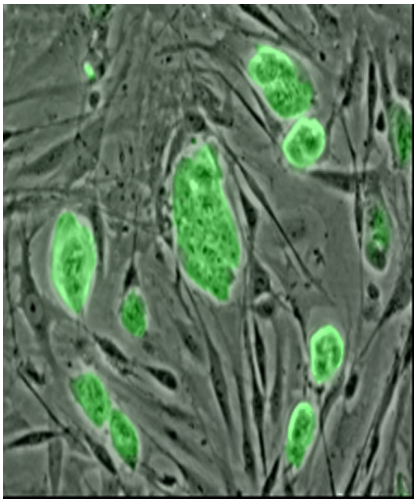

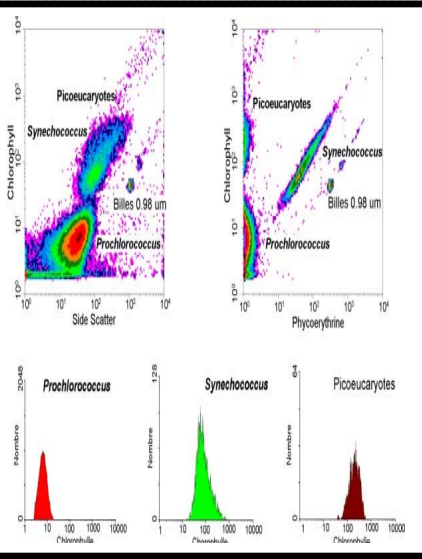

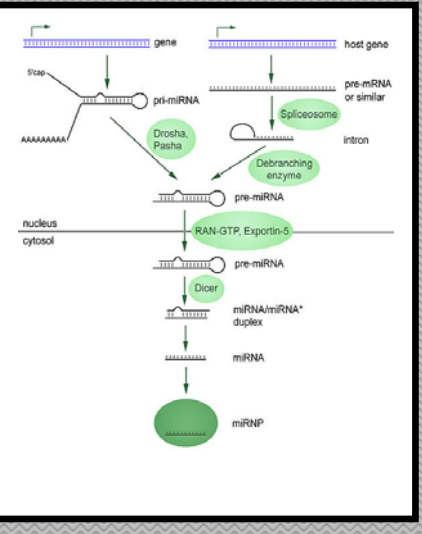

EMGEN Newsletter

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

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* EMGEN is a shortened form of EMHGBN that was approved for the ease of use and future reference by steering committee members of the member countries.

Isolation of *Exophiala dermatitidis* from endotracheal aspirate of a cancer patient

The article entitled " Isolation of Exophiala dermatitidis from endotracheal aspirate of a cancer patient" reports a case of 54-year-old Qatari female patient with a known history of cancer, suffering from pulmonary disorder. The study was carried out by S. J. Taj-Aldeen, S. El Shafie, H. Alsoub, Y Eldeeb, G. S. de Hoog. Corresponding author of this paper, S. J. Taj-Aldeen is Associate Professor of Microbiology Division, Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, and the paper was published in the journal of Mycoses. 2006 Nov; 49(6):504-9

Dr. Taj-Aldeen S. Associate Professor of Microbiology Division, Department of Laboratory Medicine and Pathology

Exophiala (Wangiella) *dermatitidis* is a darkly pigmented yeast-like organism belonging to the ascomycete order Chaetothyriales. It is occasionally found in the environment and reported from wild animals, and may cause infections in both immunocompromised and immunocompetent individuals. *E. dermatitidis* is well known to cause local skin and disseminated phaeohyphomycosis and fungemia. This species is distributed worldwide, but nevertheless cerebral cases are restricted to East Asia. It is regularly reported from sputum of patients with cystic fibrosis as colonizer of the respiratory system, or as causal agent for fungal pneumonia and pulmonary phaeohyphomycosis. In the present study we report a respiratory tract colonization of *E. dermatitidis* in a cancer patient suffering from *Candida krusei* fungemia and pulmonary disorder. A full report regarding this case, and review of the recent clinical literature on *E. dermatitidis* is presented.

Patient

Patient was 54-year-old female with diabetes mellitus, hypertension, bronchial asthma, cervical cancer with urinary bladder and colonic metastasis with radiotherapy induced rectal stricture. She was admitted to Hamad Medical Corporation with the complaint of fever and constipation for two days associated with lower abdominal colicky pain and vomiting. She had a history of a left nephrectomy for 15 years and a nephrostomy inserted in the right kidney six weeks earlier. Ultrasound confirmed the presence of moderate ascites and right pleural effusion.

CT scan 5 days after admission revealed free fluid in peritoneum and air under the diaphragm. The patient's level of consciousness deteriorated and she went into deep coma. Intravenous fluconazole was first started at 400 mg, and then 200 mg daily with extra dose of 200 mg after each haemodialysis, this regime was continued for 7 days. On day 8 the patient started to develop ventilator-associated pneumonia, on day 12 the patient become stable haemodynamically and inotrops were stopped. However, fungal cultures of endotracheal tube aspirate revealed profuse growth of *Exophiala dermatitidis* with concomitant *Candida krusei*.

Blood cultures revealed the presence of *C. krusei* repeatedly. It was not possible to further incubate the blood cultures to detect the slow growing *E. dermatitidis* as the fast growing *C. krusei* overgrew any organism in the culture within the first 48 h. Two weeks after admission she started to have fever, conventional amphotericin B was started at a dose of 30 mg every other day, two days later it was increased to 40 mg every other day, eventually increased to 50 mg every other day. Seven days after initiation of amphotericin B, intravenous fluconazole 400 mg daily was added (the cumulative amphotericin was 390 mg). The patient deteriorated for the next few days and was put back on inotrops but finally expired with persistent cancer and *C. krusei* fungemia. The black yeast-like colonies was identified based on molecular methods at Centraalbureau voor Schimmel cultures, Utrecht, The Netherlands. Molecular identification was carried out by analyzing the rDNA ITS sequencing performed according to methods outlined by Matos et al. This approach showed unequivocally that our isolate was *E. dermatitidis* genotype B.

Discussion

Exophiala dermatitidis is a darkly pigmented yeast-like fungus, due to the presence of dihydroxynaphthalene melanin. Production of melanin has been associated with virulence in diverse microorganisms. Although melanin decreases the host cell stimulation by binding to amphotericin B, *in vitro* experiments failed to detect any differences in MIC between melanized and non-melanized *E. dermatitidis*. The natural habitat of *E. dermatitidis* is still insufficiently known. It was recently shown to be abundant in public steam baths and water reservoirs. However, this organism is recognized with increasing frequency as a cause of human disease. A critical review of the literature from the year 1960 regarding the confirmed cases up to 1992 was published by Matsumoto et al. and since that review additional cases of various clinical types have been reported from diverse parts of the world (Table 1), Predisposing factors for the human infection with *E. dermatitidis* include solid organ transplant, leukemia, cystic fibrosis, neutropenia, AIDS, CAPD, and chronic diarrhea.

Because of the distinct neurotropism of *E. dermatitidis*, infections due to this fungus can be life-threatening, severe cases are observed almost exclusively in immunocompetent patients in eastern Asia, whereas mainly patients with underlying malignancies or with otherwise impaired immunity are affected outside this region.

Exophiala is a genus of dematiaceous hyphomycetes whose taxonomy and nomenclature undergo constant revision. *Exophiala dermatitidis* differs from other species of the genus by its maximum growth temperature of 42oC, absence of utilization of nitrate and nitrite, and the apparent absence of annelides, when observed with light microscopy, leading many authors to place it in a separate genus, Wangiella.

The organism grows slowly on primary isolation media, and due to the pleoanamorphic life cycle, the morphological distinction in culture between *E. dermatitidis* and other species of Exophiala can be difficult. As was recently shown, ITS1 sequencing is a highly reliable tool for species identification of strains that are phylogenetically closely related to this black yeast species. Final identification of the causative organism and attribution of our strain to genotype B is achieved by sequencing of the rDNA ITS region of the fungus. *E. dermatitidis* is frequently clinically resistant to conventional antifungal agents. Due to the rarity of the Exophiala disease no large-scale controlled analysis of the antifungal agents has been performed. The MICs of fluconazole and 5-fluorocytosine against several Exophiala isolates have been reported to vary greatly, while itraconazole and amphotericin B appear to be effective against Exophiala isolates *in vitro* at MICs > 1 µg/ml.

In vitro studies of Johnson et al. revealed the potent and fungicidal activities of amphotericin B, itraconazole, and voriconazole. This data supports our results in that amphotericin B and itraconazole are potent in vitro inhibitors of *E. dermatitidis*. Catheter associated fungemia without deep organ involvement has been treated with itraconazole. In another case amphotericin B and 5-fluorocytosine were successfully used for treatment, whereas other investigators successfully used fluconazole for the treatment. However, if the infection is systemic or it involves the central nervous system, the addition of amphotericin B is required.

When the infection is initiated by traumatic implantation into the skin, the organism remains localized to the site of inoculation, without dissemination to deeper organs. Alternatively, the organism may be acquired by inhalation of the conidia, exceptionally with hematogenous spread to distinct organs. In order to prevent local recurrence of infection due to Exophiala, treatment should include complete surgical excision of the lesions that are accessible combined with postsurgical administration of antifungal therapy such as amphotericin B, ketoconazole and itraconazole, has been advocated especially when invasive or systemic infection is present.

The present study comprises the first reported case of clinical isolation of *E. dermatitidis* in the Middle East, regarding this colonization. The organism was reported to colonize in the respiratory tract of cystic fibrosis patients. The source of the organism in the present case cannot be determined, due to the critical and complicated situation of the patient in the present study, only a limited number of tests could be performed.

Dissemination was not clear and autopsy was not possible in order to confirm any microbial disease, therefore no post-mortem specimens for culture could be obtained. The primary cause of death was probably persistent cancer and fungemia due to *C. krusei* as evident from repeated blood cultures, but it is remarkable that *E. dermatitidis* is found additionally.

Culturing techniques for isolation of *E. dermatitidis* should be employed when processing specimens from immunocompromised patients. The prolonged incubation of the cultured specimen is necessary if *E. dermatitidis* are to be recovered.

Table 1: List of Exophiala dermatitidis cases reported after 1992.

Case	Manifestation	Predisposing factor
1	Cervical lymph node, brain	None
2	Peritonitis	CAPD
3	Septicemia	ALL
4	Brain abscess	None
5	Chronic nodule	Rheumatic arthritis
6	Catheter-associated fungemia	HIV
7	Corneal ulceration	None
8	Melanonychia	None
9	Otitis externa	None
10	Keratitis	Cornea transplant
11	CSF	None
12	Peritonitis	CAPD
13	Invasive pulmonary	CF
14	Lymphadinitis	ALL
15	Invasive stomatitis	ML, neutropenia
16	Peritonitis	Immunocompromised

Abbreviations: CAPD: Continuous Ambulatory Peritoneal Dialysis; ALL: Acute lymphatic leukemia; CF: cystic fibrosis; ML: myeloid leukemia

Biosensor Application in Cancer Diagnosis

Diagnosis (plural, *diagnoses*) in medicine area is named to a process of identifying a medical condition or disease by its signs, symptoms.

The history of medical diagnosis deep rooted in past from the days of Imhotep in ancient Egypt and Hippocrates in ancient Greece but is so far from perfect despite the enormous bounty of information carried out available by medical research involving the sequencing of the human genome .

Given cancer is a multi factorial disease resulted in silent unlimited division of self body cells; its diagnosis is most difficult and critical. In fact, the most important factor in cancer treatment process is rapid detection of the tumor cells in first stages.

Most cancers are initially identified either because signs or symptoms appear or through screening. The commonly cancer investigating involved blood tests, X-rays, CT scans and endoscopy.

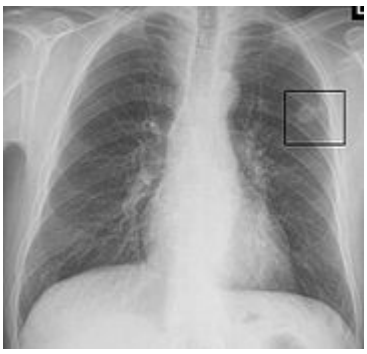

Figure 1: Chest x-ray showing lug cancer

The definitive diagnosis of most malignancies should be confirmed by histological examination of the cancerous cells. Tissue may be given from a biopsy or surgery.

The tissue diagnosis provided by the pathologist implies the type of cell that is proliferating, its histological grade, genetic abnormalities, and other data of the tumor. Cytogenetics and immunohistochemistry are other types of testing that the pathologist can perform on the tissue specimen. These tests give data about the molecular changes (for example mutations, fusions genes, and numerical chromosome changes) that has occurred in cancer cells, and also investigate the future strategies for cancer treating.

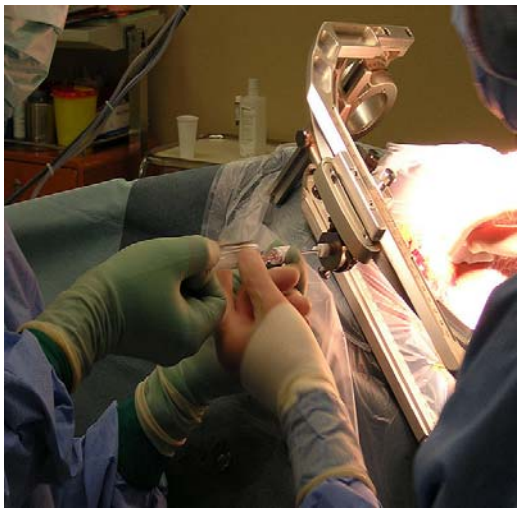

Figure 2: Brain biopsy

A diversity of biopsy techniques can be applied in suspension forms of tumors. An *excisional biopsy* names as an attempt to remove the entire lesion. When the specimen is estimate, in addition to diagnosis, the amount of straightforward tissue around the lesion, the *surgical margin* of the specimen is tested to see if the disease has extend beyond the area biopsied. "Clear margins" or "negative margins" means that no disease was initiate at the edges of the biopsy specimen. "Positive margins" defines that disease was found, and a wider excision may be required, depending on the diagnosis. When intact removal is not point to for a variety of reasons, a wedge of tissue can be taken in an *incisional biopsy*. In some cases, a sample can be together by devices that "bite" a sample. A diversity of sizes of needle can gather tissue in the lumen (‘’core biopsy’’). Smaller diameter needles gather cells and cell clusters, fine needle aspiration biopsy. Pathologic examination of a biopsy can fix on whether a lesion is benign or malignant, and can help distinguish between different types of cancer. On the contrary to a biopsy that merely samples a lesion; a larger excisional specimen identified a resection may come to a pathologist, typically from a surgeon attempting to eliminate a known lesion from a patient. For instance, a pathologist would test a mastectomy specimen, even if a previous nonexcisional breast biopsy had already created the diagnosis of breast cancer. Examination of the full mastectomy specimen would prove the exact nature of the cancer (subclassification of tumor and histologic "grading") and make known the extent of its spread (pathologic "staging").

Point-of-care diagnostic devices present a viable choice for the quick and sensitive detection and analysis of cancer markers.

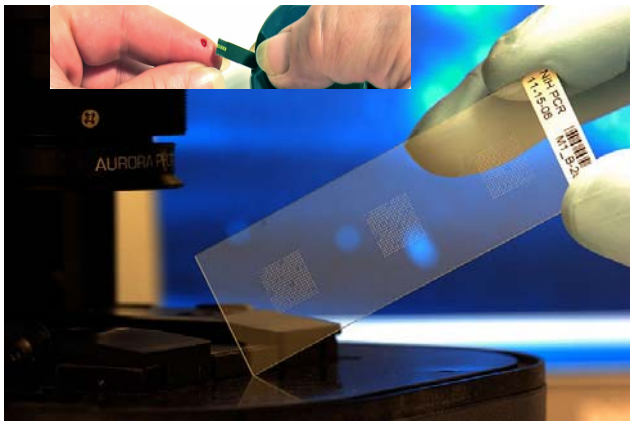

Figure 3: Biosensor application in diagnosis process

Biosensors as a device for the detection of an analyte that merges a biological component with a physicochemical detector component can cooperate an important role in the early diagnosis of cancer. Molecular profiles of patients are being gradually more studied using novel molecular tools such as genomic and proteomic techniques. These techniques jointed with bioinformatics methodologies are generating new data which is being employed in the clarification of new disease biomarkers (Tothill 2009).

Diagnosis methods on the base of biosensor are detecting techniques for investigating compounds of interest in bodily fluids, involving exhaled breath and blood. The present discovery uses biosensors that mimic naturally occurring cellular mechanisms, involving RNA oligonucleotide chains or “aptamers,” joint with molecular bonfires or nanotechnology to present an effective and efficient method for diagnosing a disease within a patient.

Quick and early diagnostics involve the use of ultra-sensitive biosensors since at the early stage of disease the concentrations of cancer marker in a person biofluids will be stumpy. As well, the larger the number of sensor molecules on a diagnostics kit the more dependable the diagnostic is, since the results will be statistically significant.

Biosensors can be categorized as point-of-care devices which can bring the capability of analysing clinical samples. With the aim of develop appropriate biosensor technologies, specific markers require to be recognized to ensure specificity of the devices. Biosensors give advanced platforms for biomarker analysis with the advantages of being easy to utilize, low-cost, rapid and robust as well as offering multi-analyte testing capability. For cancer diagnosis multi-array sensors would be useful for multi-marker diagnosis (Tothill 2009).

Biosensors commonly are consisted of:

- The *sensitive biological element* (biological material, tissue, microorganisms, organelles, cell receptors, enzymes, antibodies, nucleic acids…), a biologically derived material or biomimic) The sensitive elements can be formed by biological engineering.
- The *transducer* or the *detector element* (works in a physicochemical way; optical, piezoelectric, electrochemical, etc.) that converts the signal ensuing from the interaction of the analyte with the biological element into another signal (i.e., transducers) that can be more easily calculated and quantified;
- Associated electronics or signal processors that are primarily responsible for the present of the outcomes in a user-friendly way.

Recently, arrays of many different detector molecules have been useful in so named electronic nose devices, where the pattern of response from the detectors is employed to fingerprint a substance. Current commercial electronic noses, though, do not utilize biological elements (Wikipedia).

So as to identify specifically the cancer biomarker, the optimal identification materials should be applied as the receptor molecule in the biosensor design. This is particularly essential for medical diagnosis since the sensitivity and specificity of the sensing molecules will engage in recreation an important part in the success of the sensor device. A range of molecular recognition entities have been applied for biomarker investigation. The most broadly used is the antibody molecule, which supplies the specificity and sensitivity requisite for low levels of molecular detection. More recently, synthetic (artificial) molecular identification elements have been fabricated as affinity materials and used for analyte investigation and analysis. These types of materials can involved nanomaterials and membrane structures and can consist of molecular imprinted polymers (MIPs), aptamers, phage display peptides, binding proteins and synthetic peptides as well as metal oxides materials (Tothill 2009).

Diagnosis methodology based on biosensor as simple and sensitive diagnostics methods can detect multiple cancer biomarkers that are at low concentrations in biological fluids. Biosensors can fulfil these supplies. Though, biosensor devices necessitate to be further developed to face these novel challenges to allow, for instance, multiplex analysis of some biomarkers where arrays of sensors require to be urbanized on the same chip (Tothill, 2009).

The main requirements for a biosensor advance to be important in terms of research and profitable applications are the recognition of a target molecule, availability of a appropriate biological respect element, and the potential for non-refundable portable detection systems to be preferred to sensitive

Laboratory-based methods in cancer diagnosis as well as other detecting and analysing of pathogenic samples and will aid in the rise of the survival rate and successful advance of cancer diagnosis.

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Interview

Interview with a Medical Microbiologist and a Scientist

Dr Mohammad Katouli has an extensive international experience in medical microbiology, infectious disease and pathogenesis of bacteria. Following his PhD and post-doc experience in UK, he worked for three years at the research and development Department of the D.P Pharmaceuticals. In 1983, he took the position of the Head of Microbiology Department at Pasteur Institute of Iran where he conducted a number of nationwide research projects on the aetiology of diarrheal diseases and the prevalence of antibiotic resistance genes among *P. aeroginosa* in burn-injury hospitals.

From 1989, Dr Katouli started working at the Microbiology and Tumor biology Centre of Karolinska Institute, Stockholm, Sweden as a senior research fellow where he worked with many European scientists on several projects including “Pathogenesis of *E. coli* sepsis and bacterial translocation”, “Changes in the intestinal flora of sarcoma patients undergoing cytostatic therapy”, “Characterisation of the gut microflora after inflammation of the intestinal reservoir in pouchitis patients” and “Virulence properties of *E. coli* strains associated with ulcerative colitis”. He was also involved in the development of a microplate-based automated biochemical fingerprinting method for epidemiological investigation of pathogenic bacteria in communities and in hospital settings.

In 1998, Dr Katouli took up a teaching and research position at the University of the Sunshine Coast and established courses in Medical Microbiology and Microbial Pathogenesis. His research areas include molecular pathogenesis of bacterial translocation and the impact of probiotics, epidemiology and ecology of pathogenic clones of bacteria and microbial source tracking. He has been collaborating with many national and international scientists and research institutes and has supervised more than 28 Honours and 18 PhD and four Master students to completion during his scientific career.

Interview

Dr. Katouli has more than 147 peer-reviewed journal articles, reviews, book chapters and conference refereed proceedings in the areas of epidemiology of infectious diseases and pathogenesis of bacteria as related to human and animal health. One of his papers entitled "Bulking fiber prevents translocation to mesenteric lymph nodes of an efficiently translocating *E. coli* strain in rats" published in "Clinical Nutrition" received the 1st prize for the best original article published in clinical nutrition in 1998 at the 21th Congress of the European Society of Parenteral and Enteral Nutrition. The following is interview of EMGEN newsletter staff with him:

Dear Dr. Katouli please briefly introduce yourself and explain your educational background.

My name is Mohammad Katouli, Ph.D. in Microbiology from the University of Ulster, UK in 1980. Served as head of the microbiology department, at Pasteur Institute of Iran for 7 years and spent 11 years working as senior research fellow at the Microbiology and Tumor biology Centre, Karolinska Institute, Stockholm, Sweden. Since 1988 I have been working as senior lecturer in medical microbiology, at the University of the Sunshine Coast, Qld. Australia.

1. Could you please tell us what your main research area is?

a. Molecular mechanism of bacterial translocation and sepsis

b. Molecular epidemiology of antibiotic resistance

c. Probiotics and their mechanism of action

2. Why did you choose such fields?

It was due to my educational background in gastrointestinal microbiology, bacterial interaction, and the exchange of antibiotic resistance genes

3. Do you apply any biotechnology or genomics tools in your researches and please explain how and where?

Biotechnology and molecular biology, yes and the rest, no

4. Are there any biotechnology centers at your place?

Two groups: 1- Microbiology and biotechnology group including environmental biotechnology and bioremediation etc. and 2- Actinomycetes and biodiscovery research group

5. Are there any academic training courses in Biotechnology in there? In which level and how many students are trained annually?

Do you mean biotechnology course in my university or in Australia? If you mean the latter, yes, there are many biotechnology centers and courses around Australia and if you mean my university, also yes we have few courses in biotechnology and molecular biology. We normally have something between 30 and 40 students trained every year

6. Are you familiar with EMRO countries and EMHGBN (Eastern Mediterranean Health Genomics and Biotechnology Network)?

Unfortunately, no.

7. What is your opinion about industrial biotechnology and its development in EMRO countries?

Generally speaking, many countries are now trying to employ biotechnology and biotechnologist at different levels in order to establish a strong scientific and industry backbone.

8. Do you have any suggestions for collaborations with EMRO countries?

Organizing workshops in EMRO countries are probably the easiest way to exchange knowledge, ideas and build up a joint collaborative project. This can be followed by joint international grant applications using EMRO governments as a partner for cash and in-kind help.

9. Do you have any collaboration with biotechnology research centers in EMRO countries?

No

10. Do you have any governmental support for biotechnology in the place you work?

Yes

11. Which kinds of biotechnology facilities do you have in your laboratory and your research center?

Facilities for all types of molecular work

12. What kinds of difficulties do you face, in research and commercialization of medical biotechnology?

These are mainly supported by private enterprise and the details of research are under lock and key. These types of research are normally patented.

13. Are there enough trained biotechnologists in the field of medical biotechnology in your place?

A lot

14. What is your idea about biotechnology and its applications in improving public health?

That's why we work on that. Apart from public health, biotechnology application has now been expanded on environmental health as well.

15. What is your idea about commercialization of researches in the field of bioscience?

This is a tricky business and you have to sort out the intellectual properties issues first before stating doing anything about that. Apart from that, commercialization of the research outcome requires investment.

16. Which problems are we facing in industrial biotechnology?

Environmental pollution, vaccine development and biodiscovery.

17. Are there any late stage biological products to be commercialized in your center? Could you please explain more?

Not now

18. What is your idea about linkage improvement between research and industry?

That's how the system works. Investment by the industry on research and feed back from research to industry.

19. What is your opinion about the development of the biotechnology & genomics in your place?

There are few of them around with different focus.

20. Would you tell us about the differences of biotechnology and its applications between developed & developing countries? What should we do in this regards?

The most important issue is the lack of a long investment policy on basic research and support from private enterprise in developing country due to unstable economical situation.

Dear Dr. Katouli, Many thanks for your kind and useful response. It was a pleasure to meet you and to publish your interview and your ideas about biotechnology in our newsletter. We hope to have more of your useful ideas and cooperation.

How to improve immune response to cancer

A team of researchers at The Campbell Family Institute for Breast Cancer Research (CFIBCR) at Princess Margaret Hospital and international collaborators have revealed how to cause an improved immune response to cancer that could be included new clinical trials that use a patient's own cells to destroy tumors.

The results, available in *Nature Medicine*, express the tantalizing potential of immunotherapy in cancer therapy, says principal investigator Dr. Pamela Ohashi, co-director, CFIBCR.

In the lab study, the researchers combined interleukin-7 (IL-7) a key component of the immune system with a viral vaccine to improve the ability of the cells of the immune system to attack tumors. The consequence was clear: The combination boosted immunity to tumors.

"We are extremely excited because our research has revealed the unexpected ways IL-7 works to break down barriers that naturally block the immune response to tumors. This is important because current vaccine approaches for immune treatment bring on a response in just 1% to 3% of patients" says Dr. Ohashi, a senior scientist in signaling biology who holds a Canada Research Chair in Autoimmunity and Tumor Immunity. She is also a Professor, University of Toronto, in the Department of Medical Biophysics and Immunology".

Dr. Tak Mak, co-author and CFIBCR director, says: "The promise of using the body's own defenses to fight cancer is massive. The day is coming when immunotherapy may help spare cancer patients the toxic side effects of traditional therapies and greatly improve their quality of life while treating the disease. This is why we are planning to increase our immunotherapy research program at PMH." Dr. Mak is also a Professor, University of Toronto, in the Department of Medical Biophysics and Immunology.

This research was also financially supported by grants and fellowships from the Canadian Institute for Health Research, the Ontario Institute for Cancer Research, the Terry Fox Foundation, the National Cancer Institute of Canada, the Boninchi Foundation (Geneva) and the Irvington Institute with the Cancer Research Institute (New York).

Source: http://www.uhn.on.ca/index.htm

E-mail: uhn.info@uhn.on.ca

Genetics alone is poor indicator for drug response

In certain aspects, cells are less like machines and more like people. True, they have lots of components, but they also have lots of personality. For instance, when specific groups of people are studied in total (conservatives, liberals, atheists, evangelicals), they appear to be rather uniform and predictable. But when looked at one person at a time, individuals often break the preconceptions.

Scientists have a tendency to identify characteristics of particular cells by looking at millions at a time.
As a result, they'll find that, say, "group A" responds very well to a particular cancer therapy, whereas "group B" does not. They will then often compare group A to group B to find out why.

But often ignored is that not every cell in either group behaves in ways that the aggregate indicates. In a group of cells shown to be vulnerable to a particular cancer therapy, perhaps 10 percent resist it while 90 percent succumb. While scientists have offered various explanations for this, few have studied it.

Now a group of researchers in the lab of Harvard Medical School Professor of Systems Biology Peter Sorger have studied such "outlier" cells in the context of a new and highly touted cancer drug. They have observed that vastly disparate reactions occur within genetically homogeneous cell groups. These discrepancies result from protein levels that vary from cell to cell, even among cells that are identical genetic twins. What's more, these protein levels and their subsequent traits can be passed down to daughter cellsa heritability that has nothing to do with genetics.

"Genetics are eternally heritable, while these protein levels are momentarily heritable," says Sorger. "But this momentarily inheritance can make all the difference in the world when it comes to the effectiveness of certain medications". These findings are published April 12 online in Nature.

In order to investigate this disparate behavior among cells, graduate student Sabrina Spencer and postdoctoral researcher Suzanne Gaudet, both in Sorger's lab, looked at a molecule called TRAIL, a protein that causes cells to, literally, commit suicide, a process researchers call apoptosis. While TRAIL is a natural cell product, drug makers have been investigating ways to harness its power so that it can directly target cancer cells.

While TRAIL continues to be a promising drug candidate, its success rate isn't 100 percent, and the scientists wanted to figure out why.

The scientists took both malignant and non-malignant cells and exposed them to varying doses of TRAIL. Even though these cell lines were known to be vulnerable to the molecule, a fraction always managed to survive.

The scientists noticed that when this outlier group was isolated and once again exposed to TRAIL, the cells and their immediate progeny continued to remain highly resistant for a short time. An immediate explanation might be that this group had developed some sort of genetic defense. However, when this new "resistant" group was given several days to reproduce, the pattern soon reset to the original: 90 percent died, ten percent survived.

"We knew that there were obviously factors at work here that were not genetic," says Spencer. "Genetic resistance would remain uniform in subsequent generations. But the factors at work here were clearly more dynamic".

Using a diversity of imaging techniques, the scientists discovered soon that even though these cells were genetically identical the same cell in the same tissue doing the same thing, the actual numbers of proteins in each cell varied. Specifically, proteins involved in the cell-suicide mechanism triggered by TRAIL were affected. These protein levels altered the dynamics of the entire mechanism, sometimes making cells, for all intents and purposes, immune to TRAIL. While these protein levels were initially passed on to progeny, the heritability was transient. The researchers describe it as an extra layer of inheritance, one that is superimposed onto genetic inheritance.

As for what actually causes these protein levels to vary between identical cells, the scientists cited a simple explanation: It's completely random.

"For decades biologists have had this notion that cells produce proteins in orderly, uniform ways, like an assembly line, but they don't," says Sorger. "Rather, cells produce proteins in fits and starts, and the timing and degree varies from one cell to the next even cells that are identical in every way. This randomness is something that we're just beginning to appreciate".

These findings also propose an alternative to the cancer stem-cell hypothesis. For that, researchers have posited that certain cancers survive standard therapies because a population of tumor-specific stem cells evades chemotherapy or radiation. This paper, however, offers an alternative explanation, namely, that purely through chance, certain cells produce quantities of proteins that fundamentally alter the cell's response to therapy.

Ultimately, Sorger and his group believe that this new insight will make it possible to design anti-cancer therapies that are more effective than those available today.

Source: http://hms.harvard.edu/hms/home.asp

In the name of ALLAH

Welcome to the **10th Iranian Congress of Biochemistry and the 3rd International Congress of Biochemistry and Molecular Biology**.

The congress, to be held in July 10-14 of the year 2009 in Tehran-Iran, has been organized mainly by Tehran University of Medical Sciences and the Biochemical Society of Iran under the auspices of IUBMB. Similar to its previous counterparts, it is one of the largest scientific gatherings in the country held biannually with the participation of experts, researchers, scientists and students of various fields of life sciences.

Tehran University of Medical Sciences is pleased to be the host of this exciting event and honorably welcomes its guests who with their genuine work in research, and training of hardworking scientists have played their parts well in the overall scientific advancement of their homeland. The participation of a great number of native experts in the congress and presentation of their scientific accomplishments will sure create a precious atmosphere to enable all curious searchers to add to the value and richness of their future scientific activities.

The aim of the congress is to provide an opportunity for scientists from different parts of the world to join together to discuss recent advancements in the fields of life science and related technology and to share their recent accomplishments as they relate to the main topics covered in the congress.

Tehran University of Medical Sciences and the Biochemical Society of Iran respectfully invite all interested scientists and experts to add to the excellence and prestige of this important event by traveling to Tehran and participating in the congress.

We hope to see you there.
Organizing Committee

Congress Topics:

Nanobiotechnology; Application in Clinical Diagnosis and Treatment
Clinical Biochemistry and Biochemical Markers of Disease
Application of Proteomics in Cell and Molecular Biology
Structure, Function and Metabolism of Biomolecules
Modern Techniques in Biomedical Diagnosis
Biochemical Aspects of Herbal Medicine
Trace Elements in Health and Disease
Cellular and Molecular Biology
Molecular Basis of Disease

Webpage: http://www.biochemiran.com/congress10/index.php?&slct_pg_id=10&sid=1&slc_lang=en

Cover picture

Title: Mouse embryonic2 stem cells with fluorescent marker.

Description: Stem cells are cells fjound in most, if not all, multi-cellular organisms. They are characterized by the ability to renew themselves through mitotic cell division and differentiating into a diverse range of specialized cell types. Research in the stem cell field grew out of findings by Canadian scientists Ernest A. McCulloch and James E. Till in the 1960s. The two broad types of mammalian stem cells are: embryonic stem cells that are isolated from the inner cell mass of blastocysts, and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues.
Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.
Source: http://en.wikipedia.org/wiki/Stem_cell

Title: Flow cytometry

Description: Flow cytometry is a technique for counting, examining, and sorting microscopic particles suspended in a stream of fluid. It allows simultaneous multiparametric analysis of the physical and/or chemical characteristics of single cells flowing through an optical and/or electronic detection apparatus.
Source: http://en.wikipedia.org/wiki/Flow_cytometry

Title: MicroRNAs are produced from either their own genes or from introns

Description: In genetics, microRNAs (miRNA) are single-stranded RNA molecules of 21-23 nucleotides in length, which regulate gene expression. miRNAs are encoded by genes from whose DNA they are transcribed but miRNAs are not translated into protein (non-coding RNA); instead each primary transcript (a pri-miRNA) is processed into a short stem-loop structure called a pre-miRNA and finally into a functional miRNA. Mature miRNA molecules are partially complementary to one or more messenger RNA (mRNA) molecules, and their main function is to down-regulate gene expression. They were first described in 1993 by Lee and colleagues in the Victor Ambros lab [1], yet the term microRNA was only introduced in 2001 in a set of three articles in Science.
Source: http://en.wikipedia.org/wiki/MicroRNA