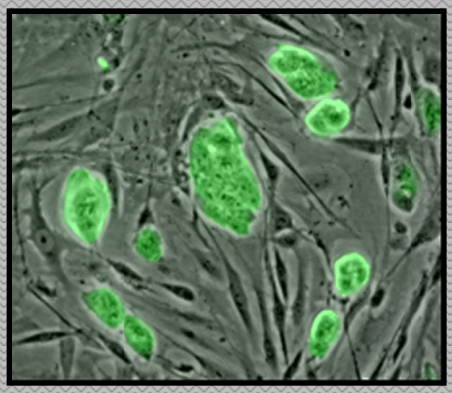

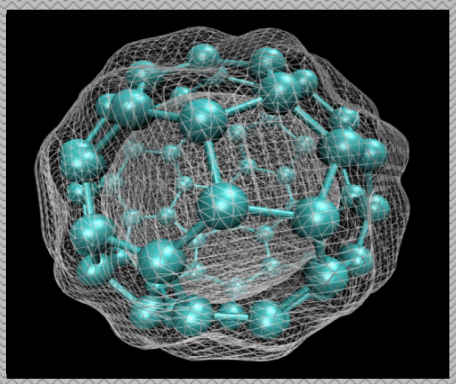

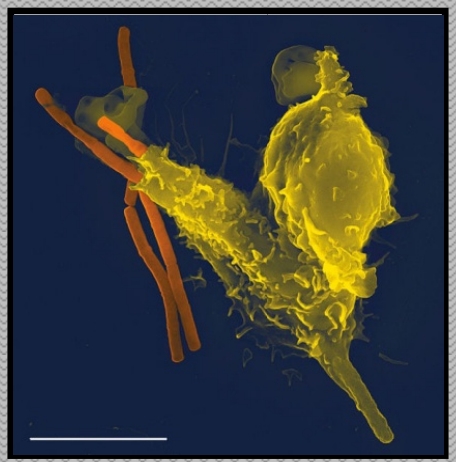

EMHGBN Newsletter

Vol. 2, Issue 4, February 14th, 2008

INSIDE THIS ISSUE:

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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GJB2 (connexin 26) Gene Mutations in Moroccan Patients with Autosomal Recessive non-syndromic Hearing loss and Carrier Frequency of the common GJB2—35delG Mutation

An article entitled "GJB2 (connexin 26) gene mutations in Moroccan patients with autosomal recessive non-syndromic hearing loss and carrier frequency of the common GJB2—35delG mutation" aims to determine the prevalence and spectrum of GJB2 mutations, including the (GJB6-D13S1830) deletion, in Moroccan patients and estimate the carrier frequency of the 35delG mutation in the general population.
The study was done by Omar Abidi, Redouane Boulouiz, Halima Nahili, Mohammed Ridal, Mohamed Noureddine Alami, Abdelaziz Tlili, Hassan Rouba, Saber Masmoudi, Abdelaziz Chafik, Mohammed Hassar, Abdelhamid Barakat. Corresponding author of this paper, Dr. Abdelhamid Barakat, is working in Human Genetic Laboratory, Department of Scientific Research, Pasteur Institute, Casablanca, Morocco and the paper was published in International Journal of Pediatric Otorhinolaryngology (2007) 71, 1239—1245.

Hearing impairment is the most common sensory disorder in humans. A severe defect that presents in early childhood has dramatic effects on speech acquisition and literacy. Later onset of severe hearing defect seriously compromises the quality of life, as the affected individual becomes increasingly isolated socially. Syndromic deafness, i.e., deafness associated with other defects, contributes to about 30% of the cases and may be conductive, sensorineural, or mixed.

In contrast, the prelingual nonsyndromic forms are almost exclusively sensorineural. Autosomal recessive nonsyndromic hearing loss (ARNSHL) accounts for approximately 80% of genetic deafness and shows extensive genetic heterogeneity and therefore understanding the various pathophysiological mechanisms causing hearing loss has an important medical impact.

In this study, we demonstrate that the GJB2 gene is a major contributor to prelingual nonsyndromic sensorineural hearing loss in the Moroccan patients, like in other ethnic groups. The 35delG constitutes the most common pathogenic mutation. Linkage analysis shows that a large consanguineous USH1 family SF11 is linked to the MYO7A/USH1B locus.

We identified the frequently described missense change p.Y1719C. In addition, we found the homozygous c.1687G>A which is predicted to result in aberrant splicing and presumably to loss of MYO7A transcript. We could show that p.Y1719C is not disease causing but represents a frequent polymorphism in the Moroccan population. On the other hand, we performed genome wide homozygosity mapping approach using GeneChip® Human Mapping 10K Array technology, and mapped two families to novel DFNB loci.

Furthermore, a novel locus, DFNB69, on 3p21.1 3p14.2 was identified in family SF33 located to a 9 Mb interval between D3S1588 and D3S3698, with a maximum multipoint LOD score of 3.01. SF27 family was linked to the novel DFNB70 locus on 2p21 2p16. The critical interval of 13 Mb is flanked by the markers of D2S119 and D2S378. Several cochlear expressed candidate genes are currently under investigation in order to find the causative genes and to identify new pathophysiological mechanisms involved in hearing loss.

Dr. Abdelhamid Barakat

Optimization of *Candida rugosa* Lipase Esterase Activity

The article entitled "Optimization of Candida rugosa lipase esterase activity" aims to optimize esterase production of Candida rugosa lipase (CRL). Active culture of C. rugosa (DSM 2031) was revived and the culture medium containing the most frequently used ingredients was optimized using a fraction of factorial design method, Taguchi. The study was done by H. Korbekandi, D. Abedi, M. Pourhossein, M. Motovali-Bashi, M. Hejazi, and M. Narimousaei. M. Kabiri. Corresponding author of this paper, Dr. H. Korbekandi is working in, University of Medical Sciences, Department of Genetics & Molecular Biology, Faculty of Medicine, Isfahan, Iran. The paper was published in Biotechnology. 2007; 6(1):273-277. This journal is accessible through Asian Network for Scientific Information.

We aimed to optimize esterase production of (CRL). Active culture of *C. rugosa* (DSM 2031) was revived and the culture medium containing the most frequently used ingredients was optimized using a fraction of factorial design method, Taguchi. Temperature and pH of the culture was also optimized using one factor at a time method.

Lipases catalyze both hydrolysis and esterification of esters. Lipases can be found in many organisms, but those originated from microorganisms are cheaper and more stable.

The yeast- *C. rugosa* is an important producer of lipase and (CRL) has been used in many biotransformations, detergent making, food and flavor industry.

It has been claimed that CRL poses versatile catalytic reactions, broad specificities, and more applications than any other biocatalyst. It has also been introduced as the best lipase for detergent industries.

Different carbon sources, nitrogen, culture temperatures and pH values have been reported for CRL production and the composition of culture medium influences on the ratio of CRL isoforms, and therefore on the catalytic activity. However, there is a lack of comprehensive optimization procedure for CRL esterase activity. There is also an inconsistency on repressive/inductive effect of glucose on CRL production. Nowadays, CRL is frequently used in esterification biotransformations for production of chiral pharmaceuticals, such as *S*-ibuprofen. Therefore, we decided to optimize esterase production of CRL and clarify the effect of glucose on this issue; to use the enzyme preparation for esterification biotransformations in future study. Active culture of *C. rugosa* (DSM 2031) was revived and the culture medium was optimized using a fraction of factorial design method, Taguchi. Considering the best previous results of the researchers studied lipase production, 9 combinations (L9 orthogonal array) of the major medium ingredients were studied. The factors to be optimized were the following 4 ones in 3 levels: oils, fatty acids, nitrogen sources, and glucose concentration.

Maximum total (internal + external) esterase activity was considered as the response factor. Using Minitab® 14 software, the levels of each factor posing the most influence on the esterase activity, and also the rank of each factor were identified. Temperature and pH of the culture were also optimized by one factor at a time method, using the best combination of Taguchi method.
The optimum combination of the major medium ingredients, in order of their magnitude, was (gl^{-1}): corn steep liquor (CSL) powder (40), triolein (glyceril trioleate) (10), glucose (0) and oleic acid (2). The optimum temperature and pH were 30 °C and 7, respectively.
Using this combination and conditions, the activity of enzyme preparation was increased to 9 Uml^{-1}, which was equivalent to 20611 Uml^{-1} of Sigma® lipolytic activity, with a productivity of 0.362 $Uml^{-1}h^{-1}$. After a semi-purification, in case of using appropriate substrates, this enzyme preparation can be considered as a potent biocatalyst for production of enantiopure pharmaceutical products. It might be concluded that 24 hours after growth in the optimized medium at the optimized conditions, will be the optimum time to extract and purify the enzyme as a biocatalyst for esterase activity.

Dr. H. Korbekandi

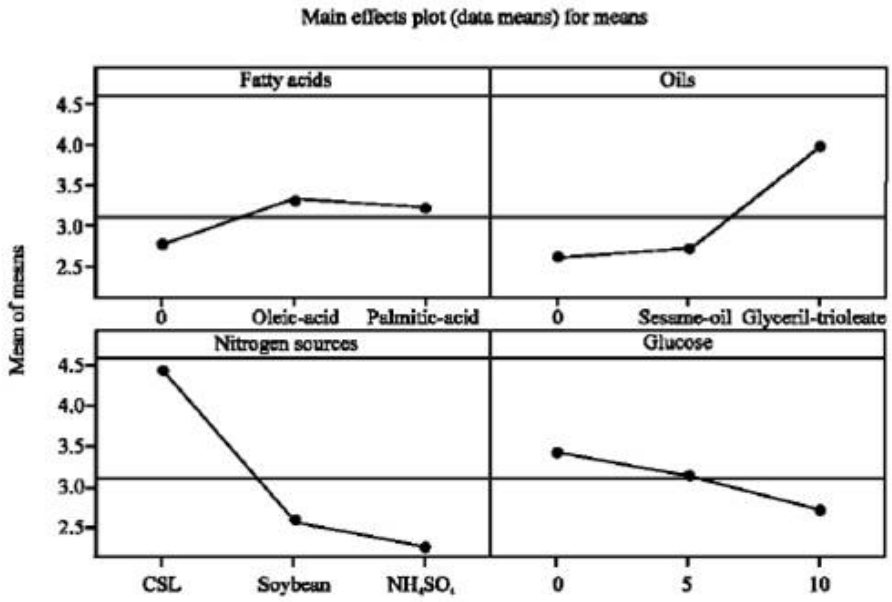


Fig. 1: The mean effects of each factor on total esterase activity. The mean effects of each factor on total esterase activity (the response factor) was plotted by Minitab®14 software

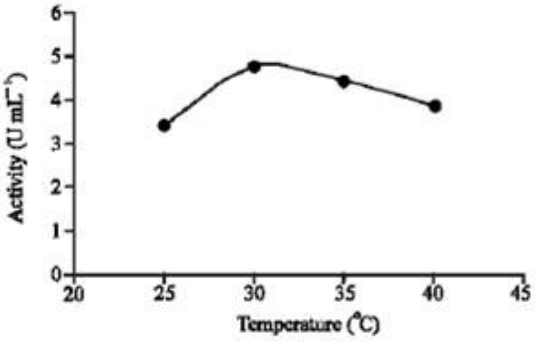


Fig. 2: Effect of different temperatures on esterase

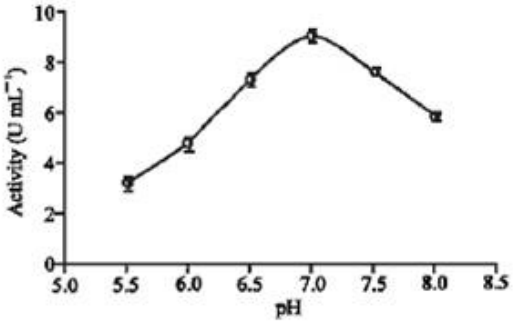


Fig. 3: Effect of different pH values on esterase activity.

Combination Drugs, an Emerging Option for Antibacterial Therapy

Abstract

The rising and sustained resistance to antibiotics and the poor pipeline of new antibacterial is creating a key health issue universally. Bacterial pathogens are increasingly becoming resistant even to the most newly approved antibiotics. A small number of antibiotics are being approved by regulatory organizations, which reveal both the complexity of developing such agents and the fact that antibiotic discovery programs have been ended at several main pharmaceutical companies in the past decade. As a result, the output of the drug pipelines is basically not well positioned to control the increasing army of resistant pathogens, though academic institutions and smaller start-ups are trying to fill that gap. An emerging alternative to fight such pathogens is combination therapy. Combinations of two antibiotics or antibiotics with adjuvant are rising as a promising therapeutic approach. We provide and discuss clinical and scientific challenges to maintain the development of combination therapy to cure bacterial infections.

Introduction

The introduction of β-lactam antibiotics in the 1940s has revolutionized medicine, and is potentially the single most significant factor in the expansion of the human lifespan. The limited variety of antibiotic drug classes allowed an alarming increase and spread of drug resistance among pathogens. Vancomycin, which was one time viewed as the antibiotic of last remedy, has lately been found to be ineffective against some isolates of *Enterococcus*. The same concern is the spread of multidrug resistant *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), which is able to resist up to eight drugs. Moreover, the application of antibiotics in livestock has increased the speed of resistant pathogens emergence and their transfer to humans. Although yet studies are required to fully document the influence of antibiotic use in livestock but strategies to control their application are now being proposed. Mathematical models that predict and simulate appearance of resistance or cell response to antibiotics are now being invented, such studies can be useful to optimize therapeutic regimen and some endorse the combination therapy method. This predictive approach although helpful, will support, but not substitute studies in a laboratory and in clinical settings.

Combination therapy in clinical settings

A small number of combination therapies have reached commercial success to date for the treatment of resistant infections. The combination of a β-lactam class antibiotic, amoxicillin, and the lactamase inhibitor, Clavulanate has led to the invention of a blockbuster drug Augmentin®.

Synercid®, is a combination with a different mode of action; two semi synthetic derivatives of metabolites created by *Streptomyces*, which individually are bacteriostatic, act as bactericidal agents when used in combination. Several studies show that combination therapy could achieve better result than monotherapy for example Chamot et al. reported the results of treating 115 patients infected by *P. aeruginosa* with monotherapy and combination therapy. The researchers concluded that the patient survival was enhanced by combination therapy that was finally followed by monotherapy.

On the other hand, scientists cautioned that controlled therapeutics trial will be necessary to determine whether combination therapy provides superior efficacy. For example, there is evidence for efficiency of some monotherapies over some combination therapies. All these studies demonstrate that the efficacy of combination therapies is to some extent dependent on the pathogen and type of infection.

In addition to the synergistic effect on drug efficiency, combination therapy has the potential to slow the emergence of resistance. In spite of these apparent successes, the combination therapy notion remains to be validated and expanded to other kinds of infectious agents.

Determining *in vitro* combination therapy efficacy

The *in vitro* effect of a combination therapy does not always result in a clear response; in fact positive interaction detected does not always result in an improved therapy in clinical trials.

The *in vitro* methods evaluate effects at static concentrations only, while *in vivo* in patient drug concentrations change owing to variables such as different dosing regimens, absorption rates and elimination rates.

However, quantification of *in vitro* interactions is the beginning for following studies. More information about this issue could be found in the original paper.

Development of novel combination therapies

Combination therapies can be generally classified by four primary modes of action by which compounds can improve the activity of each other.

(i) A second compound (an adjuvant) prevents the degradation or modification of the primary drug (an antibiotic).

(ii) A second compound (an adjuvant) allows the accumulation and retention of the primary drug (an antibiotic) by inhibiting the efflux pumps.

(iii) A second compound (an adjuvant) inhibits the intrinsic repair pathway or tolerance mechanism of cells to the primary drug (an antibiotic).

(iv) A second compound is itself an antibiotic that targets a similar or different pathway that is inhibited by the first antibiotic drug. Drug discovery and development strategies can be planned to exploit these various modes of action.

From genetic concept to chemical proof of concept

Recent works in genomics have allowed many large pharmaceutical and biotech companies to clarify these promising targets. This approach, has not yet delivered any new antibiotics.

In addition, this genomics approach can be complemented by using the genetic pool of nonessential genes. Targeting nonessential genes might result in potentiating antibiotic drugs.

This concept is supported by synthetic lethality. The synthetic lethal phenotype is observed when a combination of mutations in two nonessential and distinct genes results in cell death. Well studied in a systematic fashion in yeast, such a concept is applicable to other microbes.

The objective is to find mutant alleles of two nonessential genes that lead to a lethal phenotype when combined. This genetic concept of synthetic lethality can then potentially be chemically induced: compound A inhibits protein X; compound B inhibits protein Y. In both conditions, the cells are alive while their growth can be weakened; however, the combination of compound A and B results in a lethal mixture. This chemical synthetic lethal approach has been established in *M. tuberculosis.*

The application of transcription profiling technology is a precious and well used platform to identify the transcripts of genes that respond to drug treatments. Primary and secondary pathways targeted by drugs can be discovered as well as pathways involved in the repair of damage caused by drug action. In a study that combined both transcription profiling and the use of conditional mutants, Freiberg et al. constructed a reference compendium of *Bacillus subtilis* expression profiles that could easily identify and confirm the mechanism of action of compounds.

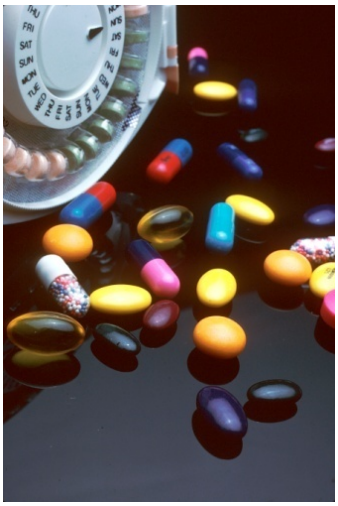
A systematic antibiotic interaction network

There is strong evidence that transcription profiling analysis, jointed with other discovery platforms, can reveal how bacteria respond to antibiotics. The synergistic effect of compounds has newly been studied systematically by Yeh et al. (2006), and Chait et al. (2007)

Although their results might not be completely applicable to a clinical setting, their studies indicate a set of potentially helpful drug-drug synergies.

For example, the protein synthesis inhibitory drugs were classified in to two groups: one group with the drugs that influence the 50S ribosome subunit was established to act antagonistically with the cell wall drugs; while the other group with the drugs that affect the 30S ribosome subunit was found to act synergistically. Their study established known drug–drug interactions, such as aminoglycosides and the inhibition of cell wall synthesis, therefore validated the approach.
Thus, the drug interaction network permits determining mode of action to as yet uncharacterized drugs or to those that have multiple targets.

Current biotech efforts



Chemogenomics might be a valuable approach that could potentially result in the identification of genetic potentiators of antibacterial medicines. We predict that novel classes of targets will be discovered by elucidating the biological processes, such as persistence, that bacteria use to defend themselves from antibiotic treatment.
These approaches are not restricted to bacteria, and they have in fact been used in human cells to recognize gene targets that, once inactivated by RNAi, can diminish cell viability in the presence of a sub-lethal quantity of a cancer drug.

Conclusion

The clinical efficiency of combination therapy has been confirmed for viral infection and for some critical bacterial pathogens such as the TB causing agent of *M. tuberculosis* but not for pyogenic infections. The approach is also being followed to treat fungal infections for which even less therapeutic options exist.

Combination therapy, with the aim to enhance the antibacterial activity of known and effective antibiotics, not only can enhance the activity of known antibiotics but also can probably support the clinical development of agents formerly found to be very effective but excessively toxic for the host. Another benefit is that this approach might result in a shorter and/or lower dosing regimens, which has the potential to decrease the rate of acquirement of resistance in pathogens.

In addition, the financial incentives to develop combination therapies are strong. A reformulation of an existing drug can generate a new intellectual property around a recognized and valuable patent portfolio; thus the effective lifetime of patent protection on existing blockbuster drugs can be extended. Combination therapy can also provide the chance to expand the therapeutic application of the approved drug.

[**Ref**: Guillaume Cottarel and Jamey Wierzbowski, Combination drugs, an emerging option for antibacterial therapy, Trends in Biotechnology Vol.25 No.12, 2007]

Centre of Biotechnology of Sfax

Biotechnology occupies a growing place in the developed countries. This place is primarily due to its significance in the domains of agriculture, food and health.

This does nothing but make more urgent the requirement for countries in the process of development, for which these domains are essential, to be equipped with necessary means to control this technology. Tunisia has crossed this step by the implementation of a biotechnological plan. This plan is materialized by the construction of the Centre of Biotechnology of Sfax (CBS).

The CBS was created by the decree N°83-1037 of November 4, 1983 reorganizing the National Institute of Scientific and Technical Research. Since January 1989, the CBS became an independent institution which budget is attached for order to the state budget.

The CBS main objectives are:

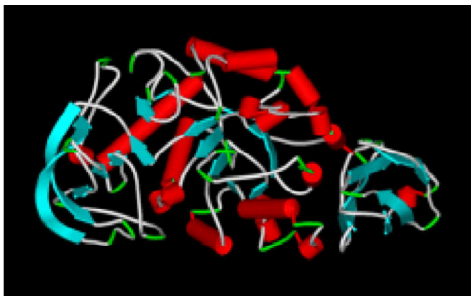
- To enhance the research in the domain of bio- industries
- To develop and adapt the techniques in this domain
- To assist the access for the industrial sector to information of a technological nature
- To provide to local industries the technical support necessary to their development and to the promotion of new industries
- To form technical experts and highly trained researchers and to continue the attempt made for their formation, principally in the domain of biotechnology; this objective is achieved by the organization of advanced courses, seminars, training courses and by the preparation of dissertation in cooperation with local university structures.
- To establish direct collaborations with the developed countries.

Introduction of some Laboratories in Sfax Biotechnology Centre

Laboratory of Enzymes and Metabolites of Prokaryotes

Alpha-amylase production:

These enzymes are involved in bio-transformation of starch, production of specific maltodextrines, in the bakery and in the composition of detergents.



3D Structure of AmyUS100

Alpha amylase of the *B. stearothermophilus* strain (AmyUS100):

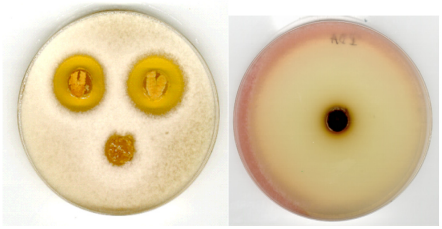
This amylase was isolated and studied from a newly isolated *B.stearothermophilus* strain. This amylase is characterized by its thermostability (T1/2 de 40 mn à 110°C). AmyUS100 is an atypical amylase producing maltohexaose and maltopentaose as major end products of starch hydrolysis. The encoding gene was cloned and sequenced and the analysis of the sequence shows some originalities.

The study of the structure-function relationship allowed us to identify two implicated in the end product of starch hydrolysis. We also succeeded the construction, by site directed mutagenesis, of a derivative mutant more thermostable and having a low demand of calcium (25 ppm instead of 100 ppm for AmyUS100 which is very useful for an industrial application)

Laboratory of Enzymes and Metabolites of Prokaryotes

Antifungal activity detection:

Fungi cause many troubles in the agricultural domain and public health. In agriculture, many damages are results of fungal infection. For the public health, several illnesses are caused by fungi and new non polyenic activities are required more and more.



Detection of Antifungal activities in solid and liquid media

In our study, the selection of *Streptomyces* strains producing antifungal activities having

Agricultural benefit was done using the inhibitory tests against some fungi such as *Fusarium sp, Verticillum dahalea* and fus*arium oxysporum f. sp. Albedinis*. For medical interests, scientists use as indicator organisms, two yeasts *Candida tropicalis R2* and *Candida albicans*.

At this time, researchers have selected 29 *Streptomyces* strains producing antifungal activities.

Actually our effort is concentrated on the studies of six strains which produce high antifungal activities. Among them two, seems to be producing non-polyenic active compounds. Using morphological and molecular techniques, researchers have identified three from the six maintained strains.

There are three new bacteria belonging to the genus *Streptomyces*. We have optimized their culture situation for antifungal activities production, the extraction and the purification of their active molecules. Three pure active molecules were separated from one of the studied strains and their chemical structures were recognized using different spectroscopic techniques. These molecules hold antifungal and antibacterial activities and belong to the macrolide families.

Laboratory of Enzymes and Metabolites of Prokaryotes (LEMP)

Anti-tumors

Streptomyces strains are the source of several anti-tumors activities. We have tried to test the capacity of our collection to produce these kinds of biomolecules.

Until the moment, we have tested about one hundred strains using cytotoxic tests against two specific cell lineages. For this conception, we have performed the culture conditions and concluded a protocol of extraction and concentration of these molecules. From the one hundred tested strains, twenty seven possess cytotoxic activities of which, 10 against the two lineages of the tested cells and 17 against one of the lineages.

[**Ref**: Center of Biotechnology of Sfax, http://www.cbs.rnrt.tn/en_accueil.php.]

Interview with Dr. Ahmed Rebai from Tunisia

First of all introduce yourself and your research area in biotechnology?

I am the director of the Bioinformatics and signalling research unit. Our research group is composed by four senior researchers and twelve PhD and Master Students. Our research activities covers issues in health biotechnology by a reverse engineering approach of signalling pathways involved in complex human diseases and particularly cancer. Currently, for four years our interest has been in Tyrosine kinase (TKR) and nuclear hormone receptors (NHR), two protein families of primary interest in cancer, some of them such as EGFR, Her2 and estrogen receptor, are already used as cancer biomarkers or therapy targets. Our research strategy is based on three complementary components: Bioinformatics, Genetics and Proteomics. We try to look for genome variation or mutation in the receptor genes in tumours (breast and thyroid) and then study their impact on the activity of the proteins by functional genomics and proteomics methods and molecular structure modelling. We also try to model the effect of these variations on the signalling pathways of TKR and NHR and understand the cross talking between these pathways using probabilistic approaches such Bayesian networks and Markov models. We also have collaborations with chemists in order to find new molecules of therapeutic effect that target TKR.

Did you have any research projects in Sfax which led to medical biotechnology products?

Yes, but not in medical biotechnology. We have biotechnology products (enzymes and processes) for bio-industries and the environment that have been patented by our colleagues. Some of them are being used by multinational companies.

Are there any biotechnology products that have been made in your country? (i.e. your native researchers involved in the project)

As far as I know, we do not have any biotech companies neither governmental nor private! The first one to my knowledge is a start-up that have been recently created (end 2007) in our Centre for antibody production.

Would you please explain your cooperation with EMRO countries, in the field of biotechnology and health genomics?

We have collaboration with Kuwait (Faculty of Allied Health) with student exchange, with Egypt, Morocco and Algeria.

Do you have other biotechnology centres in your country?

Yes, we have particularly the Pasteur Institute of Tunisia in biomedical field and the Centre of biotechnology of BorjCedria for plant biotechnology.

Do you have any governmental supports in biotechnology centres in Tunisia?

Yes, the government provides more than 50% of funds.

Which kinds of biotechnology facilities do you have in your laboratories?

We have all the equipments needed for molecular biology, genomics, proteomics and biotechnology. These include facilities for DNA sequencing and genotyping, protein identification (LC-MS/MS), medium-scale production (1-liter fermenter), etc.

What kinds of difficulties do you face, in research and commercialization of medical biotechnology in your country?

The availability of consumables and kits for experimental work in molecular biology. Commercialization is a real issue, but we are not already at this stage.

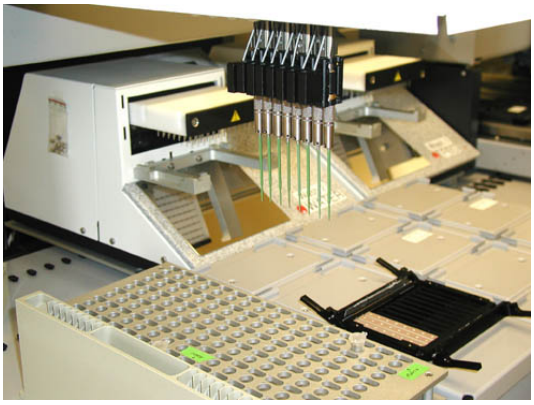
Do you have any training courses or workshops in your research centre?

Yes, this is a major activity of our centre. We organize regularly, courses and workshops on biotechnology and related issues. We already organized, for example an International Bioinformatics courses in 2005. The next big event will be the International Symposium on Biotechnology in May 2008.

Do you have enough trained staffs in the field of medical biotechnology in your country?

I think that we have skilled human resources in biomedical but few of them are concerned with biotechnological issues. We still need specialized persons that can easily move from the lab to the industry.

Biotechnology Time Line



Here is a look back at 10,000 years of biotechnology

8000 B.C.

Humans bring under control crops and livestock.

4000-2000 B.C.

Biotechnology first used to leaven bread, using yeast (Egypt).

1590

Janssen invent the compound microscope.

Ibn al-Haytham is regarded as the father of optics for his influential *Book of Optics*, which correctly explained and proved the modern intromission theory of vision, and for his experiments on optics.

1663

Hooke discovers survival of the cell.

1675

Leeuwenhoek discovers bacteria.

1830

Proteins discovered by Antoine Fourcroy.

1857

Pasteur suggests microbes cause fermentation.

Timeline

1865

Science of genetics start: Austrian cleric, Gregor Mendel studies garden peas and discovers that genetic traits are passed from parents to children in a predictable way-the laws of heredity.

1878

The first centrifuge is developed by Laval.

1888

The chromosome is discovered by Waldyer.

1911

The first cancer-causing virus is discovered by Rous.

1915

Phages, or bacterial viruses, are discovered.

1928

Penicillin discovered as an antibiotic: Alexander Fleming.

1941

The word genetic engineering is first used, by Danish microbiologist A. Jost in a lecture on reproduction in yeast at the technical institute in Lwow, Poland.

1944

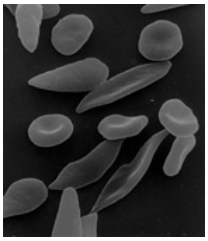
DNA is proven to hold genetic information-Avery et al.

1953

The scientific journal Nature publishes James Watson and Francis Crick's manuscript describing the double helical structure of DNA, which results the beginning of the modern age of genetics.

1956

Kornberg discovers the enzyme DNA polymerase I.



1958

Sickle cell anemia is shown to occur due to a change of a single amino acid.

Also in the 1950s

Discovery of interferon.

First synthetic antibiotic.

Timeline

1960

Messenger RNA is discovered.

1966

The genetic code for DNA is cracked.

1971

First entire synthesis of a gene.

1975

The first monoclonal antibodies are created.

1976

Researchers successfully introduce a human gene-one that codes for the protein interferon-into a bacterium.

1981

The first gene-synthesizing machines are developed.

1986

First anticancer drug produced through biotech: interferon.

1988

Congress funds the Human Genome Project, a massive effort to plan and sequence the human genetic code as well as the genomes of other organisms.

1990

The Human Genome Project-an international attempt to map all the genes in the human body-is launched.

1995

The first baboon-to-human bone marrow transplant is performed on an AIDS patient.

1996

Biogen's Avonex is approved for the treatment of multiple sclerosis.

Timeline

1997

First animal cloned from a mature cell: a sheep named Dolly in Scotland.

1998

Human embryonic stem cell lines are recognized.

2000

Rough draft of the human genome sequence is announced.

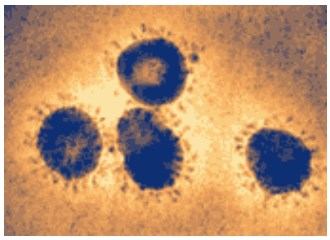
2001

Complete DNA sequencing of *Agrobacterium tumefaciens*.

2002

Scientists are forced to rethink their view of RNA when they discover how important small pieces of RNA are in controlling many cell functions.

2003



The SARS (severe acute respiratory syndrome) virus is sequenced three weeks after its discovery.

2004

The FDA approves the first anti-angiogenic drug for cancer, AVASTIN® (bevacizumab).

2005

Using new genome sequence data, scientists at the Centers for Disease Control & Prevention partially synthesize the flu virus that killed at least 20 million people worldwide in 1918-1919.

2006

A recombinant vaccine against human papillomavirus (HPV) receives FDA approval.

The virus induces genital warts and can cause cervical cancer.

2007

Biologists make skin cells work like stem cells.

[**Ref**: http://www.biotechinstitute.org/what_is/timeline.html, http://www.biotech.org and http://www.biology.iupui.edu/biocourses/Biol540/2bkgrnd6CSS.html].

Announcement

Hamdard International Integrative Medicine Conference 2008

Hamdard Foundation Pakistan
Pakistan Association for Eastern Medicine
Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan

On behalf of the organizing committee Pakistan Association for Eastern Medicine (PAEM), it is with deep regret we announce that Hamdard International Integrative Conference 2008 on Expanding the Horizon of Integrative Medicine to be held on 10-12 March, 2008 at Hamdard University, Karachi, Pakistan has been postponed due to the prevailing situation in Pakistan.

Hk. Qalb-e-Saleem
General Secretary,
Pakistan Association for Eastern Medicine,
Hamdard University,
Karachi, Pakistan.
Web address: http://www.hamdard.edu.pk/hucon2008/

Cover Picture Description (Up to down):

Title: A light programmable biofilm.

Description: According to Who-is-me, this is a biofilm made by the UT Austin / UCSF team for the 2004 Synthetic Biology competition. It displays the "Hello world" message commonly used in sample computer programs. Courtesy of Jeff Tabor and Randy Rettberg
Source: http://en.wikipedia.org/wiki/Main_Page

Title: Mouse embryonic stem cells with fluorescent marker

Description: Embryonic stem cell lines (ES cell lines) are cultures of cells derived from the epiblast tissue of the inner cell mass (ICM) of a blastocyst or earlier morula stage embryos.
Source: http://en.wikipedia.org/wiki/Main_Page

Title: fullerene C60 with isosurface of ground state electron density as calculated with DFT.

Description: The Fullerenes are a family of carbon allotropes named after Richard Buckminster Fuller. In fact, C60fullerene possesses a variety of interesting biological properties, such as HIV-P inhibition, DNA photocleavage, neuroprotection, apoptosis, etc.
Source: http://en.wikipedia.org/wiki/Main_Page and http://pubwww.carnet.hr/ccacaa/CCA-PDF/cca2001/v74-n4/cca_74_2001_743-755_Da-Ros.pdf

Title: A scanning electron microscope image of a single neutrophil (yellow), engulfing anthrax bacteria (orange).

Description: Neutrophil granulocytes, generally referred to as neutrophils, are the most abundant type of white blood cells in humans and form an integral part of the immune system.
Source: http://en.wikipedia.org/wiki/Main_Page