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Genetic toxicology: Web resources

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Abstract

Genetic toxicology is the scientific discipline dealing with the effects of chemical, physical and biological agents on the heredity of living organisms. The Internet offers a wide range of online digital resources for the field of Genetic Toxicology. The history of genetic toxicology and electronic data collections are reviewed. Web-based resources at US National Library of Medicine (NLM), including MEDLINE®, PUBMED®, Gateway, Entrez, and TOXNET®, are discussed. Search strategies and Medical Subject Headings (MeSH®) are reviewed in the context of genetic toxicology. The TOXNET group of databases are discussed with emphasis on those databases with genetic toxicology content including GENE-TOX, TOXLINE®, Hazardous Substances Data Bank, Integrated Risk Information System, and Chemical Carcinogenesis Research Information System. Location of chemical information including chemical structure and linkage to health and regulatory information using CHEMIDPLUS at NLM and other databases is reviewed. Various government agencies have active genetic toxicology research programs or use genetic toxicology data to assist fulfilling the agency's mission. Online resources at the US Food and Drug Administration (FDA), the US Environmental Protection Agency (EPA), the National Institutes of Environmental Health Sciences, and the National Toxicology Program (NTP) are outlined. Much of the genetic toxicology for pharmaceuticals, industrial chemicals and pesticides that is performed in the world is regulatory-driven. Regulatory web resources are presented for the laws mandating testing, guidelines on study design, Good Laboratory Practice (GLP) regulations, and requirements for electronic data collection and reporting. The Internet provides a range of other supporting resources to the field of genetic toxicology. The web links for key professional societies and journals in genetic toxicology are listed. Distance education, educational media resources, and job placement services are also available online in the field of genetic toxicology. As molecular biology and computational tools improve, new areas within genetic toxicology such as structural activity relationship analysis, mutational spectra databases and toxicogenomics, now have resources online as well.

Keywords: Genetic toxicology; Web resources; Mutagenicity

1. Introduction

Genetic toxicology is the study of the toxic effects of damage to deoxyribonucleic acid (DNA). Genetic information, encoded chemically in DNA, is maintained, replicated and transmitted to successive generations with high fidelity. Damage to DNA can occur through normal biologic process or as the result of interaction of DNA, either directly or indirectly, with chemical, physical or biological agents (Brusick, 1980).

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The goal of this article will be to discuss and identify various types of online, digital resources that are available to workers in genetic toxicology including bibliographic, data, regulatory, and educational websites. The article will not be encyclopedic in listing websites but instead will outline the types of online resources available and provide examples.

2. The evolution of genetic toxicology

The field of genetic toxicology began its development before the biochemical basis of heredity was understood. Early investigators observed that physical and chemical agents could cause heritable mutations. The role of radiation in producing heritable changes in a living organism was first reported by Muller (Muller, 1927). Auerbach was the first to report the ability of chemicals to cause mutations (Auerbach et al., 1947). These early observations of induced change in heritable traits formed a core of study that evolved into the field of genetic toxicology.

One major role of genetic toxicology over the years has been to investigate mechanisms of heredity by providing tools to study DNA and RNA structure (Cloutier et al., 2001), DNA repair (Hanawalt and Haynes, 1965; Rasmussen and Painter, 1966), and the role of mutation at both the individual (McDiarmid et al., 1995) and population levels (Jacobson-Kram et al., 1993; Robinson et al., 1994). The study of mutagenesis has proved invaluable in many diverse areas including environmental monitoring (Pesch et al., 1984), occupational health (Galloway et al., 1986), risk assessment (Dearfield, 1995), product safety (Malyapa et al., 1997), and understanding the genetic component of human health (Trosko, 2000; Tomlinson, 2001). As different assay systems were developed over the years to measure genotoxicity, a Darwinian process of selection operated that identified the more robust tests that, when performed together as a battery, were most efficient in detecting mutagenic chemicals or drugs (Tennant et al., 1987; Zeiger et al., 1990). This process has led to the use of genetic toxicology in regulatory toxicology. This role deals in part with hazard assessment of chemicals (including drugs) in commerce or about to enter into commerce. One result of this process has been the development of standardized test designs such as provided by the Organization of Economic Cooperation and Development (OECD, 1998). Other outcomes of this process have been the establishment of globally harmonized guidelines of what tests to perform for different types of products such as provided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 1995, 1997) and various standards for the conduct of these tests collectively known as Good Laboratory Practice (GLP) guidelines.

While work has been done using acellular systems to investigate the biochemical or biophysical interactions of mutagens with DNA (Pouwels et al., 1968; Kuhnlein et al., 1979), most work in the field of genetic toxicology has involved the use of intact organisms. Test systems that have been used include bacteriophages (Weigle, 1953), viruses (Seidman, 1989), bacteria (Ames et al., 1975; Green and Muriel, 1976), yeast (Zimmermann and Schwaier, 1967), mammalian cells in culture (Chu and Malling, 1968; Kao and Puck, 1968), plants (Sparow et al., 1972; Grant, 1994), insects (Valencia et al., 1984; Vogel et al., 1999) and animals (Russell et al., 1981; Kohler et al., 1991). Endpoints that have been used over the years to measure genotoxicity include DNA adducts (Randerath et al., 1989; Reddy, 2000), DNA strand breakage (Larsen et al., 1982; Skare and Schrotel, 1984), mutations (Clive and Spector, 1975; Mitchell et al., 1997), changes in chromosome number or structure (Evans, 1976; Galloway et al., 1994), DNA repair (San and Stich, 1975; Mitchell et al., 1983), and cell transformation to malignant phenotypes (Kakunaga, 1973; LeBouf and Kerckaert, 1987). In the early years of genetic toxicology there was a large increase in both the types of organisms used for mutational research and in the number of endpoints used to measure mutagenic damage. The rapidly increasing number of researchers and amount of published material in genetic toxicology through the 1960s led to the formation of

professional societies focused on genetic toxicology. One of the first societies founded to focus on mutagenesis was the Environmental Mutagen Society (EMS) founded in 1969. This was followed in 1970 by the founding of the European Environmental Mutagen Society and in 1977 the UK Environmental Mutagen Society.

Simultaneous with the establishment of professional societies focusing on genetic toxicology was the recognition of the need to electronically collect, organize, and disseminate genetic toxicology data. While bibliographic indexing of genetic toxicology publications was already available in printed form through services such as *Index Medicus*, there was an effort in the 1970s to develop specialized electronic databases for genetic toxicology. The first such database was the Environmental Mutagen Information Center (EMIC) sponsored by Oak Ridge National Laboratory (ORNL), Oak Ridge, TN (Wassom, 1973). This program started as a result of the vision of Dr Alexander Hollaender, Director of the Biology Division, ORNL and the first President of EMS. EMIC was sustained through the leadership and efforts of Dr John Wassom, Dr Heinrich Malling, Dr Fred de Serres, and Elizabeth VonHalle, among others. EMIC was the prototype for future computer-based scientific data storage and retrieval services. EMIC exists today as an archived collection within TOXNET® at the National Library of Medicine (NLM).

3. National Library of Medicine

3.1. MEDLINE® and PUBMED®

The best source for web-based bibliographic references in the field of genetic toxicology are the various databases maintained by the NLM. The NLM databases and the means to access them have evolved over time. The traditional way to search for biomedical citations 20 or more years ago was to consult the many volumes of *Index Medicus*, a printed list of indexed citations from biomedical, medical and health science journals. *Index Medicus* continues to this day with full or selected indexing of slightly more than 3500 medical journals (http://www.nlm.nih.gov/tsd/serials/lji.html).

In 1971, the NLM made available an electronic version of the biomedical database. This new database, MEDLINE, could be searched online using command language from remote computer terminals. A major improvement in accessing data online occurred in 1986 when the NLM released the DOS-based software program GRATEFUL MED. This program helped format searches and facilitated citation retrieval using personal computers. In 1996, another improvement occurred with the release of the WINDOWS-based Internet Grateful Med (IGM). This enhancement of the earlier GRATEFUL MED software permitted web-based searches of 15 different NLM databases, including MEDLINE.

In 2000, and continuing into 2001, major changes occurred in the philosophy, structure and access to the NLM databases that MEDLINE users should be aware of. Key changes include the elimination of IGM as the access point to MEDLINE, elimination of on-line search charges, expanded searches across multiple databases (including images, molecular structures, DNA sequences and protein sequences), web linkage to outside resources (e.g. providing full-text journal articles at web sites of participating publishers) and greater accessibility for the general public. The main web page of NLM (www.nlm.nih.gov) guides users to an index of health related web resources (www.nlm.nih.gov/hinfo.html). Notable for genetic toxicologists in this health resource index are links to MEDLINE/PUBMED (Entrez) and the NLM Gateway. Access to MEDLINE has been switched from IGM to the Entrez search and retrieval system developed by the National Center for Biotechnology Information (NCBI) at NLM (www.ncbi.nlm.nih.gov/entrez/query) and the NLM Gateway developed by the Lister Hill National Center for Biomedical Communications at NLM (http://gateway.nlm.nih.gov). Both Entrez and Gateway use the PUBMED database that includes the original MEDLINE database as well as additional citations that are related, but beyond the scope of, the core MEDLINE journals. Currently, MEDLINE contains over 11 million journal citations drawn from nearly 4500 worldwide journals.

It is helpful to have an understanding of how the search engines work to make the most efficient use of the databases and to ensure the most accurate results of the search. Both the Entrez and Gateway search screens are intuitive to use and are supported with good online tutorials. There are free courses offered by NLM on the campus of NIH and at sites throughout the country (www.nnlm.gov/mar/online/index.html). There is also a listing of sites outside the US, some of which offer courses (www.nlm.nih.gov/pubs/factsheets/intlmedlars.html). The fundamental concept to understand is that all journal entries are indexed according to many items including, but not limited to, content, authors, journal, date, and language. Indexing by content uses the NLM's controlled vocabulary thesaurus called Medical Subject Heading (MeSH®) (www.nlm.nih.gov/pubs/factsheets/mesh.html). MeSH vocabulary provides both an alphabetical and hierarchical structured nomenclature to index articles by keywords. The hierarchical structure contains over 19 000 linked terms and concepts with more that 100 000 additional supplemental terms in a linked chemical thesaurus. Table 1 provides an example of the hierarchical approach to indexing mutagenicity tests in the MeSH nomenclature. All mutagenicity tests fall under Genetic Techniques which is under the heading Investigative Techniques and in turn is under the broader heading Analytical, Diagnostic and Therapeutic Techniques and Equipment. The MeSH nomenclature currently does not provide separate indexing for the standard mutagenicity tests with the exception of micronucleus assays and Comet assays. MeSH terms also have additional Entry Terms that are cross-references for synonyms. For example, a query for Genotoxicity Test would be interpreted and searched as if Mutagenicity Test were entered. Complex searches can be constructed by using Boolean operators such as AND, OR and NOT with additional terms including chemical names, title words, author names, date ranges, specific journals or special data subsets.

Table 1
Example of MeSH indexing for micronucleus tests

MeSH Heading with Mesh Tree Number
Analytical, Diagnostic and Therapeutic Techniques and Equipment [E]
Investigative Techniques [E05] +
Genetic Techniques [E05.393] +
Mutagenicity Tests [E05.393.560] +
Alternate indexing words for Mutagenicity Tests: Genetic Toxicity Tests; Genotoxicity Tests; Mutagen Screening; Tests, Genetic Toxicity; and Toxicity Test, Genetic
Micronucleus Tests [E05.393.560.598] +
Alternate indexing word for Micronucleus Tests: Micronucleus Assays

One data subset within MEDLINE of particular interest to Genetic Toxicologists is the 'Toxicology' subset. This subset represents the TOXLINE® Core database which covers the standard toxicology literature. TOXLINE Core and the companion database TOXLINE Special are described in Section 4.5 below.

3.2. National Library of Medicine Entrez

The Entrez search screen (www.ncbi.nlm.nih.gov/Entrez/) permits integrated searches across various databases at NCBI and NLM of interest to researchers in genetic toxicology and toxicogenomics (Table 2). To access PUBMED and the MEDLINE database from the Entrez search screen, select PUBMED from the menu bar at the top of the screen or from the pull down pick list in the 'Search' field at the top of the screen. Searches are then constructed and executed as described above. The power of Entrez is the ability to search multiple databases. For example, PUBMED can be searched for articles dealing with the *lacI* gene as a mutational target in transgenic mice. Abstracts of retrieved citations can be printed out and even the full text of the articles, if published electronically. The nucleotide sequence of the *lacI* gene (NUCLEOTIDE and GENOME databases) or the *lacI* protein (PROTEIN database) can be studied and the 3D structures (STRUCTURE database) of both can be viewed. The corresponding gene in humans with associated chromosome mapping and sequences can be viewed through Online Mendelian Inheritance in Man (OMIM

Table 2
Entrez databases

Database	Description
PUBMED	Biomedical and health science literature including MEDLINE and additional literature resources
Nucleotide	Nucleotide sequence search and relationship analysis
Protein	Protein sequence search and relationship analysis
Structure	Three-dimensional structure of macromolecules or fragments
Genome	Complete genome assemblies
PopSet	Population study data sets
OMIM	Online Mendelian Inheritance in Man
Taxonomy	Phylogenetic information of organisms in GenBank
Books	Collection of biomedical books with online searching
ProbeSet	Gene Expression Omnibus (GEO)
3D Domains	3D structure viewer of structures and sequences
BLAST	Basic Local Alignment Search Tool for searching nucleotide and protein sequences for alignment

database). Two related tools available through NCBI Entrez is the Basic Local Alignment Search Tool (BLAST®) which permits searching of protein and DNA databases for sequences homologous to a submitted sequences (www.ncbi.nlm.nih.gov/BLAST) or BLAST2 which produces the alignment of two given nucleotide or protein sequences based on local alignment www.ncbi.nlm.nih.gov/gorf/bl2.html). Other Entrez databases available from the Entrez toolbar are TAXONOMY, POPSET, BOOKS, PROBESET and 3D DOMAINS (www.ncbi.nlm.nih.gov/Entrez).

3.3. National Library of Medicine Gateway

The still evolving NLM Gateway permits the user to search multiple databases at NLM, including PUBMED/MEDLINE, and provides menu driven access to other NLM databases (http://gateway.nlm.nih.gov). The NLM Gateway was designed to be a single point of entry for all NLM resources. Experienced users may wish instead to search directly their database of interest. Databases formerly accessible by the older IGM webpage were gradually updated and transferred to Gateway. IGM was retired on 28 September 2001. The Gateway main menu provides a link to TOXNET, a group of toxicology-related databases maintained by Specialized Information Services at NLM (www.toxnet.nlm.nih.gov).

4. Toxicology Data Network (TOXNET®)

TOXNET is a group of databases, many of which are of particular interest to genetic toxicologists (http://toxnet.nlm.nih.gov). TOXNET is maintained by the Toxicology and Environmental Health Information Program (TEHIP), (http://sis.nlm.nih.gov/Tox/ToxMain.html) within the Specialized Information Services Division (http://sis.nlm.nih.gov) of the NLM. TEHIP is responsible for information resources and services in toxicology, environmental health, chemistry, HIV/AIDS, and specialized topics in minority health. TOXNET contains 11 different databases organized into four groups according to whether the database provides toxicology data, bibliographic information, chemical releases to the environment, or nomenclature information on chemicals (Table 3). The one actively maintained database in TOXNET that focuses primarily on genetic toxicology is GENE-TOX. Another database with genetic toxicology information is the EMIC. This database is no longer being updated but is available as an archival collection through TOXNET. Some TOXNET databases such as Developmental and Reproductive Toxicology and Environmental Teratology Information Center (DART/ETIC) and the Toxics Release Inventory (TRI) provide little genotoxicity information. Other databases include genetic toxicology data as part of a more comprehensive review of the toxicity of a chemical while still others provide supporting information. Once a search has been run in one TOXNET database, the same search strategy can be run against other TOXNET databases by using the 'Other Database' menu option.

4.1. Hazardous Substances Data Bank (HSDB®)

The HSDB provides a comprehensive review of human and animal toxicology data on over 4500 potentially hazardous chemicals. This peer-reviewed database includes some mutagenicity data but genotoxicity data is not a major focus of the database. The database includes additional information on human exposure, industrial hygiene, emergency handling procedures, environmental fate and regulatory requirements.

4.2. Integrated Risk Information System (IRIS)

IRIS provides data in support of human health risk assessment on over 500 chemicals. The chemicals reviewed in the IRIS database are primarily chemicals in commerce that are of regulatory interest. This database was begun by the EPA in the mid-1980s and is maintained by the EPA. The database provides carcinogenicity and other data used in support of human health risk assessments. When mutagenicity data are available for a chemical, it is usually reviewed in section II.A.4, 'Supporting Data for Carcinogenicity', of the chemical record.

4.3. Chemical Carcinogenesis Research Information System (CCRIS)

CCRIS is a toxicology data file that provides data from carcinogenicity, tumor promotion, mutagenicity and tumor inhibition studies on over 8000 chemicals. The data comes from a variety of sources including the peer-reviewed primary literature as well as from publications from the National Cancer Institute (NCI), National Toxicology Program (NTP) and other secondary sources.

4.4. GENE-TOX

GENE-TOX is a toxicology datafile that contains genetic toxicology test data from over 3000 chemicals. The database was created by the EPA to provide a core of genetic toxicology data from a variety of different assay systems that could then be used recommend proper study designs and assay evaluation criteria. The GENE-TOX records are structured to provide basic substance information and a summary of each study referenced. The summary includes information on the test system, the assay name, the mutagenicity evaluation, the dose response evaluation, and links to the supporting citations. Much of the data used in GENE-TOX were reviewed by expert panels organized by EPA and published as panel reports in the peer-reviewed literature.

4.5. TOXLINE®

TOXLINE is a bibliographic database contain-

Table 3
Toxicology Data Network (TOXNET®) databases

Database	Database type	Description and Gene Tox interest
HSDB	Data	Hazardous Substances Data Bank. Contains some gene tox information.
IRIS	Data	Integrated Risk Information System
CCRIS	Data	Chemical Carcinogenesis Research Information System
GENE-TOX	Data	Genetic toxicology database from the US Environmental Protection Agency
TOXLINE	Literature	Literature on biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals.
DART/ETIC	Literature	Developmental, reproductive and teratology literature information
TRI	Chemical release	Toxic release inventories from EPA for various years
CHEMIDPLUS	Chem Info	Chemical names, synonyms, structures, regulatory list information, and links to other databases.
HSD Structures	Chem Info	2D chemical structures of chemicals in HSDB
NCI-3D	Chem Info	2D and 3D chemical structures from National Cancer Institute

ing over 3 million citations covering biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. TOXLINE includes a large number of genetic toxicology citations to both the general literature, a wide-variety of government technical reports, and archival databases that are no longer being maintained. Searches can be targeted to genetic toxicology topics by combining a chemical name with a mutagenicity-specific term such as 'mutation' or 'cytogenetics'.

TOXLINE has been recently reconfigured and is now divided into two separate parts based on the underlying database searched. The TOXLINE Core searches the toxicology-specific general literature within MEDLINE/PUBMED, and replaces the former TOXBIB subfile. TOXLINE Core is accessed through the TOXLINE search page by selecting the 'TOXLINE Core on PUBMED' radio button or from the MEDLINE/PUBMED search screen by selecting the 'Toxicology' subset as a Limits option in the basic search screen. TOXLINE Core searches have all the features of a general PUBMED search.

TOXLINE Special is designed to supplement TOXLINE Core by indexing a variety of specialized journals, technical reports and archived electronic databases. TOXLINE Special is accessed through the TOXLINE search page by selecting the 'TOXLINE Special' radio button. Another special database in TOXNET that focused on genetic toxicology was the EMIC database. This database is no longer being actively maintained but is available as one of the archived databases available for searching through the TOXLINE Special database. Additional information on TOXLINE appears on the Factsheet for TOXLINE (www.nlm.nih.gov/pubs/factsheets/toxlinfs.html).

4.6. CHEMIDPLUS

CHEMIDPLUS is a NLM database that provides information on chemicals, including the structure, names, synonyms, CAS number, formula, and regulatory list information (http://chem.sis.nlm.nih.gov/chemidplus). This database is very useful to genetic toxicologists due to the powerful search engine and visualization tools that link chemicals and chemical structures to the bibliographic databases, factual databases, and regulatory lists within the NLM using Chime Pro and ChemSymphony. Information on a specific chemical can be located from the database of over 350 000 chemical records and over 100 000 chemical structures. The search engine permits searches on substructures or functional groups within a molecule to locate chemicals that share either the substructure or similar substructures. Chemical structures can be entered, viewed and searched using Chime Pro which is a free plug-in program designed to work with CHEMIDPLUS and the Chemscape webserver (www.mdlchime.com/chime). ChemSymphony is a package of customizable and flexible JAVA tools for creating chemistry resources on a network for visualizating, manipulating and processing chemical structures (www.chemsymphony.com/index2.htm). Custom chemical structures can be drawn using the free plug in program called ISIS/DRAW 2.3 to pass chemical structures to the CHEMIDPLUS search engine through the Chime structure search window (www.mdli.com/downloads/isis.draw/isisdrawreg.html). The power of CHEMIDPLUS is that not only can information on a chemical be retrieved but the chemical, as represented by either words or structural drawing, can also be used as the basis for a search in different 'Locators'. Locators are the various bibliographic or data files on TOXNET, resources on other Internet servers, or various Superlist documents. Superlist documents as defined by NLM are documents prepared by various regulatory or governmental agencies that deal with chemical substances of interest to international, national and state regulatory agencies (http://sis.nlm.nih.gov/Chem/ChemSuperAbout.html).

5. Chemical information resources

There are many web resources for finding information on the chemical, physical and general

biological properties of chemicals. Genetic toxicologists need to evaluate the mutagenicity of both established and new compounds. Access to a good digital resource of chemistry data provides a starting point for an evaluation. Identifying information such as accurate chemical name, synonyms, registry numbers, structure, and existing regulatory status is an essential starting point for evaluating the genotoxicity of a compound. One of the best sources for chemical information integrated into a biological data base is CHEMIDPLUS discussed above as part of the NLM TOXNET.

There are a number of other free, online databases that provide chemical, biological and regulatory information on chemicals. One similar website, provided by CambridgeSoft Corporation, is www.chemfinder.com. This site provides basic chemical and structural information, as well as information on the biochemistry, health effects, physical properties, relevant regulatory documents, plus information on purchasing the chemical.

Material Safety Data Sheets (MSDS) provide detailed information on established chemicals. There are many online sources for MSDS information, often with providers specializing in specific market segments such as agricultural chemicals or industrial chemicals. Websites such as Interactive Learning Paradigms, Inc. (www.ilpi.com/msds) and MSDS Solutions (www.msdssolutions.com) provides a through listing of weblinks to other sites providing MSDS information. MSDS Solutions permits 30 days free access and also provides information in French. A good source for primary MSDS information is provided by Safety Information Resources, Inc. supported by the University of Vermont (http://siri.uvm.edu/msds/). Many companies provide free MSDS information for their products but often these sites require user registration. A good example of a corporate site providing MSDS information on products is maintained by Sigma-Aldrich Company (www.sigmaaldrich.com for the Americas and www.sigmaaldrich.com/Europe for Europe, the Middle East and Africa).

6. Genetic toxicology programs at government agencies

There are active governmental genetic toxicology programs supported by various countries. These programs provide basic scientific research, scientific research in support of regulatory toxicology, and non-laboratory scientific expertise for regulatory toxicology. There are also programs funded by international organizations and even state governments. Web resources of several representative government programs are described.

6.1. US Food and Drug Administration

The US Food and Drug Administration (FDA) (www.fda.gov) has groups responsible for genetic toxicology issues in most of the different Centers at FDA. Each Center maintains individual webpages with varying amounts of genetic toxicology-specific information. There are selected databases such as the 'Everything Added to Food in the United States' (EAFUS) database (http://vm.cfsan.fda.gov/~dms/eafus.html) maintained by the Center for Food Safety and Applied Nutrition (CFSAN) (http://vm.cfsan.fda.gov) that provides access to toxicology data, including mutagenicity data. The EAFUS database provides indexing to toxicology data for direct and indirect food additives, food contact materials and 'Generally Recognized As Safe' (GRAS) compounds. The original FDA guideline for mutagenicity testing of chemicals was developed by CFSAN and codified in the *Draft Redbook II* originally issued in 1993. A revised version, *Redbook 2000: Toxicological Principles for the Safety of Food Ingredients*, is available with portions available electronically at http://vm.cfsan.fda.gov/~redbook/red-toct.html.

Most genetic toxicology programs and regulatory review within FDA occurs at the Center for Drug Evaluation and Research (CDER) (www.fda.gov/cder). Guidance documents on genetic toxicology testing at FDA are discussed in greater detail in Section 7.1. These documents, such as the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guide-

lines for mutagenicity testing (Guidelines S2A and S2B), can be searched for at the CDER Guidance Page (www.fda.gov/cder/guidance) or retrieved directly from the ICH webpage (www.ifpma.org/ich5s.html). Since the pharmaceutical industry is responsible for performing the majority of genotoxicity testing as part of Investigational New Drug (IND) submissions, the CDER website provides a wealth of information on the IND process www.fda.gov/cder/handbook/index.htm. Access to the other centers within FDA (Center for Biologics Evaluation and Research, Center for Veterinary Medicine, and Center for Devices and Radiological Health), is possible through the main FDA webpage.

6.2. US Environmental Protection Agency

The US Environmental Protection Agency (EPA) was an early leader in supporting genetic toxicology research and incorporating genetic toxicology testing into the regulatory approval process of industrial chemicals and pesticides. The EPA maintains active regulatory oversight in registering new chemicals entering commerce and sponsoring basic research in genetic toxicology at EPA laboratories and through contracts. Basic research programs in genetic toxicology at EPA are located in the Environmental Carcinogenesis Division (ECD) of the National Health & Environmental Effect Research Laboratory (NHEERL) (http://www.epa.gov/NHEERL/ecd/background.html).

The Office of Prevention, Pesticides and Toxic Substances (OPPTS) (http://www.epa.gov/opptsfrs/home) is responsible for the regulation of both industrial chemicals and pesticides. Industrial chemicals and toxic substances are the responsibility of the Office of Pollution Prevention and Toxic Substances (OPPT) (www.epa.gov/opptintr), formerly the Office of Toxic Substances, which regulates toxic substances according to the Toxic Substance Control Act (TSCA) (http://www.epa.gov/opptintr/chemtest/notice7.pdf). Pesticides are controlled by the Office of Pesticide Programs (OPP) (www.epa.gov/pesticides) according to the Federal Insecticide, Fungicide and Rodenticide Act (http://www.epa.gov/pesticides/fifra.htm). OPPTS has developed a new series of harmonized test guidelines that describe the acceptable conduct of product testing. Series 870, Health Effects Test Guidelines, describes the conduct of both in vitro and in vivo genetic toxicology studies (http://www.epa.gov/opptsfrs/OPPTS_Harmonized). These guidelines are discussed further in Section 7.2.

The Chemical Right-to-Know Initiative (Chem-RTK) was started by EPA in 1998 to ensure that basic toxicity information is publicly available on most of the high production volume (HPV) commercial chemicals made and used in the US (www.epa.gov/chemrtk). Initially, EPA will seek voluntary toxicology testing, including genetic toxicology assays, to provide complete data sets for HPV chemicals through the EPA HPV Challenge Program (www.epa.gov/chemrtk/hpvtest.htm). EPA intends to require testing under the HPV Test Rule for those chemicals with inadequate data sets. HPV testing will use the same tests, testing protocols, and basic information summary formats as required by the OECD Screening Information Data Set (SIDS) program (www.oecd.org/ehs/guide/index.htm and www.oecd.org/ehs/sidsman.htm).

The Genetic Activities Profiles (GAP) program is a collaboration between EPA and the International Agency for Research on Cancer (IARC) (www.iarc.fr) that provides graphic display of mutagenicity data and other related short-term tests on over 500 agents including over 250 priority chemicals of interest to EPA (www.epa.gov/gapdb). The GAP database includes short-term test results abstracted from approximately 8000 references on genetic toxicity and includes chemicals from recent volumes of the IARC Monographs on the Evaluation of Cancer Risks to Humans(http://193.51.164.11/monoeval/allmonos.html) and from various EPA projects. The database and viewing software can be downloaded free from www.epa.gov/gapdb/download.htm.

6.3. National Institute for Environmental Health Science (NIEHS)

The NIEHS, an institute of the National Institutes of Health, maintains an active genetic toxi-

cology program as part of its mission to reduce human disease from environmental causes (www.niehs.nih.gov/home.htm). The NTP (http://ntp-server.niehs.nih.gov) is an interagency program supported by the NIEHS, the National Institute for Occupational Safety and Health (NIOSH, an institute of the Centers for Disease Control and Prevention) (www.cdc.gov/niosh/homepage.html), and the National Center for Toxicological Research (NCTR, a laboratory of the FDA) (www.fda.gov/nctr/index.html). The NTP website provides a large amount of genetic toxicology information synthesized from NTP-sponsored studies. A good example of this type of data is found in the NTP Testing Information and Study Results webpage (http://ntp-server.niehs.nih.gov/main_pages/NTP_ALL_STDY_PG.html) where one of the special reports provides a comparison of NTP carcinogenicity and mutagenicity data (http://ntp-server.niehs.nih.gov/htdocs/Carc_SA/NTP_Res_Compare.html).
NIEHS and NTP have been instrumental in supporting the validation of various in vivo transgenic mouse models such as BigBlue® mice for mutation testing and $p53^{+/-}$ and Tg.AC mice for carcinogenicity testing (http://ntp-server.niehs.nih.gov / Main_Pages / Transgen / Transgen_Default.html).

7. Regulatory guidelines that apply to genetic toxicology

The majority of genetic toxicology testing in the world is performed for hazard assessment of new drugs and chemicals. This testing is required by various guidelines issued by national governments and states (ICH, 1995, 1997). In recent years there has been a major effort to harmonize testing guidelines for pharmaceuticals and industrial chemicals. These harmonized guidelines tend to describe either how to perform tests or what tests should be performed under certain circumstances. A good listing of global regulatory agencies that deal with drugs and chemicals in commerce can be found at www.fda.gov/oia/agencies.htm. Other guidelines, generically known as 'Good Laboratory Practice' standards describe how the testing should be conducted, recorded and reported. Individual countries maintain regulatory information on their webpages. The Society for Quality Assurance maintains an excellent link of webpages related to the various GLP guidelines (www.sqa.org/gov%20links.htm).

7.1. Pharmaceutical genetic toxicology guidelines

The FDA, Japanese Ministry of Health and Welfare (JMHW) and the European Union (EU) have developed harmonized guidelines for preclinical genotoxicity testing of drugs before they are used in humans. Nearly every drug in development will be tested in a battery of genetic toxicology tests that include a bacterial reverse mutation assay, an in vivo rodent bone marrow micronucleus assay, and either an in vitro mammalian cell gene mutation assay or an in vitro mammalian cell chromosome aberration assay. The use of these tests is described in the ICH guidelines S2A and S2B. Copies of these guidelines are available from ICH at www.ifpma.org/ich5s.html. The various GLP guidelines for FDA studies are located at www.fda.gov/ora/compliance_ref/bimo/default.htm. A major topic in laboratories performing preclinical toxicology testing, including genetic toxicology laboratories, involves electronic data collection, signatures, submission, and review. Information on FDA CDER's approach to electronic records may be found at www.fda.gov/cder/regulatory/ersr/default.htm. The guidance for FDA electronic records and electronic signatures are contained in the Code of Federal Regulations (CFR) at 21 CFR Part 11. These rules, known as 'Part 11', are described at www.fda.gov/ora/compliance_ref/part11.

7.2. Industrial chemical and pesticide test guidelines

The lead agency on harmonizing genetic toxicology test guidelines has been the Organization for Economic Cooperation and Development (OECD). The OECD adopted a decision that

data collected according to OECD Test Guidelines and Principles of GLP would be accepted in member countries for assessment purposes relating to protecting human health and the environment (www.oecd.org/ehs/mad.htm). OECD test guidelines are organized into four sections: physical chemical properties, effects on biotic systems, degradation and accumulation, and health effects. The titles of individual OECD test guidelines may be viewed at www.oecd.org/ehs/test/testlist.htm. There are 15 approved genetic toxicology test guidelines for various genetic toxicology assays. This includes the four commonly performed assays: bacterial reverse mutation assay (OECD 471), In Vitro Mammalian Chromosome Aberration Test (OECD 473), Mammalian Erythrocyte Micronucleus Test (OECD 474), and In Vitro Mammalian Cell Gene Mutation Test (OECD 476). The entire test guidelines must be purchased from OECD. OECD GLP guidelines are available at www.oecd.org/ehs/glp.htm. Both the ICH guidelines for drugs and the EPA harmonized guidelines for industrial chemicals and pesticides used the OECD guidelines as a basis for study design.

The EPA has developed a new series of harmonized test guidelines for both industrial chemicals and pesticides based on the study designs provided in the OECD Health Effects test guidelines. The harmonized guidelines have blended previous guidelines issued separately by OPPT (Toxic Substances) and OPP (Pesticides) with the genetic toxicology test guidelines issued by the Organization of Economic Cooperation and Development (OECD). Eighteen final genetic toxicology test guidelines have been issued including some for assays that are not in routine use for regulatory submission. Guidelines are available for the most commonly performed genetic toxicology assays for EPA submission including: Bacterial reverse mutation assay (870.5100), in vitro mammalian cell gene mutation test (870.5300), in vitro mammalian cell chromosome aberration test (870.5375), and Mammalian erythrocyte micronucleus test (870.5385). The EPA has separate GLP guidelines for pesticides regulated under FIFRA (www.ovpr.uga.edu/qau/epaglp_a.html) and for industrial chemicals regulated under TSCA (www.ovpr.uga.edu/qau/tscatoc.html). The EPA has started a program for electronic submission and review of data and reports similar to the efforts by the FDA under 21 CFR Part 11. The EPA program, called Cross-Media Reporting and Record-keeping Rule (CROMERRR), is described at http://alpha.lmi.org/epa/electronic_reporting/cromerr.html.

7.3. Access to US federal laws

In the US, the Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register (FR) by the Executive departments and agencies of the Federal Government. All of the controlling regulations for genetic toxicology testing and GLP's are published in the CFR and FR and are searchable electronically through the Government Publishing Office (www.access.gpo.gov/nara/cfr/index.html). This search can be done by keyword, CFR citation, CFR title, or volume number. Laws and regulations governing the FDA may be located at www.fda.gov/opacom/laws/lawtoc.htm. Laws and regulations governing the EPA may be found at www.epa.gov/epahome/lawreg.htm.

7.4. European government web resources

The UK Medicines Control Agency (MCA) website provides useful detail on the history of the enabling legislation governing drug licensing in the UK under The Medicines Act and then later throughout Europe under various European Legislation (www.mca.gov.uk). This website also provides linkage to drug authorities throughout Europe (www.mca.gov.uk/links.htm). Information on the OECD Good Laboratory Practice (GLP) and Compliance Monitoring program, including references to the governing laws and published GLP guidelines, is available at www.oecd.org/ehs/glp.htm.

8. Professional societies related to genetic toxicology

Professional societies have played a key role in the formation within toxicology of the subspecialty of genetic toxicology. Early practitioners of genetic toxicology tended to belong to more general toxicology societies such as the Society for Toxicology (www.toxicology.org) or professional societies organized around traditional scientific disciplines such as the American Society for Microbiology (www.asmusa.org).

In 1969, the EMS was organized in the US to support the growing field of genetic toxicology. This society is the primary genetic toxicology society in the US. The EMS website, www.ems-us.org, provides information on membership, annual meetings and publications. There are a number of regional genetic toxicology societies in the US. The Genetic Toxicology Association (GTA) serves the mid-Atlantic region (www.ems-us.org/gta/index.html). The Genotoxicity and Environmental Mutagen Association (GEMS) serves the North Carolina and southeast region of the US (www.ncneighbors.com/312). The Genetic and Environmental Toxicology Association (GETA) serves northern California (www.ems-us.org/geta/index.html).

The European EMS, founded under the leadership of Dr Frits Sobels in 1970, maintains a website where programs, meetings and publications are listed (http://193.51.164.11/eems/index.htm). The United Kingdom Environmental Mutagen Society (UKEMS) serves genetic toxicologists in the UK with a website at www.swan.ac.uk/cget/newuk1.htm. The Société Française de Toxicologie Génétique serves the French genetic toxicology community with a website that is maintained in both French and English (www.sftg.org). The Japanese Environmental Mutagen Society (JEMS) maintains a website with both Japanese and English versions (http://wwwsoc.nii.ac.jp/jems/jems-e.html). The Sociedade Brasileira de Mutagênese Carcinogênese e Teratogênese Ambiental (Brazilian Mutagen, Carcinogen, and Teratogen Society, SBMCTA) maintains a website in Portuguese at www.sbmcta.org.br. The Asoc. de Mutagenesis, Carcinogeneisi Y Teratogenesis Ambiental represents Latin America (www.iaems.nl/alamcta.htm). The Mutagenicity and Experimental Pathology Society of Australasia (www.mepsa.org) was formed in 1999 by combining two Societies: the Australia and New Zealand Environmental Mutagen Society (ANZEMS) and the Australasian Society for Experimental Pathology (ASEP). In Asia, genetic toxicology societies include the China Environmental Mutagen Society (CEMS, www.iaems.nl/cems.htm), the Korean Environmental Mutagen Society (KEMS, www.iaems.nl/kems.htm), the Philippines Environmental Mutagen Society (PhEMS, www.iaems.nl/pems.htm), the Thai Environmental Mutagen Society (www.iaems.nl/tems.htm), and the Environmental Mutagen Society of India (EMSI, www.iaems.nl/emsi.htm). Information on the Pan-African Environmental Mutagen Society (PAEMS) is available at www.iaems.nl/paems.htm.

Many of the various national genetic toxicology societies formed an international coordinating society called the International Association of Environmental Mutagen Societies (IAEMS). This organization was formed to facilitate international contacts and cooperation in all aspects of mutagenesis research, to facilitate formation of regional or national mutagenesis associations and to hold periodic international meetings. Information on the IAEMS may be found at www.iaems.nz. The member associations of the IAEMS may be found at www.iaems.nl/member.htm.

9. Journals that focus on genetic toxicology

The personal computer and the Internet have revolutionized how information is collected, stored and distributed. This revolution has continued into the laboratory and has changed how we collect, analyze and report scientific observations. The process of publishing scientific papers has accelerated through the process of electronic submission, review and printing. Even the process of 'printing' has taken on new meanings with electronic typesetting, on-demand printing, full text retrieval online or even fully electronic journals online. In nearly all cases, journals are indexed by

MEDLINE and other fee-based indexing services such as Current Awareness in Biological Sciences (CABS) (www.elsevier.nl/locate/inca/600715) and Science Citation Index (ISI) (www.isinet.com/isi/products/citation/sci/index.html). A new concept in online journal publishing and access is HighWire Press (http://mywire.stanford.edu). HighWire Press, controlled by Stanford University, was started in 1995 to publish or disseminate journals online. Initial journals included Journal of Biological Chemistry, Science and Proceedings of the National Academy of Science and now HighWire includes nearly 300 journals mainly in the biological and medical sciences. HighWire provides immediate online access to subscribers of a journal, but based on varying types of licenses, other HighWire journals are available online also. Some journals are made available to nonsubscribers after a delay period—commonly 6 months to 1 year after publication. Another source of access to multiple journals is ScienceDirect® provided by Elsevier Science B.V. (www.sciencedirect.com). Elsevier, publisher of over 1100 journals in the sciences including several core journals in the field of mutagenesis research, has established links to other publishers and science content providers to provide an online resource for full text retrieval of scientific literature.

Mutation Research, published by Elsevier Science B.V., has a number of separate journals dealing with genetic toxicology and mutagenesis (www.mutationresearch.com/mutat/show). Journal sections include Fundamentals and Molecular Mechanisms of Mutagenesis, Genetic Toxicology and Environmental Mutagenesis, DNA Repair, Reviews in Mutation Research, and Mutation Research Genomics. Mutation Research articles are available online through www.sciencedirect.com. The official journal of the Environmental Mutagen Society, Environmental and Molecular Mutagenesis, is published by Wiley-Liss, Inc. Abstracts of all journals are available through MEDLINE and other indexing services. Subscription information and full text access online for members is available at www.interscience.wiley.com/jpages/0893-6692. Mutagenesis, published by Oxford University Press, is the journal of the UKEMS (http://www.swan.ac.uk/cget/ukems/mutagenesis/mutagenesis.htm). The European Journal of Genetic and Molecular Toxicology is an online journal published by the European Environmental Mutagen Society (www.swan.ac.uk/cget/ejgt1.htm). The Japanese Environmental Mutagen Society publishes Environmental Mutagen Research three times per year with both print and electronic copies available (http://wwwsoc.nii.ac.jp/jems/no6.files/journale.htm).

There are a number of professional associations in the field of toxicology that include articles in the field of genetic toxicology. One of these more general toxicology journals is Toxicology (www.elsevier.nl/locate/toxicol), the official journal of The British Toxicology Society (www.thebts.org/index.html), published by Elsevier Science, B.V. The Society of Toxicology (www.toxicology.org) publishes Toxicologic Sciences and Toxicology and Applied Pharmacology (www.toxicology.org/Information/Publications/journals.html).

10. Online resources for education in genetic toxicology

The Internet has been used as an educational delivery medium for distance education classes, as a repository for educational material and as a medium of exchange of ideas. One of the first web-based training class in genetic toxicology has been developed by the IAEMS through a grant from the NIEHS, Research Triangle Park, NC, USA. The tutorial couse on the Rodent Erythrocyte Micronucleus Assay In Vivo is available on the web (www.iaems.nl/mainNC.html). Courses on other standard genetic toxicology assays, including the bacterial reverse mutation assay, are in preparation. There are also online educational resources for teaching general concepts in toxicology. One example are the toxicology tutorials available from the Specialized Information Services branch of NLM (http://sis.nlm.nih.gov/Tox/ToxTutor.html).

There are a variety of lecture outlines and course notes in various areas of genetic toxicology provided by university professors. One example is an introductory online tutorial in genetic toxicology presented by Dr David H. Evans, Department of Molecular Biology and Genetics, University of Guelph, Guelph, Ont., Canada. This course provides an overview of the field of genetic toxicology, basic concepts of DNA damage, DNA repair, the consequences of mutations, and how mutations are detected (www.uoguelph.ca/mbgwww/courses/94200/Toxicology.html). Another example of an online course overview is the webpage on DNA repair developed by Dr Joel Huberman, Department of Cancer Genetics, Roswell Park Cancer Institute, Buffalo, NY(http://mcbio.roswellpark.org/RPN530/DNA–Repair/DNA_Repair.html). Many laboratories and research programs have webpages that also contain instructional material to provide background information. A good example of this is the website on the p53 gene maintained by the Institut Curie, Paris, France (http://perso.curie.fr/Thierry.Soussi/index.html).

Large professional associations have developed extensive websites to support education within their sphere of influence. One example is the American Society for Microbiology that has developed an extensive online resource with digital images for teaching, curriculum guides, online reviews of teaching materials and websites (www.micrpbelibrary.org).

The Internet is also a resource for locating academic programs in genetic toxicology. Professional societies such as the Society of Toxicology provides listings of graduate programs in toxicology with programs specializing in genetic toxicology identified (www.toxicology.org/PublicOutreach/CareerResources/careerprograms.html). Examples of university webpages providing information about graduate research in mutagenesis are provided by the University of Texas Medical Branch, Galveston, TX (http://www2.utmb.edu/pmch/geToxicology.htm) and the Center for Environmental Health, University of Victoria, Victoria, BC (http://web.uvic.ca/ceh/).

11. Structure Activity Relationship (SAR) analysis

SAR analysis can be considered to be computational toxicology. SAR combines toxicology data, bioinformatics, and computational analysis to create expert computer systems that can predict biological or toxicological effects of a new compound. This is accomplished by identifying reactive chemical structures in the new molecule and then using either previously gathered information or using statistical algorithms developed from previously gathered information to predict an effect (Rosenkranz et al., 1999; Matthews et al., 2000).

One early SAR program based on statistical algorithms was developed by Dr Herbert Rosenkranz, University of Pennsylvania and Dr Jilles Klopman, Case Western Reserve University. Their academic research lead into the formation in 1996 of MultiCase, Inc, Beachwood, OH. This company offers a variety of SAR software including CASETOX, TOXALERT and MULTICASE (www.multicase.com) that, with the appropriate databases, provide predictions of various toxicology endpoints including genotoxicity. Another early program based on statistical algorithms, TOPKAT®, provides separate modules for Ames mutagenicity as well as a variety of other short-term toxicology endpoints (www.accelrys.com/products/topkat/index.html). The Oncologic® SAR program, developed by Logichem, Inc. Boyertown, PA in cooperation with the EPA, predicts carcinogenic potential within specific classes of chemicals (www.logichem.com).

Both the FDA and EPA have established programs to evaluate and use SAR modeling and prediction. The mission of the Regulatory Research and Analysis Program with in FDA CDER is to construct electronic databases for pre-clinical toxicology studies for pharmaceuticals and to develop structure activity relationship (SAR) software programs to provide reliable estimates of the potential toxicities of FDA-regulated chemicals (www.fda.gov/cder/otr/rras2.htm # prog7). The EPA has a number of SAR programs including the use of SAR in the High Production Chemicals Challenge Program (www.epa.gov/opptintr/chemrtk/sarfinl1.htm).

One forum for publication of articles related to SAR is 'SAR and QSAR in Environmental Research' published by Taylor and Francis Group, London, UK (www.tandf.co.uk/journals/titles/1062936x.html).

12. Mutational spectra databanks

As laboratory techniques in genetic toxicology have improved over the years the focus of research has moved from the organism to the cell and finally to the molecule. Mutation assays using intact organisms or intact cells to investigate genetic damage generally use phenotypic change in a marker to infer mutation in the controlling gene. The ability to sequence specific gene sequences from recovered putative mutant cells now permit molecular confirmation that a mutant phenotype actually results from an altered, mutated DNA sequence. Different types of genotoxins can produce characteristic genetic lesions that can be identified through sequencing. Information can be gathered on the mechanism of action of a genotoxic chemical by looking at the spectrum of mutants produced by the chemical. Sequence analysis can help identify hotspots in a gene where a specific mutation may result in altered function of the corresponding protein. Germline mutations can result in heritable genetic diseases and somatic mutations may result in cancer. Gene sequence analysis can help in diagnosis and identifying the mutational basis of a disease. For these reasons a large number of mutation databases with associated software tools have been developed. These databases tend to be been structured to serve distinct needs and research communities. Some databases are organized around a specific locus or disease such the p53 mutation database maintained by the Laboratoire de Genotoxicologie des Tumeurs, Institut Curie, Paris, France (http://perso.curie.fr/Thierry.Soussi/) or the p53 mutation database maintained by International Agency for Research on Cancer, Lyon, France (www.iarc.fr/p53/Index.html).

Other mutational databases have been developed to serve specific research communities. The Mammalian Gene Mutation Database, maintained by Center for Molecular Genetics and Toxicology at the University of Wales, Cardiff, Wales (http://lisntweb.swan.ac.uk/cmgt/index.htm), collects the sequences of mutagen-induced gene mutations in mammalian tissues. Users may submit mutant gene sequences or search the database for specific mutants. Search criteria include type of mutagen, species or cell line, tissue, specific mutational event or author. Results include all matching mutational events with hypertext links to literature citations. This database is designed to complement the Human Gene Mutation Database maintained by the Institute of Medical Genetics, at the University of Wales (http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html).

An example of how mutational spectra analysis has become part of genetic toxicology can be seen with the development of transgenic rodents for mutagenicity research. In the field of genetic toxicology, one goal has been to develop an easy, quick and inexpensive in vivo gene mutation model. The use of bacteria and mammalian cells in culture with homogenized rodent liver to simulate mammalian metabolism has become, by default, an alternative to predicting mutagenesis in vivo. Development of the molecular tools to insert recoverable shuttle vectors with target and reporter genes into the genomic DNA of animals led to the development of transgenic rodents such as BigBlue™ mice (Kohler et al., 1991; Young et al., 1995). These types of animals can be used to measure genotoxicity of chemicals in various tissues by recovering bacteriophage lambda shuttle vectors containing mutated *lacI* or *cII* target genes. Target genes in recovered shuttle vectors can be sequenced to confirm the underlying molecular basis for the change to the mutant phenotype (Shane et al., 2000). As mutants are sequenced, the sequence of each mutant can be submitted to a shared database and then analyzed relative to the spectra of mutants produced by other known mutagens. One such database used by researchers with the BigBlue model was developed by Dr Johan de Boer at the University of Victoria, Victoria, BC (http://eden.ceh.uvic.ca/bigblue.htm). Another site that maintains searchable mutant spectra databases, including the transgenic *lacI* gene, is maintained by Dr Neal

Carriello at 'Neal's DNA Mutation Site', (www.ibiblio.org/dnam/mainpage.html).

13. Toxicogenomics

Development of cDNA microarray technology has provided a powerful tool for the study of gene sequence, structure and expression (Nuwaysir et al., 1999; Cooper, 2001). Using current microarray technology and analytical software, the expression of thousands of genes can be monitored simultaneously in two biological samples of interest, and the expression patterns compared. Traditional toxicology studies usually have relied on measuring the presence of an altered cell type that takes time to develop. For example, if the endpoint is a specific type of cancer, the process may take months or years to give a detectable tumor following exposure to a genotoxic carcinogen. The process from carcinogen exposure and tumor formation may follow predictable sequences of cellular events involving differential gene expression with different sequences occurring with different mechanism of action. Complementary DNA (cDNA) microarray technology, can be used to analyze such changes in genome-wide patterns of gene expression between treated and control groups. Toxicogenomics using microarray technology may be able to identify toxic substances, to identify mechanisms of action, determine no effect levels, determine susceptible tissues and cell types, and extrapolate effects from one species to another (Medlin, 1999). In the related field of pharmacogenomics, microarray analysis gene expression profiles can be used as a proof of principle assay to show an effect of a candidate drug in vivo.

The National Center for Toxicogenomics was established by NIEHS, Research Triangle Park, NC to provide a center of excellence for cDNA microarray technology in predictive toxicology (http://dir.niehs.nih.gov/microarray/home.htm). This project is a natural complement to the long-term program in chemical carcinogenicity and genotoxicity supported by NIEHS and the NTP. One outcome of this project to date has been the development of 'The Toxchip' (http://ehpnet1.niehs.nih.gov/docs/1999/107-5/innovations.html). Early versions of this chip contain over 2000 human genes selected for relevance to basic cellular processes and response to different types of toxic injury including DNA replication, DNA repair, apoptosis, cell cycle control, oncogenes and tumor suppressor genes. New versions of the chip will contain over 12 000 genes. While not intended to replace short-term genotoxicity or long-term carcinogenicity assays, toxicogenomics could prescreen new chemicals and also reduce the time, expense, and use of animals in the process of drug and chemical development. Many others are involved in the development of cDNA microchip arrays for genomics including academic, governmental, nonprofit and corporate groups. Examples of toxicogenomic research within academic groups include the Department of Biochemistry at Stanford University (http://cmgm.stanford.edu/pbrown/) and the Department of Molecular Genetics, Max-Planc-Institure, Berlin, Germany (www.molgen.mpg.de/research/lehrach/groups.html). The Microarray Gene Expression Database group provides a forum and structure for exchange of information for workers in the field (www.mged.org).

Underlying much of the revolution in toxicogenomics and pharmacogenomics is basic work being done in the field of genomic research by such institutions as The Institute for Genomic Research, Rockville, MD (www.tigr.org/tdb), Celera Genomics, Rockville, MD (www.celera.com), and by the NCBI, Rockville, MD (www.ncbi.nlm.nih.gov). NCBI has developed programs such as the Gene Expression Omnibus to support the public use and dissemination of gene expression data, to build a gene expression data repository, and to provide an online resource for the retrieval of gene expression data from any organism or artificial source (www.ncbi.nlm.nih.gov/geo/). Trade associations have established committees to help in the validation of microarray analysis in toxicogenomics. For example, the Health and Environmental Sciences Institute of the International Life Sciences Institute has established a subcommittee called

Application of Genomics and Proteomics in Mechanism-Based Risk Assessment Subcommittee (http://hesi.ilsi.org/activities/index.cfm).

14. Careers in genetic toxicology

One practical area that the Internet has served the field of genetic toxicology has been in student development and job placement. Most professional societies offer information on career planning, fellowship opportunities, mentoring programs and travel awards. Professional associations with student programs include the Environmental Mutagen Society (www.ems-us.org), the Federation of Societies for Experimental Biology (https://career.faseb.org/marc/index.html), the Society for Toxicology (www.toxicology.org/PublicOutreach/EducationOutreach/education.html#) and the American Society for Microbiology (ASM) (www.asmusa.org/mbrsrc/studentsection.htm).

Professional societies also provide job-matching services such as offered by the Environmental Mutagen Society (www.ems-us.org/placemnt.html), ASM (www.asmusa.org/empinfo.htm), and the Society for Toxicology (www.toxicology.org/PublicOutreach/placement/placement.html). Depending on the level of service, some of the job placement services are on a fee basis. There are also a number of online job matching services such as ScienceJobs.com (www.sciencejobs.com). A final webpage that has significantly contributed to the field of genetic toxicology by providing humor and insight has been the Dilbert Homepage (www.unitedmedia.com/comics/dilbert/).

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