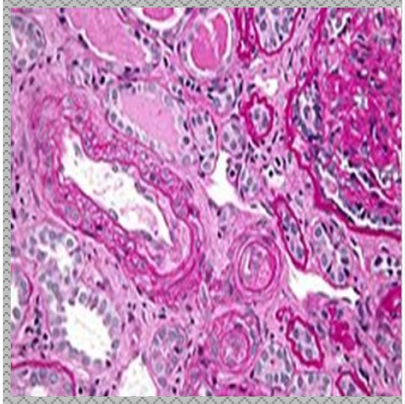

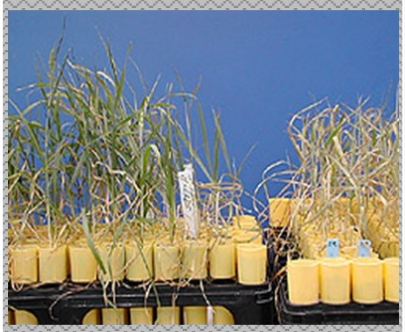

EMGEN Newsletter

Vol. 5, Issue 3

IN THIS ISSUE:

Eastern Mediterranean Health Genomics and Biotechnology Network (EMGEN) 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. Sponsored by Iran Biotechnology Development Council.

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Article

The paper entitled: "Microbial biotechnology for decolorization of textile wastewaters" which is published in Reviews in Environmental Science and Biotechnology summarizes the findings of recent studies directed on decolorization of raw textile wastewaters. This is the only review reporting the biodegradation of azo dyes in raw textile sewage. Physicochemical and biological tactics have been invented to remove dye pollution from such wastewaters. The study was carried out by Dr. Muhammad Imran from the Department of Environmental Sciences, University of Gujrat, Pakistan and et al.

Wastewater emanating from the textile industry is one of the main origin of contamination for groundwater and surface waters in countries where textiles and other dye-products are made. Biotechnological approaches have attracted worldwide consideration for their relative cost-effectiveness and environmental friendly nature. During recent years, various microbial cultures such as microbial enzymes have been specified and applied for eliminating such dyes from simulated wastewaters which having determined chemical combination. However, there are still very challenges in promoting this microbial and enzymatic technologies for discoloring of raw textile wastewater that possess metals, salts and other toxic combinations.

Azo dyes contains one of the greatest classes of synthetic dyes that are widely used in the textile industry and indicate about 80 % of commercial dyes manufactured in the world with an annual production of 7×10^5 tones. In developing countries, textile wastewater comprising azo dyes is mostly consume to drench Agricultural products , which adds detrimental azo dyes to agricultural soils. Keeping the widespread use and harmful effects of azo dyes in view, their elimination from the wastewaters is a topic of concern in recent research.

Although, some of physicochemical procedures are applied to cure dye contaminated wastewater in developed countries, they are scarcely applied in developing countries where textile products are made in hundreds of small factories. Physical method produce solid absorbent which their disposal is a big problem and the use of chemical methods has limited applicability due high cost. Alternatively, the use of microorganisms for decolorizing textile wastewater is remarked relatively affordable. Once, microorganisms added to waste water it reproduces itself further; and also, the biological approach will eliminate pollution completely.

Research with simulated wastewater show that the amount of destruction of the dye by microbial cultures and purified enzymes differs depending on the anatomy of the dye molecule. The degradation usefulness of different microbial cultures may be repressed when practiced to the raw sewage. In this review, Dr. Muhammad Imran and et al. evaluated the potential of microbial processes for the treatment of raw sewage discharged by textile units including:

1. Physicochemical characteristics of textile raw wastewater like chemical diversity of azo dyes in textile effluent, soluble salts, heavy metals, high temperature, variable pH, high biological oxygen demand (BOD), and chemical oxygen demand (COD).
2. Using of biotechnology for the treatment of colored textile wastewater like action mode and microbial enzymology for decolorizing colored wastewater (Azoreductases, Lactases, and Peroxidases), potential of microbial activities to discoloring raw textile wastewater (wastewater treatment by pure fungi or bacteria cultures), and finally, wastewater treatment by mixed microbial cultures.
3. Wastewater treatment by microbial enzymes.

Wastewater discharged by the textile producing industry is a twisted blend of various materials that companion in a big diversity of dyes with various chemical compositions. Thus, finding specific organism and understanding of its role is important to omitting waste water contamination. In addition, genetic and biotechnological solutions for producing more resistant and effective methods all will build on understanding of available solutions.

BACTERIAL APPLICATION IN CANCER THERAPY

Nowadays, there is a different look at bacteria than in the past. They are more than little devilish pathogens, they have converted to our new, excellent, multipotent devices. Their role extended from mines for bioleaching to application into the human body i.e. new strategies for cancer therapy. Bacteria have been utilized with different manners in battle against the cancer and tumor cells.

Bacterial cancer therapy is not a novel viewpoint. There is almost hundred years history beyond use of bacteria as an anticancer therapeutics. The physician, William B. Coley was one of the pioneers for use of bacteria in cancer therapy with well documented works. He had observed neck cancer regression in one of his patients after erysipelas infection. Consequently, he began to investigate about bacteria and their toxins effects on cancer therapy. At the end of 18th century, Coley created a vaccine derived from *Streptococcus pyogenes* and *Serratia marcescene* calling Coley's toxin, for simulate infection with purpose of treat cancer without risk of actual infection. The vaccine became popular in medical society and was widely used to treat various range of cancers such as sarcomas, carcinomas, lymphomas, melanomas and myelomas with successful results.

According to a recent comparative study, the ten years survival rate for persons who treat with Coley's toxin is same as persons who treat with other conventional non-radiotherapeutic cancer therapy methods in 1983.

After Coley's observations, other researchers which understand the important role of bacteria in cancer therapy, discovered that several bacterial genera could accumulate in tumor tissues. This finding provided logical base to investment on apply of bacteria in cancer therapy over the past.

The accumulating bacteria could divided into two primary classes according to oxygen metabolism, the first one comprise of obligate anaerobes such as Bifidobacteriums and Clostridiums, second group comprise of facultative anaerobes such as *Salmonella*, *Escherichia* and *Listeria*. Anaerobic strains because of special anaerobic condition in necrotic regions of tumors have potential to live and generate in these regions. These bacteria with some manipulation by genetic or metabolic engineering, will acquired competency to apply in cancer therapy as a vector or a competitor for supplements. Tumor microenvironments are safe room for such bacteria in human body because of immune system restricted ability to access and nutrition enriched environment of tumors. Actually, bacteria could colonize 10000 times faster in tumor niches compared with healthy tissues. Moreover, with aid of flagella exist in bacteria, they could to penetrate in out of hand regions for conventional drugs such as regions far from vasculature.

After colonization, bacteria continue to produce and release therapeutic proteins or toxins in tumor regions. These products must be toxic for cancer cells. In strategies based on protein secretion, smaller proteins keep production in higher rate. Protein coding sequence can be achieved. By the way, there is different secretion pathways in bacteria that can be used based on condition. The lethal therapeutic proteins concentration in tumor environment could grantee by long-term secretion from bacteria. the final volume of protein released by bacteria related to protein and applied secretion pathway. The other strategy to release protein from bacteria is inducing the bacteriolysis. It can be achieved by expression of lysis genes of phage which is inserted into the bacteria genome.

Regulation of expression of these genes by inducible promoters allow control of gene expression in appropriate time and condition. For delivery of cytotoxic compounds by bacteria, gene expression under precise control is critical. Several chemicals or irradiations can activate inducible promoters. There are several bacterial inducible gene expression systems which respond to chemicals that are safe and do not produce in human body naturally. Live attenuated bacteria could be used as a vector to delivering cytotoxic genes. Bacteria are considered as a mammalian cell vectors to delivery genetic materials. *Listeria monocytogenes*, *Escherichia coli* and *Salmonella* spp. have been used as DNA vaccine-based vectors. *S. choleraesuis* that is carrying Thrombospondin-1 gene, significantly inhibit tumor growth when used to treating primary melanoma. The anti-tumoral effect of an attenuated *Salmonella typhimurium* strain that carry a recombinant plasmid known as DIABLO was evaluated with tumor growth inhibition by 70-90%, so it is proposed as an antitumor strategy.

One of the proteins with anticancer activity is FASL but it cannot be administered systemically because of its lethal liver injury and apoptosis induction. FASL express in *Salmonella* successfully suppressed 59 and 82% of D2F2 and CT-26 tumors respectively.

Although, immune system has important role in cancer treatment; however, cancerous cells have strategies to escape the immune system. Loss of MHC class I molecules on the cancerous cells or blocking the immune system by production of TGF and IL10 are two well-known examples of two strategies. There are some novel cancer treatment strategies based on immune therapeutics.

The immune system responses trigger by use of attenuated *S. typhimurium*. Melanoma could be under invasion by *S. typhimurium* successfully and immune response could be observed. Experimental melanomas prohibited growth exhibition caused by genetically engineered attenuated strain of *S. typhimurium* with murine cytokines expressing capacity. *C. novy* is a famous bacteria to induce inflammation and leukocytosis. The inflammation has well-known antitumor effects.

Tumor cell destruction by reactive oxygen species production, proteases and other degradative enzymes activities occur during inflammation. Therefore, it is not surprising that *C. novi's* NT spores destroy adjacent cancer cells. It is reported that, phase I clinical trial are underway for use of LM-LLQE7 produced by recombinant *Listeria monocytogenes* as an immune therapeutic agent for cervical cancer. Bacteria could be used as an adjuvant for immune therapy for cancer cells, to this aim there are options such as *Mycobacterium bovis* and *Bacillus calmette*. All of these indicates great potential of bacteria as immune therapeutic agents at cancer therapy.

Bacteria have incredible property for production and it is well-known for every scientist work in life science, so use of their products such as enzymes, toxins and secondary metabolites are another applications of bacteria in cancer therapy. Bacterial toxins could be very powerful with high cytotoxic potential, actually, some of them have the highest rank among toxins has found in nature. One method to use of them against tumor cells is producing chimeric proteins comprise of bacterial toxins and monoclonal antibody to cancer cell diagnosing.

The most commonly used toxins for cancer therapy include Diphtheria toxin and exotoxin A from *Corynebacterium diphtheria* and *Pseudomonas aeruginosa* respectively. This products have high toxicity because of protein synthesis inhibition by EF-2 inactivation. To safe use of them in human body, several modifications of these have been applied. A large number of proteins and peptides have been described with anticancer activities which produces by bacteria. SSL10 and approved SSL5 are super-antigen like proteins with anticancer activities approved by *in vitro* tests.

Romidopsin and Spiruchostatin B are structurally related peptides which display anticancer activities. Sometimes, peptide engineering could help to design more efficient products against cancerous cells. For example, Pep 27 anal 2 analog of pep 27 is a peptide extracted from *Streptococcus pneumonia* which plays a role in cell death programming. The minimum content for anticancer activity begins at 70 micromole. With help of peptide engineering methods by amino acid substitution, anti cancer activity begin at 30 micromolar. There are several US patent related to cancer therapy with use of Azorin and Laz protein. Azorin is a small cooper protein which produce in *P. aeruginosa* and Laz is a surface exposed, Azorin-like protein produce in Gonococci and Meningococci. Azorin do the duty by stabilizing tumor suppressor p53 protein.

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APTAMERS

Aptamers are single-stranded amino acid or nucleic acid polymers that identify and attach to targets with a great affinity and selectivity. Nature uses these molecules before we recognize them. In fact, Riboswitches, regulatory segment of messengers RNA resulting in a change in production of the protein encoded, also can be considered as aptamers.

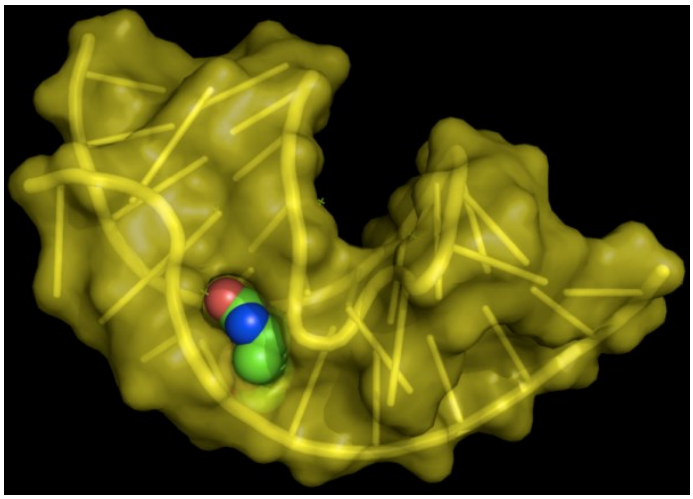

Figure 1. Structure of an RNA aptamer specific for biotin. The external view and backbone of aptamer are shown in yellow.
Biotin (spheres) fits into the RNA surface.

Function correlation of DNA and RNA based compounds of aptamers experimented. DNA aptamer is analogue of RNA aptamer with thiamin replacing uracil; but, thrombin, interferon, prostate specific antigen DNA and RNA aptamers have unique sequence.

These molecules produced by selecting them from a great accidental sequence reservoir. Systematic Evolution of Ligands by Exponential Enrichment (SELEX); besides, reference to as *in vitro* selection or *in vitro* evolution, is a combinatorial technique in chemistry and molecular biology for generating oligo nucleotides of both single-stranded DNA or RNA that obviously bind to a target ligand or ligands.

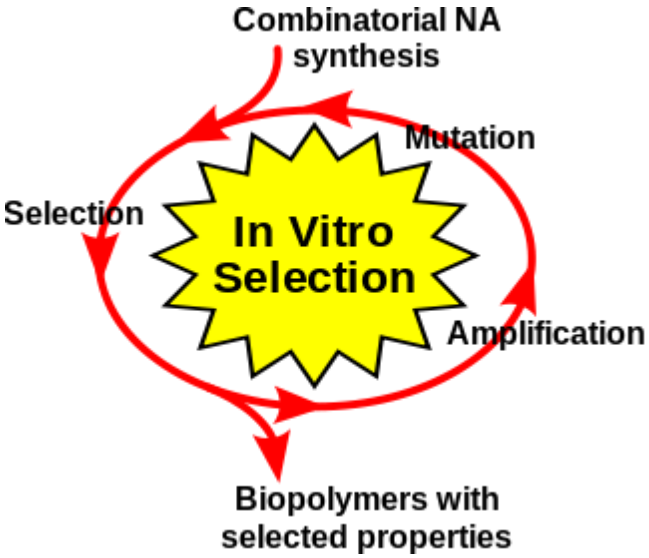

Figure 2. A general overview of *in vitro* selection protocol for aptamers. NA stands for Nucleic Acids which start as a random pool, and are enriched through the selection process.

SELEX technique has several divisions for optimize its use; also, we have AptaBiD or Aptamer-Facilitated Biomarker Discovery (AFBD) which is a technology for biomarker discovery. AptaBiD is based on multi-round genesis of an aptamer or a reservoir of aptamers for discriminant molecular targets on the cells which assist descriptive detection of biomarkers. The significant specification of the AptaBiD technology is that it produces aptamers simultaneously with biomarker discovery and aptamers are developed for cell surface biomarkers in their native state and conformation.

Peptide aptamers composed of a changeable peptide loop attached at both ends to a protamersein scaffold. The length of a peptide is usually 10 to 12 amino acids, scaffold may be any protein.
Currently, most used peptide aptamer selection method is the yeast two-hybrid system. The peptide aptamer can also be chosen from synthetic peptide libraries created by phage display and other surface display technologies such as ribosome display, yeast display, bacterial display, and mRNA display.

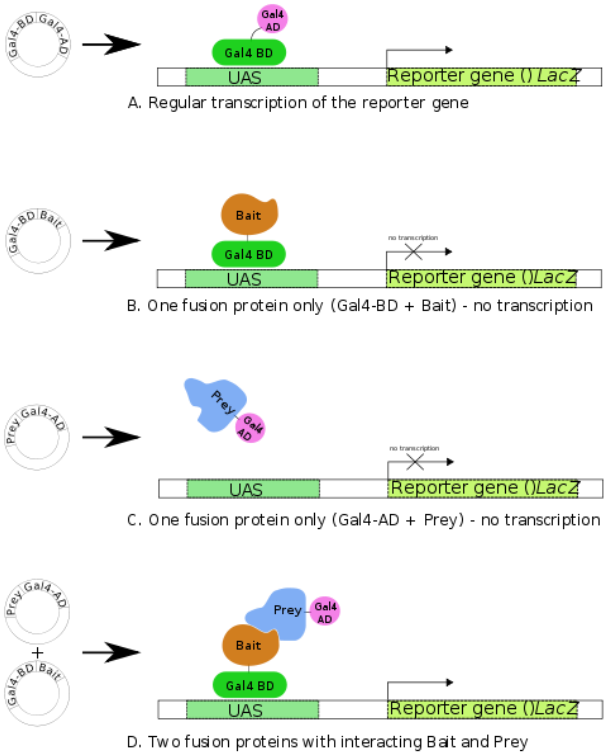

Figure 3. Overview of two-hybrid assay, checking for interactions among two proteins, named here Bait and Prey. **A.** Gal4 transcription factor gene translates two domain proteins (BD and AD), which are necessary for the transcription of the reporter gene (LacZ).

B,C. Two combined proteins are ready: Gal4BD+Bait and Gal4AD+Prey. Any of them, lonely is not enough to begin the transcription (of the reporter gene).

D. When both fusion proteins are generated, the transcription process of the reporter gene will began.

Advantage of these molecules over antibodies include: Engineered completely in test tube, produced by chemical synthesis, possess desirable storage properties, show little or non immunogenicity, small sized aptamers can easily and effectively get entered into the biological sections, non-modified aptamers can be cleared quickly from the bloodstream, mainly owing to nuclease degradation and elimination from the body by the kidneys, a result of the aptamer's low molecular weight, several modification are available to increase the serum half-life to day or even week time scale.

Aptamers databases were developed in the internet as resources for all *in vitro* selection and SELEX experiments. These resources are provided to collect, organize, and distribute all the known information regarding aptamer selection.

Smart aptamers include aptamers selected with defined equilibrium, rate constants and thermodynamic parameters of aptamer –target interaction. Kinetic capillary electrophoresis is a novel method applied for the selection of smart aptamers. It obtains aptamers in a few rounds of selection.

The first aptamer based drug was developed for age related macular degeneration (AMD) and called Macugen. In agriculture, the first aptamer based diagnostic platform for parsing of mycotoxins developed in grain. Imaging, tenascin-binding aptamer is presented for cancer imaging due to rapid clearance advantage of aptamers. Also, unmodified aptamer applications are centralized on solving the momentary conditions e.g. blood clotting or treating organs e.g. the eye where positional transfer is feasible.

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UNIQUE NANO-CAPSULES PROMISE THE TARGETED DRUG DELIVERY

The scientists have become busy with drug delivery systems for a long time, as the benefits of this method are numerous. A lot of "nano-carriages" for drug delivery to the correct target were produced, but the scientists still confront many challenges. One of these challenges is how to avoid a medicine to act before it reaches to its target in the body.

"Many accessible carriers encapsulate drugs through the long-distance electrostatic interplays; the carrier attracts oppositely charged drug. Our technique does not cope with the electrostatics in any way. Filling in the nanogel by the exotic molecules, locking them in the pore and subsequent discharge are restricted by the temperature. Hence, the drugs can be charged or neutral" declares one of the co-researchers, Professor Igor Potemkin.

According to the researchers, there are other tools to generate the discharge of drugs, for example, a peripheral magnetic field and pH. But in every case researchers confront the problem of effectiveness of the drug discharge.

The scientists tried to unravel this problem by construction a carrier, which its inner cavity, like an egg with two shells, is enclosed by two "membranes" of various chemical compositions. The outer permeable shell plays a protecting role and prevents congestion of the nano-capsules, while the pores of the internal shell can be open and close conditional on the temperature due to the unstable exchanges between its monomeric units.

The inventor is confident that in every case the produced nano-containers are the perfect carriers for targeted drug delivery. Furthermore, their synthesis is neither difficult nor actually costly. While at undergoing phase of research it is hard to state the exact cost, the cooperation strategies already comprise the construction of the large-scale, commercially suitable manufacture of nanogels.

Reference: https://www.sciencedaily.com/releases/2016/05/160504121448.htm

NEW CANCER DRUGS COULD TREAT LETHAL RESISTANT PROSTATE CANCERS

Men with progressive prostate cancer that has stopped reacting to conventional therapy could potentially be curved by a new category of cancer drugs created to conquer drug resistance. Researchers realized that the drugs, called Hsp90 inhibitors, purposely aim and disable a mechanism normally applied by prostate cancer cells to escape the effects of normal treatment. The results show very important information about the function of Hsp90 in drug-resistant prostate cancers, and open up new paths to cancer treatment based on blocking this or related proteins.

A team at the Institute of Cancer Research, London, found that Hsp90 inhibitors inhibited the effect of dysfunctions in the androgen receptor, which regularly happen in resistance to hormone therapy. The research proposes that Hsp90 inhibitors could be useful in prostate cancers that have turned out to be resistant to therapy and begun spreading in the body. Hsp90 inhibitors are among the inventive new types of therapy planned to attack cancer not directly, by destabilizing numerous diverse proteins necessary for the growth and endurance of cancer cells.

Hsp90 inhibition also hampered generation of atypical forms of the androgen receptor, covering cancer cells against hormone therapy. Prostate tumors need male hormones called androgens to grow and spread, and obstructing androgen receptors can be an efficient therapy. Though, cancer cells regularly produce atypical forms of the androgen receptor that can be switched on permanently without the need for androgen hormone stimulation. Hsp90 inhibition also decreased the levels of the ordinary androgen receptor, and other significant prostate cancer molecules called AKT and GR.

Study co-leader Prof. Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"We name Hsp90 inhibitors 'network drugs' since they fight with several signals of the cancerous cells all together, across a network instead of just a single signaling pathway. These drugs can strike cancer harder than those targeting only one protein, and seems talented for prohibiting or overcoming drug resistance. This study showed that Hsp90 inhibition can purposely stop resistance to hormone treatments in prostate cancer, throughout a totally new mechanism of action relating the processing of messenger RNA."

Reference: https://www.sciencedaily.com/releases/2016/05/160501142556.htm

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TITLE: Thrombotic microangiopathy

Thrombotic microangiopathy (TMA), is a chronic disease which results in thrombosis in blood vessels, because of an endothelial damage. This disease may occur with other disease such as purpura, anemia, thrombocytopenia and disability of kidneys.

The classic TMA causes by thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Other causes of TMA are extreme hypertension, diffused intravascular coagulation, antiphospholipid antibody syndrome, atypical hemolytic uremic syndrome, scleroderma renal tension, and drug toxicities, e.g. calcineurin inhibitor toxicity.

The particular etiology is associated to the type of TMA, but the two major causes of TMA are extrinsic factors (e.g. viruses, endo and exotoxins, antibodies, drugs and etc.) and hereditary elements (e.g. shortages or lack of clotting factors, and etc.). Each of these will cause damage to endothelium, decreased endothelial thrombo-resistance, complement consumption and abnormal vWF fragmentation disorders.

Reference: https://en.wikipedia.org/wiki/Thrombotic_microangiopathy

TITLE: Plant breeding and plant Pharming

One of the methods to produce recombinant proteins is using plant biotechnology. This method can produce biopharmaceuticals and protein vaccines. Plant breeding is the science and art of modifying the nature of plants in the event of generating favorable traits. Plant breeding can be achieved through various methods including simple selection of plants with favorable traits for proliferation, to more intricate molecular techniques. Plant breeding is an ancient procedure which has been experienced for too many years, close to beginning of human civilization. It is used universal by people such as gardeners and farmers, or by professional plant breeders. International R&D companies daresay that producing new crops is fundamental for warranting food security by expanding new species that are resistant to pests and diseases, higher-yielding, drought-resistant or regionally suited to various environments and growing situations.

Plant breeding began with nonimmigrant agriculture and solely the domestication of the ancestor agricultural plants, an operation which is guesstimated to date back about 10,000 years ago. In the beginning, early farmers simply chose edible plants with specific favorable specifications and used these as predecessors for subsequent descendants, lead to an accumulation of noteworthy traits over time.

Gregor Mendel's experiments with plant hybridization caused his creating laws of inheritance.

When his works became when informed, it created the basis of the new science of genetics, which agitated the research by many plant scholars worldwide appropriated to improving crop production through plant breeding. Modern plant breeding is using genetics, but its scientific background is more extensive, covering molecular cytology, entomology, chemistry, biology, pathology, physiology, and statistics (biometrics).

Reference: https://en.wikipedia.org/wiki/Plant_breeding
https://en.wikipedia.org/wiki/Pharming_%28genetics%29

TITLE: Immunology

Immunology is a sub-branch of medical science that covers the research in all perspectives of the immune system in all creatures. It is associated with the physiological operation of the immune system in all aspects of the health and diseases; immune deficiency, malfunctions of the immune system, the physical, chemical and physiological specifications of the ingredients of the immune system *in vivo, in vitro*, and *in situ*. Immunology has usages in different fields of science.

Even before the advent of science of immunology, a large number of early physicians have identified too many organelles of the body which could have a significant effect on the immune response. The most important and primary lymphoid organs of the immune system are bone marrow and thymus, and auxiliary lymphatic tissues are liver, lymph nodes, lymph vessels, spleen, tonsils, adenoids, and skin.

The immune system cells are a group and in some cases a subdivision of the adaptive immune system (vs. innate immune system ; e.g. skin) which do their duty by phagocytosis and secreting antibodies in the body against pathogens and their toxins.

Reference: https://en.wikipedia.org/wiki/Immunology