

Off-the-Shelf Technologies for Space Biology

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A summary of available technologies that can be applied now to implement the cell and molecular research recommendations of the 1998 Space Studies Board Committee on Space Biology and Medicine, and conduct research on the biomolecular level objectives of the Fundamental Space Biology Program.

Introduction

The 1998 Space Studies Board (SSB) Committee on Space Biology and Medicine report, *A Strategy for Research in Space Biology and Medicine in the New Century*, “calls for an integrated, multidisciplinary approach (to space research) that encompasses all levels of biological organization – the molecule, the cell, the organ system, and the whole organism – and employs the full range of modern experimental approaches from molecular and cellular biology to organismic physiology.” (<http://www.nas.edu/ssb/csbmmenu.htm>).
(See Attachment 1 below)

The *NASA Fundamental Space Biology Program Description* states, “The major scientific objective of Fundamental Space Biology is to expand our understanding of fundamental biological processes and the mechanisms by which these processes sense, respond, adapt to, and evolve in the space environment.
(See Attachment 1 below)

Over the past 5 years technologies have been developed that enable, for the first time, the discovery of biology’s diverse and complex cell molecular mechanisms. The mapping of the primary model species’ genomes, plus the rapid development of high through-put research tools and computer aided research methods have already started producing a bounty of information on how biology’s basic mechanisms work. NASA can effectively and economically use these tools to address the basic questions of how Earth life responds to space. They can be applied now to start accomplishing the above recommendations and objectives. They also provide unprecedented research return for the cost of required resources. The benefits of this knowledge include:

- Characterization of the molecular mechanisms behind biological reaction to space;
- Identification of the fundamental processes underlying space medicine problems;
- Development of more effective countermeasures;

- Discovery of DNA targets to genetically engineer plants and other organisms for space;
- Provide a unique control and additional data set for related ground research.

The technologies presented in this report were selected based on four criteria. (1) They are in operation and available. (2) They can be applied to basic model species: bacteria, yeast, *C.elegans*, *Drosophila*, mice, rats, mammalian cells and tissues, and plants (*arabidopsis*), all of which can be supported in space using currently available space flight research hardware. (3) They provide data that directly address the cell biology research priorities identified in the SSB 1998 report. (4) They can be applied to samples fixed in-flight using simple fixation methods (one to three steps) or frozen at -20°C or both.

They are grouped according to the type of information they provide; for example, techniques that inventory the molecular population of a cell, or, ones that discover a molecule's function.

Better and better, faster and faster, cheaper and cheaper.

The technology survey that was conducted for this report also provided a measure of biotechnology's high rate of advancement, and the increasing rate of molecular biology discovery that is being realized. Almost all technologies listed in the table were released in the past 2 years. The breakthroughs are not only in new abilities to study biology but also in the economy and efficiency of the techniques. There are substantial and increasing benefits for NASA due to the decline in resource and flight costs for biomolecular studies while the research value is rising.

The lesson learned from this study is that a technology watch should be maintained, technology shopping should be practiced, and that the inventory of important new tools should be updated and reported to decision makers quarterly to ensure that NASA continues to deliver the maximum scientific yield from space flight research.

Attachment 1.

1) 1998 SSB Report recommended research on the following specific biological questions:

- 1) How do single cells detect gravity?
- 2) How are cell functions influenced by gravity?
- 3) How do cells transduce gravitational stimuli?

2) From the *NASA Fundamental Space Biology Program Description*

“The major scientific objective of Fundamental Space Biology is to expand our understanding of fundamental biological processes and the mechanisms by which these processes sense, respond, adapt to, and evolve in the space environment.

The objectives include, but are not limited to, discovery of:

- (*) How physical forces encountered in space flight impact biological structure and function.
- (*) The role of the genome and cellular structures in sensing and responding to gravitational force.
- (*) Whether, and to what extent, normal development of cells, systems, and organisms depends on gravitational force.
- How and for what purposes different organisms in the animal and plant kingdoms sense and use gravity.
- (*) The role of gravity in evolution.
- The role of gravity in determining how the structure, function, and interactions of space and planetary ecosystems change over time.”

These questions concern cells’ molecular activity either directly (*) or as part of an integrated study. The currently available ‘high-throughput’ research tools described in Table 1 allow research to be conducted on each of these questions, sometimes simultaneously.

With methodical tissue collection of all species flown, this format enables comparative cell biology studies that are longitudinal over time, lateral across species, and vertical across organisms and biological hierarchies (single cell, local cell groups, tissues, organs, multi-cell organisms, complex organisms). This approach should provide sufficiently detailed data for initial research into the causes and processes of observed physiological responses to space. And it will serve as a basis for a comprehensive program of basic discovery.

These capabilities were demonstrated by Hammond et al on STS 106. The Hammond investigation confirmed the ability to differentiate the genomic and protein responses to the space, launch vibration, launch acceleration, and rotating wall vessel environments through genomic and proteomic analyses. This investigation also demonstrated the capability to preserve specimens in space in a manner that allows researchers to track the movement of specific transcription factors from the cytoplasm to the nucleus via fluorescent probes. The entire flight portion of the experiment (for one time point) was conducted within the volume of a coffee can.

Attachment 2

The following method uses a broad survey approach to catalog, in detail, how the space environment affects the cell's molecular activity. From this catalog, researchers can study the source of gravity sensing and trace the information flow within the cell to the metabolic and structural outcome. Subsequent studies can apply the same techniques to more focused and detailed research on specific questions based on the resulting knowledge.

Example Research Method:

- 1) Collect tissues in space.
 - a) Harvest tissues from all available model species at predetermined times of mission.
 - b) Fix, fix and chill at 4°C, and/or fast freeze each sample at -20°C or below.
 - c) Store and return to ground for post-flight analysis.
- 2) Catalog the change, compared to controls, in bio-molecules in the cells.
 - a) High throughput biomolecular assays
 - b) Metabolic analysis – e.g., nutrient uptake, motility, growth rates, reproduction rates.
- 3) Identify changed biomolecules' and discover their functions.
 - a. Bioinformatics, 2d gels, knockouts etc.
- 4) Correlate biomolecular activity to higher level effects.
 - a. Signal transduction, cell phenotype, organ and organismal effects.
- 5) Compare samples over time to characterize adaptive response to Space.
 - a. Datamining,
 - b. Structural analysis – molecular probes, fluorescence tagging, electron microscopy, 3-D computational reconstruction, near field optical microscope.
 - c. Dynamics – such as the movement of transcription proteins into the nucleus.
- 6) Perform comparative cell biology studies across species to identify differences in response between single cell, multi-cellular and complex organisms.

Other uses for this accumulative space derived data:

- a) becomes part of the world's accumulation of protein and gene data for future research;
- b) starts the process of finding protein or other molecular targets for developing countermeasure therapeutics;
- c) establishes the space-related branch of bioinformatics and
- d) can be used as a control for ground based bio-molecular studies of osteoporosis, immune deficiencies, radiation effects, geotropism, etc.

Note: One of the new approaches possible because of these capabilities is opportunistic science. A considerable amount of biological information can be obtained within coffee can sized research systems comprised of a container, power system, incubator, fixation system. For example, the cell biology system designed for the Nano-satellite flight could replace ballast. A single Bioserve incubation container can yield a high quantity of information as demonstrated on STS 106 by Hammond et al.

Table 1: Current state-of-the-art technologies for the study of the cell molecular response to the space environment.

The following table shows tools that are currently available for research on cell molecular activity. They are applicable to all the organisms that can provide tissue samples for simple fix and freeze strategies. Together the technologies can provide an avenue to addressing, at the molecular level, NASA's goals to discover how earth life responds to the space environment.

Tissue collection: Planned or opportunistic sample collection for biomolecular analysis can be done on ISS or free flyers. Bioserve and microfluidics packages can be programmed for automated small species sample preservation. Samples can also be collected on a non-interference basis from species flown for other reasons. These tissues can then be analyzed on the ground, employing the listed methods to discover and begin to understand the space-specific cell molecular activity.

After the tissues are returned to Earth the process could have the following steps. These steps form the Table's sections:

- 1) Detect the changes in cells' biomolecules as result of exposure to space.
- 2) Determine the function of changed proteins.
- 3) Discover the signaling pathways that cause expression changes and coordination with other cells.
- 4) Research the mechanisms of the effect these expression changes have in local cells, organs, etc.
- 5) Research correlations of molecular activity to observed organismal effects (e.g., bone demineralization).

Related information is summarized at the bottom. These additional sections are not meant to be exhaustive or review established capabilities, but indicate recently available capabilities:

- Computer Aided Research / Desk-top Biology
- Online Resources For Model Species
- Imaging

1) Detect the changes in cells' biomolecules as result of exposure to space.

- 1) Catalog the inventory of transcripts, proteins and other molecules in cells exposed to the space environment.
- 2) Compare with controls to identify changes.

Research use	Technology	Org	Product name	Description
Id all RNA in cells	SAGE, Serial analysis of gene expression. Sensitive, nonspecific capture of mRNA	Invitrogen	I-SAGE Kit	<p>http://www.invitrogen.com/content.cfm?pageid=2911&cfid=351245&cftoken=55922709</p> <p>Identification and digital quantification of transcripts from small samples. Capture the RNAs with magnetic beads, make cDNA, and cut a fourteen-letter tag from each one. Glue single tags together into long molecules called concatemers. Sequencer reads these molecules, counts them and analyzes them, and computer programs give you a list of the genes: Id'ed if known or will list previously unknown genes for discovery.</p> <p>Can be referenced to a public gene expression database SAGEmap: http://ncbi.nlm.nih.gov/sage.</p> <p>EMBL used SAGE to monitor the activity of the complete genome of the fruit fly (http://www.flybase.org.) to watch what happens as cells receive a signal that helps form tissues.</p> <p>http://www.developmentalcell.com/cgi/content/abstract/1/4/579/ http://www.sagenet.org/ http://www.sagenet.org/SAGEData/sagedata.htm SAGE data for 600,000 transcripts.</p>
Highly parallel biomolecular assay	Quantum-dot-tagged microbeads Broad RNA, protein detection	Indiana University	Quantum-dots	<p>http://www.nature.com/cgi-taf/DynaPage.taf?file=/nbt/journal/v19/n7/abs/nbt0701_631.html&dyoptions=doi1005069355</p> <p>Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots (nanocrystals) into polymeric microbeads at precisely controlled ratios. ID up to one million different biomolecules. Their novel optical properties (e.g., size-tunable emission and simultaneous excitation) make them sensitive fluorophores for wavelength-and-intensity multiplexing. This spectral coding technology is for gene expression studies, high-throughput screening, and medical diagnostics.</p>

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Highly parallel bio-molecular detection	Nano-barcodes	SurroMed Inc. Penn. State U		http://www.sciencemag.org/cgi/content/full/294/5540/137 www.surromed.com For highly multiplexed analysis of genes, proteins and other analytes in solution . Cylindrically shaped, "striped" metal nanoparticles are used to simultaneously carry out large numbers of biological assays in a small volume. Chemistry allows coupling of a wide variety of capture reagents onto bar-coded particles. The striping pattern can be used to identify which chemistry has been immobilized on the particle, in much the same way as position encodes information in conventional microarray experiments.
Highly parallel gene assays	premade micro arrays off the shelf RNA detectors	Affymetrix	GeneChip®	Pre-made GeneChip® arrays featuring probes from human, rat, mouse, Drosophila, Arabidopsis, yeast, Pseudomonas aeruginosa, or Escherichia coli . Chips are generated using proprietary light-directed chemical synthesis process, which combines solid-phase chemical synthesis with photolithographic fabrication, and are used in conjunction with GeneChip instrumentation.
Highly parallel gene assays	premade micro arrays	BD Biosciences-CLONTECH	Atlas™	Application-targeted or broad-coverage arrays, which are used to simultaneously profile many cellular pathways and functions. E.g., array bearing 80-bp long synthetic oligonucleotides probes for all 8,300 currently named human genes. Also arrays of probes for 140-3,800 genes from human, mouse, or rat .
Whole yeast genome arrays	premade micro arrays	Corning Inc		Genome-wide array that contains 6,160 PCR products corresponding to unique genes representing the entire yeast genome .
Off the shelf Highly parallel gene assays	premade micro arrays	Incyte Genomics		Broad coverage arrays with probes corresponding to genes of human, rat, mouse, Arabidopsis thaliana, yeast, and Staphylococcus aureus
Mutation detection	Accurate genetic comparison	John Hopkins School of Medicine.		http://www.hopkinsmedicine.org/press/2001/NOVEMBER/011113.htm Highly accurate gene chips to detect differences from a reference gene map. Radiation, evolution monitoring.

2) Determine the function of the changed proteins and other biomolecules.

- Bioinformatic analysis: Gene and protein database lookup. Reference other studies of specific proteins.
- Discover unknown proteins: 2D gel pattern comparisons via database lookup.
- Analyze with commercial yeast, etc. chips for further ID.
- Computational methods – protein maps, sequence comparisons, modeling etc
- Follow-up studies with custom chips on same samples, new samples

Database lookup of SAGE results	SAGE package includes internet lookup of RNA on existing databases	Invitrogen	I-SAGE Kit	<p>http://www.invitrogen.com/content.cfm?pageid=2911&cfid=351245&cftoken=55922709</p> <p>During sequential reading of collected RNA, SAGE software compiles a list of all discovered RNA and counts them. This data is then compared to existing SAGE databases. It outputs a list of the known genes and also the unknown.</p> <p>http://www.sagenet.org/SAGEData/sagedata.htm SAGE data for 600,000 transcripts.</p> <p>SAGEmap, public gene expression database: http://ncbi.nlm.nih.gov/sage.</p> <p>EMBL used SAGE to monitor the activity of the complete genome of the fruit fly for JNK protein function discovery. http://www.flybase.org.)</p> <p>http://www.developmentalcell.com/cgi/content/abstract/1/4/579/</p>
HTS protein id.	2-d gel image database	NCI, or ExPASy U. Geneva	Flicker, or Swiss-2DPage	<p>www.lecb.ncifcrf.gov/2dwgDB.</p> <p>ca.expasy.org/ch2d</p> <p>Archive of standardized gel images for computer comparison to new gel images. Aides identification of proteins.</p>
Protein maps		U. of Washington		<p>http://www.hhmi.org/news/fields.html</p> <p>Nature Biotechnology, 12/2000</p> <p>Protein Interaction networks by analyzing published data on the interactions among thousands of yeast proteins. A first step toward providing scientists with a reference guide to aid detailed exploration of the functions of yeast proteins. Report 72% accuracy in predicting protein function from its place in the map.</p> <p>Can complement other approaches</p>

2b) Discovery of unknown proteins

Follow-on research using same or new tissue samples to target still unknown proteins.

Genetic function discovery	Knock outs using isogenic cell lines	DuPont Pharmaceuticals Company		http://www.nature.com/cgi-taf/DynaPage.taf?file=/nbt/journal/v19/n10/full/nbt1001-919.html Top-down screening strategy that integrates fluorescence protein technology with somatic cell genetics, thereby capturing some of the appeal of molecular approaches. Uses fluorescent protein technology in isogenic cell lines that differ by a single genetic change to identify space reactions with gene-selective properties.
mRNA function discovery	Antisense at mRNA level	Isis	Gene Trove	www.dddmag.com/feats/0109anti.asp Highly selective antisense inhibitors to genes of interest for in vitro and in vivo functional genomic studies. For use in cell culture-based assay systems. 100 genes in parallel per run. Also a database product that provides information to partners on the roles that gene products play in different physiological models. Tested on entire array of yeast genes.
Custom gene arrays	Made to order gene chips	Agilent		Offers custom-made, in situ synthesis-based arrays for use with their complete microarray system. These arrays are generated using inkjet-based technology.
Microarrays for regulatory pathways		OriGene Technologies Inc	SmartArray	Microarrays for specific regulatory pathways: chips focus on nuclear hormone receptors; two different subsets of transcription factors; phosphotyrosine kinases; G-proteins, G-protein-coupled receptors, and their regulators; cytokines, chemokines, and their receptors; ion channel proteins; transporter proteins; proteinases; and adhesion molecules.
Targeted Human gene Microarrays	Off-the-shelf Microarrays with specific focus	Perkin-Elmer	MICROMAX gene expression analysis system	http://lifesciences.perkinelmer.com/products/micromax/prod_serv.asp Six targeted arrays: 194 known human kinases and 56 phosphatases; 290 human transcription factors; 281 human cancer-related genes; 135 ion channel and transporter genes, and 134 receptor genes; over 250 probes for apoptosis research; and more than 300 neurobiology cDNA probes.

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HTS protein id.	2-d gel image database	<u>NCL</u> , ExPASy U. Geneva	<u>Flicker</u> , Swiss-2DPage	www.lecb.ncifcrf.gov/2dwgDB , ca.expasy.org/ch2d Archive of standardized gel images for comparison to new gel images. Aides identification of proteins.
Id of proteins	MALDI-TOF MS	Ciphergen		http://www.ciphergen.com/F1_prod1.html Mass spectrometry of a spot from 2-d gel is analyzed by masses of its peptide pieces. Computer conducted comparisons against known mass data to id. protein.
Integrated protein id.	MALDI-TOF MS to recognition in one system	Sequenom	MassARRAY	http://www.sequenom.com/genotyping/overview/techno/techno.html MALDI-TOF MS system combines separation, detection and characterization (by software) in one step: recognizes genotype.
Software Protein analysis tools	Automated protein analysis tools	UCSF	ProteinProspector	prospector.ucsf.edu MS-Fit, MS-Tag, MS-Seq, MS-Pattern, MS-Digest, MS-Product, MS-Comp, MS-Isotope, and DB-Stat
Protein repository	Bioinformatic databases	Protein DataBase, SWISS-PROT, ...	Many	http://www.rcsb.org/pdb/ Repository for the processing and distribution of 3-D biological macromolecular structure data on proteins, nucleic acids, protein-nucleic acid complexes, and viruses.
Characterize genes	Uses MS data to characterize genes	MDS Proteomics	PepSea suite	From MS data, identifies gene location, intron-exon boundaries, and reading frames . Can identify novel proteins that may be missed by standard in silico gene predictions.
Protein characterization	Protein Chips for variety of protein types	Ciphergen		http://www.ciphergen.com/F1_prod1.html Hydrophobic ProteinChip Arrays Hydrophilic ProteinChip Arrays Anion Exchange ProteinChip Arrays Cation Exchange ProteinChip Arrays Immobilized Metal Affinity ProteinChip Arrays Preactivated ProteinChip Arrays

2c) RNA to protein correlation, protein editing, protein-protein interaction.

Protein interactions	two-hybrid systems and online access to maps	Hybrigenics, Paris	Protein Interaction Maps (PIM)	pim.hybrigenics.com/pimriderlobby/current/PimRiderLobby.htm Bacterial and yeast two-hybrid technology to create "protein interaction maps" (PIMs), which graphically display protein-protein interactions and access annotations.
Protein interactions	Two-hybrid systems	Myriad Genetics'	ProNet	www.myriad-pronet.com High-throughput version of the yeast two-hybrid system. For study of interactions between intracellular, secreted, membrane-bound proteins and pathways.
Protein interactions	Two-hybrid systems	Myriad Genetics'	ProSpec	High-throughput MS analysis of multi-protein complexes to identify macromolecular complexes, and characterize individual protein domains involved in those interactions.
Protein structure		U. of Houston		Molecular recognition using nuclear magnetic resonance spectroscopy , which allows researchers to look at the three-dimensional structure of molecules and DNA binding sites at the atomic level. Can determine structure of large proteins in solution.
Id of proteins	enzyme-linked immunosorbent assays (ELISAs) Targeted Protein detection	Pierce Boston Technology Center	SearchLight Proteome Arrays	http://www.dddmag.com/feats/0110pier.asp Simultaneous detection and quantification of two to nine proteins in each well of a 96-well plate. Rapid, sensitive, and multiplexed protein assay platform that requires little sample (5 to 50 mL) and provides a large amount of quantitative information.
custom-designed biochips DNA, RNA, peptides, other organics		U. of Houston		http://www.uh.edu/admin/media/nr/102001/biochip.htm Custom-designed biochips containing not only DNA, but other types of molecules, such as RNA, peptides or libraries of organic molecules

3) Discover the signaling pathways related to changes.

Transcription factor / signal transduction tracking	OTS chip for transcription factors	Panomics Inc	TranSignal™ Protein/DNA Array	http://www.panomics.com/index.html Assess the differential activation of 54 SH3 transcription factors simultaneously.
Signal transduction bioinformatic platforms.	Database and tools for molecular interaction			http://bioinfo.mshri.on.ca/ A database of the molecular interactions among proteins . Although, the database is not fully populated yet, the project intends to provide information about molecular interactions, complexes, and pathways from references to 3-D structure to experimental conditions defining interactions. (Free)
Cell Signaling Database	Database for human signaling pathways	NIH	Cell Signaling Networks Database	http://geo.nihs.go.jp/csndb/ Data- and knowledge- base for signaling pathways of human cells. It compiles the information on biological molecules, sequences, structures, functions, and biological reactions that transfer the cellular signals. Signaling pathways are compiled as binary relationships of biomolecules and represented by graphs drawn automatically. Our final goal is to make a computerized model for various biological phenomena.
EST database				http://www.sciencemag.org/cgi/content/summary/294/5543/747a Contains nearly 4 million entries.
Transcriptional regulation.	Database for proteins involved in transcriptional regulation.		Transfer	http://transfac.gbf.de/ Database for regulatory genomic signals and regions, especially those that govern transcriptional control. To analyze and characterize the underlying sequence elements and their context. Provides database and software tools for identification of unraveled genomic sequences.

4. Correlate molecular activity to cell structure effects.

50 – 100nm resolution optical microscope	Near-Field Scanning Optical Microscope (NSOM)	U. of Arizona		http://pubs.acs.org/subscribe/journals/ancham/jtext.cgi?ancham/73/i14/html/ac0100906 Raman, visible, infrared, fluorescence and photoluminescence spectrometers linked to a NSOM using CW and femtosecond-pulsed lasers. Measurements are made with a spatial resolution of 50 – 100 nm.
3-D microscopy of cell communities and software analysis	three-dimensional digital microscopy and micro-analysis	Resolution Sciences Corp.	Digital Volumetric Imaging (DVI)	http://www.adpath.com/ Micron resolution, high-fidelity three-dimensional digital visualization and microanalysis of up to a volume of 100 mm ³ of biological tissue = 3D data. Resolution's RESLabs™ data analysis software converts samples of tissue into DVI data sets. Analysis can be performed via RESView™ Workstation. http://www.adpath.com/slideshow/trabecular.html
High thru-put Cell phenotype analysis	Phenotype MicroArrays	Biolog	Phenotype MicroArrays (PMs)	http://www.genome.org/cgi/content/abstract/11/7/1246 Array based identification of changes in cellular phenotype using cell respiration as a universal reporter. Able to define the effects of gene knockouts or drug exposure on cellular pathways. Currently, PMs can test the phenotypes of bacterial and fungal cells, human cells ‘soon’. The company ultimately intends to offer researchers the ability to scan 2,000 different phenotypes with these arrays.

5) Correlate molecular activity to observed higher level phenotype effects (e.g., bone demineralization)

Transgene studies of biomolecular effects on organisms	Mouse transgenetics	Taconic Farms Inc., Germantown, N.Y		http://www.dddmag.com/feats/0110tran.asp For study of genetic regulation, development, and protein function effects on higher levels. Uses viral vectors, pronuclear microinjection, and homologous recombination to transfer genes.
Multi-field research collaborations	Integrated research on molecules, cell, cell groups, organs, organisms		Bioinformatic research and analysis	Chemists, Mathematicians, statisticians, computer scientists, bioinformatics researchers, computational biologists, modelers, others and molecular biologists cross-pollinate.
Combinatorial knockout biology research		Max Planck Institute of Molecular Plant Physiology		http://www.telegraph.co.uk:80/et?ac=000343180237640&rtmo=0KbbieXq&atmo=9999999&pg=/et/01/11/1/ecnweed01.html Using a 'research assembly line' approach Metanomics, Inc, has created more than 100,000 different genetic types of arabidopsis . Just one gene is altered in each line to shed light on what it does. About 70,000 of the lines have a gene turned off and the remainder have genes turned on. Each year, Metanomics produces more than 20 million data files on the mutants.
Comparative genomics using single gene mutants	functional studies where physiology is poorly understood	Howard Hughes Medical Institute	Isogenic cell lines	http://www.nature.com/cgi-taf/DynaPage.taf?file=/nbt/journal/v19/n10/abs/nbt1001-940.html Isogenic cell lines that differ by a single genetic change can be used to identify compounds with gene-selective properties. A drug screen in which they co-cultured two isogenic colon tumor cell lines, one that expressed a mutant K-Ras allele and the other in which that allele was deleted by homologous recombination.

Computer Aided Research / Desk-top Biology

Use of software, computer databases and the internet to leverage and share the information produced by High Throughput Research.

Tools to discover protein function

Technology	Org	Product	Description
Online Gel databases	ExPASy NCI	Swiss-2Dpage Flicker	ca.expasy.org/ch2d www.lecb.ncifcrf.gov/flicker Assists protein identification with tools for comparing standardized gels against online archive of gel images.
Protein data bases		PDB, ExPASy, etc	Comprehensive Protein data for bioinformatics. There are also a number of specialized databases.
Online Consolidated Gene database	OSU, LabBook, Inc	OSU Human Genome Database	www.labbook.com EST, cDNA and protein sequences in an annotated human gene index. Resulted in human gene count of ~70,000
Protein interaction maps	Hybrigenics, Paris	Protein Interaction Maps (PIM)	pim.hybrigenics.com/pimriderlobby/current/PimRiderLobby.htm Bacterial and yeast two-hybrid technology used to create "protein interaction maps" (PIMs), which graphically display protein-protein interactions and access , etc..
Online bioinformatics portals	Biocarta, PDB, DoubletWist		Web based portals for general public use.
Online analysis tools	University of Salzburg		CASP pages -Evaluation and assessment data for CASP 1-4 ProSup -Protein Structure Superimposition Server WILMA- Structural genome annotation for C.elegans PROSAIL -Protein Structure Analysis Tool BENCHMARK -A protocol for testing the accuracy of alignments. MATRICES -Structure derived substitution matrices. http://lore.came.sbg.ac.at/services.html ProNet online -protein- protein complexes www.myriad-pronet.com
Protein structure			http://news.bmn.com/conferences/list/view?rp=2001-ICMSB-3-S5 Tools to integrate and predict structural information; links information on fold, sequence, and function.

Image informatics	Scimagix and Tissue Informatics	image data mining	http://www.the-scientist.com/yr2001/apr/tools_010416.html Tools for image data mining Oracle®/Web-based SIMS™ (Scientific Image Management System), is a database package for the storage, analysis, and mining of annotated experimental image data.
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Online Resources For Model Species

Model species virtual library

<http://ceolas.org/VL/mo/>

<http://godot.ncgr.org/home.html>

arabidopsis database

http://www.sanger.ac.uk/Projects/C_elegans/index.shtml

C. Elegans Genome project

<http://flybase.bio.indiana.edu/>

<http://sdb.bio.purdue.edu/fly/aimain/1aahome.htm>

Berkeley Drosophila Genome Project

<http://www.flybase.org>

drosophila meglanogaster

Mouse genome informatics

<http://www.informatics.jax.org/>

The **Mouse** Atlas and Gene Expression Database Project

<http://genex.hgu.mrc.ac.uk/>

Stanford's **yeast** genome database

<http://genome-www.stanford.edu/Saccharomyces/>

Imaging

Use	Tech	Org	Product	Description
Tracing cell molecules	fluorescence resonance energy transfer (FRET)			<p>http://www.hopkinsmedicine.org/cellbio/devreotes/ New fluorescent dyes and optical methods have increased the spatial resolution, distance range, and sensitivity. one of the few tools available for measuring nanometer-scale distances in biological molecules. Energy is transferred from a donor fluorophore to an acceptor fluorophore over a range of 2-10 nm. Real time viewing of subunits of G protein splitting apart following GPCR activation, an event that unleashes the G protein on downstream effector molecules. http://www.nigms.nih.gov/news/reports/single_molecules.html</p>
3-D microscopy	three-dimensional digital microscopy and micro-analysis	Resolution Sciences Corp.	Digital Volumetric Imaging (DVI)	<p>http://www.adpath.com/ Digital Volumetric Imaging (DVI) Micron resolution, high-fidelity three-dimensional digital visualization and microanalysis of up to a volume of 100 mm³ of biological tissue = 3D data. Resolution's RESLabs™ data analysis software converts samples of tissue into DVI data sets. Analysis can be performed via RESView™ Workstation. http://www.adpath.com/slideshow/trabecular.html</p>
50 – 100nm resolution optical microscope	Near-Field Scanning Optical Microscope (NSOM)	U. Arizona		<p>http://pubs.acs.org/subscribe/journals/ancham/jtext.cgi?ancham/73/i14/html/ac0100906 Raman, visible, infrared, fluorescence and photoluminescence spectrometers linked to a NSOM using CW and femtosecond-pulsed lasers. Measurements are made with a spatial resolution of 50 – 100 nm.</p>
Electro-static properties		UCSD		<p>8/21/01 PNAS Electrostatic models portray how the charges on individual atoms of a molecule interact to produce a distribution of electric fields throughout the molecule. These models have proven useful to researchers analyzing the stability and dynamic motions and interactions of biological molecules, including proteins, DNA and RNA. Leap from modeling molecules of 50,000 atoms to those of more than a million atoms.</p>

Virtual reality molecular imaging	nanoManipulator	UNC - CH	NanoManipulator	<p>http://pubs.acs.org/subscribe/journals/tcaw/10/i11/html/11simon.html</p> <p>TRL 3-4</p> <p>NanoManipulator: a, virtual reality (3-d and tactile) user interface to scanning probe microscopes such as scanning tunneling microscopes (STM) and atomic force microscopes (AFM).</p> <p>nanoManipulator uses VR goggles and a force feedback probe as an interface to a scanning probe microscope, providing researchers with a new way to interact with the atomic world. Researchers can travel over genes, tickle viruses, push bacteria around, and tap on molecules.</p>
Penetrating optical imagers		NIH	Multi-spectral imaging	<p>multispectral imaging uses a camera and certain wavelengths of visible and infrared light to take pictures. It can photograph internal structures, like the brain, because some wavelengths can penetrate the body without harming it. By choosing wavelengths tuned to different constituents of biological tissues, such as water and fat, researchers can pick up otherwise invisible details, much as satellites can "see" the heat of a dense urban area using the right wavelengths of infrared light.</p>
Viewing intact neurons	Head mounted microscope	Lucent		<p>http://www.neuron.org/cgi/content/abstract/31/6/903/?highlight=denk</p> <p>Two-photon microscopy has enabled anatomical and functional fluorescence imaging in the intact brain of awake, freely moving rats, using a miniaturized head-mounted microscope. Capillary blood flow and dendritic calcium transients were measured with high time resolution using line scans.</p>