	43.75	31.70%
Morocco	10,113	33.1 (9)	9.70%
Nigeria	9,105	7.5 (12)	-8.40%
Pakistan	7,832	5.3 (13)	24.50%
Jordan	6,384	119.33	24.30%
Kuwait	5,930	254.5	-0.50%
Lebanon	5,341	152.6	12.45%
Indonesia	5,118	2.35	12.50%
Bangladesh	4,745	3.5 (14)	15.50%
United Arab	4,389	108.64	30.00%
Uzbekistan	3,924	15.1 (11)	-11.00%

Percentage change in publication rate over 2002-2004 compared with the 1998-2004 average
www.comstech.org.pk

Science deficits

The OIC study looked at total scientific output of member countries ,which holds about 8,700 research journals as well as monographs and conference proceedings. Turkey leads the pack by a long way (see Table 1).

The figure shows that, Muslim countries contribute just 2.5 per cent of more than 11.5 million papers published worldwide each year. This reflects the low value placed on scientific research in general, and publishing research findings in particular, within much of the Islamic world. It is also clear that the three largest Muslim countries by population — Indonesia, Pakistan and Bangladesh — are not the most scientifically and technologically productive. This disparity between countries suggests that a vast number of Muslims around the world are virtually excluded from the worldwide scientific enterprise. A closer look at the study's findings shows that there is also a lack of diversity in subject in scientific publications.

"Scientists in the Muslim world tend not to publish in some of the technological fields that have contributed to economic growth in the West"

In addition, scientists in the Muslim world tend not to publish in some of the technological fields that have contributed to economic growth in the West — for example, semiconductors, information technology, genetics and nanotechnology. This absence represents a weakness in these countries' ability to translate scientific research into useful technologies that support economic development.

Finally, not one of the 25 most productive (by publication count) scientific institutes in Islamic countries such as Ankara University, Cairo University or King Fahd University — appear on the list of top institutions worldwide. As scientists' decisions and motivations are affected by institutional quality, environment and incentives, this institutional deficit may, in part, explain the low scientific productivity in the Muslim world.

But ,there are some indicators of a change sweeping across the Muslim world. Iran, Pakistan and Turkey show a clear upward trend in scientific output all of which have recently made large increases to scientific spending. Pakistan has, for example, increased funding for tertiary education by 5,000 per cent over the last 5-7 years.

Even after adjusting for secular trends in publication counts, the number of annual scientific publications has grown in six of the 15 countries listed in Table 1. Several of these are building up their scientific infrastructure through substantial investments in tertiary education and research.

A female laboratory technician in Sudan.

For example, the Emirate of Qatar, through its Doha Education City, is trying to become the education and knowledge hub of the region. Similarly, Nigeria recently announced plans to invest US$5 billion in science and research over the next decade with the hope of making substantial gains in economic growth and development.

A study of scientific research in the muslim world shows that it lags far behind the rest of the world, but there are encouraging signs of improvement

But, in order to make the most of these — and other less ambitious — initiatives, the Muslim world will need policies that can support the use and development of science and technology infrastructure. Islamic countries also need to promote the value of science and technology to the general population. And they must learn to use science to solve socio-economic problems such as disease, resource shortages, and economic development.

Only through an intelligent use of policy, followed by patient and committed implementation, can the Muslim world move out of the scientific backwaters to become equal participants and beneficiaries of the scientific age.

Iran, Pakistan and Turkey show a clear upward trend in scientific output all of which have recently made large increases to scientific spending

The objectives of the workshop

1. Perform research in all fields of medicine including medico-legal cases.
2. Develop specific aim for research study.
3. Help researcher in design and methods of the study, and how the research will be conducted.
4. Edit research at all stages and prepare preliminary results or progress report.
5. Encourage researchers to publish their research studies in medical/science journals and books.
6. Help the researcher to prepare budget and justification for all the expenses required to achieve the project aim and objectives.
7. Adhere and abide by ethical principles and guidelines for the protection of human subjects and animal in research.

"The Spoken Word is often buried with one's bones – it is the written word that Lives long after."
Shakespeare

Research Writing & Editing Workshop

June 15-16, 2007

Venue: Lecture Room
(2nd Floor, Near Ward 23)
BDF Hospital
Kingdom of Bahrain

Dr Jaffar M Al-Bareeq
Chief Editor
Bahrain Medical Bulletin-
Established 1979

Research Writing & Editing Workshop Program

Friday, June 15, 2007

Introduction	5 min	Dr. Mohammed Al Khalifa
Opening & Introduction	20 min	Dr. Hilli
The Art of Writing I	60 min	Dr. Bareeq
Coffee Break	15 min	
The Art of Writing II	60 min	Dr. Bareeq
How to do Research & Generate Ideas	60 min	Dr. Hilli
Statistics,Research,Design & Illustration	45 min	Dr. Das
Hypothetical Study	10 min	Dr. Hilli
Lunch Break	45 min	
Ethics in Research	60 min	Dr Bareeq
Introduction	30 min	Dr Bareeq
Coffee Break	30 min	
Methods	30 min	Dr. Hilli
Results	30 min	Dr Bareeq
Discussion	30 min	Dr. Bareeq
Abstract	30 min	Dr. Bareeq
Conclusion	30 min	Dr. Bareeq
References	30 min	Dr. Bareeq
Positive Thinking and Creativity	60 min	Mohd Ali

Saturday, June 16, 2007

Letter to the Editor	30 min	Dr. Hilli
Poster Presentation	30 min	Dr. Hilli
Authorship/Contributorship	30 min	Dr. Hilli
Coffee Break	15 min	
Literature Search	60 min	Dr. Bareeq
CV Writing	30 min	Dr. Hesham
Case Presentation & Submission	45 min	Dr. Hilli
The Art of Interview	45 min	Dr. Hesham
Lunch Break	45 min	
Oral Presentation	30 min	Dr. Sindi
Research Ideas in Dentistry	30 min	
Discussion of Hypothetical Study	60 min	Dr. Hilli
Coffee Break	30 min	
Discussion of candidates' Research paper, design or Proposal with the organisers	150 min	Dr. Hilli/Dr. Bareeq/ Dr. Hesham/Dr. Sindi
Concluding Discussion	30 min	Dr. Hilli
Certificate of Attendance	15 min	Dr. Mohammed Al Khalifa

Research Writing and Editing Workshop will be held on June 15-16, 2007 in BDF Hospital, Kingdom of Bahrain

Gene variation linked to heart attacks

www.consumeraffairs.com

"Risk of developing heart disease is about one in two for men and one in three for women"

The lifetime risk of developing heart disease is about one in two for men and one in three for women. If they can identify genetic factors which influence heart disease risk over and above known risk factors, we can do a better job of identifying those people who will benefit most from early intervention to reduce their risk. Those early interventions include lifestyle changes such as quitting smoking and getting high blood pressure or high cholesterol levels under control through diet, exercise and medication.

About one in four Caucasians are thought to carry the mutations. Africans did not appear to carry the mutations, and in African-Americans, the mutations were not linked with heart disease risk.

The findings may explain why heart disease is common among people who do not smoke, have high blood pressure or high cholesterol. The tiny stretches of mutated DNA, called single nucleotide polymorphisms or SNPs, were not previously identified as a gene, which may make it more difficult to determine how they contribute to disease. McPherson's team looked at two SNPs called rs10757274 and rs2383206.

"A common gene variant more than doubles the risk of heart attack in white people under the age of 60"

A common gene variant more than doubles the risk of heart attack in white people under the age of 60, new research suggests. Two studies involving more than 40,000 people have identified three gene mutations, each linked to a substantially increased risk of heart disease, particularly among middle-aged adults. The researchers hope their findings will lead to new drugs to treat cardiovascular disease.

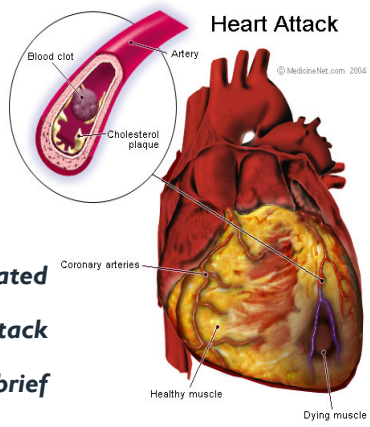
Ruth McPherson, at the University of Ottawa Heart Institute in Canada, and colleagues analyzed blood samples taken from more than 28,000 people with heart disease and healthy control subjects.

The team attached fluorescent molecules to specific DNA sequences to identify genetic differences between the two groups – a technique known as "gene chip" technology.

The tests revealed a small but striking difference on chromosome 9. There was a much higher prevalence of two gene variants in the DNA of heart disease patients.

The variations were "single nucleotide polymorphisms" (SNPs) – differences between single letters of the DNA code. Individuals of European descent who carried one or two copies of the SNPs were 25% and 40% more like to have coronary heart disease, respectively.

The variants are quite common. More than half of Caucasians have one chromosome with these SNPs and a quarter have two affected chromosomes, the study found.



Illustrated Heart Attack in brief

However, the same link to heart disease was not found for African Americans with the newly identified gene variants, the researchers say.

A separate survey of 17,000 people's DNA, by deCODE Genetics in Iceland, identified another SNP which was linked to a 60% increased risk of heart attack among Caucasians. This newly identified SNP, also on chromosome 9, appears to contribute to an elevated risk of early-onset heart disease, which strikes men and women before the ages of 50 and 60, respectively.

People with two copies of this variant – 20% of Caucasians – have a doubled risk of heart attack before these ages, the researchers found.

Change your Blood type?

news@nature.com – 1 April 2007; Journal reference: Nature Biotechnology - 25, 454 - 464 (2007) (DOI: 10.1038/nbt1298),Qiyong P Liu, Gerlind Sulzenbacher, Huaiping Yuan, Eric P Bennett & et.al. , NewScientist.com news service

Scientists have discovered enzymes that can efficiently convert blood groups A, B and AB into the 'universal' O group – which can be given to anyone, but is always in short supply.

The ABO group blood-type system is based on the presence or absence of the sugar-based antigens 'A' and 'B' on red blood cells. Type O blood cells have neither A nor B antigens, so may be safely transfused into anyone. Both types A, B, and AB blood do, and cause life-threatening immune reactions if they are given to patients with a different blood group. In the 1980s, a team in New York, US, showed that an enzyme from green coffee beans could remove the B antigen from red blood cells. It proved too inefficient for practical use, but Henrik Clausen at the University of Copenhagen in Denmark and colleagues have now screened bacteria and fungi for more powerful enzymes. Qiyong P Liu' Henrik Clausen and et.al., report two bacterial glycosidase gene families. One, from a gut bacterium called Bacteroides fragilis, and the other, from Elizabethkingia meningosepticum – which causes opportunistic infections in people that capable of efficient removal of A and B antigens at neutral pH with low consumption of recombinant enzymes. The bacterial glycosidase enzymes strip these antigens away from A, B and AB blood. Enzymatic removal of blood group ABO antigens to develop universal red blood cells (RBCs) was a pioneering vision originally proposed more than 25 years ago. Although the feasibility of this approach was demonstrated in clinical trials for group B RBCs, a major obstacle in translating this technology to clinical practice has been the lack of efficient glycosidase enzymes. The enzymatic conversion processes hold promise for achieving the goal of producing universal RBCs, which would improve the blood supply while enhancing the safety of clinical transfusions.

Enzymes convert all donor blood types to group O

The enzymatic conversion processes hold promise for achieving the goal of producing universal RBCs

If so, the technology should be in hot demand, because group O blood – the only safe option if there is any doubt about the recipient's blood group – is a precious commodity.

New Link Between Down Syndrome And Alzheimer's

news.myspace.com

Scientists have shown that a protein involved in cholesterol metabolism may cause the accelerated onset of Alzheimer's Disease in individuals affected with Down Syndrome.

People with Down Syndrome -- a genetic disorder due to the presence of an extra chromosome 21 -- develop Alzheimer's disease (AD) earlier (mid- to late 30s) than the general population (mid- to late 70s). To understand why, scientists have studied genes from chromosome 21 that are also involved in AD. One of those genes has already been found: It produces a protein called amyloid precursor protein (APP) that helps create protein clusters that are the hallmark of AD. Cheryl L. Wellington and colleagues have found another gene on chromosome 21 that produces a protein that regulates the amount of cholesterol present in a cell. The scientists showed that this protein influences the distribution and processing of APP and that it is present at high levels in the brains of Down Syndrome individuals. The new discovery may provide new ways to halt AD symp-

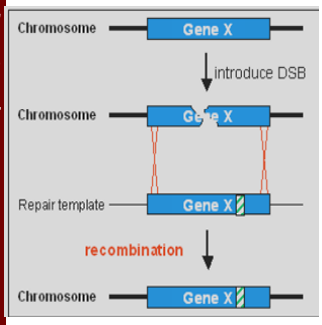
TRAINING

Zinc Finger Nucleases

www.Zincfingers.org

Zinc finger nucleases (ZFNs) are synthetic proteins consisting of an engineered zinc finger DNA-binding domain fused to the cleavage domain of the FokI restriction endonuclease. ZFNs can be used to induce double-stranded breaks (DSBs) in specific DNA sequences and thereby promote site-specific homologous recombination and targeted genomic manipulation of genomic loci in a variety of different cell types (a process known as ZFN-mediated gene targeting). A long-term goal of the Zinc Finger Consortium is to develop ZFNs as broadly applicable and readily accessible molecular tools for performing targeted genetic alterations. The ability to alter the sequence or structure of any gene of interest would be enormously useful for biological research and molecular therapeutics.

Figure 1: DSB-enhanced gene targeting



"ZFNs promote site-specific homologous recombination and targeted genomic manipulation of genomic loci in a variety of different cell types"

Gene targeting by ZFNs:

Gene targeting is a method to repair or inactivate any desired gene of interest. Gene targeting strategies use the introduction of a double-stranded break (DSB) into a genomic locus to enhance the efficiency of recombination with an exogenously introduced homologous DNA "repair template" (Figure 1).2 DSBs can stimulate recombination efficiency several thousand-fold, approaching gene targeting frequencies as high as 20%.3-5 Early experiments utilized highly specific homing endonucleases, enzymes that bind and cleave extended DNA sequences, to introduce DSBs into specific genomic loci.2 Unfortunately, since robust techniques to alter the DNA-binding specificites of these enzymes do not currently exist, the use of homing endonucleases to enhance gene targeting is limited to loci into which the target cleavage sequence can be introduced. Zinc finger nucleases (ZFNs) provide an alternative to homing endonucleases for introducing site-specific DSBs. ZFNs consist of a DNA-binding zinc finger domain (composed of either three or four fingers) covalently linked to the non-specific DNA cleavage domain of the bacterial FokI restriction endonuclease (Figure2A).

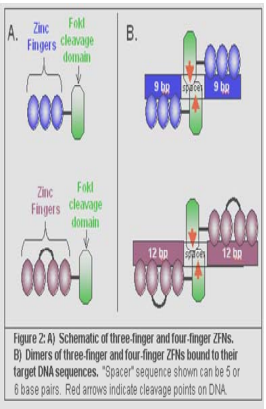


Figure 2: A) Schematic of three-finger and four-finger ZFNs. B) Dimers of three-finger and four-finger ZFNs bound to their target DNA sequences. "Spacer" sequence shown can be 5 or 6 base pairs. Red arrows indicate cleavage points on DNA.

6-10 ZFNs can bind as dimers to their target DNA sites, with each monomer using its zinc finger domain to recognize a "half-site" (Figure 2B).

11,12 Dimerization of ZFNs is mediated by the FokI cleavage domain13-15 which cleaves within a five or six base pair "spacer" sequence that separates the two inverted "half sites" (Figure 2B).4,11,12,16 Importantly, because the DNA-binding specificities of zinc finger domains can be re-engineered using various methods,17-21 customized ZFNs can theoretically be constructed to target nearly any gene sequence. Recent work has shown that ZFNs can be used to direct gene targeting events to specific endogenous loci or genes in insect, plant, and human cells. ZFNs can stimulate recombination in plant22 or human cells3 between two reciprocally defective copies of a reporter gene. ZFN-mediated gene targeting has been used to effect correction of disease-associated mutations in an endogenous gene

Genome wide single gene specificity

In human cells (SCID-associated mutations in the IL2Rg gene)4 and mutation of an endogenous gene in Drosophila.23,24 Collectively, these studies suggest that ZFNs will be immediately useful as research tools and, in the longer term, as therapeutic reagents to manipulate the sequence of any endogenous gene.

Zinc Finger Engineering

Widespread testing and application of the ZFN-mediated gene targeting will depend upon the ability of the typical scientific researcher to rapidly construct engineered zinc finger domains.

In addition, given that the ranges of desirable ZFN affinity and specificity needed to minimize ZFN cytotoxicity remain poorly understood, for any given target DNA site it will be important to obtain multiple zinc finger domains with various affinities and specificities for testing in cells. Therefore, an ideal method for generating multi-finger proteins would provide a user-friendly approach for generating a series of candidate proteins with a range of affinities and specificities for each target DNA site of interest. Although a variety of different zinc finger engineering methods have been described in the literature, no large-scale test of any of these approaches for constructing ZFNs has yet been performed and therefore the relative and absolute efficacies of these methods remain unknown. Furthermore, a variety of factors have made zinc finger engineering technology inaccessible to the non-specialist researcher. The various engineering methods Described utilize different zinc finger protein scaffolds that are not readily inter-convertible. One of these platforms requires access to a proprietary archive of zinc fingers (owned by the biotechnology company Sangamo Biosciences) and requires labor-intensive efforts to generate domains with optimized binding capabilities. Furthermore, implementation of existing zinc finger engineering technology can require specialized experimental expertise that is not easily learned simply by following published protocols. The Consortium believes that these various factors have limited (and will continue to limit) the development and application of ZFN technology. Modular assembly of zinc finger domains.

Various reports in the literature have described rapid "modular assembly" methods in which pre-existing finger "modules" with known, optimized specificities are linked together to create a multi-finger domain. This strategy can use modules consisting of single fingers (obtained by selection from randomized libraries,25-27 by rational design,28 or from naturally occurring domains29) to assemble domains composed of three or six fingers (Figure 3A).

Modular assembly has also been used with one-and-a-half30 and two-finger modules4 (obtained by selection) to construct three- and four-finger proteins, respectively (Figure 3B).

Although conceptually appealing in its simplicity, the overall success rate of this approach for creating zinc finger nucleases that function well in cells remains unknown. In addition, a variety of different approaches and module archives have been described in the literature and the relative efficacies of these various methods have not been tested.

Finally, modular assembly approaches yield only a single multi-finger domain for any given DNA site and therefore provide only one candidate for making a ZFN for that target. If that one zinc finger domain yields a non-functional and/or cytotoxic ZFN, these methods do not provide any simple alternatives for creating additional domains capable of binding the DNA site of interest. Context-sensitive optimization of engineered multi-finger proteins.Recently, an optimization strategy that permits the simultaneous selection of fingers in a multi-finger protein has been described.1 This method accounts for context-dependent effects on the DNA-binding activity of individual zinc fingers. This strategy (illustrated in Figure 4) consists of two stages of selection performed using a bacterial cell-based two-hybrid system31-33 and ultimately yields multiple candidates that bind to the target DNA site. In Stage 1, parallel low stringency selections for each finger in the desired protein are used to identify pools of fingers (from master randomized libraries) that bind to each target DNA "subsite." In Stage 2, these pools of fingers are randomly recombined to create "shuffled" libraries of multi-finger domains and then high-stringency selections are performed to isolate the final optimized candidates. This strategy yields multiple zinc finger domains that bind

with various levels of affinity and specificity to their respective target DNA sequences of interest.1 Although this method can yield proteins with excellent affinities and specificities (as judged by in vitro assays), at present the efficacy of this approach for generating ZFNs that function well in cells remains unknown. Another drawback to this context-sensitive selection-based approach is that it is not amenable to widespread adoption because it requires multiple, labor-intensive selections to be performed for each target site.

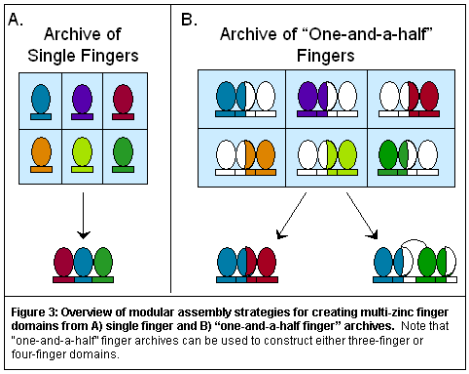


Figure 3: Overview of modular assembly strategies for creating multi-zinc finger domains from A) single finger and B) "one-and-a-half finger" archives. Note that "one-and-a-half" finger archives can be used to construct either three-finger or four-finger domains.

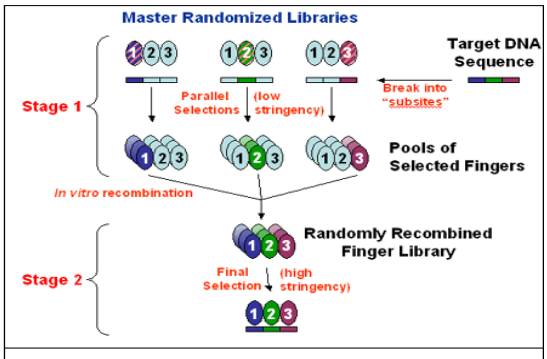


Figure 4: Overview of Multi-Zinc Finger Domain Optimization Strategy
Details provided in text. Ovals represent individual finger units. DNA "subsites" are represented by colored rectangles. Adapted from ref. 1.

Regional Health Genomics & Biotechnology Newsletter

Eastern Mediterranean Health Genomics and Biotechnology Network was created in 2004 with collaboration of representatives of selected centres of excellence in (health related) molecular biology, biotechnology & genomics in the Eastern Mediterranean region by recommendations and efforts of WHO/EMRO.

The ultimate goals of this network are:

* *to induce collaboration in production, training, research & development*
* *to be self-reliant in biotechnology*
* *to facilitate cooperation between wealthy and poor countries to upgrade health standards.*

Address: *Biotechnology building, #69, Pasteur Ave., Pasteur Institute of Iran Tehran, Iran, 13164*

Tel: +98-21-66954324

Fax: +98-21-66465132

E-mail: emhgbn@gmail.com, secretariat@emhgbn.net

Website: www.emhgbn.net

Prepared by:
F. Sarvi, S. Z. Mirmoradi & S. Mostaan

Page design: S.Mostaan

Editor: Dr. S. Sardari