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Occupational exposure to antineoplastic agents

The adverse health effects associated with antineoplastic agents in cancer patients and some others treated with these drugs are well documented. Cyclophosphamide, ifosphamide, paclitaxel and methotrexate confer significant health risks such as immediate nervous system effects, acute and long-term reproductive effects, liver, lung, heart and kidney damage, hearing impairment and subsequent risk of haematological malignancies.

For cancer patients with a life-threatening disease, there is certainly a great benefit to treatment with these agents. However, for the health care workers who are exposed to antineoplastic agents as part of their work practice, precautions should be taken to eliminate or reduce exposure as much as possible.

Pharmacists who prepare these drugs or nurses who may prepare and/or administer them are the two occupational groups who have the highest potential exposure to antineoplastic agents. Additionally, physicians and operating room personnel may also be exposed through the treatment of patients. Hospital staff, such as shipping and receiving personnel, custodial workers, laundry workers and waste handlers, all have potential exposure to these drugs during the course of their work.[1]

Antineoplastic agents

The International Agency for Research on Cancer (IARC) in Lyon, France has identified a number of antineoplastic agents and two combination therapies as having an association with cancer in patients who are treated with them. These include both cancer and non-cancer patients. IARC currently lists eleven agents and two combined therapies as Group 1 (Human carcinogens), twelve as Group 2A (Probable human carcinogens) and eleven as Group 2B (Possible human carcinogens) (Table 1).

Effects of occupational exposure

Acute effects

The most frequent acute toxicities noted include nausea, vomiting, headaches, dizziness, hair loss, and liver damage. These acute symptoms were positively correlated with the number of doses handled and the use of protective equipment. Additionally, body mass was significantly associated with the development of acute symptoms. Hepatocellular damage was noted in nurses employed on an Oncology Unit. This symptom was associated with the employee's duration of work exposure and the volume of handling.[2]

Long term effects on fertility and reproductive outcomes

Exposure to chemotherapeutic agents poses a significant risk to female reproductive health. The literature reports the incidence of such reproductive deficits as infertility, spontaneous abortions, fetal abnormalities, and menstrual cycle abnomalities.[3–6]

It has been found that women exposed to antineoplastic drugs during the first trimester of pregnancy were more than twice as likely to experience fetal loss as women who were not exposed and carried their pregnancies to full term. Stucker *et al.*.[7] showed a relative risk of 1.7 (95% CI = 1.0–2.8) among nurses who, on average, prepared and administered 18 chemotherapy infusions per week without personal protective equip-

In this issue

ment. Valanis and colleagues[8,9] reported that spontaneous abortions were associated with chemotherapy handling during pregnancy (Odds ratio [OR] = 1.5; 95% CI = 1.2–1.8).

Several additional negative reproductive outcomes have been noted following cytotoxic drug exposure. Savitz *et al*[10] found that women who were occupationally exposed to antineoplastic agents reported an increased risk of preterm deliveries and small-for-gestational-age births. This study did not delineate, however, whether the noxious drug exposure was pre-conception or during pregnancy. The effects of potential chromosomal aberrations are reflected in increased incidences of miscarriages and malformations in offspring. Two studies of nurses occupationally exposed to cytotoxic drugs showed relative risks for miscarriages of 2.3 and 1.7 respectively.[11,12]

Hemminki *et al*.[4,5] found an OR of 4.7 for malformations in the offspring of nurses handling cytotoxic agents.

Genetic effects

Genotoxic activity of some antineoplastic agents in humans has been noted in both patients treated with the agents as well as those healthcare personnel administering the agents.[13,14] The incidence of DNA single-strand breaks in peripheral mononuclear blood cells was 50% higher in nurses not utilising recommended safety precautions.[15,16]

This finding is significant since other major carcinogens, such as exposure to smoke, present with the identical DNA strand breaks.[16]

Chromosomal aberrations were also noted in nurses and physicians handling antineoplastic drugs. The length of handling exposure was the predominant factor that correlated with the degree of chromosomal damage.[17]

Table 1. Antineoplastic agents classified as known or probable human carcinogens

Group 1 (Human carcinogens)	Group 2A (Probable carcinogens)	Group 2B (Possible carcinogens)
Arsenic trioxide	Azacitidine	Amsacrine
Azathioprine	BCNU	Azaserine
Chlorambucil	CCNU	Aziridine
Chlornaphazine	Chlorozotocin	Bleomycin
Cyclophosphamide	Cisplatin	Dacarbazine
Myleran	Doxorubicin HCl	Daunomycin
Melphalan	*N*-Ethyl-*N*-nitrosourea	Mitomycin C
Semustine	Etoposide	Mitoxantrone
Tamoxifen	Mechlorethamine HCl	Sreptozocin
Thiotepa	*N*-Methyl-nitrosourea	Uramustine
Treosulfan	Procarbazine HCl	
Mustargen-Oncovin-Procarbazine-Prednisone (MOPP)	Teniposide	
Etoposide-Cisplatin-Bleomycin (ECB)		

Adapted from the International Agency for Research on Cancer. [13]

Association of exposure to antineoplastic agents with cancer

There are a few case reports that have appeared in the literature and two epidemiological studies that address this issue. In addition, Sessink et al[18] have calculated the risk of excess cancer in workers exposed to cyclophosphamide.

Minor amounts of cyclophosphamide were reported in the urine of pharmacy technicians and nurses handling the drug even when taking special safety precautions.[19] Another study showed surface wipe samples with measurable cyclophosphamide even away from the handling site.[20] These studies strongly implicate the importance of skin absorption as an exposure route. Also accidental spillage is never completely avoidable.[21]

An increased risk of malignancy, predominately leukemia, among healthcare workers in general has been previously reported.[22-24]

Blair and colleagues[4] reported that hospital workers were 2.9 times (95% CI = 1.4–6.9) more likely to

develop acute myelogenous leukemia than non-hospital workers in the Iowa area of the US. The literature regarding the risk of cancer among healthcare personnel who handle antineoplastic drugs is limited and has focused predominantly on leukemia. Skov *et al.*[25,26] reported a non-significant increased risk of developing leukemia among physicians who handled chemotherapy (relative risk [RR] = 2.85; 95% CI = 0.51–16.02).

A significant increased risk for leukemia was noted among oncology nurses who handled chemotherapy agents (RR = 10.65; 95% CI = 1.29–38.5).

There is a wealth of information in the literature regarding occupational chemotherapy exposure and elevated levels of nonspecific markers for carcinogen exposure, such as sister chromatid exchanges and chromosomal aberrations.[19,27-32] Sister chromatid exchanges are symmetrical rearrangements of DNA within chromosomal structures in T lymphocytes; they were noted after exposure to a known carcinogen.[33]

Occupational monitoring[21, 34]

Biological studies

Several biological endpoints have been employed to monitor healthcare workers' exposure to antineoplastic agents. Most of these endpoints measure various types of genotoxic damage. These include, urine mutagenicity, chromosomal damage, sister chromatid exchange, micronuclei induction, DNA damage, HPRT mutations, and thioether excretion.

Urinary mutagenicity

Since most antineoplastic agents and/or their metabolites are excreted in the urine and a large percentage of them are mutagenic, the analysis of the urine of workers handling antineoplastic agents is a means to document exposure. However, relatively high doses are needed in order to detect an effect and, because the assays are nonspecific, confounding factors must be controlled for. Concentrated urine from workers is usually tested with a bacterial mutagenicity assay (Ames test) that is sensitive to many of the antineoplastic agents and/or their metabolites and the results compared to a control population.

Chromosomal aberrations

Chromosomal aberrations represent damage to DNA that is visible in stained cells. Usually, lymphocytes are obtained from exposed populations and examined for various types of chromosomal damage. This methodology has been applied to numerous occupational and environmental exposures to chemicals and radiation in addition to extensive animal studies. A number of chromosomal aberration studies have demonstrated an increase in chromosomal damage in the lymphocytes of nurses and pharmacists handling antineoplastic agents.

Sister chromatid exchanges

Although sister chromatid exchanges (SCEs) are typically measured in lymphocytes, similar to chromosomal aberrations and micronuclei, they are involved with DNA repair. This endpoint has been used extensively in other occupational settings as a marker for agents that may damage DNA, thus resulting in its repair. Several studies of workers exposed to antineoplastic agents have shown an increase in their frequency as compared to control populations.

Micronuclei induction

Micronuclei induction results from exposure to many chemicals that react with DNA. This assay has been employed extensively in animal studies, and to a lesser extent in occupational studies, to determine the ability of a chemical agent to damage DNA resulting in the formation of small fragments of DNA termed micronuclei. Micronuclei are usually measured in peripheral lymphocytes, but also can be evaluated in other cell types.

DNA damage

A number of methods are available to measure DNA damage directly. These include alkaline elution, and more recently, the Comet assay. These as-

says have been used in vitro and in animal studies, but only sparingly in occupation exposure studies. They usually measure DNA strand breaks. Since most antineoplastic agents target DNA, this is a sensitive and relevant endpoint to study.

HPRT mutations

HPRT mutations are typically measured in lymphocytes and targets mutations in a specific gene. This method had been employed recently in other occupational setting as a marker for exposure to agents which mutate DNA. A small number of studies of occupational exposure to antineoplastic agents has shown an increase in HPRT mutations.

Thioether excretion

The excretion of thioethers in the urine has been used in a limited number of occupational studies as a marker for exposure. The method is nonspecific and may be seen with other exposures, including smoking.

Urinary excretion of antineoplastic agents

Urinary analysis is the direct measurement of antineoplastic agents and/or their metabolites in the urine of exposed workers by analytical methods. Typically, gas chromatography/mass spectrometry (GC-MS or GC-MS-MS), high performance liquid chromatography (LC-MS or LC-MS-MS) or high performance liquid chromatography with UV detection (LC-UV) are employed to identify the drugs and/or their metabolites in the urine. For platinum-containing compounds, voltammetry or inductively coupled plasma mass spectrometry (ICPMS) are used to determine the presence of platinum in the urine.

Environmental sampling, decontamination, protective equipment, closed system transfer devices (CDTDs) and work practice[35]

Environmental sampling for antineoplastic agents

Although the studies on air sampling are limited due to technical problems associated with air sampling methods for these drugs, there have been numerous studies published on environmental wipe sampling for these drugs. Typically, work surfaces are sampled with a moistened wipe and the material is extracted and analyzed for specific antineoplastic agents. Currently, it is possible to identify and quantitate six to eight agents with this technique.

Decontamination and deactivation of antineoplastic agents

Several reports have dealt with methods for the decontamination and/or deactivation of antineoplastic agents. Although bleach (hypochlorite) is often recommended for the decontamination purposes, it is not effective with all classes of agents. Therefore, it cannot be assumed that cleaning with bleach solutions will destroy all types of antineoplastic agents. Some antineoplastic drugs are listed by the US Environmental Protection Agency as Hazardous waste and must be disposed of accordingly.

Evaluation of protective equipment for handling antineoplastic agents

These include biological safety cabinets, gloves, protective gowns and closed-system devices. NIOSH defines a closed system drug transfer device (CDTD) as: "A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system." There are several CDTDs currently available from different manufacturers. CDTDs have been shown to reduce the levels of surface contamination present where antineoplastic drugs are handled and to reduce the percentage of wipe samples that have detectable amounts of antineoplastic drugs.

Workers handling hazardous drugs need protection to prevent potentially harmful exposure.

Work practice evaluation

Several approaches have been developed for evaluating work practice techniques for drug preparation and drug administration. These approaches typically rely on a non-toxic substitute for the drug that can be easily visualized by ultra violet light or other means. Some test kits are available for various manufacturers.

CASE REPORTS

The following cases illustrate the range of health effects reported after exposure to antineoplastic drugs:

Case 1

A female oncology nurse was exposed to a solution of carmustine when the complete tubing system fell out of an infusion bottle of carmustine, and all of the solution poured down her right arm and leg and onto the floor.[2] Although she wore gloves, her right forearm was un-protected, and the solution penetrated her clothing and stockings. Feeling no sensation on the affected skin areas, she immediately washed her arm and leg with soap and water but did not change her clothing. A few hours later, while at work, she began to experience minor abdominal distress and profuse belching followed by intermittent episodes of non-bloody diarrhea with cramping abdominal pain. Profuse vomiting occurred, after which she felt better. The nurse went to the emergency room, where her vital signs and physical examination were normal. No specific therapy was prescribed. She felt better the following day. Carmustine is known to cause gastric upset, and the investigators attributed her gastrointestinal distress to its systemic absorption.

Case 2

A 39-year-old pharmacist suffered two episodes of painless hematuria (blood in the urine) and was found to have cancer (a grade II papillary transitional cell carcinoma).[36] Twelve years before her diagnosis, she had worked full time for 20 months in a hospital IV preparation area where she routinely prepared cytotoxic agents, including cyclophosphamide, fluorouracil, methotrexate, doxorubicin, and cisplatin. She used a horizontal laminar-flow hood that directed the airflow toward her. Because she was a nonsmoker and had no other known occupational or environmental risk factors, her cancer was attributed to her antineoplastic drug exposure at work- though a cause and effect relationship has not been established in the literature.

Case 3

A 41-year-old nurse who had worked on an oncology ward for 13 years suffered from nasal discharge, difficult breathing, and attacks of coughing 1 to 2 hours after beginning work.[37] During the third year of her employment on the ward, she developed difficult breathing while away from work. Her total IgE was low, and specific IgE antibodies to common agents and skin prick tests to common allergens (including latex) were all negative. The patient was subjected to a number of single-blind bronchial challenge tests with antineoplastic drugs, and she was monitored by spirometry and peak expiratory flow measurements. On the basis of clinical findings, the investigators concluded that the evidence was con-sistent with a diagnosis of allergic asthma.

Case 4

A malfunctioning biological safety cabinet (BSC) resulted in possible exposure of nursing personnel to a number of antineoplastic drugs that were prepared in the BSC.[38] Blood samples from the nurses were analyzed for genotoxic biomarkers 2 and 9 months after replacement of the faulty BSC. At 2 months, both sister chromatid exchanges (SCEs) and micronuclei were significantly elevated compared with those of a matched control group. At 9 months, the micronuclei concentrations were similar to those of the 2-month controls. SCEs were not determined at 9 months. The investigators concluded that the elevation in biomarkers had resulted from the malfunctioning of the BSC, which resulted in worker exposure to the antineoplastic drugs. They also concluded that the subsequent replacement with a new BSC contributed to the reduced effect seen with the micronucleus test at 9 months.

Case 5

A 41-year-old patient-care assistant working on an oncology floor developed an itchy rash approximately 30 min after emptying a commode of urine into a toilet.[39] She denied any direct contact with the urine,

Table 2. List of hazardous drug handling activities in workers

Activity	Primary Group of Workers Exposed
Handling drug-contaminated vials Reconstituting powdered or lyophilized drugs and further diluting either the reconstituted powder or concentrated liquid forms of hazardous drugs Expelling air from syringes filled with hazardous drugs Compounding potent powders into custom-dosage capsule	Pharmacists, pharmacy technicians
Administering antineoplastic drugs by intramuscular, subcutaneous, or intravenous (IV) routes Generating aerosols during the administration of drugs, either by direct IV push or by IV infusion Priming the IV set with a drug-containing solution at the patient bedside Handling body fluids or body-fluid-contaminated clothing, dressings, linens, and other materials	Nursing personnel
Handling contaminated wastes generated at any step of the preparation or administration process (Nursing personnel) Counting out individual, uncoated oral doses and tablets from multidose bottles Unit-dosing uncoated tablets in a unit-dose machine Crushing tablets to make oral liquid doses	Pharmacists, pharmacy technicians, nursing personnel
Contacting measurable concentrations of drugs present on drug vial exteriors, work surfaces, floors, and final drug products (bottles, bags, cassettes, and syringes) Handling unused antineoplastic drugs or antineoplastic drug contaminated waste Decontaminating and cleaning drug preparation or clinical areas	Pharmacists, pharmacy technicians, nursing personnel, housekeeping personnel
Performing certain specialized procedures (such as intraoperative intraperitoneal chemotherapy) in the operating room	Physicians, nursing personnel, operating room personnel
Transporting infectious, chemical, or hazardous waste containers	Nursing personnel, housekeeping personnel, waste disposal personnel
Performing repairs or maintenance on biological safety cabinets or isolators used to prepare antineoplastic drugs	Maintenance personnel, biological safety cabinets certification personnel

Adapted from the National Institute for Occupational Safety and Health [40]

wore a protective gown and nitrile gloves, and followed hospital policy for the disposal of materials contaminated with antineoplastic drugs. The rash subsided after 1-2 days. Three weeks later, she had a similar reaction approximately 1 h after performing the same procedure for another patient. It was found that both hospital patients had recently been treated with vincristine and doxorubicin. The patient-care assistant had no other signs or symptoms and reported no changes in lifestyle.

Preventing occupational exposure to antineoplastics

In September, 2004, The National Institute for Occupational Safety and Health (NIOSH) published an Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings *(DHHS (NIOSH) Publication No. 2004-165)*.[40]

Health care workers should take the following steps to protect themselves from hazardous drugs:

Table 3. NIOSH recommendations for safe handling of antineoplastic and other hazardous drugs

Activity	Recommendations
Receiving and storage of drugs	Wear PPE* suitable for task being performed Properly label all hazardous drugs Store and transport drugs in proper containers
Preparation and administration of drugs	Evaluate drug preparation and administration policies Wear suitable PPE, including double gloves for task being performed Limit access to areas where drugs are prepared Use proper engineering controls when preparing drugs Wash hands with soap and water before donning and after removing gloves Prime intravenous tubing in a ventilated cabinet Use needleless or closed systems when preparing and administering drugs Do not disconnect tubing from an intravenous bag containing a hazardous drug Dispose of used materials in the appropriate container
Ventilated cabinets	Perform all preparations with hazardous drugs in a ventilated cabinet designed to reduce worker exposure Do not use supplemental engineering controls as a substitute for a ventilated cabinet When asepsis is required, select a cabinet designed for both hazardous drugs containment and aseptic processing Horizontal laminar-flow clean benches should not be used for preparation of hazardous drugs Properly maintain engineering controls as required by the manufacturer
Routine cleaning, decontamination housekeeping, and waste disposal	Use suitable PPE for the task being performed Establish periodic cleaning routines for all work surfaces and equipment used where hazardous drugs are prepared or administered Consider used linen and patient waste to be contaminated with the drugs and/or their metabolites Separate wastes according to institutional, state, and federal guidelines and regulations
Spill control	Manage spills according to written policies and procedures Locate spill kits in areas where exposures may occur Adhere to Occupational Safety & Health Administration (OSHA) respiratory protection program Dispose of spill material in a hazardous chemical container
Medical surveillance	Participate in medical surveillance programs at work, or see your private health care provider if one does not exist Medical surveillance should include the following: • Reproductive and general health questionnaires • Complete blood count and urinalysis • Physical examination at time of employment and annual health status questionnaire review • Follow up for workers who have shown health changes

*Adapted from the National Institute for Occupational Safety and Health[40] ;*PPE = personal protective equipment.*

1. Prepare hazardous drugs inside a ventilated cabinet designed to protect workers and others from exposure and to protect all drugs that require sterile handling.
2. Use ventilated cabinets for preparation. These include biological safety cabinets (BSCs) and containment isolators designed to prevent escape of hazardous drugs into the work environ-

ment.

3. Filter the exhaust from ventilated cabinets with high-efficiency particulate air filters (HEPA filters). Make sure these cabinets are exhausted to the outdoors wherever feasible.
4. Use two pairs of powder-free, disposable chemotherapy gloves, with the outer one covering the gown cuff and wear face shields.
5. Consider providing supplemental equipment to protect workers further—for example, glove bags, needleless systems, and closed-system drug-transfer devices.
6. Establish and oversee appropriate work practices for handling hazardous drugs, patient wastes, and contaminated materials.
7. Provide workers with proper PPE on the basis of a risk assessment and train workers how to use it—as required by the Occupational Safety and Health Administration (OSHA) PPE standard [29 CFR* 1910.132]. PPE may include chemotherapy gloves, nonlinting and nonabsorbent polyethylene-coated polypropylene disposable gowns and sleeve covers, and eye and face protection.
8. Ensure the proper use of PPE by workers.
9. Use NIOSH-certified respirators. Note: Surgical masks do not provide adequate respiratory protection.
10. Provide syringes and IV sets with Luer-Lok™ fittings for preparing and administering hazardous drugs. Also provide containers for their disposal.
11. Consider using closed-system drug-transfer devices and needleless systems to protect nursing personnel during drug administration.
12. Periodically evaluate hazardous drugs, equipment, training effectiveness, policies, and procedures in your workplace to reduce exposures as much as possible.

For additional information, check Tables 2 and 3.

Conclusion

The toxicity of anticancer chemotherapy has been well known since its initial clinical use. Indeed, it has often been these drugs' toxic side effects that have limited their therapeutic value. The risk-benefit equation for a cancer patient often determines these drugs' appropriate use despite acknowledged side effects. Although these drugs present the same potential toxicities to exposed health care workers, that risk-benefit ratio is altered. A balance must be achieved to continue the use of these beneficial drugs in patients, while assuring the health of personnel administering them. A body of guidance now exists on how to achieve this goal. Much of the new guidance revisits the long standing elements of a comprehensive safe handling program and reminds us that the risk remains and our vigilance is required, but that a harmonized safe handling approach has been adopted that assures minimal risk to workers who provide lifesaving therapies to their patients.

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Article compiled by Leyla H Sharaf

TEST YOUR KNOWLEDGE

Answers to MCQs on back

1. Which of the following are the most frequent acute toxicities found with occupational exposure to antineoplastic agents?

a) Hair loss
b) Vomiting
c) Headaches
d) Dizziness
e) All of the above

2. Which of the following is used to monitor healthcare workers' exposure to antineoplastic agents?

a) Micronuclei induction
b) HPRT mutations
c) Urinalysis
d) A & B
e) A, B & C

3. Which of the following is classified as Group 1 Human Carcinogen?

a) Mitomycin C
b) Mitoxantrone
c) Semustine
d) Sreptozocin
e) Uramustine

Is there a problem?

A 55 year old patient was prescribed digoxin for atrial fibrillation. Is there any major error in the prescription?

PEC HOSPITAL

Patient Name: Mr. Ricky Age: 55 years
Address: Street No.10

Rx

Digoxin tablets
250 mg once daily
Send one pack

Dr. DSB
Signature Date: 25/02/14

Answer
(Prescription Exercise)

Wrong unit.
It should be 250 micrograms and not milligrams.

TOPICAL ISSUES AND CONTROVERSIES

Is there a role for "Junk DNA"?

In 30 papers published simultaneously, the five-year Encyclopedia of DNA Elements (ENCODE) project reports the mapping of more than four million regulatory sites across the human genome. In an effort that rivals the original human genome project in scale and scope, researchers from around the world have been collaborating for the past five years to understand the non-coding regions of the human genome-the more than 95% of the genome that's been dubbed "*junk DNA*" in the past. Now, with these simultaneous publications describing their findings, the team has reported that more than 80% of the human genome does indeed have a function.

ENCODE involved 440 scientists from 32 labs in the USA, UK, Spain, Singapore, and Japan. Since 2007, they have collected more than 15 terabytes of raw data that describes places in the genome that contain regulatory binding sites, areas of frequent DNA modification, or roles in managing the larger chromatin structure of DNA.

The ENCODE data represent a powerful resource for exploring fundamental questions about how life is encoded in our genome and for more clinically oriented researchers, the ENCODE data provide key information about which genome sequences are functionally important.

While determining the placement and function of regulatory sites in DNA has been done in individual

regions before, the new map is the most complete picture, and provides a launching-off spot for future studies in almost every avenue of genetic research.

The maps were created using a variety of techniques, including chromatin immunoprecipitation (ChIP) to locate binding sites for 119 transcription factors and histones as well as chromatin conformation capture, methylation analysis assays, and RNAseq. These experiments were performed in 150 cell types from different organs and developmental stages to create a full picture of functionality. Because of the millions of these switches, only a small percentage of them are on in any given type of cell, and the pattern of switches is different for each kind of cell. One has to survey a lot of different cells to gain a complete picture that can then be compared with a disease landscape.

As a first step toward applying the new functional genome data to clinical relevance, a multi-institutional team analysed gene variants that have already been discovered in genome-wide association studies (GWAS) for their overlap with the newly mapped out functional areas. To see how much of previously identified disease-associated variation is located within DNA regulatory elements, the team treated hundreds of cell types with the nuclease DNAse1. Sites with high levels of cleavage by DNAse1– so-called DNAse I hypersensitive regions (DHS) -are known to contain DNA regulatory elements. From this data, they determined the placement of these DHSs and then aligned them with more than 5,000 gene variants associated with 207 diseases and 447 traits identified in GWAS.

In a paper published on September 5, 2012 in *Science,* the team reported that 76% of these disease-associated gene variants fell within DHSs.[1] The next step is to home in on each variant and determine the exact function of the regulatory region it affects and how it may cause disease. It is now known that a majority of these changes that are associated with common diseases and traits that don't fall within genes actually occur within the gene controlling switches. This phenomenon is not confined to a particular type of disease. It seems to be present across the board for a very wide variety of different diseases and traits.

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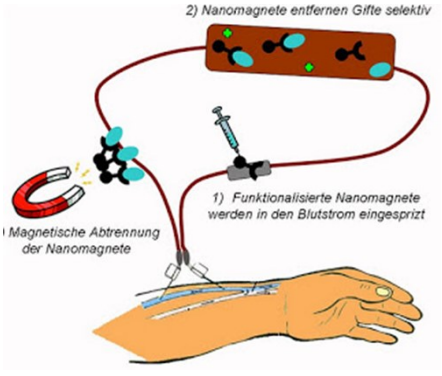
Source:http://www.biotechniques.com/news/biotechniquesNews/biotechniques-334767.html?utm_source=B

Clearing diseases from the blood by tiny magnets

Researchers in Switzerland, are developing nanomagnets that could someday remove potentially harmful substances from the blood. The technology could be used to treat people suffering from drug intoxication, certain cancers and bloodstream infections.

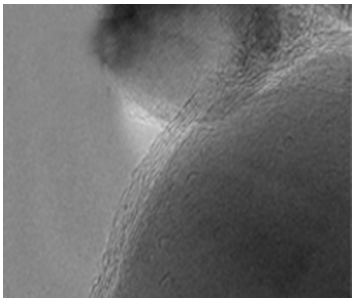
In this strategy, magnetized nanoparticles are coated with carbon and studded with antibodies specific to the molecules the researchers want to purge from the blood, for example inflammatory proteins such as interleukins, or harmful metals like lead. The researchers can filter out the unwanted compounds by adding the nanomagnets to blood, then running the blood through a dialysis machine or similar device. The nanomagnets capture the target substances, and right before the nanoparticles would be recirculated, the magnetic separator accumulates the toxin-loaded nanomagnets in a reservoir and keeps them separated from the recirculating blood. According to a study published in the journal *Nephrology Dialysis and Transplantation,* the researchers were able to remove 75 % of digoxin, a drug that can prove fatal if given in too high a dose, in a single pass through a blood-filtration device. The nanomagnets had removed 90 % of the digoxin after 1.5h of cleansing.



One big challenge is that the researchers must demonstrate that the particles aren't toxic to the body and won't interfere with the blood's ability to clot. But early results are promising. In a 2011 paper in *Nanomedicine*, it was shown that the nanomag

nets did not damage cells or promote clotting-two critical safety milestones. At the annual meeting of the American Society of Anesthesiologists in October, 2011, they presented data showing that the nanomagnets are partially taken up by monocytes and macrophages, two forms of immune cells, which is an important proof of principle for any future application of the technology in fighting serious infections. They are also conducting a study of the technology in rats with sepsis -a severe bloodstream infection marked by the massive buildup of damaging immune molecules.

The potential uses of the Swiss group's method could extend beyond sepsis to other diseases, including blood cancers. For example, it might be possible to design nanomagnets that pair up with circulating leukemia cells and take them out of the body, thus reducing the risk of metastasis. However, it is noted that the human body is a highly oxidative environment, and oxidation of iron weakens the magnetic properties of the material. By coating their magnets in carbon, the Swiss group may have come up with a way to prevent this corrosion. However, the viability of the technique remains to be seen as the real challenges are in having high circulation times, no immune response, and ensuring that the magnets do not cluster with each other.



Blood cleaner: *A microscope image shows one of the carbon -encapsulated nanomagnets used in the study.*

Source: *http://www.technologyreview.com/news/426203/tiny-magnets-could-clear-diseases-from-the-blood/*

FDA Reviews and approvals

Drugs and devices

The FDA issued a Drug Safety Communication regarding the potential risk for *Clostridium difficile* diarrhea in patients taking prescription or nonprescription proton pump inhibitors (PPIs). Patients should be instructed to take PPIs at the lowest effective dose and for the shortest duration appropriate for the medical condition. In addition, patients should be instructed to contact their healthcare professional immediately if they develop watery stool that does not improve, abdominal pain, and fever while taking PPIs.

The FDA has approved a once-weekly, extended-release formulation of exenatide injection (Bydureon™, Amylin Pharmaceuticals, California). This glucagon-like peptide-1 receptor agonist is indicated as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus (DM) and is administered subcutaneously once every 7 days. Bydureon is not recommended as first-line therapy and should not be used to treat type 1 DM or diabetic ketoacidosis. Use with insulin and in patients with a history of pancreatitis is not recommended. A Risk Evaluation and Mitigation Strategy (REMS) is required with Bydureon to help ensure that the benefits outweigh the risks for medullary thyroid carcinoma and acute pancreatitis.

The FDA approved a combination of the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin and biguanide metformin hydrochloride (Jentadueto™, Boehringer Ingelheim Pharmaceuticals, Connecticut; and Eli Lilly and Company, Indiana) as an adjunct to diet and exercise in adult patients with type 2 DM. Jentadueto should be given twice daily with meals, using slow dose escalation to decrease the adverse gastrointestinal effects associated with metformin. Jentadueto should not be used for type 1 DM or diabetic ketoacidosis, and use has not been evaluated in combination with insulin. Labeling contains a black-box warning about the risk for lactic acidosis associated with metformin accumulation.

Once-daily Janumet® XR (Merck & Co., New Jersey) was approved by the FDA for adjunct management of type 2 DM in combination with diet and exercise in adults. Janumet XR is the combination of the DPP-4 inhibitor sitagliptin and extended-release metformin. Janumet XR is not indicated for type 1 DM or diabetic ketoacidosis and has not been evaluated in patients with a history of pancreatitis. To decrease the adverse gastrointestinal effects of metformin, administration with the evening meal is preferred, and dosing should be gradually escalated. Labeling contains a black boxed warning regarding the risk for lactic acidosis associated with metformin accumulation. Decrease of insulin or insulin secretagogue (eg, sulfonylurea) dose requirements may be needed with concomitant use of Janumet XR to minimize risk for hypoglycemia.

The FDA granted approval of a pneumococcal 13-valent conjugate vaccine (Diphtheria CRM_{197} Protein) (Prevnar 13®, Wyeth Pharmaceuticals, Pennsylvania) for prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in patients aged 50 years or older. The vaccine has prior approval for children aged 6 weeks to 5 years. Approval was granted under accelerated approval regulation, which requires further study to describe clinical benefit. That trial is underway, with results expected December 2013

The FDA approved lisdexamfetamine dimesylate (Vyvanse®, Shire US Inc., Wayne, Pennsylvania) for maintenance treatment of attention-deficit/hyperactivity disorder (ADHD) in adults. This central nervous system stimulant is a schedule II controlled substance and has previous approval for ADHD in children and adolescents. Patients taking Vyvanse should be counseled about the risk for serious cardiovascular events and sudden death with use.

A single, shared-system REMS was approved for transmucosal immediate-release fentanyl (TIRF) drugs prescribed for outpatient use. This strategy, called "TIRF REMS Access Program," consists of a restricted distribution programme. TIRF medicines include but are not limited to fentanyl sublingual tablets (Abstral®, Novartis Consumer Health, Nebraska), fentanyl citrate transmucosal lozenges (Actiq®, Cephalon, Pennsylvania), and fentanyl nasal spray (Lazanda®, Archimedes Pharma US, New Jersey). Until this programme goes into effect, healthcare professionals should continue to enroll in individual REMS programmes for immediate-release fentanyl products; those who are already enrolled in at least 1 individual REMS program will be automatically enrolled in the TIRF REMS Access Program. Providers who prescribe only for inpatient use do not have to enroll in the TIRF REMS Access Programme

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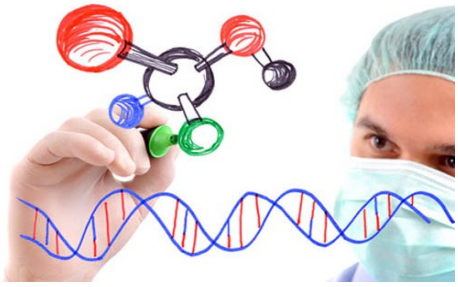
The FDA approved a new fentanyl sublingual spray (Subsys™, DPT Laboratories, New Jersey) for breakthrough pain in adult patients with cancer who are tolerant to opioid therapy. Subsys is supplied in single-use 100-, 200-, 400-, 600-, and 800-µg strengths; however, dosing should only begin with 100 µg. Subsys is not equivalent to other fentanyl products on a µg-per-µg basis. Clinicians who prescribe Subsys for outpatient use must be enrolled in the TIRF REMS Access Programme

The FDA approved ingenol mebutate gel (Picato®, LEO Pharma, New Jersey) for short-term treatment of actinic keratosis. Ingenol mebutate, which induces cell death, is available in 2 strengths: 0.015% for use on the face and scalp once daily for 3 consecutive days, and 0.05% for use on the trunk and extremities once daily for 2 consecutive days. Exposure to the periocular area should be avoided because eye disorders have occurred with use. Local skin reactions, including severe reactions, can also occur. Ingenol mebutate should not be applied to skin that has not yet healed from other drug or surgical treatment.

IN THE NEWS

Gene therapy on its way to clinical approval, after 20 y of high-profile failure



The concept is simple: replace or supplement a mutated gene with a new, accurate copy. In theory, such a strategy could not just treat, but cure countless human genetic diseases. In practice, however, developing safe and effective gene therapies has not been easy. Even when identifying a disorder's genetic basis is fairly straightforward, finding the appropriate delivery vector to target the diseased tissues in the body, while avoiding unintended consequences, has challenged would-be gene therapists for more than 20 years. But more and more researchers are convinced that the technique is on the brink of becoming a common medical practice.

In 2011 alone, major breakthroughs have been published for the use of gene therapy in patients with hemophilia, solid tumors, and leukemia, not to mention the dozens of trials yielding positive results for gene therapies to treat various types of blindness. It hasn't always been such high times for gene therapy, however. The field was booming in its early days, with approvals for gene therapy clinical trials rising exponentially from the first one in 1989 to 116 in 1999. But that year, a gene therapy trial participant who had an unusually mild form of liver disease caused by mutations in a gene on the X chromosome, died 4 days after receiving an injection of an adenovirus carrying an unmutated copy of the gene meant to correct his condition. The viral vector apparently triggered a massive immune response that caused multiple organ failure and brain death.

Then, starting in 2002, reports from Paris and London told of patients developing a leukemia-like disease following treatment in clinical trials for a rare autoimmune disorder called severe combined immunodeficiency (SCID), or "bubble-boy" disease. SCID patients lack a functioning immune system, and must live in highly sterile conditions to prevent infections. The studies started out extremely well: most of the infant boys were able to live relatively normal lives, no longer confined to their "bubbles." The trials were hailed as the first unequivocal gene therapy success.

But in the years that followed, 5 of the 20 patients developed a leukemia-like disease -an effect that was traced to the retroviral vector used to deliver the corrective gene to bone marrow cells *ex vivo*. The vector had inappropriately inserted the gene into the babies' genomes close to a proto-oncogene involved in white blood cell proliferation, activating the gene and triggering a flood of T cells. After the second child fell ill, the FDA suspended 30 US trials using the same retrovirus, or about 15% of the 200 gene therapy trials under way at that time -a move the agency called a precautionary measure. Of the five patients that developed leukemia, one died; the rest are in remission.

Events like these had a big negative impact in the field. Interest in gene therapy started to wane, and treatments that might have been expected to hit the market years ago are still plugging through the clinical trial process.

But things are looking up. In 2011, researchers published long-term survival data for two UK gene therapy trials for SCID: the original London trial for X-linked SCID (SCID-X1) and a second trial for adenosine deaminase SCID.[1] Up to 9y after treatment, 14/16 children treated have had their immune systems restored and have been able to live relatively normal lives.

Many other gene therapy trials are currently underway -and yielding positive results -for numerous other diseases, including various forms of hereditary blindness, HIV, hemophilia, neurodegenerative diseases, and a variety of cancers.

Though no gene therapies have yet received FDA approval, nearly 2,000 clinical trials have been initiated in the last 5y alone, many with seemingly miraculous results and- thanks to improved vectors and techniques -none of the devastating side effects that plagued the field in its earlier days.

References

1. Gaspar HB et al. Sci Transl Med; 2011: 3:97ra79-80.

Source: *http://the-scientist.com/2012/06/01/targeting-dna/*

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from June to December 2013

Alevo Tablets 250, 500mg; Levofloxacin-250, 500mg; Alkem Lab. Ltd. - India
Amlo Tablets 10mg; Amlodipine-10mg; Oman Pharm.Prod. Co. (Zynova) – Sultanate of Oman
Antiplex Tablets 75mg; Clopidogrel-75mg; Dar Al Dawa-Jordan
Apotel Plus Soln. for Injn; Paracetamol – 600mg Lidocaine HCl-20mg; Uni-Pharm. S.A. Pharma Lab, Greece
Apotel Soln. for Intravenous Infn; 1000mg/6.7ml, Paracetamol-1000mg; Uni-Pharma S.A. Pharma Lab, Greece
Aprovasc Tablets 150/10mg; Irbesartan-150mg, Amlodipine-10mg; Sanofi Aventis De Mexico- Mexico
Aprovasc Tablets 150/5mg; Irbesartan-150mg, Amlodipine-5mg; Sanofi Aventis De Mexico- Mexico
Aprovasc Tablets 300/10mg; Irbesartan-300mg,Amlodipine-10mg; Sanofi Aventis De Mexico- Mexico
Aprovasc Tablets 300/5m; Irbesartan-300mg, Amlodipine-5mg; Sanofi Aventis De Mexico- Mexico
Atacand Plus Tablets 32mg/12.5ml;Candesartan Cilexetil-32mg, Hydrochlorothiazide-12.5mg; Astrazeneca AB- Sweden
Atorva Tabs 10, 20, 40mg; Atorvastatin 10,20,40mg; Jazeera Pharma Ind. - Saudi Arabia
Azipar – 500 Tabs; Azithromycin Anhydrous -500mg; Plethico Pharma Ltd. - India
Azitrox Tablets 250, 500mg; Azithromycin-250, 500mg; Zentiva K.S. - Czech Republic
Cefrax Oral Suspension 100mg/5ml; Cefixime-100mg; National Pharm. Ind. Co.- Sultanate of Oman
Cinfaletro Tablets 2.5mg; Letrozole-2.5mg; Laboratoires Cinfa, S.A. - Spain
Cinfaval Tabs 160mg; Valsartan-160mg; Lab Cinfa S.A. - Spain
Cinfaval Tabs 40, 80, 320mg; Valsartan-40, 80, 320mg; Lab Cinfa S.A. - Spain
Claritide Tablets 500mg; Clarithromycin-500mg; Plethico Pharma Ltd. - India
Co-Cinfaval Tabs 160/12.5mg; Valsartan-160mg Hydrohlorothiazide-12.5mg; Lab Cinfa S.A. - Spain
Co-Cinfaval Tabs 160/25mg; Valsartan-160mg Hydrohlorothiazide-25mg; Lab Cinfa S.A. - Spain
Co-Cinfaval Tabs 80/12.5mg; Valsartan-50mg, Hydrohlorothiazide-12.5mg; Lab Cinfa S.A. - Spain
Compound Sodium Lactate IV Infusion BP (RL); Sodium Lactate-0.32gm, NaCl 0.600gm, KCl 0.04gm, $CaCl_2$ 0.027g; Claris Lifesciences Ltd
Devarol-S-Ampoules for IM inj. 200,000 I.U; Cholecalciferol-200,000 IU; Memphis Co. for Pharma & Chemical Ind. - Egypt
Dexaton Soln. for Inj. 4mg/ml; Dexamethasone Phosphate-8mg; Vianex S.A. - Greece
Dobine Conc. for IV Infn. BP 12.5mg/m;, Dobutamine-12.5mg; Claris Lifesciences Ltd. - India
Ferrinject Soln. for Inj./ Infusion 100mg/2ml; Iron-100mg; Vifor International Inc.- Switzerland
Ferrinject soln. for Inj/ Infusion 500mg/10ml; Iron-500mg; Vifor International Inc.- Switzerland
Gliafor Tablets 500, 850, 1000mg; Metformin HCl-500, 850, 1000mg; Dar Al Dawa-Jordan
Glycine Irrigation USP 1.5%, Glycine USP -1.5g; Claris Lifesciences Ltd. - India
Immodium Instant Orodispersible Tablet; 2mg, Loperamide HCl-2mg; McNeil Products Ltd. - U.K.
Intelence Tablets 100mg; Etravirine-100mg; Janssen-Cilag Int'l N.V. – Belgium
Irbea Tablets 75, 150, 300mg; Irbesartan-75, 150, 300mg; Laboratoires Cinfa, S.A
L-Cet Tablets 5mg; Levocetirizine Dihydrochloride-5mg; Oman Pharm.Prod. Co. (Zynova) – Sultanate of Oman
Levitra Orodispersible Tablets 10mg; Vardenafil-10mg; Bayer Pharma AG - Germany
Lipitin 10, 20mg Tabs; Atorvastatin-10, 20mg; KSPICO - Kuwait
Livazo Tablets 2, 4mg; Pitavastatin-2, 4mg; Algorithm S.A. L- Lebanon
Loractive-D Capsules; Loratadine-5mg,Pseudoephedrine Sulphate-120mg; Plethico Pharma Ltd. - India
Lukakline Tablets -10mg; Montelukast – 10mg; Glaxo Smithkline-Ireland
Maxirox Tablets 300mg; Roxithromycin-300mg; Aegis Ltd. - Cyprus
Medygraine Tablets 100mg; Sumatriptan-100mg; Actavis Group PTC ehf - Iceland
Medygraine Tablets 50mg; Sumatriptan-50mg; Actavis Group PTC ehf - Iceland
Micogel Cream 2%; Miconazole Nitrate-20mg; Cipla Ltd. - India
Minirin Melt 240mcg; Desmopressin – 240mcg; Ferring AB- Sweden
Mono-Embolex Prophylaxis Soln. for Inj; 3000 IU/0.3ml PFS for subcutaneous use, Certoparin Sodium-3000 IU; Novartis Pharma Schweiz AG- Switzerland
Motrinex Tablets 10mg; Montelukast-10mg; Dar Al Dawa-Jordan
Nata Drops; Natamycin-50mg; Cipla Ltd. - India

NovorRapid Flextouch PFP 100 U/ml Soln for Inj; Insulin Aspart – 100 U; NovoNordisk A/S - Denmark
Novoseven Powder & Solvent for Soln. for Inj; 1mg (50 KIU); Epta cog Alfa - 1mg L-Histidine in water for Inj; 1.1ml; Novo Nordisk A/S- Denmark
Novoseven Powder & Solvent for Sol for Inj; 2mg (100 KIU); Epta cog Alfa - 2mg L-Histidine in water for Inj; 2.1ml; Novo Nordisk A/S- Denmark
Novoseven Powder & Solvent for Soln for Inj; 5mg (250 KIU); Epta cog Alfa - 5mg L-Histidine In water for Inj; 5.2ml; Novo Nordisk A/S- Denmark

Olankline Tablets 5, 10mg; Olanzapine-5, 10mg; GlaxoSmithkline-Ireland
Olimel N5E Emulsion for infusion 1000, 2000ml; May ingredients; Baxter S.A. Belgium
Olimel N9 Emulsion for infusion 1000ml; May ingredients; Baxter S.A. Belgium
Olimel N9E Emulsion for infusion 1000, 2000ml; May ingredients; Baxter S.A. Belgium
Panadol Cold & Flu Vapour Release & Decongestant Powder for Oral Solution; Paracetamol-600mg Phenylephedrine HCL 10mg; GlaxoSmithkline Beecham-Spain

Periolimel N4E Emulsion for infusion 1500, 2000ml; Many ingredients; Baxter S.A. - Belgium
Plagrel Tablets 75mg; Clopidogrel -75mg; KSPICO- Kuwait
Pramokline Tablets 10mg; Escitalopram-10mg; Glaxo Smithkline-Ireland
Predo Syrup 15mg/5ml; Prednisolone-15mg; Jazeera Pharma Ind. - Saudi Arabia
Qutenza Cutaneous Patch 179mg; Capsaicin-179mg; Astellas Pharma Europe B.V. – The Netherlands
Rectacure Cream, Tribenoside-50mg; Lidocaine-20mg; Jazeera Pharma Ind. - Saudi Arabia
Renvela Powder for Oral Susp. 2.4g Sachet; Sevelamer Carbonate-2.4g; Genzyme Europe B.V. – The Netherlands
Respal Tablets 2, 4mg; Risperidone-2, 4mg; Joswe-Jordan
Sativex Oromucosal Spray; Cannabidiol- 25mg Delta (9)- Tetrahydrocannabiol-27mg; Novartis Pharma Schweiz Ltd. - Switzerland
Simponi Soln. for Inj. 50mg/0.5ml in PFP; Golimumab-50mg; Janssen Biologics B.V. - The Netherlands
Simponi Soln. for Inj. 50mg/0.5ml in PFS; Golimumab-50mg; Janssen Biologics B.V. - The Netherlands
Sodium Chloride 0.9% & Glucose 5% IV Infn. BP (DNS); Glucose -5g NaCl - 0.9g; Claris Lifesciences Ltd. - India
Sodium Chloride IV Infusion B.P. 0.9% w/v (NS); NaCl-0.9gm; Claris Lifesciences Ltd
Somazina Oral Solution 100mg/ml; Citicoline-100mg; Ferrer International S.A. - Spain
Sycrest Sublingual Tablets 5, 10mg; Asenapine-5, 10mg; N.V. Organon- The Netherlands
Telzap Tablets 40, 80mg; Telmisartan-40, 80mg; Zentiva Sagkuj Yrunk
Tobi Podhaler Inhalation Powder Hard Caps. 28mg; Tobramycin-28mg; Novartis Pharma Schweiz AG - Switzerland
Tussidane Oral Solution (Sugar free) 1.5mg/ml; Dextromethorphan Hydrobromide-1.5mg; Lab. Elerte - France
Valcyte Pwd. For Oral Soln. 50mg/ml; Valganciclovir-50mg; F. Hoffmann-La Roche - Switzerland
Xeljanz Tablets 5mg; Tofacitinib-5mg; Pfizer Inc. - U.S.A.
Yondelis Powder for Conc. for soln. for Infn. 1mg/vial; Trabectedin-1mg; Janssen Cilag Int. M.V. - Belgium

Zenoril Tablets 5mg; Lisinopril – 5mg; Ram Pharm. Ind. Co. Ltd. – Jordan
Ziquin Tablets 500mg; Levofloxacin-500mg; Laboratoires Cinfa, S.A.
Zocef Tablets 500mg; Cefuroxime-500mg; Alkem Lab. Ltd. - India

Answers to: Test your knowledge

Correct answers:
1-e; 2-e; 3-c

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