MARKET FORESIGHTING

Biomarkers & surrogate endpoints

July 2004

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Biomarkers – Summary (1)

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Definition & Details

•**Biomarker;** any quantifiable biological entity or characteristic

•**Clinical Biomarker:** a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention[1]

•**Surrogate endpoint;** a laboratory or physical sign that is used in therapeutic trials for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives and that is expected to predict the effect of therapy[1]

[1]; http://www.fda.gov/cder/Offices/Biostatistics/Chakravarty_376/

Market Dynamics & Emerging Markets

Substantial Diverse Market splits broadly into Bio-Medical & Non-Medical. Bio-Medical includes pharmaceutics, diagnostics, theranostics and associated reagents, services, consumeables. Non-Medical very fragmented and difficult to define at present.

Worldwide forecasts for medical-biomarkers

Segment	Revenue 2003 ($m)	Revenue 2008	CAGR (%)
Services	120	367	25
Products	224	634	23
Diagnostics	108	1914	77
Total	452	2915	45

Emerging Technologies & Platforms

Biomarker development is driven by genomic, bioinformatic and proteomic technologies.

- Sample identification e.g. quantitative mass spec
- Functional analysis e.g. arrays
- Miniaturisation e.g. microfluidics
- Multiplex testing e.g. biochips
- High sensitivity detection
- Massively parallel processing
- Point-of-care productisation e.g. biosensors

Drivers & Trends

- Better validation of targets Improve clinical trial selection (e.g Herceptin)
- Reduce late stage attrition rates
- Marginal efficacy “drug rescue’ for niche populations
- IP barrier; block drugable pathways using patent-protected biomarkers
- Difficult to diagnose disease (NSCLC)
- Differential diagnosis (CHF vs MI)
- Markers of pre-disease (Syn X)
- Prognostic indicators and drug labeling.
- Medical trends (e.g. iprimary prevention and early diagnosis)

Company Landscape

- Big Pharma
- Biotechs
- Diagnostic
- Proteomic
- Genomic
- Bioinformatic
- CRO & Special Services
- Reagent Companies

Deal Space

- > 25 deals since Jan ‘03
- Pharma interest main driver
  - Roche & Epigenomics
  - GSK & Beyond Genomics
  - AstraZeneca & Cell Signalling Technologies
  - Abbott & Celera
  - Merck & Surromed

Challenges

- Pharma Blockbuster mentality
- Gaining regulatory approval for novel biomarkers
- Approval and access to clinical samples
- Integration into design of large-scale prospective clinical trials
- Technology infancy & acceptance
- Avoiding commoditization

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Biomarkers – Summary (2)

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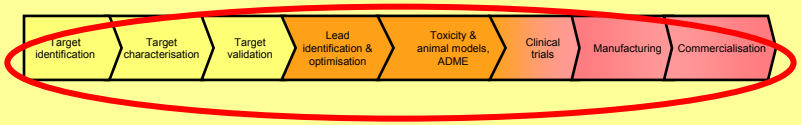
Business models



- Impact into all areas of Pharmaceutical value chain and key areas of Healthcare provision.

Business models

- Reagent manufacturer biomarker assays (but if not clinically validated lower value)
- Platform diagnostics company (e.g. AFFX)
- Collaborations between Pharma and Technology providers (e.g. Abbott & Celera)
- New Theranostic entities (JVs of drug & diagnostic players)
- Biotechs adopt biomarker-directed niche discovery model (Genzyme, Millenium)

Scottish Context

- Strong academic base in genomics, proteomics & Bioinformatics
- Industrial strength in diagnostics, reagents and CROs
- Clinical Excellence in Cardiovascular, Cancer & Diabetes.

Market Demand

Strong in discovery and all disease markets; especially

- **In Cancer**
- **In Heart Disease**
- **In Diabetes**
- **In Neurobiology**

Expert Commentary

- "50% of patients with lung cancer do not get benefits from Iressa…..but there is a small group who get an almost miraculous response, and their whole life can be transformed and extended for years" Sir Tom McKillop – AZ CEO
- "Pharmacogenomics is a new field, but we intend to use it to promote the development of new medicines" Mark McClellan – FDA Commissioner.

Foresighting

Pharmaceutical drug development

- **Efficacy testing**
- **ADMET/toxicology**
- **Target/lead identification**
- **Clinical trials design**

Clinical Management

- **Treatment decision tools**
- **Improved Diagnostics**
- **Monitoring of treatment**

Disease Areas

- **Aggressive Cancers**
- **Global CV**
- **Metabolic Syndrome**

GAPS

- **Access to well designed clinical samples**
- **Standardized sample isolation protocols**
- **Rapid low cost reagent preparation**
- **Precise reproducible chips**
- **High sensitivity & dynamic range detection**
- **Data integration & analysis tools**
- **Clinician access to technology**

Barriers

- Reluctance of clinicians to accept surrogate endpoints instead of morbidity and mortality data e.g. homocysteine, CRP and even HDL in chronic diseases like CHD
- Pharmaco-economic benefits of use must be proven and significant.
- Funding expensive large-scale prospective clinical studies.
- Collaboration with big-pharma and biotech to develop test and establish biomarkers for therapeutics e.g. "HercepTest"
- Overcoming current commoditization

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BIOMARKERS

SUPPORTING SLIDES

These slides are intended to support the summary slides. The ordering of this slide set does not lend itself to use as a presentation

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Biomarkers Supporting Information Contents

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- Scottish Context
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- Foresighting
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- Company Landscape
- Appendix

Definition & Details

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Biomarkers encompass any quantifiable biological entity or characteristic.

Discovery of appropriate Biomarkers will enable a diversity of applications & open markets;

- Diagnose disease
- Stage and monitor disease
- Select for ‘high-yield’ livestock and plants
- Oil typing and genetic localization

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Biomarkers will contribute substantial value to areas as diverse as environmental remediation, quality assurance in food manufacturing, livestock strain improvement and pathogen identification in bio-warfare as well as bio-medical applications.

This widespread utility will ensure a large market potential; however, marked fragmentation will promote segment specific market dynamics and technology drivers

This report specifically analyses the current and future uses of biomarkers in clinical, bio-pharmaceutical and life science applications and markets.

In 2003, the global market for biomarker related products and services in the bio-medical field generated revenues of $452 mm. Growth of 45% p.a. is forecast, generating revenues of $2.9bn in 2008.

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Clinical biomarkers & Surrogates

Biomarker; a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention.[1]

Surrogate endpoint; a laboratory or physical sign that is used in therapeutic trials for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives and that is expected to predict the effect of therapy.[1]

[1]; http://www.fda.gov/cder/Offices/Biostatistics/Chakravarty_376/

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- Medical biomarkers that are efficient, minimally invasive and present early in the disease process could revolutionise the treatment of difficult-to-diagnose diseases such as diabetes, CVD and numerous cancers (including Non small cell lung cancer, colorectal cancer and pancreatic cancer).

- However, diagnostics for diseases where few treatment options are available have little utility; the value of biomarkers lies in informing and improving treatment options.

- In a pharmaceutical setting, users of biomarkers include; pharmaceutical and biotechnology companies; clinician researchers; clinicians performing clinical trials; basic researchers studying pathways and processes; contract research organizations; clinical labs; and government bodies analyzing epidemiology and public health trends.

- Characteristics desired in biomarkers include; reproducibility; sensitivity; specificity; ease of use; potential for automation; close correlation with disease state; ease of sample handling; low technological requirement; minimally-invasive; potential for multiplexing; quantitative; reliability.

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The identification and use of biomarkers is not new; rather it is the availability of emerging technologies that is driving rapid progress in this area.

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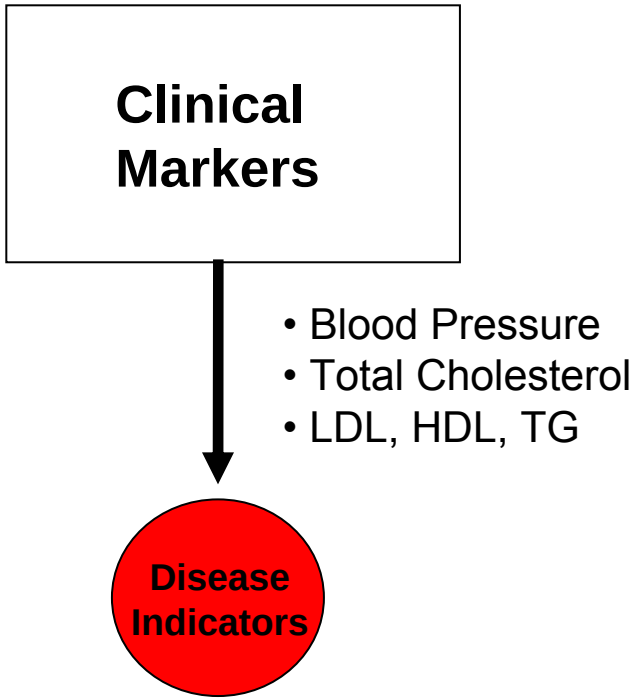
Evolution of Biomarkers in Cardiovascular Disease

The evolution of biomarkers reflects changes in our understanding of disease aetiology and pathophysiology. For example, hypertension was previously considered a disease *per-se*; its current status as a (bio)marker for underlying cardiovascular disease reflects the importance of elevated blood pressure as both a symptom of nascent cardiovascular disease and a prognostic indicator for disease outcome.



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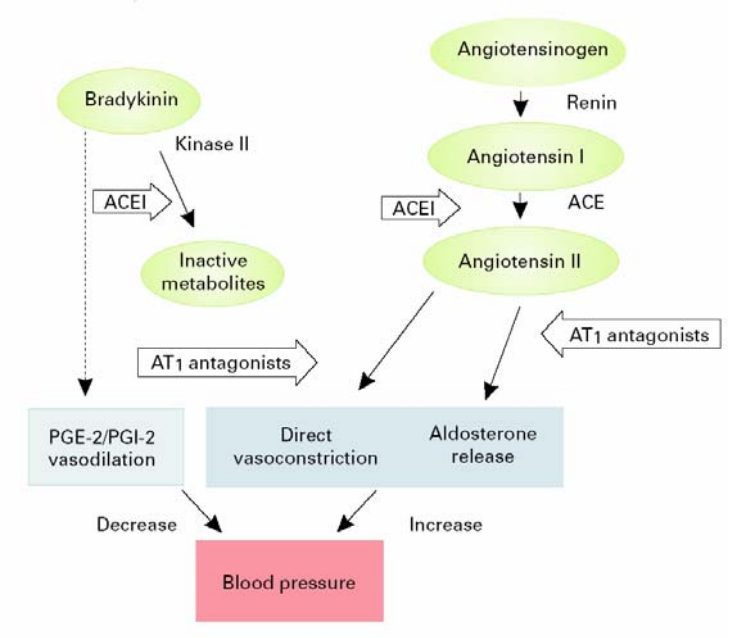
Evolution of Biomarkers in Cardiovascular Disease

The evolution of biomarkers reflects changes in our understanding of disease aetiology and pathophysiology. Two decades of basic and clinical research laid the foundations for clinical marker validation.



Clinical Marker Validation

Disease Indicators

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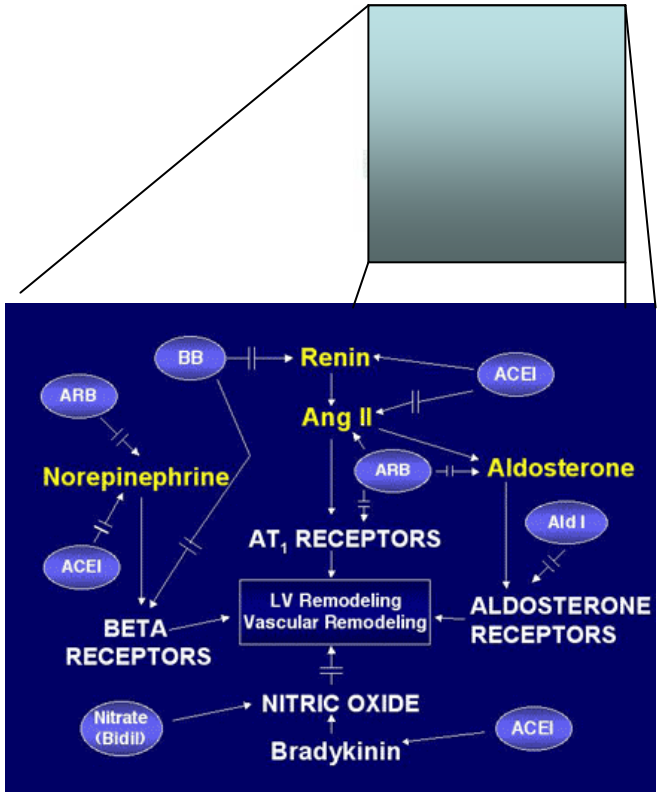
Evolution of Biomarkers in Cardiovascular Disease

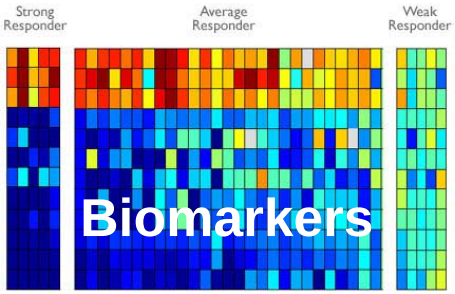
Genomics

Proteomics

Clinical Expertise

Bioinformatics





Disease Indicators

New technologies are dramatically accelerating understanding of disease processes, and both cellular and systems biology

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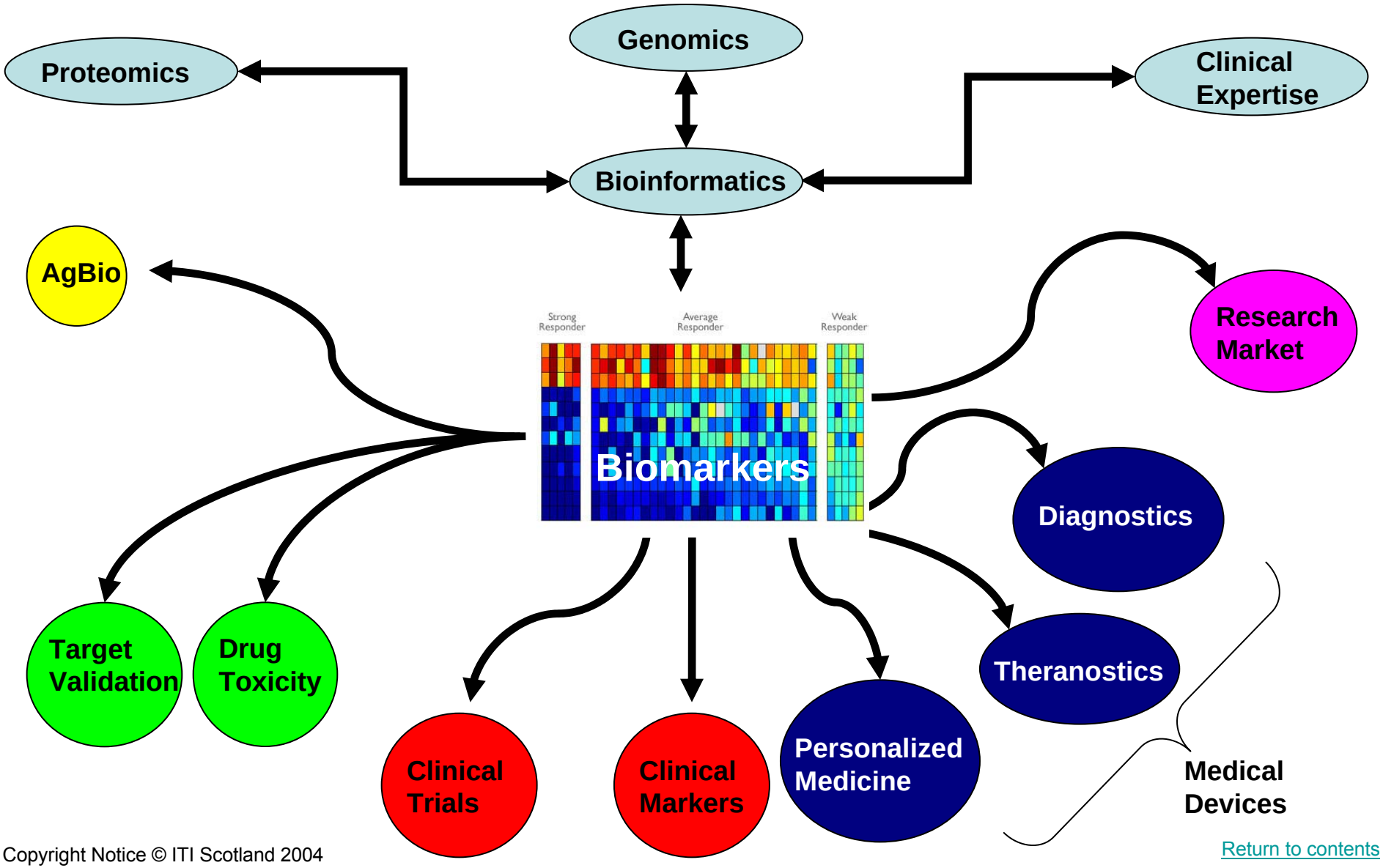
Biomarker technology can potentially impact all areas of Life Sciences



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Market Dynamics & Emerging Markets

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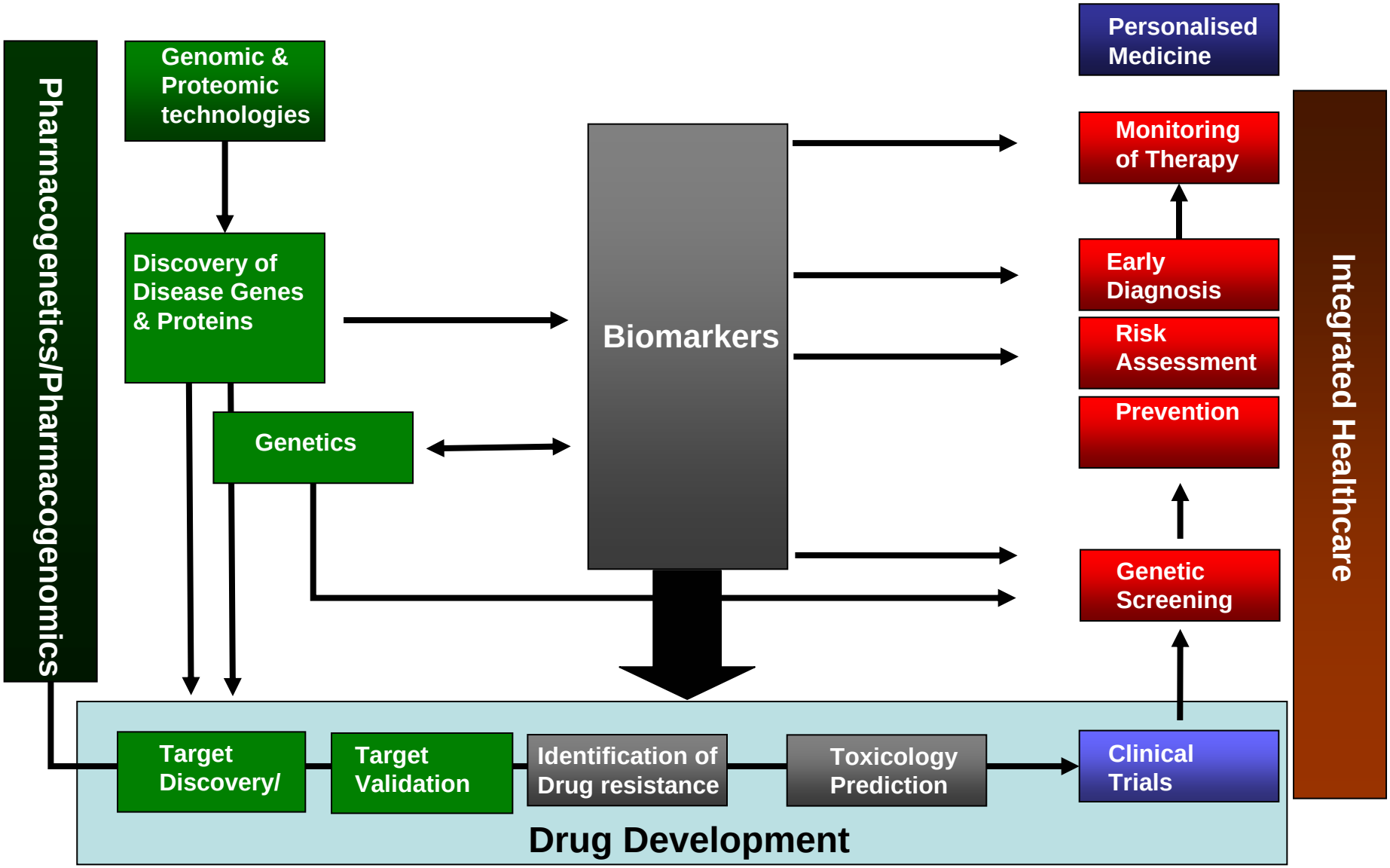
Clinical and pharmaceutical markets for biomarkers



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The clinical/pharmaceutical biomarker market has seen a surge of interest due to the availability of genomic and proteomic technologies and needs of users

- Biomarkers facilitate SAR studies and toxicity prediction during lead optimisation, reduce patient counts in clinical trials through pre-qualification for drug response and provide for earlier and more accurate proof of concept and dose ranging studies.
- Biomarkers have a significant role to play in improving R&D productivity.
- Up to 10% of drug development programmes are favourably impacted by biomarkers in 2004 and this figure increases to 50% of projects by 2008.

Worldwide Revenue projections for biomarker related products and services

Segment	Revenue 2003 ($m)	Revenue 2008	CAGR (%)
Services	120	367	25
Products	224	634	23
Diagnostics	108	1914	77
Total	452	2915	45

Source: Drug & Market Development

Potential impact of biomarkers on Pharmaceutical R&D Costs

Year	R&D Costs ($bn)	% of Projects	% Savings	Cost Reduction	Adjusted R&D cost ($bn)	% Saved
2004	37.4	10	15	0.6	36.8	2
2005	40.4	20	22	1.8	38.6	4
2006	43.6	30	30	4.2	39.4	10
2007	47.1	40	37.5	7.1	40	15
2008	50.9	50	45	11.5	39.4	23

Source: Drug & Market Development

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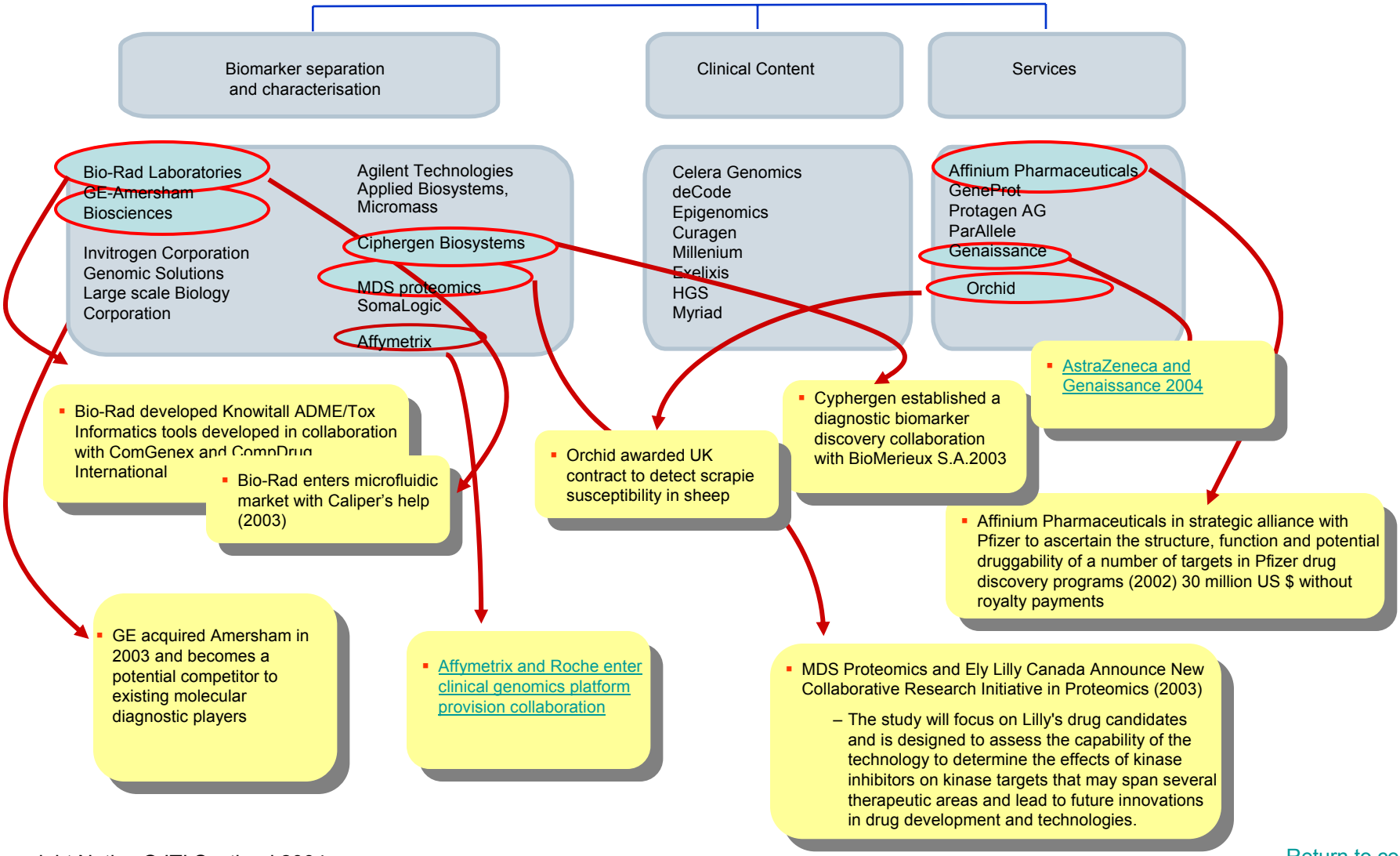
The level & pace of activity is also reflected in the number of emerging companies and their collaborations with big Pharma



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Deal Space

Main activities currently show Pharma sourcing

- AstraZeneca & Genaissance *(statin pharmacogenomics)*
  (Following Baycol withdrawal from market and safety concerns associated with Crestor)
- Roche & Affymetrix
  (Clinical Genomics $70MM upfront)
- Roche & Parallele
  (Type II Diabetes)

VC interest is increasing;

- '2004 is the year of the biomarker' (IDG Ventures)

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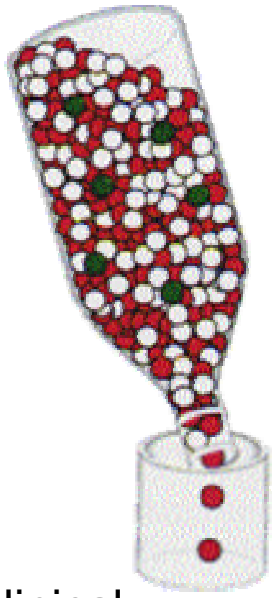
Biomarkers have the potential to make a substantial impact in pharmaceutical R&D…….

Of the estimated $800m cost of bringing a drug to the market, up to 60 % is spent pursuing leads which turn out to be useless. Nearly 50% of drug candidates fail because of lack of efficacy and up to 40% fail due to safety concerns.



- Biomarkers will improve the efficiency of drug development
  - Relieving the bottleneck in target validation:
  - Reducing drop-out rate of drug candidates in pre-clinical and clinical development – using Toxicoproteomics early in the discovery process
  - Undertaking large-scale protein profiling of clinical samples to generate prognostic and diagnostic biomarkers - better disease diagnosis allows more efficacious treatment and monitoring of disease progression

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Biomarkers have the potential to impact general clinical medicine/adverse reaction

- Adverse drug reactions each year kill 106,000 people in the US, account for 28% of all hospital admissions, and have an economic impact of $182 billion dollars. *American Medical News. Jan 15, 1996, p.11*

- In the UK, adverse drug reactions are estimated to account for 6.5% of hospital admissions, at an annual cost of $847 mm. *http://bmj.bmjjournals.com/cgi/content/full/329/7456/15*

- Early diagnosis using biomarkers could reduce the incidence of CRC by 50%. A reduction in deaths from CRC by 50% would mean approx $11 billion per year additional total benefit to the Australian economy.

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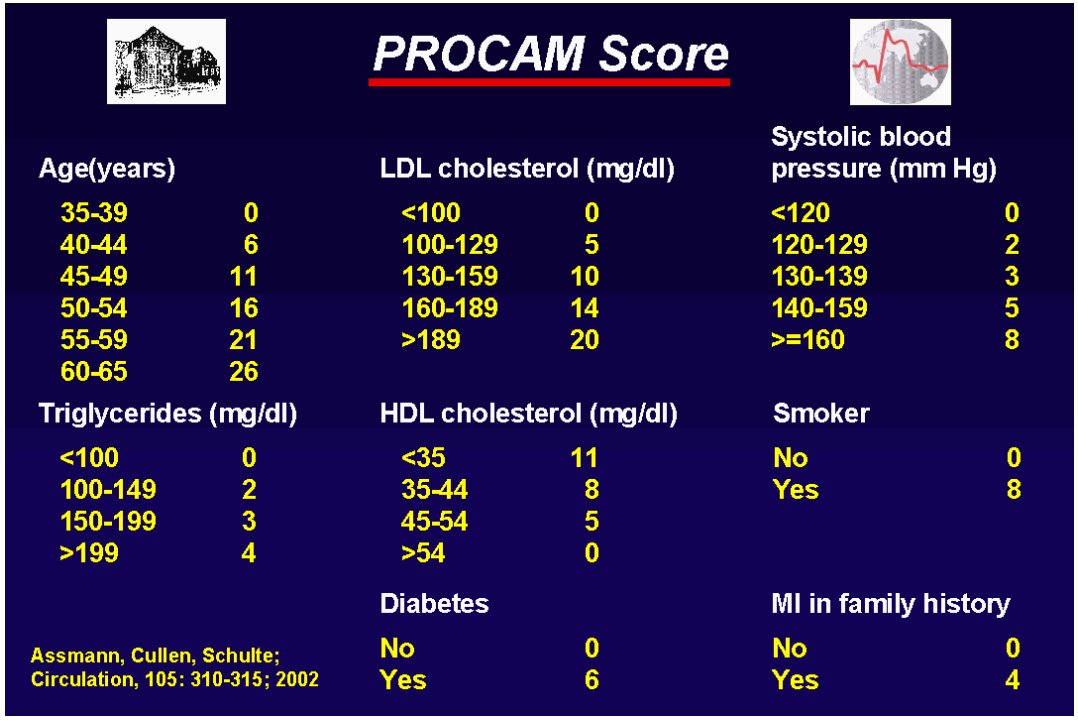
Biomarkers have the potential to impact cardiovascular medicine……



..initially by augmenting current diagnostic tests used in treatment algorithms such as PROCAM and FRAMINGHAM e.g. diaDexus Plactest.
Ultimately this will enable a single, simple measure of 'global cardiovascular risk', the provision of clinical decision tools for treatment and allowing individual rather than population measures of risk.

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Biomarkers have the potential to impact cancer medicine…

Table 1: CCN recommendations on the use of tumor markers in common malignances[1]

SITE	ANALYTES	SCREENING	DIAGNOSIS AND PROGNOSIS	TREATMENT SELECTION AND MONITORING	SURVEILLANCE
Acute myelogenous leukemia	Immunophenotyping markers		●		
Bladder	NMP-22, BTA, M344		●	●	
Breast	Her-2/*neu*		●	●	
Colorectal	CEA		●	●	●
Esophagus					
NSCLC					
Ovarian	CA-125		●	●	●
Pancreas	CA 19-9		●	●	●
Prostate	PSA	●	●	●	●
SCLC					
Stomach					

● *Recommended in NCCN practice guidelines* ● *Marker in development (no current consensus on utility) or used in investigational settings*

- filling the gaps in cancer screening, diagnosis, prognosis, treatment selection and monitoring and surveillance. Uses include; Screening for risk of developing cancer; e.g. NSCLC, Ovarian Cancer, Pancreatic Cancer, Stomach Cancer etc.
- generating tailored treatment regimens e.g. flat-fixed dosing of irinotecan based on CYP3A4 activity.
- generating prognostic indicators/markers of recurrence e.g. presence of PSA following prostatectomy

Source; Gander T et al., 2003

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Herceptin theranostic tests: paving the way for personalised medicine

- Therapy specific diagnostics (theranostics) are being developed specifically for predicting and assessing drug response in individual patients (rather than diagnosing disease)
- There are currently two protein marker based theranostic tests on the market for selecting patients for anti cancer treatment with Herceptin:
  - FISH (Fluorescence in situ Hybridisation) and IHC (immuno histochemistry). Both techniques require a tissue sample of patient's tumour to be analysed in the pathology lab.
  - In phase III of the clinical trials of Herceptin, patients with breast cancer that over-expressed HER-2 receptor were selected (25-30 % of patients with breast cancer show over-expression of HER-2 receptor). A 22.5% improvement in survival rate was demonstrated in this group of patients. This effect wouldn't have been clear if breast cancer patients were selected without regard to HER2 expression.
  - Herceptin recorder revenues in 2003 of $424.8 million; without the availability of a test to identify the 25% (HER-2 positive) women who will respond to this agent, it is unlikely that Herceptin would have gained approval.
- Novartis recently received approval for a diagnostic test which allows identification of patients that would be suitable for treatment with Gleevec in CML; Gleevec recorded revenues of $1128 mm in 2003.
- DakoCytomation recently received marketing approval for the EGFR PharmDx test which is required to assess suitability for treatment with BMS/IDEC's Cetuximab in CRC.
- **BUT** no diagnostic test is yet required by the FDA for the prescription of Genetech's Avastin (targeting VEGFR in CRC) or Tarceva (targeting EGFR/Her-1 in NSCLC).

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Political

- What are the political issues surrounding population-based primary prevention screens using biomarkers?
- What data will the FDA require to accept biomarkers as surrogate end points in chronic indications?
- What data will the FDA require to accept biomarkers as surrogate end points acute and orphan indications?
- When will the FDA allow use of ASR designation versus full approval as a diagnostic test?

Economic

- What are the reimbursement issues surrounding diagnostic and theranostic biomarkers?
- How expensive are clinical trials requiring theranostic biomarkers to run?
- How expensive are the epidemiological studies validating biomarkers?
- How do manufacturers avoid commoditization and extract value from their tests?
- What is the pricing potential of theranostic biomarkers?

Sociological

- What are the sociological issues surrounding ethics, privacy and the use of biomarkers for predicting future disease risk and provision of medical insurance?
- What are the sociological issues surrounding ethics, privacy and access to clinical samples in biomarker discovery?

Technological

- What are the technological issues surrounding measurement of complex biomarkers at the point of care? Reproducibility? Robustness? Ease of use?
- What are the GMP and GLP issues regarding the manufacture and use of clinical biomarker assay kits?

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The regulatory issues associated with pharmacogenomics and biomarkers are evolving…….

The FDA recently issued its first guidelines on the use of pharmacogenomic data in drug approval. This long awaited initiative, published under the title "Pharmacogenomic Data Submissions", intended to solicit public comment is a noteworthy move toward integrating pharmacogenomic data into, and ultimately transforming the entire drug discovery process.

http://www.fda.gov/cder/guidance/5900dft.pdf

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However, the ethical, legal, social and governmental policy implications of pharmacogenomics and biomarker analysis are unclear……..

- The Nuffield Council on Bioethics, in its latest report 'Pharmacogenetics: ethical issues' recognizes that it is too early to know exactly how the science of pharmacogenetics will be applied in practice, but stresses that it is not too soon to begin considering the potential ethical, legal, social and policy implications.

  Nuffield Council on Bioethics

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But impact, for example, the future provision of health insurance.

- **The Genetics and Insurance Committee (GAIC), has published its second report covering September 2002 to December 2003.**

- Currently, GAIC has only approved one genetic test from which results can be used in setting insurance premiums, the Huntington's disease test, and only for life insurance policies over £500 000. GAIC has, however, advised the Association of British Insurers on how applications for 17 other tests should be rewritten so that they may be resubmitted for further consideration.

- GAIC monitors the insurance industry's compliance with an existing moratorium on using the results of predictive genetic tests in setting insurance premiums. The moratorium is in place until November 2006.

Source; http://www.wellcome.ac.uk/en/genome/

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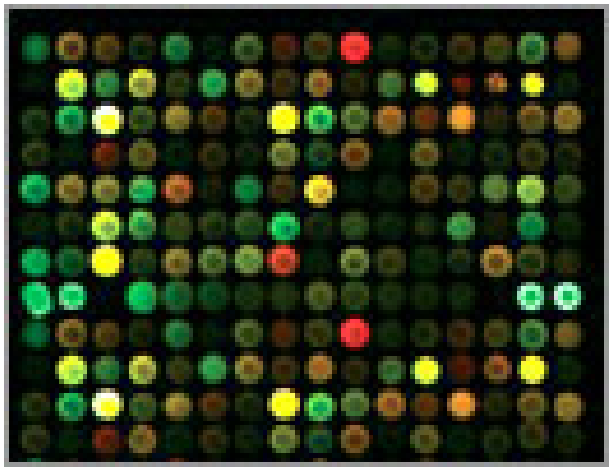
Genomics – Gene Expression Analysis

Key principles: RNA isolated from a particular cell type or tissue comprises a complex mixture of different RNA transcripts. The abundances of individual transcripts in the mixture reflect the expression levels of the corresponding genes.



How does it work?

- Microarrays can be used to analyse the expression of tens of thousands of genes simultaneously.
- A microarray is a small device, about the size of a microscope slide, with thousands of different known DNA sequences immobilized at different addresses on the surface.
- Each of these DNA sequences can participate in a specific hybridization reaction.
- Complex mixtures of isolated RNA are copied (reverse transcribed) to the more stable DNA form allowing their labeling, usually with fluorescent dyes and are hybridized to the microarray.,
- The hybridization process occurs with such specificity that a single immobilised DNA probe can pick out a matching partner target, in a complex mixture containing millions of different sequences.
- Microarrays allow highly parallel analysis enabling use of thousands of different DNA probes.
- The abundances of individual labelled DNA molecules reflect the expression levels of the corresponding genes.
- The strength of the signal thus represents the level of gene expression in the original sample; abundant sequences will generate strong signals and rare sequences will generate weak signals.

How is it used?

- Expression analysis with microarrays can be used to determine what genes are expressed in a particular cell type or tissue and to compare the expression levels of different genes.
- It can also be used to compare gene expression across different but related samples, such as disease vs healthy tissue. A gene expressed only in the disease sample, for example, might represent a useful drug target. Comparative expression analysis can be achieved by comparing duplicate microarrays hybridized to complex probes prepared from the alternative samples.

Source; http://www.wellcome.ac.uk/en/genome/

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Genomics - Genotyping

SNP Genotyping

- The Human Genome Project has shown that there are minor variations between each individual's genetic sequence or DNA. These are know as polymorphisms and as the most common variations are due to single nucleotide polymorphisms they are referred to as SNPs. Most SNPs are benign, but some key SNPs are being discovered to be associated with a higher risk of specific diseases. For example, specific SNPs are now known to make carriers be more likely to develop diabetes or Alzheimer's disease. Equally, differences in genetic make-up may determine whether or not an individual reacts poorly to a particular drug.

Key principles

- There are believed to be over 10 million SNP variants between individuals. In order to associate any one SNP with a certain trait or disease very large scale (either in parallel or high throughput) pharmacogenomic analyses are needed.
- Microarrays offer the potential to study 1,000s of SNPs at one time.
- Oligonucleotide chips contain thousands of short DNA sequences immobilized at different positions. Such chips can be used to discriminate between alternative bases at the site of a SNP.

How does it work?

- Two chip-based typing methods are widely used. One method relies on allele-specific hybridization. Short DNA sequences on the chip represent all possible variations at a polymorphic site; a labelled DNA will only stick if there is an exact match. The base is identified by the location of the fluorescent signal.
- Alternatively, the oligonucleotide on the chip may stop one base before the variable site. In this case typing relies on allele-specific primer extension. A DNA sample stuck onto the chip is used as a template for DNA synthesis, with the immobilized oligonucleotide as a primer. The four nucleotides, containing different fluorescent labels, are added along with DNA polymerase. The incorporated base, which is inserted opposite to the polymorphic site on the template, is identified by the nature of its fluorescent signal. In a variation of this technique, the added nucleotide is identified not by a fluorescent label but by mass spectrometry.

How is it used?

- Two of the most important applications are 'association studies', which attempt to correlate SNP profiles with predisposition to disease, and pharmacogenomic studies, which attempt to correlate SNP profiles with drug response patterns.
- A disadvantage of chip-based assays is that they are somewhat inflexible - new SNPs cannot easily be incorporated onto a chip, requiring a new chip to be made. This is being overcome by the use of bead arrays.

Source; http://www.wellcome.ac.uk/en/genome/

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Genomics - Haplotyping

- **Haplotypes are groups of closely linked alleles that tend to be inherited together and can be used to map human disease genes very accurately.**
- All our chromosomes come in pairs, one in each pair inherited from each parent. While each chromosome of a pair contains the same genes in the same order, the sequences are not identical. For example, there are single SNPs approximately every 1000 nucleotides. It is therefore possible to distinguish sequence variants (alleles) that come from our mother and our father and this allows human disease genes to be mapped by linkage analysis.
- In germ cells the maternal and paternal chromosomes pair up and exchange segments of DNA, a process called recombination. After recombination, the chromosomes contain a mixture of alleles from each parent. Recombination will occur frequently between DNA sequences that are a long way apart but only rarely between sequences that are close together. Therefore, by measuring the frequency of recombination between the disease gene and other DNA sequences whose location is already known, the position of the disease gene can be established.
- A consequence of recombination is that blocks of sequences on the same chromosome tend to be inherited together, a phenomenon known as linkage disequilibrium. Such groups of alleles, which are rarely separated by recombination, are known as haplotypes. In the human genome, haplotypes tend to be approximately 60,000 bp in size and therefore contain up to 60 SNPs that travel as a group.
- Haplotypes can be exploited for the fine mapping of disease genes.
- Thus a new mutation responsible for a specific genetic disease always enters the population within an existing haplotype. Over several generations, recombination events may occur within the haplotype but the disease allele and the closest SNPs still tend to be inherited as a group. If this haplotype can be identified in a group of patients with the disease, typing the alleles within the haplotype allows a conserved region to be identified, which pinpoints the mutation responsible for the disease.
- The abundance of SNPs and their ease of analysis means that this technique has the potential to map genes very accurately.
- There is therefore now much interest in developing a haplotype map of the entire human genome.

Source; http://www.wellcome.ac.uk/en/genome/

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Genomics - Haplotyping

The Hap Map Project

The Human Genome Project has established an international team of scientists to collaborate in determining most common haplotype variations of the human genome in a project known as the 'HapMap'. Their most recent report was in the 18 December 2003 issue of the journal Nature.

The team will obtain and identify genetic variations in DNA samples from 270 people in Nigeria, Japan, China and the USA. Once finished, the HapMap will provide a freely available catalogue of common patterns, or haplotypes.

Our individual predisposition to disease and our response to medicines are, in part, encoded within our DNA, in the differences (called single-nucleotide polymorphisms, or SNPs) scattered through our genetic sequence. However, we tend to share regions of SNPs with others, and these regions, termed Haplotypes, can be mapped onto the reference genome sequence and tagged by a subset of SNPs.

As a result of the HapMap Project, researchers will not have to search through the 10,000,000 SNPs that occur in the human genome, but instead will be able to use the map developed by the Project to obtain as much information using a massively reduced number of SNPs, about 500,000.

Source; http://www.wellcome.ac.uk/en/genome/

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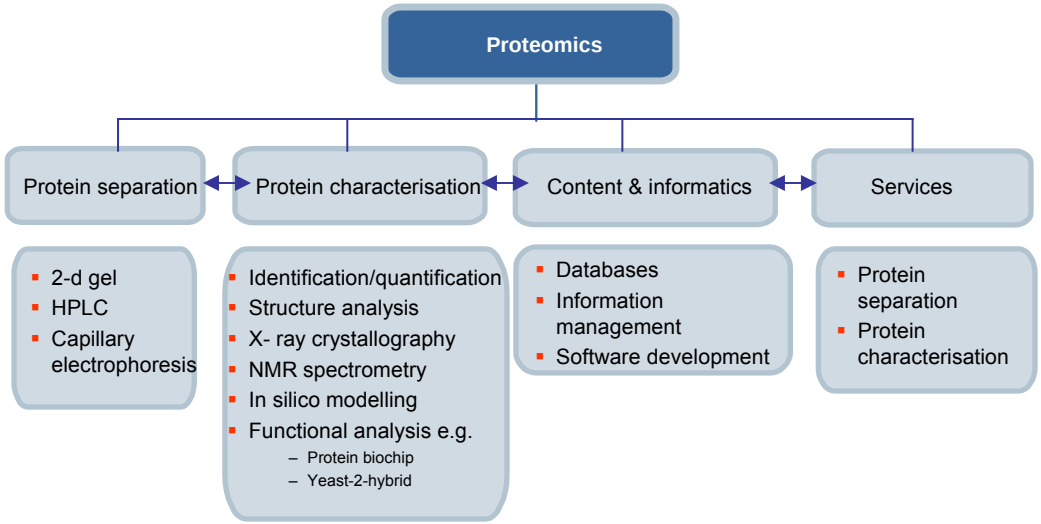
Proteomics

- Proteomics integrates fundamental technologies such as protein separation and profiling, mass spectrometry for characterisation, proteomic databases for data storage and management, and bioinformatics tools and techniques to extract information from these databases.
- Proteomics can be divided into three main areas;-
  - The identification of all the proteins in a particular cell, tissue or organism;
    - Differential display proteomics for comparison of protein levels from e.g. healthy versus diseased tissue with the aim to identify cellular pathways and the cause of the disease
  - The discovery of how these proteins work together;
    - Studies of protein-protein interactions and post-translational modification
  - Finding out the precise three-dimensional structure of each protein.
    - Knowledge of the three-dimensional structure is crucial in in helping with the formulation of new drugs as it could indicate which part of the protein is susceptible to a drug's effects.



Proteomics asks: questions like: -

- What proteins are there
- What do they do
- How do they work together
- What do they do in signalling pathways
- What are the changes in proteins that drive development, repair, breakdown and death of an organism

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Proteomics is a rapidly emerging set of key technologies that are being used to identify proteins and map their interactions in a cellular context.

Sample Preparation technologies	Separation technologies	Sample identification technologies	Functional analysis
▪ Technologies for universal protein sample preparation, automated systems for sample preparation ▪ Better expression systems for protein production - individual or multiple proteins	▪ Methods for complex mixture analysis ▪ Improved methods for protein separation (ICAT, MudPIT, LC) ▪ High throughput systems for characterisation e.g.2-D gel analysis, mass spectrometry	▪ Quantitative Mass spec ▪ Developing technologies that allow systematic analysis of post-translational modifications (phosphorylation, glycosylation)	▪ Tools for analysing protein complexes *in vivo* (e.g. TAP purification technology) ▪ Tools for scaling up protein interaction studies ▪ Chips and Array technology – potential to generate highly detailed information with minimum use of materials – Improved microarray surfaces – Specific interaction microarrays – Reverse screening microarrays – Differential capture protein microarray assays – Antibody, aptamer, lectin chips
Miniaturisation	▪ Microarrays ▪ Microfluidics		

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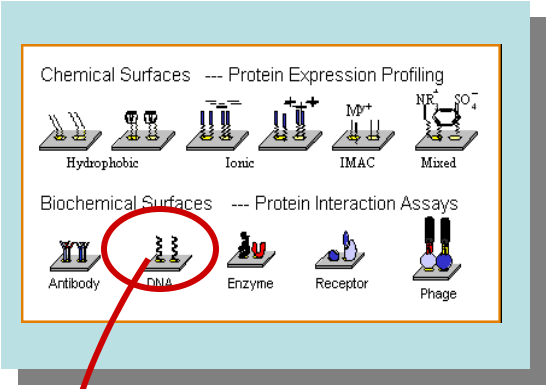
Within the space, molecular arrays is one of the fastest growing sectors and is providing opportunities for newcomers



- Protein microarray technology allows the simultaneous determination of a large variety of parameters from a minute amount of sample within a single experiment
- Analytical arrays employ high density matrices of peptide, antibodies, carbohydrates, ligands, aptamers (DNA,RNA) or chemically modified surfaces and are used to detect proteins in a complex mixture
  - Analytical arrays enable protein profiling which analyses hundreds or thousands of proteins from given samples and achieve higher levels of prognostic or diagnostic accuracy compared to traditional analysis of individual proteins
- Functional protein microarrays (chips) are constructed by immobilizing large numbers of purified proteins on a solid surface. They have the potential in assaying for a wide range of biochemical activities (protein-protein, protein-lipid, protein-nucleic acid and enzyme substrate) as well as drug and drug target identification

Source: Zhu and Snyder. Curr Opin Chem Biol. 2003, 7:55-62

- Market opportunities for aptamer technology are significant due to
  - superior specificity and affinity of aptamers combined with direct detection and
  - synthetic manufacturing leads to a more cost-effective tool for both research and clinical settings …

"…Aptamer arrays are a nice thought but antibody arrays are more versatile…"
Large pharma

However, the lag in bringing protein arrays to market reflects the significant barriers to overcome, including protein stability, attachment of proteins to solid supports and sensitive detection methods.

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Challenges

- The Pharmaceutical Industry's "blockbuster mentality" and resistance to market segmentation; thus even Genentech with their successful development of Hercetpin through incorporating a biomarker (targeting Her2/EGFR in Breast Cancer) are resisting similar use of a biomarker in their development of Tarceva (targets Her1/EGFR in CRC).
- Regulatory requirements and approval for biomarkers are still evolving and provide challenges for biomarker commercialisation; e.g. Amplichip CYP450
- Gaining access to clinical samples for biomarker development is challenging; approval and access to clinical samples is restricted by consent legislation.
- Integration of biomarker development into drug development programs and the design of large-scale prospective clinical trials is challenging for small biomarker discovery companies.
- Avoiding commoditization will be an issue if maximum value is to be extracted from biomarker discovery and development programs.
- Pharmaco-economic issues; e.g. population based screening for CHF not economically beneficial
- Fostering close collaboration with drug-development programmes
- Widespread adoption of microarrays for clinical research is restricted by their high cost and lack of precision, but costs are coming down as the number of suppliers is increasing.
- Proxies in chronic disease; convincing clinicians of the value of proxies, e.g. homocysteine and CRP in metabolic syndrome, or the benefit of raising HDL (a proxy for outcomes) by drug intervention in cardiovascular disease.
- Recognising the need for patient segmentation using biomarkers where drugs have marginal efficacy.
  - AstraZeneca failed to do so with Iressa; "50% of patients with lung cancer do not get benefits from Iressa…..but there is a small group who get an almost miraculous response, and their whole life can be transformed and extended for years" (Note that Iressa is approved only as final line therapy in NSCLC).
  - However Genentech did with Herceptin; the effect of Herceptin wouldn't have been clear if breast cancer patients in phase III had been selected without regard to HER2 expression.

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Business models

Multiple strategies –

- Reagents manufacturers provide reagents for biomarker assays *(but if not clinically validated, low value)*
- Platform diagnostics company *(e.g. Multiplex chip based systems)*
- Collaborations between pharma and technology providers
- New Theranostic entities *(JVs of drug & diagnostic players)*
- Biotechs adopt biomarker-directed niche discovery model

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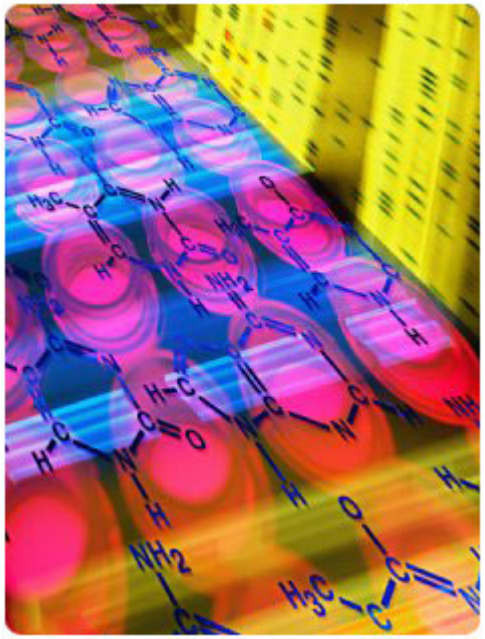
- Drug discovery – a key area of focus for biomarkers

- Drug discovery – a significant market need



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The pharmaceutical research and development market is significant with a high unmet need

Market size -

- The global pharmaceutical market is estimated to be worth over $400 bn.
- National healthcare expenditure was estimated at over $1.66 tn in the US in 2003.
- The top 10 Pharmaceutical companies account for 53% of market revenues.
- In 2002, the FDA approved 78 new medicines, a 20% increase over 2001.

Market size – costs

- In 2003, $33.2 bn was spent on pharmaceutical R&D in the U.S. alone (a 7% increase over 2003 levels).
- In 2003, US R&D spending represented approximately 17% of total US pharmaceutical sales revenues.
- Since 1990, more than 300 completely new medicines, vaccines and biologics have been approved by the FDA.
- The rate at which drugs reach the market has remained broadly constant over the last 20 years, despite massive increases in R&D spend.

Market Need

- Only 3 out of every 10 marketed prescription drugs produce revenues that match or exceed average R&D costs
  - Improve Pharma R&D efficiency
  - Surrogates for outcomes in chronic diseases
  - Marker for drugs with efficacy in subsets of patients
- Market need is for tools that improve the efficiency of R&D, simultaneously reducing the cost of development.
- The average time taken for a product to reach market over the last 20 years has Increased almost 20% to 15 years.

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Large scale biomarker analysis – Toxicoproteomics & Toxicogenomics

- A major hurdle in drug development is the occurrence of adverse drug responses (side effects) i.e. drug toxicity. Such responses cannot generally be predicted. They reveal themselves late in the drug development process, either in pre-clinical trials on animal models or in clinical trials on human patients. In many cases, the candidate drug has to be abandoned at this stage.
- A major application of biomarker technologies is the prediction and investigation of adverse drug responses. These fields have even been given their own names: toxicoproteomics and toxicogenomics.
- If for example tissue samples from an untreated patient and from a patient treated with a candidate drug are compared for differences in the presence or abundances of their protein profiles then particular marker proteins may be evident. These differentially expressed proteins may be useful as biological markers for drug toxicity. Further, if they can be identified, the mechanism of toxicity may also become clear.
- Much toxicology research has focused on the liver and kidneys as these break down and excrete drugs and so are the major sites of toxicity in the body. Many drugs that have been investigated in this manner including some of the medicines we take for granted, such as paracetemol and the antibiotic gentamicin.
- One of the major side effects of the immunosuppressant drug, cyclosporin A, is kidney toxicity, which occurs in nearly 40 per cent of patients. The toxicity is associated with the loss of calcium in the urine and resulting calcification of the kidney tubules.
- Proteomic analysis of rat, and subsequently human, kidneys from untreated patients and those treated with cyclosporin A showed a striking difference in the level of one particular protein, the calcium-binding protein calbindin. This protein was much less abundant in the kidneys of humans and rats treated with cyclosporin A, and immediately suggested the mechanism of cyclosporin A toxicity.

Source; http://www.wellcome.ac.uk/en/genome/

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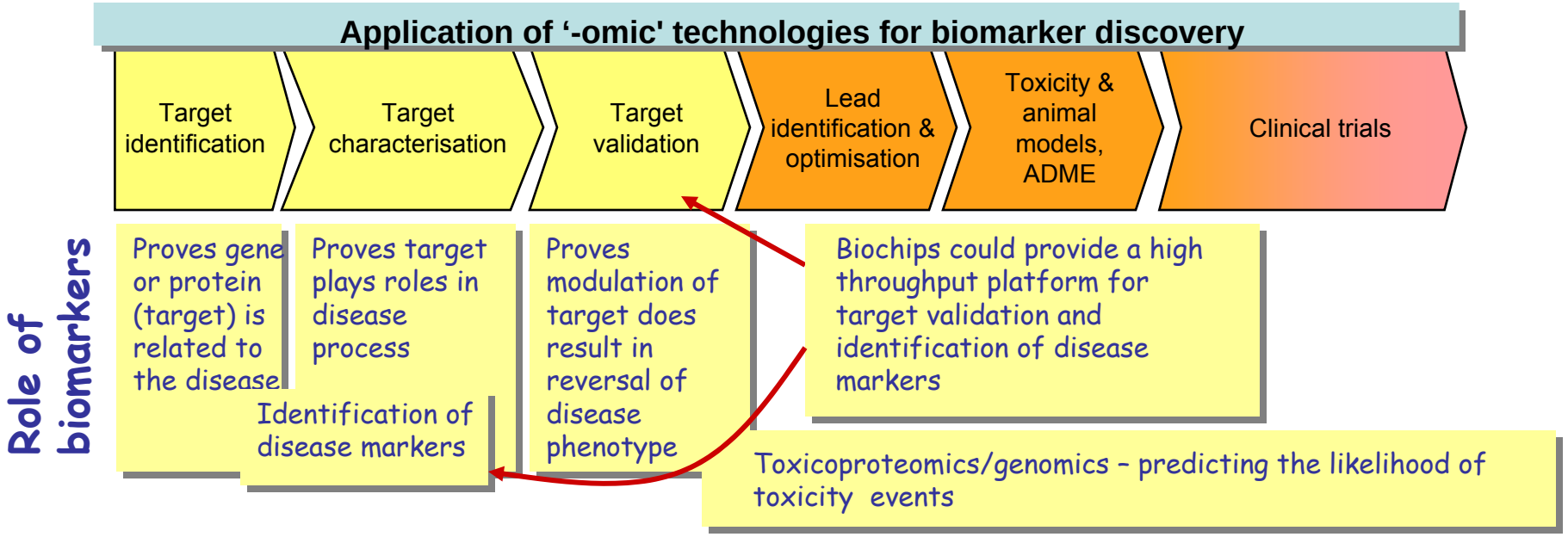
Biomarker discovery has the potential to impact on all stages of the drug discovery process



- **Target Validation**
  - As a result of genomics, there is no shortage of drug targets – the need is to convert as many of these as possible into validated drug targets
  - Biomarkers can relieve the target validation bottleneck in Pharma R&D by identifying efficient proxies for efficacy.
- **Toxicology markers**
  - Evaluation of gene and protein expression for understanding toxic events in pre-clinical safety can reduce high attrition rates due to toxicity issues
  - Used to screen the number of drugs for likely toxicity before they go into clinical trials – toxicoproteomics
- **Identifying clinical biomarkers**
  - Disease classification
  - Disease progression markers for pre-clinical and clinical testing
  - Markers for patients' individual response to drugs

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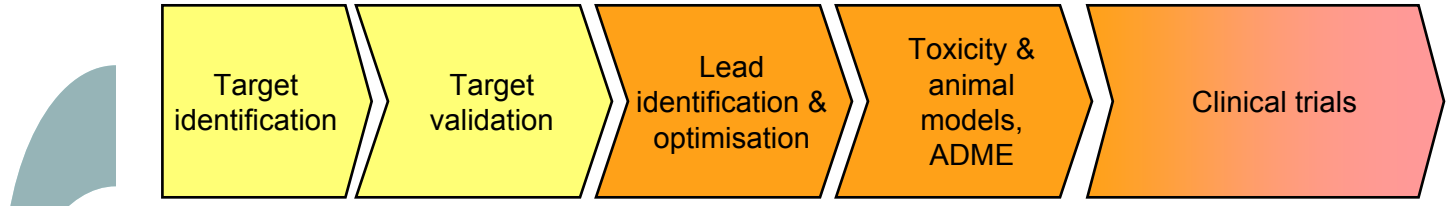
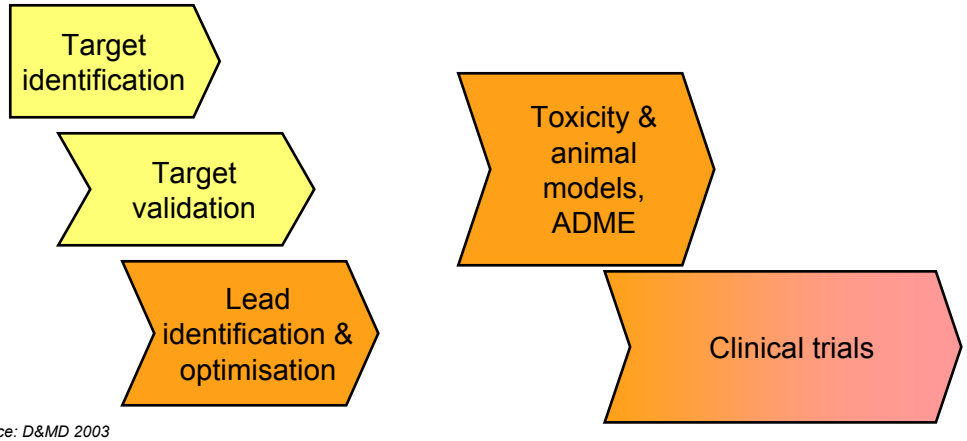
It is the ability to transition from serial optimisation of compounds to parallel optimisation - using efficient and easy-to-quantify measures of efficacy and toxicology- that makes biomarker research such a hot area in drug discovery



Integration of the processes of the drug discovery development timeline will lead to increased efficiencies and productivity - two current issues in Pharmaceutical Industry



Source: D&MD 2003

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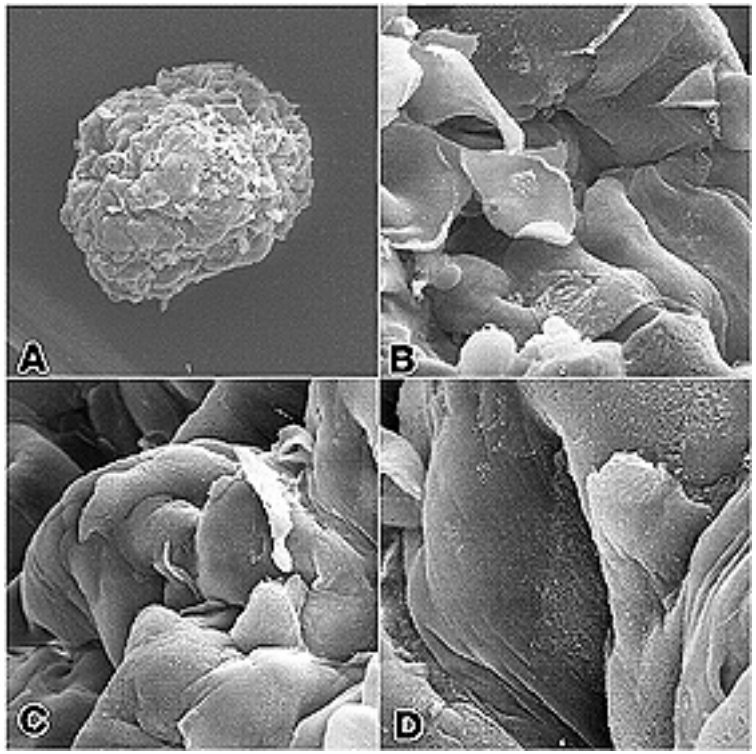
- Cancer – a key area of focus for biomarkers
- Cancer – a significant market need



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The cancer market is significant with a high unmet need

Market size - patients

- 20 million people worldwide
- 10 million new cases per years
- 2nd leading cause of death worldwide
- Lung cancer – 25-30% of all cancer deaths
- Breast cancer most common type in women
  - 400,000 women diagnosed annually
- Prostate cancer most common type in men

Market size – revenues

- Global Cancer market currently a $20 bn dollar market
- Estimated to increase to $45 bn by 2011
- Treatments for breast cancer ~ $3 bn
- Cost of cancer in the US estimated at $171.6 bn
  - $60.9 bn direct costs
  - $15.5 bn indirect costs

Source: Datamonitor 2003, American Cancer society 2003

Market Need

- Above normal cancer rates driven by
  - Improved diagnostic screening
  - More public awareness
  - New knowledge on cellular basis of cancer
- Market need is for effective, less toxic cancer therapeutics. In view of the anticipated growth in cancer cases, it is becoming too expensive to continue prescribing drugs that are largely ineffective.
  - With cancer- and patient- specific drugs, there will be a need of in vitro diagnostics to match the drug to cancer and patient and to monitor the drug's action on the disease

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"The difficulty of the search is complicated by the breadth and subtlety of the clinical questions that arise in the management of cancer patients:

- *Does this asymptomatic patient have ovarian cancer?*
- *How aggressive is it?*
- *Are there distant metastases?*
- *What is the preferred treatment?*
- *Has the cancer recurred?"*[2]

2; Gander, T et al., Medical Laboratory Observer, January 2003.

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Major applications for biomarkers in cancer include; early diagnosis, prognosis and the application of tailored treatment regimens

- Biomarkers promise;-
  - the discovery of tumour and disease markers for early cancer detection and diagnosis,
  - novel protein based drug targets for anticancer therapy, and
  - surrogate endpoints for the assessment of therapeutic efficacy and toxicity.
- Biomarkers ***have already shown*** promising results in the diagnosis of cancer:
  - Specific proteins have been identified that can be used to diagnose breast cancer, colon cancer and bladder cancer.
  - Unusually high levels of the phosphorylated form of the protein stathmin have been found in childhood leukaemia cases.
  - In bladder cancer, several keratin proteins have been identified that are expressed in different amounts as the disease progresses from early stage to full blown squamous cell carcinoma –
    - disease progression can now be monitored through measurement of the keratin levels in bladder biopsies
  - Psoriasin, another protein found in urine of bladder cancer patients can be used as an early diagnostic marker for the disease

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One of the biggest applications for biomarkers in cancer is the application of genomics and proteomics to discover diagnostic, prognostic and theranostic markers of disease

- Cancer proteomics encompasses the identification and quantitative analysis of differentially expressed proteins from normal tissue, premalignant and malignant tissue
- Petricoin *et al* recently discovered that pathologic changes within an organ might be reflected in the proteomics patterns in the serum.
  - Bioinformatics tools using proteomic spectra has been developed
  - Correctly identified out 63 of 66 cases ovarian cancer (including stagings)
- NCI's early detection research network is using proteomics in the discovery and identification of biomarkers for cancer detection.
- Specific cancer proteins have been identified
  - Oncoprotein 18 (OP18) increased in acute lymphoid leukaemia
  - FK506 binding protein overexpressed in ovarian cancer
  - HSP70 stress inducible anti-apoptotic protein in ovarian cancer

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DNA arrays can be used to classify different types of cancer

- There are over 200 different types of cancer, each of which has a unique set of clinical characteristics, and specific treatment regimens.
- Acute myeloid leukaemia (AML) and acute lymphoblastoid leukaemia (ALL) cells look very similar but they respond to different therapies. For AML,drugs such as daunorubicin and cytarabine are favoured while ALL patients respond better to vincristine and methotrexate.
- Traditional diagnosis relies on a combination of techniques. Skilled clinicians look for subtle cell shape differences in biopsies and smears. Cytogeneticists may be able to identify particular chromosome rearrangements specific for each cancer. In certain cases, cells produce different enzymes and stain in distinct ways or produce a marker protein identified using an antibody. However, none of these tests is 100 per cent accurate and results can be conflicting and in some cases inconclusive.
- For AML and ALL it has been found that accurate classification is achieved by analyzing the expression of 50 genes on an array representing nearly 7000 genes in total. In one study, 36 out of 38 patients were classified correctly using this single test.
- Only 40 per cent of patients with non-Hodgkins lymphoma respond to current therapy. Until recently, it was impossible to tell which patients would respond until treatment was underway. However, DNA microarray analysis reveals two, previously unrecognised, subtypes of the disease that match the different clinical outcomes and drug responses.

Source; http://www.wellcome.ac.uk/en/genome/

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Protein analysis can identify diagnostic markers and targets for drug development.

- Proteins have been identified that can be used to diagnose breast cancer, colon cancer and bladder cancer; e.g. Stathmin is expressed at unusually high levels in cases of childhood leukaemia.

- The stathmin protein is phosphorylated in cancer patients; only the phosphorylated form is associated with childhood leukaemia. This emphasises the importance of proteomics in disease diagnosis, because a change in protein modification associated with cancer cannot be detected using DNA arrays.

- In the case of bladder cancer, proteomics analysis has identified several keratin proteins that are expressed in different amounts as the disease progresses from the early transitional epithelium stage to full blown squamous cell carcinoma.

- The measurement of keratin levels in bladder cancer biopsies can therefore be used to monitor the progression of the disease. Another protein, psoriasin, is found in the urine of bladder cancer patients and can be used as an early diagnostic marker for the disease. This provides another example of how proteomics, but not DNA arrays, can be used in cancer diagnosis. Urine, in common with most bodily fluids, contains proteins but no RNA.

Source; http://www.wellcome.ac.uk/en/genome/

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National Comprehensive Cancer Network recommendations for the use of biomarkers in cancer (2003)

Table 1: CCN recommendations on the use of tumor markers in common malignances[1]

SITE	ANALYTES	SCREENING	DIAGNOSIS AND PROGNOSIS	TREATMENT SELECTION AND MONITORING	SURVEILLANCE
Acute myelogenous leukemia	Immunophenotyping markers		●		
Bladder	NMP-22, BTA, M344		●	●	
Breast	Her-2/*neu*		●	●	
Colorectal	CEA		●	●	●
Esophagus					
NSCLC					
Ovarian	CA-125		●	●	●
Pancreas	CA 19-9		●	●	●
Prostate	PSA	●	●	●	●
SCLC					
Stomach					

● *Recommended in NCCN practice guidelines* ● *Marker in development (no current consensus on utility) or used in investigational settings*

Source; Gander T et al., 2003

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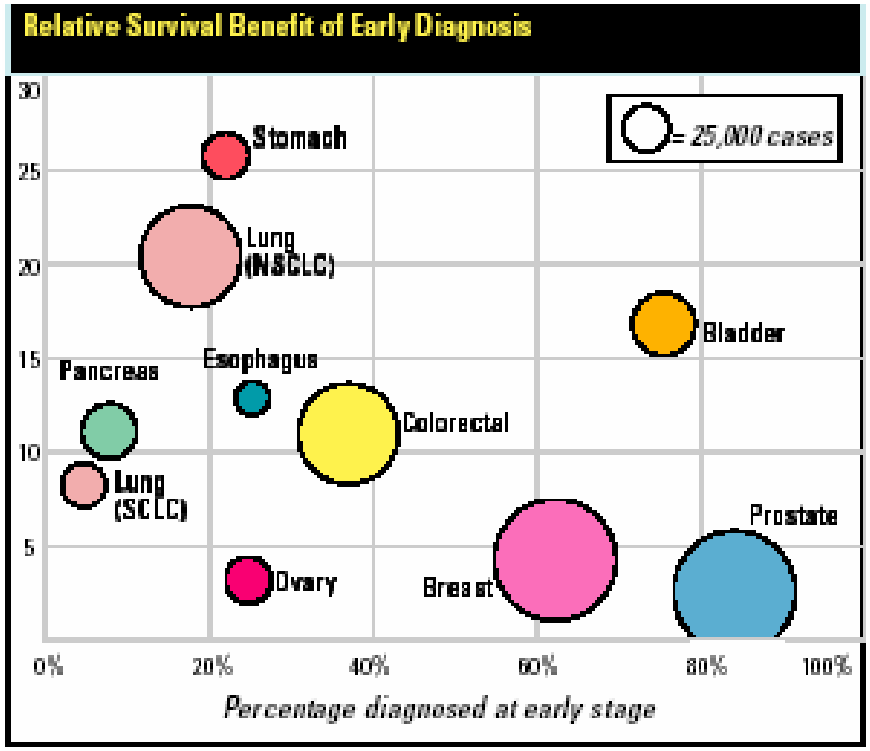

"There is general agreement that earlier cancer detection is preferable since it is associated with improved survival. Unfortunately, early detection is the exception for most cancers. For example, patients diagnosed with localized non small cell lung cancer (NSCLC) are approximately 20 times more likely to survive five years than patients whose disease is diagnosed with distant metastases. However, fewer than 20% of NSCLC cases are diagnosed at the localized stage"[2]

Source; Gander T et al., 2003

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Current Themes

- Women with a family history of breast cancer are now routinely tested for BRCA1 and BRCA2 mutations.

- For women who have been treated for breast cancer, recommended surveillance and follow-up procedures include periodic histories and physical exams; mammography and pelvic exams (for women taking tamoxifen who have not undergone hysterectomy). **Routine measurement of biomarkers is not currently recomended.[2]**

- Physicians and patients often turn to tools without proven value in the desperate hope of detecting recurrences or metastases earlier. **Up to 62% of surveillance costs for breast cancer survivors are attributable to "excess testing"** that exceeded recommendations and is unlikely to be effective.[3] Only 22.6% of recurrences are detected at scheduled follow-up surveillance, and symptoms are the primary indicator if relapse in 57.6% of cases.[4]

- Examples of biomarkers assuming important roles in clinical management of cancer include the assessment of Bcr-Abl oncogenes in leukemias, Her2/neu gene amplification in breast cancer and EGFR amplification in colorectal cancer.

- Researchers at Fox Chase Cancer Centre have identified a biomarker –thymidine phosphatase- which will predict how patients with colon cancer will respond to treatment with capecitabine (Roche's Xeloda; Pfizer's Campostar).

- In parallel with its approval of Erbitux, the FDA also cleared an EGFR pharmDx kit from DakoCytomation; this biomarker is used to identify patients eligible for treatment with Erbitux. Erbitux is expected to achieve blockbuster status in CRC.

- The European Patent Office (EPO) has revoked a patent granted in 2001 to Myriad Genetics Inc. and other collaborators on a 'Method for diagnosing a predisposition to breast and ovarian cancer.'

3; Srinivas P, Clinical Chemistry, 2001. 4; Vastag B, Journal of the National Cancer Institute, 2000

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Unmet biomarker needs in Cancer include:

- A panel of biomarkers to allow accurate genotyping of cancers and predict response to different therapeutic agents.
- Biomarkers that allow patient selection and accurate assessment of emerging agents in niche populations, e.g. Iressa.
- Accurate/efficient diagnostic and prognostic tests for multiple cancers e.g. Ovarian cancer.
- Non-invasive tests for cancers e.g. pancreatic cancer.

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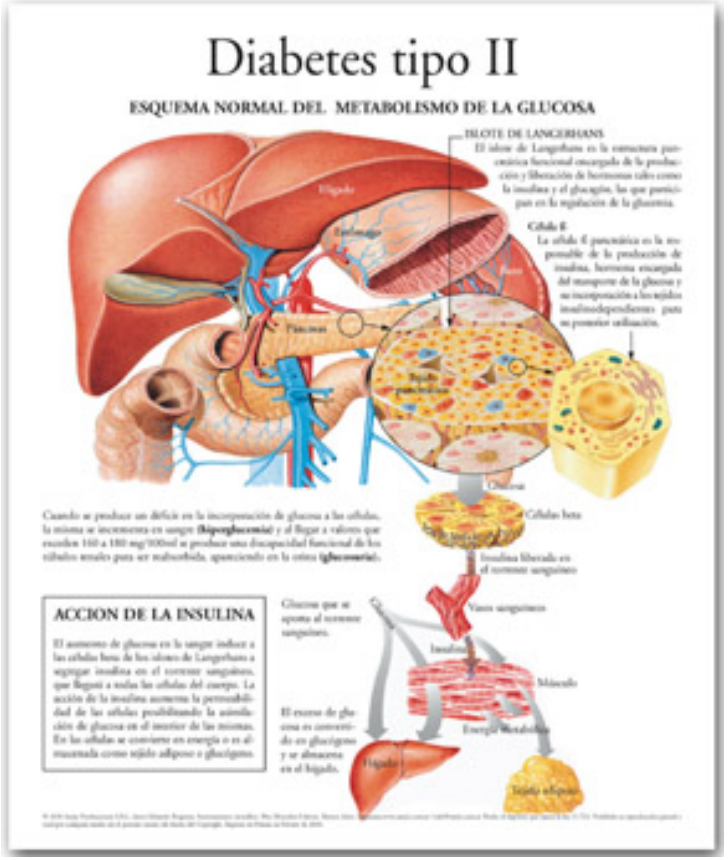
- Diabetes – Key applications for Proteomics
- Diabetes – A significant market need
- Diabetes – Players with proteomics programmes



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The major application for proteomics in diabetes is the application of protein screening methods to drug discovery and design

- Programmes undertaken in the field of proteomics at US National Institute of Diabetes and Digestive and kidney disease (NIDDK) include;
  - Identification of surrogate markers indicating different stages of diabetes
  - Use of proteomics to study signal transduction networks for insulin receptors and other cell surface receptors relevant to diabetes
  - Characterisation of the proteome of animal & cell models relevant to diabetes, its complications and other metabolic diseases
  - Use of proteomic approaches for identifying surface markers for monitoring pancreatic beta cell differentiation
  - Identification of novel drug targets or therapeutic agents using proteomic approaches relevant to diabetes

- A number of proteins have been identified that are differentially expressed between pancreatic islets from mice that are glucose intolerant and islets from normal mice. The expression of some of these proteins was further modulated by treatment with rosiglitazone.

Sanchez J-C et al, Mol. Cell. Proteomics2002, 1, 509-516

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Interest in Proteomics for Diabetes is increasing due to the sheer size and cost of the diabetes problem worldwide

Areas of Unmet Need & Market Dynamics

- Diabetes – management and treatment of – represents a significant area of unmet need.
- Currently diabetes is being managed as a ongoing condition representing significant costs to healthcare systems in the western world
- Diabetes is estimated to cost $105 bn worldwide with numbers of patients increasing
  - 18.2 million people in the US have diabetes
  - 5.2 million of this population are unaware they have the disease
  - Cost of diabetes to US $132 billion
    - Direct medical costs $92 bn
    - Indirect costs $40 bn (disability, work loss, premature mortality, etc.)

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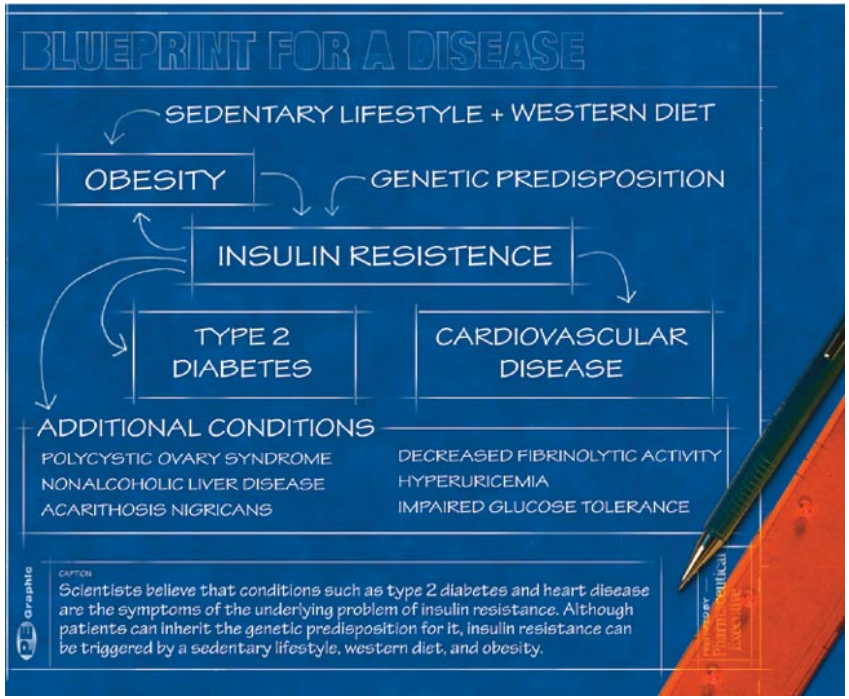
Unmet biomarker needs in Diabetes:

- Markers that can identify patients at high risk of disease progression from large asymptomatic patient populations. These markers must offer improvements over current tests such as HBA1c, IGT, CRP, Homocysteine etc. (Markers for metabolic syndrome)

- Markers of drug action that will be accepted by physicians as surrogates for efficacy. e.g. physicians are unwilling to accept PPAR action on HBA1c as a surrogate for morbidity and mortality outcomes data in diabetic patients.



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- **AKT2 gene linked to insulin resistance**

- This is the first demonstration of a mutation in a human gene downstream in the signal pathway from the insulin receptor leading to insulin resistance and diabetes in some people.
- In type 2 diabetes, tissues of the body are insensitive to the action of insulin. In a study of patients with severe impairment of insulin action, researchers have identified a new mutation in a gene called AKT2 that is responsible for the symptoms in affected individuals in one family.
- Mutation of a critical region of the AKT2 protein produces signalling changes responsible for insulin resistance and diabetes in some people.

Source; http://www.wellcome.ac.uk/en/genome/

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- **International research teams studying two distinct populations have found variants in the HNF4A gene that may predispose people to type 2 diabetes, the most common form of the disease.**

- Researchers identified four SNPs which are strongly associated with type 2 diabetes in Finnish and Ashkenazi Jewish populations.
- All four SNPs cluster in the regulatory region of a single gene, hepatocyte nuclear factor 4 alpha (HNF4A), a transcription factor that acts as a 'master switch' regulating the expression of hundreds of other genes. HNF4A turns genes on and off in many tissues, including the liver and pancreas. In the beta cells of the pancreas, it influences the secretion of insulin in response to glucose.
- "It's a nice coalescence of findings," said Francis Collins, director of the National Human Genome Research Institute (NHGRI) "What we found is a common variation in this gene. If you have this variation, it appears to raise your risk of type 2 diabetes about 30 per cent. The variation isn't going to cause diabetes unless you have it in combination with other, yet-to-be-identified genetic susceptibility factors, together with certain environmental influences such as obesity and lack of physical exercise."

Source; http://www.wellcome.ac.uk/en/genome/

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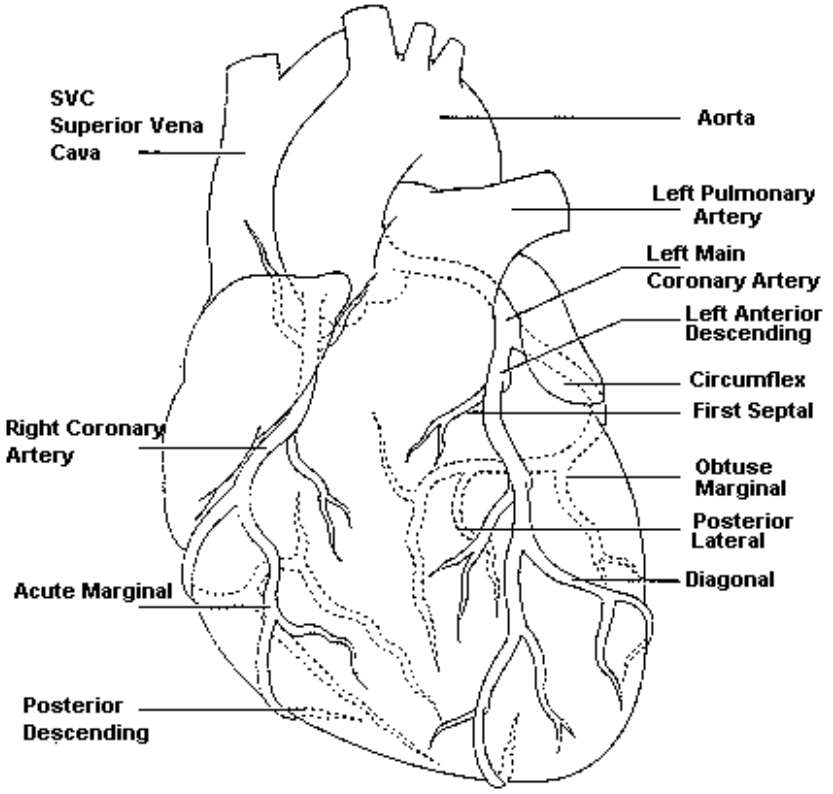
- Heart disease – Key applications for Proteomics
- Heart disease – A significant market need



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Application of proteomics in heart disease

- Proteomics allows examination of global alterations in protein expression in the diseased heart and will provide new insights into cellular mechanisms involved in cardiac dysfunction. It should also result in the generation of new diagnostic and therapeutic markers.

McGregor E and Dunn MJ. *Hum Mol Genet. 2003*

- Types of collaborations are between companies/Research Institutes with Databanks for Cardiovascular disease, companies with the technologies for mining and analysing proteins and larger companies with a franchise in the area, e.g. Duke university (holds largest database of cardiac patients), GeneProt (sophisticated capabilities in proteomics technologies) and Novartis (Major interest in cardiovascular disease).

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Heart Disease - a variety of diseases representing a significant opportunity driven by market size and need

Prevalence (US numbers)

- 64,400,000 Americans have heart disease
  - 50,000,000 have high blood pressure
  - 13,200,000 have coronary heart disease
  - 5,000,000 have congestive heart failure
  - 4,800,000 suffer stroke
  - 1,000,000 have congenital cardiovascular defects
- 1 in 5 males and females has some form of heart disease

Drivers & Trends

- The aging of the population resulting in increased incidence of chronic disease including coronary artery disease, heart failure and stroke
- Explosive increase in incidence of diabetes & obesity
- Estimated Cost of cardiovascular disease in US estimated at $368 bn

Source: American Heart Association

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Current Themes

- Axis-Shield recently announced a licensing agreement with Azwell Inc, of Osaka, Japan, to allow marketing of Azwell's homocysteine assay in the USA and Canada. Azwell's exclusively-licensed partner in the USA is Polymedco of Cortlandt Manor, New York. Polymedco will market Azwell's assay solely on its proprietary Poly-Chem analyser. Under the agreement, Axis-Shield will receive a royalty on each test sold by Polymedco.

- Biosite Diagnostics' BNP assay, a fully automated test for use as an aid in the diagnosis of HF, has been a strong commercial success. Research shows that elevated levels of BNP indicate HF, although the assay is less useful for the rapid diagnosis of ischemic events, such as MI. Roche also markets a BNP diagnostic test, while in December Abbott labs submitted a 510(k) application to the FDA for its own BNP test. (Source Burrill 2004).

- In June 2003, Bayer Diagnostics received FDA clearance for its automated BNP assay, an for the diagnosis of HF. Roche and Abbot have also received clearance for their BNP assays.

- In September I-Stat received FDA approval for a ten-minute I-Stat System Cardiac Troponin test, the first diagnostic in the market that allowed doctors to measure at the bedside any elevation in troponin levels in the blood – which is indicative of heart damage. Before approval of the 10 minute point of care test, emergency doctors often waited 30 minutes or more for test results. I-Stat is being acquired by Abbot labs. (Source Burrill 2004).

- The FDA recently cleared the Albumin Cobalt Binding test, manufactured by Ischemia Technologies, that significantly increases the ability of doctors to rule out a heart attack when a person shows up in ER with severe chest pain. Typically the ACB test is used in combination with an ECG and a troponin test. (Source Burrill 2004).

- In July 2003, diaDexus received FDA marketing approval for its PLAC blood test used to predict the risk of CHD. PLAC works by measuring the lipoprotein associated phospholipase A_2 Enzyme; elevated levels indicate CHD. This test may one day be used to identify potential patients for GSK's experimental LP-PLA_2 inhibitor. (Source Burrill 2004).

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Current Themes

- **Icelandic researchers have identified two variants of the ALOX5AP gene that may increase the risk of heart attack and stroke.**

- Although many of the clinical features of cardiovascular diseases have been determined, the contribution of genetic factors to these diseases remains uncertain.
- Research by deCODE Genetics has now identified two variants in the ALOX5AP gene, encoding the arachinodate 5-lipoxygenase-activating protein (FLAP), which may increase the risk of myocardial infarction or stroke.
- The researchers studied 713 Icelanders who had suffered a heart attack and found that 29 per cent carried a variant of ALOX5AP (HapA). This variant was associated with an 80 per cent increase in heart attack risk; carriers of HapA may also be at a 67 per cent increase in the risk of stroke.
- The ALOX5AP gene product, FLAP, has been implicated as playing a role in regulating the production of substances that trigger inflammation – such as leukotrienes, which are potent vasoconstrictors of coronary arteries. It is proposed that increased FLAP activity may lead to the accumulation of leukotrienes on fatty deposits on the arterial wall.

Source; http://www.wellcome.ac.uk/en/genome/

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Unmet biomarker needs in Heart Disease:

- Markers that can identify patients at high risk of disease progression from large asymptomatic patient populations. These markers must offer improvements over current tests such as CRP, Homocysteine etc. (Markers for metabolic syndrome)

- Markers that accurately integrate and reflect all CV risk factors (e.g. B.P., LDL, TG, HDL, etc) to give a measure of global CV risk.

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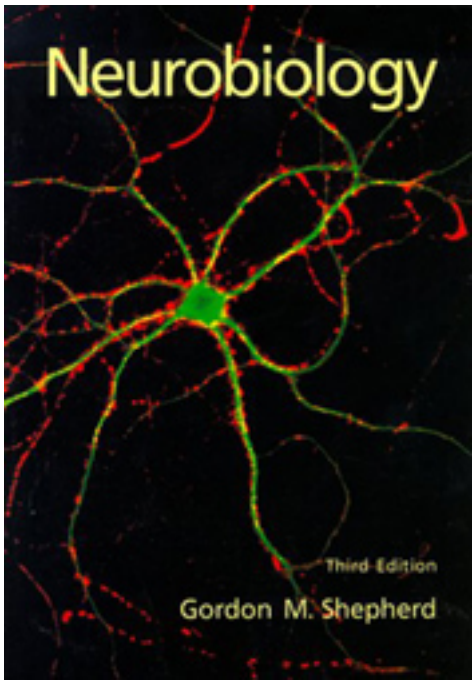
- Neurobiology – Key applications for Proteomics
- Neurobiology – A significant market need



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Neurogenomics – Application of biomarkers to CNS

- Bodily fluids such as cerebrospinal fluid (CSF) and serum can provide indicators on CNS related disorders
  - Changes in the protein composition of CSF may be indicative of altered CNS protein expression pattern with a causative or diagnostic disease link.
  - Recently large scale proteomic studies have identified more than 500 proteins, including phosphoproteins
  - The existence of a CNS database will accelerate development of more specific diagnostic and prognostic disease markers as well as new selective therapeutics
- Application of proteomics to CNS disorders covers a number of indications
  - Neurodegenerative diseases (Parkinson's & Alzheimer's disease),
  - Neurological diseases (Stroke, trauma,)
  - Psychiatric disorders (Schizophrenia, depression, addiction, anxiety)
- Data is being generated and targets identified through gene expression profiling, pathway mapping, genome mining, SNP mining and bioinformatics analysis and interrogation of data sets
  - Differences in protein expression and post-translational modification (mostly oxidative modification) of proteins from AD brain and peripheral tissue, as well as in brain from rodent models of AD, have yielded insights into potential molecular mechanisms of neurodegeneration in this dementing disorder.

Source: spectroscopynow.com

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Neurobiology an area of significant unmet need –

Disease	Approx No Patients
Parkinson's disease	1,500,000
Alzheimer's disease	4,000,000
Stroke	3,500,000
MS	300,000
Huntington's disease	30,000

- Neurobiological disorders are many, varied and many do not have effective treatments
- Current treatments treat symptoms and do not provide cures
- CNS drugs represent $50 bn annually and the market is growing 20% each year
- Over 160 million people worldwide suffering from CNS related illnesses

Source: D&MD Oct 03

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Scottish Context

Example Companies

Adgen

Albachem Ltd

Arrayjet

Auvation Ltd

Axis Shield Ltd

Crucial Diagnostics

CXR BioScience Ltd

Cyclacel

Diagnostics Scotland

Haptogen

Inveresk

Invinity Bioscience

Lux biotech

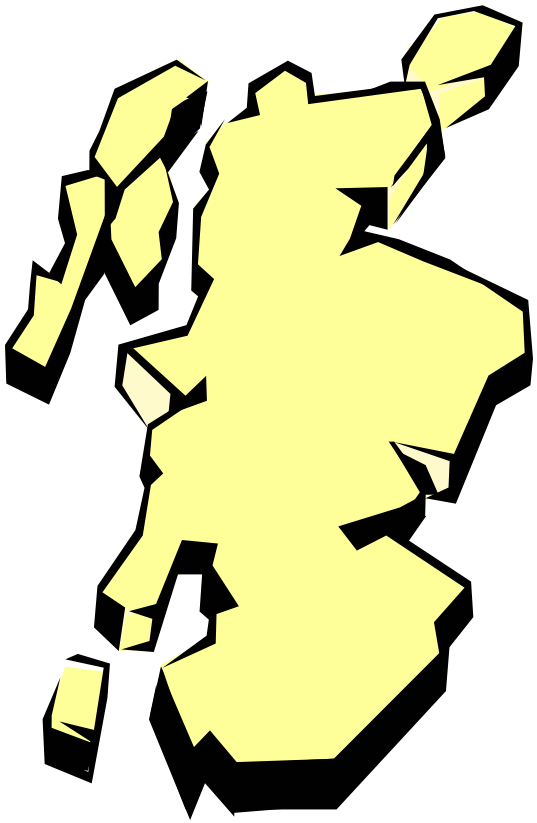
Organon

Quintiles

Scottish BioMedical

Serologicals

Upstate



Research Institutes/Academia

Scottish Structural Proteomics Facility

Edinburgh Protein Interaction Centre

Institute of Biomedical and Life Sciences, University of Glasgow

MRC Human Genetics Unit,, Edinburgh,

Wellcome Trust Centre for Cell Biology, Institute of Cell and Molecular Biology,

Department of Medical Microbiology
Department of Pathology
University of Aberdeen

Post Genomics and Molecular Interaction Centre

sc-GTI, Edinburgh

Beatson Institute

Scottish Diabetes Group

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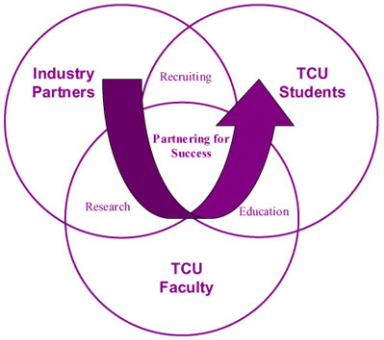
Select Global Current & Future Players

- Big Pharma
  Roche (Avastin)
  GSK (for HIV typing)
- Biotech companies
  Genentech (Herceptin)
- Diagnostic companies
  Roche, Celera Diagnostics, Diadexus, Axis-Shield
- Proteo/Genomic companies
  Ciphergen, Zynomics, ParAllele, Perlegen deCode, Sequenom, Illumina
- CRO & Special Services
  Quintiles, Charles River, LabCorp
- Reagent Companies
  Upstate, Invitrogen, Cell Signalling, Seralogicals



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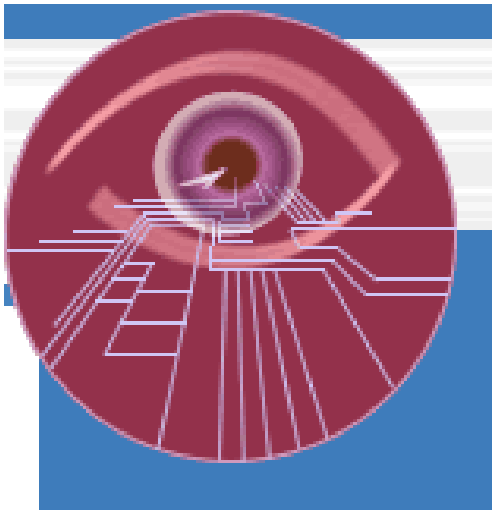
Foresighting



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Opportunity

Pharmaceutical drug development

- Efficacy testing
- ADMET/toxicology
- Target/lead identification
- Preclinical testing
- Clinical trials/drug labelling

Clinical Management

- Treatment decision tools
- Improved Diagnostics
- Monitoring of treatment
- Pre-disease identification

Disease Areas

- Aggressive Cancers
- Global CV
- Metabolic Syndrome

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What are the opportunities in Biomarkers in the next 10 years

"…most value for proteomics at the moment is in biomarkers – ideally these are identified early in the drug discovery process …" *Lge Pharma*

"...Pharmacoproteomics – assigning the right drugs to the right patients by using proteins as indicators (biomarkers)…" *Academic*

"…Tools for systematic analysis of post-translational modifications of proteins…"
Academic & advisor to proteomic company…

*"…*tools that enable in vivo protein complex identification for pathway analysis…"
Academic

"…toxicogenomics and toxicoproteomics …for predicting drug efficacy and selection of least toxic compounds…" *Lge Pharma*

*"….*Disease progression markers – definitely very attractive in cancer…" *Lge Pharma*

*"…*The holy grail is protein chips – simultaneous analysis of all relevant diagnostic parameters or multiple tumour markers from biopsy material …"
Lge Pharma

What are the major gaps (problems) in the market

"…there are no tools for systematically studying post-translational protein modification…"
Academic & Advisor to biotech company
*"...*Lack of an exhaustive set of good antibodies against all proteins…" *Lge Pharma*
"…Current gap in market is for universal sample preparation methods…" *Academic*
"…More sensitive methods for detecting low abundance proteins and detection over a wide dynamic range
Academic
*"…..*a lack of well-defined clinical samples with appropriate patient consent *.."* *Lge Pharma*

What are the major gaps (problems) in the market

"…not a lot of pharma companies devote resources to new technologies…"
Lge Pharma
*"...*most proteomic technolgies look promising, but sensitivity, reproducibility, robustness and automation will have to be demonstrated…"
Lge Pharma
"…Current gap in market is for universal sample preparation methods…" *Academic*
"…

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Barriers

- Pharmacoeconomic benefits
- Clinicians' acceptance of surrogate endpoints
- Chronic diseases require expensive large scale prospective studies
- Overcoming current commoditization

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iti Life Sciences

Gaps

- Access to well designed clinical samples
- Standardised sample isolation protocols
- Rapid low cost reagent preparation
- Precise reproducible chips
- High sensitivity & dynamic range detection
- Data integration & analysis tools
- Clinician access to technology

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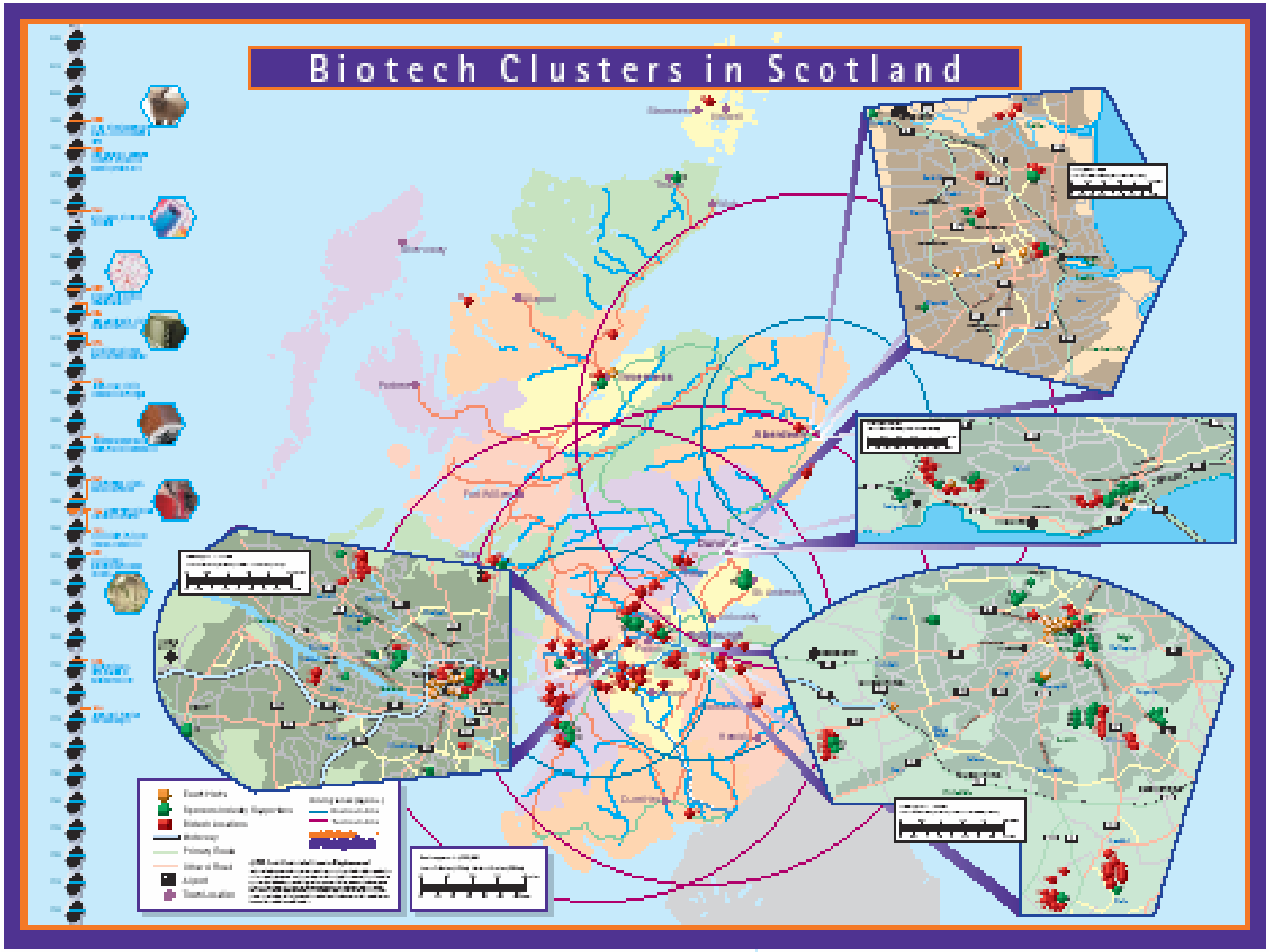
Company Landscape



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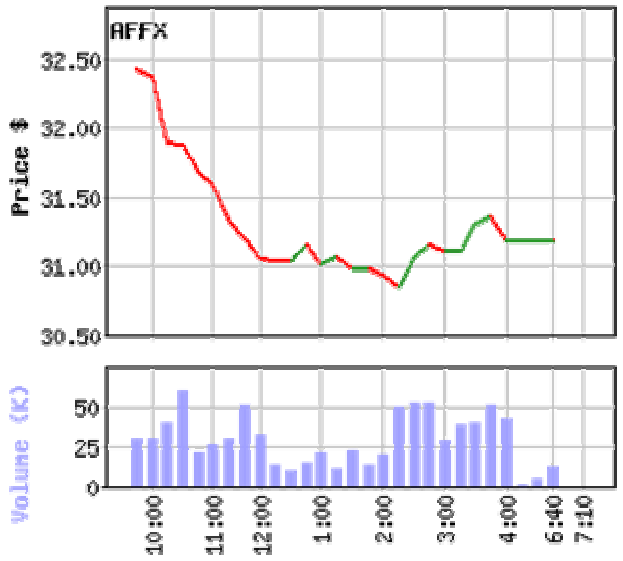
iti Life Sciences

AFFYMETRIX

Affymetrix's GeneChip system and other products identify, analyze, and manage genetic data to help develop new treatments for use in biomedical research. It sells its products directly to customers, including Schering AG, Amgen, and Roche. Affymetrix and Millennium Pharmaceuticals are developing the next generation of GeneChip technology. The company owns about 40% of Perlegen Sciences, which uses Affymetrix's technology to map genetic variations called single nucleotide polymorphisms (SNPs) and tie them to human health for drug development.



GeneChip arrays are applied in a wide variety of DNA and mRNA analyses. Recent analytical accomplishments include the elucidation of interactions between signaling pathways involved in development, the discovery of a new class of leukemia, and the development of new assays to track drug metabolism.

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ABAXIS.com POINT OF CARE CHEMISTRY AND HEMATOLOGY SYSTEMS FOR PEOPLE AND THEIR PETS

Abaxis' point-of-care blood analyzers can perform more than 20 types of tests on humans and animals. The analyzers are designed to be portable, require little training, provide on-the-spot results, and offer built-in quality control and calibration. They come with reagent discs for performing common blood tests. Abaxis markets the system under the name VetScan in the veterinary market and Piccolo in the human medical market. It is developing a wider range of tests to better penetrate the human diagnostic market. Abaxis sells its products to veterinarians, hospitals, managed care organizations, and the military. A comprehensive metabolic, renal and hepatic function panel is available (Source Jay Koenig, Hoovers.com/Araxis)

PANEL	ANALYTE																										
General Chemistry 12 # 400-0012	ALB	ALP	ALT	AMY	AST	BUN	Ca^{++}	CHOL				CRE			GLU						TBIL		TP			
Liver Panel Plus # 400-0003	ALB	ALP	ALT	AMY	AST									GGT							TBIL		TP			
General Chemistry 7 # 400-0007						BUN	Ca^{++}	CHOL				CRE			GLU						TBIL				UA	
General Chemistry 6 # 400-0006			ALT		AST	BUN						CRE		GGT	GLU											
Electrolyte Panel # 400-0022											Cl^-						K^+		Na^+			TCO_2				
MetLyte 8 # 400-0023						BUN				CK	Cl^-	CRE			GLU		K^+		Na^+			TCO_2				
Basic Metabolic Panel # 400-0024						BUN	Ca^{++}				Cl^-	CRE			GLU		K^+		Na^+			TCO_2				
Lipid Panel # 400-0025								CHOL	CHOL/HDL RATIO*							HDL		LDL*					TRIG		VLDL*	
Renal Function Panel # 400-0027	ALB					BUN	Ca^{++}				Cl^-	CRE			GLU		K^+		Na^+	PHOS		TCO_2				
Comprehensive Metabolic # 400-0028	ALB	ALP	ALT		AST	BUN	Ca^{++}				Cl^-	CRE			GLU		K^+		Na^+		TBIL	TCO_2	TP			
Hepatic Function Panel # 400-0026	ALB	ALP	ALT		AST								DBIL								TBIL		TP			

* *Calculated Value*

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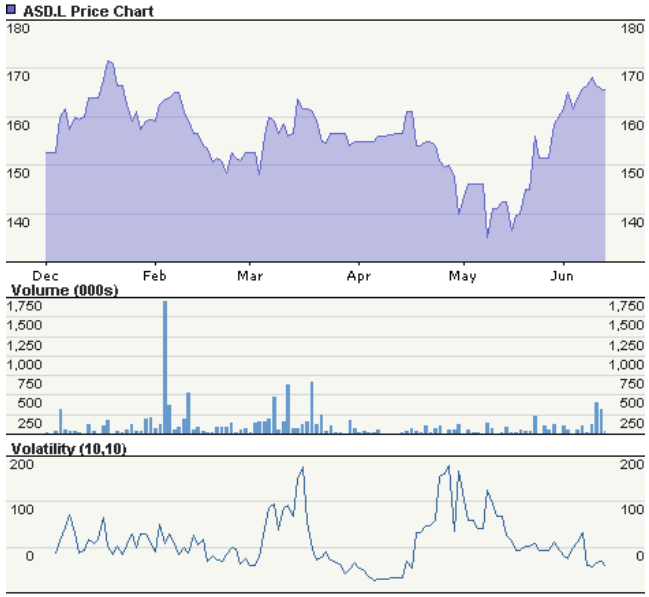

Axis-Shield makes diagnostic tests centered on diabetes and autoimmune, infectious, cardiovascular, and alcohol-related diseases. Its leading products are assays that measure heart disease potential and detect thrombotic risk. The company also distributes a range of products from third parties. Subsidiary Plasmatec Laboratory Products makes latex and febrile reagents. Axis-Shield has research and development agreements with several biotechnology companies. The company was formed by the 1999 merger of Axis Biochemicals and Shield Diagnostics.
(Source Jay Koenig, Hoovers.com)

NycoCard::: CRP Single Test
NycoCard::: HbA1c
NycoCard::: READER II
NycoCard::: U-ALBUMIN
NycoCard::: D-DIMER Single Test

Axis-Shield recently announced that it has concluded a licensing agreement with Azwell Inc, of Osaka, Japan, to allow marketing of Azwell's homocysteine assay in the USA and Canada. Azwell's exclusively-licensed partner in the USA is Polymedco of Cortlandt Manor, New York. Polymedco will market Azwell's assay solely on its proprietary Poly-Chem analyser. Under the agreement, Axis-Shield will receive a royalty on each test sold by Polymedco.

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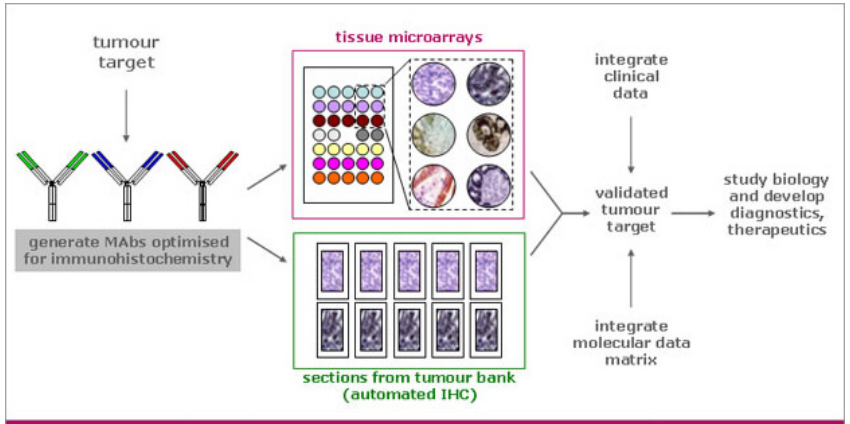
AUVATION

Auvation develops innovative technologies for the diagnosis and treatment of cancer. Its core capabilities are in the identification and validation of protein targets within tumour cells. Auvation's flagship technology targets the detoxifying enzyme cytochrome P450 1B1 (CYP1B1), the only tumour marker molecule found in all types of cancer. CYP1B1 is being exploited as a point-of-attack in three ways: CYP1B1-activated prodrugs; Inhibitor co-therapy, which offers enhancement of drug efficacy; and Immunotherapy. The IPR relating to immunotherapeutic use of CYP1B1 has been licensed to US drug development company, Zycos Inc.



Auvation tumour target discovery: part 2

Auvation also has exclusive rights to collections of patient tumour samples with matched normal tissue and comprehensive clinical data. They are using this resource to screen for new disease markers and therapeutic targets using antibody and proteomics technologies, and to validate these targets using automated immunohistochemistry and tumour microarrays.

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BIOSITE®
NEW DIMENSIONS IN DIAGNOSIS®

Biosite's diagnostic products include its Triage Drugs of Abuse Panel and Triage TOX Drug Screen, single-sample urine tests that indicate illegal drug use, including amphetamines, cocaine, marijuana, and opiates. The firm's Triage *C. difficile* and Triage Parasite Panels detect intestinal parasites and other pathogens. The company's Triage BNP Test assists in diagnosing congestive heart failure. The Biosite Discovery program is a collaborative research effort to identify new protein markers for strokes, cardiovascular and pulmonary diseases, and sepsis.

Triage® BNP TEST

Biosite recently rolled out the Cardiac ProfilER panel, a test providing results on four cardiac markers – troponin I, myoglobin, CK-MB and BNP – in 15 minutes using a whole blood sample.

Biosite's BNP assay, a fully automated test for use as an aid in the diagnosis of HF, has been a strong commercial success. Research shows that elevated levels of BNP indicate HF, although the assay is less useful for the rapid diagnosis of ischemic events, such as MI. Roche also markets a BNP diagnostic test, while in December Abbott labs submitted a 510(k) application to the FDA for its own BNP test. (Source Burrill 2004)

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BIO-RAD

Biorad makes and sells clinical diagnostics systems and instruments used in life sciences research. Bio-Rad supplies products to customers worldwide, including hospitals, universities, government agencies, biotechnology firms, and pharmaceutical companies. Products include laboratory instruments, disease tests, and imaging systems. Bio-Rad also makes spectrometers and spectral-related software, marketing products through its own sales force. The Schwartz family owns more than 80% of Bio-Rad.

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CELERA

Celera Genomics Group cleared a major hurdle when it mapped the human genome, but the firm, a tracking stock of Applera, believes studying proteins will make it a profitable drugmaker. Sister firm Applied Biosystems handles the marketing of Celera's genomics databases (which offer info about the genomes of mice, fruit flies, various bacteria, and other life forms) to life sciences companies so that Celera can focus on drug discovery and development, in part with the help of Applera and Applied Biosystems. The firm looks to partner with other biotech and pharmaceutical companies to develop antibody therapies, particularly for cancer.

Celera has also undertaken several programs to identify differentially expressed proteins on the surface of cells. Proteins that have clear differences in abundance in diseased cells relative to healthy cells may represent targets for therapeutic antibodies.

ANTIBODY TARGET PROGRAM	STATUS
Pancreatic Cancer	Identified over 110 differentially expressed cell surface proteins. Selected 25 proteins for validation as targets for antibodies and small molecules.
Non-small Cell Lung Cancer	Processing tumor and normal tissue to identify differentially expressed proteins. Identified approximately 100 differentially expressed cell surface proteins.
Colon Cancer	Processing tumor and normal tissue to identify differentially expressed proteins.
Breast Cancer	Processing tumor and normal tissue to identify differentially expressed proteins.

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CELERA DIAGNOSTICS
A Joint Venture With Applied Biosystems

A joint venture between siblings Applied Biosystems Group and Celera Genomics Group, Celera Diagnostics is using the best of both companies to develop new diagnostic tools. The company's products help health care providers better diagnose, monitor, and treat diseases. A key focus is the ViroSeq HIV-1 genotyping system. The diagnostic, which has received FDA clearance, may help doctors better assess drug resistance in HIV patients by pinpointing the exact strain of HIV they have. Celera Diagnostics and Abbott Laboratories have teamed to research and develop a variety of molecular diagnostics; Abbott Diagnostics markets ViroSeq HIV-1. (Source Barbara Redding, Hoovers.com)

Luminex Applied Biosystems m1000

Biomarkers/technologies offered by Celera Diagnostics;

- ViroSeq™ System
- Cystic Fibrosis
- Hepatitis C Virus
- HLA Typing
- Instrument Platforms
- ABI PRISM® 7000 Sequence Detection System
- Luminex 100™ Total System
- ABI PRISM® 3700 DNA Analyzer
- ABI PRISM® 3100-*Avant Genetic Analyzer*
- ABI PRISM® 3100 Genetic Analyzer
- ABI PRISM® 377 DNA Sequencer
- ABI PRISM® 310 Genetic Analyzer

In June 2004, Celera Diagnostics presented data at Annual European Congress of Rheumatology linking variation in the gene PTPN22 to a two-fold increase in risk for rheumatoid arthritis (RA).

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Cepheid develops products for genetic profiling, to purify DNA, to detect biological contaminants, and for other scientific uses. The Smart Cycler System, its flagship product, amplifies and analyzes DNA for life science research faster than other analyzers. Partners Fisher Scientific and Takara Shuzo sell the system in select markets in North America and Asia, respectively; the company has distributorship deals with regional players in Europe. Cepheid has developed GeneXpert, a system designed to extract and examine DNA from blood samples, spores, and other samples in about 30 minutes. (Source Barbara Redding, Hoovers.com)

The GeneXpert System combines cartridge-based sample preparation with amplification and detection functions in a fully integrated and automated nucleic acid analysis instrument. These products are designed to purify, concentrate, detect, and identify targeted nucleic acid sequences, delivering answers from unprocessed sample in less than 30 minutes. The SmartCycler® System is an automated rapid, real-time thermal cycler used for identifying DNA/RNA from prepared biological samples. (Source Cepheid)

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CIPHERGEN®

Ciphergen Biosystems is enabling the next step in biotechnology -- deciphering proteins. The firm focuses on proteomics, or protein-based research. Its ProteinChip System includes disposable ProteinChip arrays, a chip reader, and software that allow biologists and drug developers to discover new protein biomarkers and to identify protein function by connecting DNA and protein research. The system can also analyze protein interactions. Its BioSepra Process Division develops chromatographic sorbents used to manufacture vaccines, proteins, and antibodies. Customers include Amgen, Human Genome Sciences, and Merck. (Source Jay Koenig, Hoovers.com).

Recently, Affymetrix's GeneChip and Ciphergen's ProteinChip technologies were used synergistically for gene and protein expression profiling, revealing unique cellular targets and putative signaling pathways of the tumor suppressor gene FHIT in lung cancer. (Source Ciphergen)

Ciphergen have Biomarker Discovery Center® facilities in Fremont California, Malvern Pennsylvania, Copenhagen Denmark, and Yokohama Japan. Ciphergen operates Biomarker Discovery Center facilities as expert resource centers for ProteinChip® System customers. Biomarker Discovery Center facilities are dedicated to helping Ciphergen customers solve complex and time-sensitive biological research problems. (Source Ciphergen)

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CYGNUS®

Cygnus develops glucose-monitoring systems. The company's star product is the GlucoWatch Biographer, a wrist-worn device that monitors blood-sugar levels for diabetics without breaking the skin. Through its AutoSensor, the GlucoWatch utilizes the company's "electro-osmosis" system, which extracts glucose from fluid between skin tissue rather than blood. Diabetics can use the device's frequent glucose readings to better manage their diabetes through changes in diet, exercise, and insulin dosage. (Source Jay Koenig, Hoovers.com)

The GlucoWatch® Biographer was Cygnus' first approved product. The device and its second-generation model, the GlucoWatch G2® Biographer, are the only products approved by the U.S. FDA, that provide frequent, automatic and non-invasive measurement of glucose levels. (Source Cygnus)

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CYTYC

Cytyc makes sample-preparation systems used in medical testing. Its ThinPrep System stores patients' samples in liquid and incorporates an automated slide-preparation process that results in clearer samples for clinical diagnosis. The system is used as a replacement for the conventional Pap smear to detect the human papillomavirus, a cause of cervical cancer. The ThinPrep System can also be used to perform cancer analysis on tissues from the breast, liver, lung, thyroid, or other organs. (Source Jay Koenig; hoovers.com)

Cytyc's FirstCyte® Breast Test is a minimally invasive method of collecting cells from a woman's breast to search for atypical cytological changes. The FirstCyte® Breast Test is an office-based procedure1 that is comfortable for most patients.

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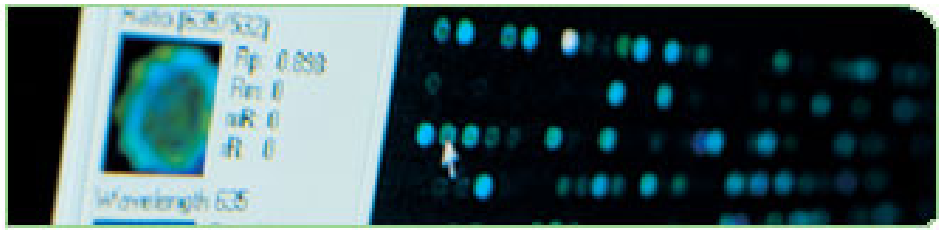
CuraGen Corporation

CuraGen uses its experience as a one-time gene researcher to discover and develop new therapies (including traditional small molecule drugs, as well as protein-based drugs and monoclonal antibodies) for a host of diseases, including cancer, inflammatory conditions, metabolic disorders, and central nervous system diseases. Like many struggling development-stage firms, CuraGen partners with other companies to ease the burden of R&D costs. The company is working with Bayer to develop therapies for diabetes and obesity. With Abgenix it is creating fully human monoclonal antibodies for cancer and cardiovascular and renal diseases. (Source Barbara Redding, Hoovers.com)



CuraGen has developed a genomic tool to assess the safety of new candidate drugs. The Predictive Toxicogenomic Screen (PTS™) is a high throughput, cost-effective test system that screens and prioritizes new drug candidates based upon a predicted safety profile for the liver. This information is combined with potency information and chemical attributes to select the best new drug candidates, improving the efficiency and reducing the costs of drug development. (Source Curagen)

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DakoCytomation

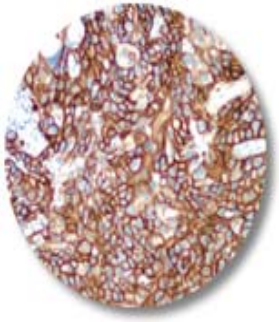
HER2 protein overexpression

DakoCytomation and its nearly 20 subsidiaries around the world make research equipment. Products include equipment for flow cytometry (the study of cells using lasers); immunocytochemistry (a method for diagnosing cancer); immunochemistry (the study of bodily fluids to diagnose disease and other medical purposes); and microbiology products used to identify sexually transmitted diseases, stomach ulcers, and other ailments, as well as diseases and infections in animals. (Source Michael Mclellan, Hoovers.com)

In February 2004, DakoCytomation received approval from the U.S. FDA for use of its EGFR pharmDx™ kit as an aid in identifying colorectal cancer patients eligible for treatment with ERBITUX™ (cetuximab). DakoCytomation also markets the Hercep test to assay for Her2/neu overexpression.

DakoCytomation offer biomarker products in the following areas;

- Pharmacodiagnostics
- Antibodies
- Detction Reagents
- Immunostaining Systems
- Flow Cytometry
- Clinical Diagnostics
- Molecular Pathology
- Microbiology



EGFR pharmDx strongly positive colorectal adenocarcinoma.

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deCODE genetics

deCODE created databases of Icelanders' gene samples, medical records, and genealogy records, some dating back to the ninth century. It sells this data and other bioinformatics products to drugmakers; the firm's flagship Clinical Genome Miner Discovery system is co-marketed with IBM. deCODE uses its data to develop drugs on its own and with such partners as Hoffmann-La Roche, Pharmacia (now merged with Pfizer), and Merck. The company and Roche Diagostics are developing tests to predict a person's risk for osteoporosis, type 2 diabetes, stroke, and other conditions. deCODE is developing pharmacogenomics tests with Affymetrix. (Source Barbara Redding, Hoovers.com)

CGM Discovery ™

In December 2003, Roche and deCODE Genetics announced the development of gene expression assays that can predict responsiveness to common treatments for asthma and hypertension. The research assays were able to predict with 85% accuracy which patients would respond to which drugs. The next step will be validating findings and refining assays into diagnostic tests, which could help doctors individualize treatment options for their patients. (source Burrill 2004)

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diaDexus

diaDexus' products test primarily for cancer, but also for heart disease and other conditions. Lead product candidate PLAC Test –which detects a person's risk for coronary heart disease– was recently approved by the FDA. Its Cathepsin-K and Colon-101 candidates do the same for osteoporosis and colon cancer, respectively. The firm is also developing therapeutic monoclonal antibody cancer vaccines. Founders SmithKline Beecham (nowGlaxoSmithKline) and Incyte Genomics provided diaDexus with initial genomic data and potential molecular targets. (Source Jay Koenig, Hoovers.com)

diaDexus targets five major solid tumor types in its oncolgy discovery and development efforts: colon, breast, lung, ovarian and prostate. More than 800 potential diagnostic candidates have been evaluated and 13 are currently under development. (Source diaDexus)

In July 2003, diaDexus received FDA marketing approval for its PLAC blood test used to predict the risk of CHD. PLAC works by measuring the lipoprotein associated phospholipase A_2 Enzyme; elevated levels indicate CHD. This test may one day be used to identify potential patients for GSK's experimental LP-PLA_2 inhibitor. (Source Burrill 2004).

PLAC

The Test for Lp-PLA2

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In March 2003, Epigenomics signed a three year collaboration with Roche to develop biomarkers based on DNA methylation.
In June 2004, Epigenomics announced positive results from clinical studies showing that its proprietary DNA methylation markers can identify the likelihood of disease recurrence in women following breast cancer surgery.
Epigenomics is also collaborating with Wyeth to analyse drug response markers in xenograft mice

Epigenomics is committed to significantly improving the treatment of cancer and other complex diseases by developing novel diagnostic and pharmacodiagnostic products based onDNA methylation. By detecting and interpreting DNA methylation patterns, the "on" and "off" signs for genes, Epigenomics can create a digitized readout for each cell. The comparison of a patient's cells against healthy and sick reference samples enables an exact diagnosis of disease at a very early stage and provides physicians with essential information to help guide an appropriate therapy. The combination of diagnosis and therapy, based on this information and robust proprietary technology, is “personalizing” medicine. (Source Epigenomics)

Epigenomics has the following products in development;
Early detection and molecular classification tests in
- colon
- prostate
- breast cancer

under development with Roche

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EXACT sciences Applying Genomics to Eradicate Cancer.®

EXACT is working on tests that may aid in the early detection of colorectal cancer and precancerous lesions by isolating human DNA in stool samples and identifying genetic mutations associated with cancer. Focusing on colorectal cancer because it is one of the most common (and one of the deadliest), EXACT believes its method is superior to those currently in practice because it may be able to discern colorectal cancer in its early stages, when it is most treatable. The company is conducting clinical trials in conjunction with the Mayo Clinic. It is also developing its technology to detect lung, pancreatic, and other cancers. (Source Jay Koenig, Hoovers.com)

PreGen-Plus™
Non-Invasive Colorectal Cancer Screening

Exact Sciences (in partnership with LabCorp), launched PreGenPlus, the first non-invasive DNA based test available for the detection of colorectal cancer. Pregen Plus is being marketed to doctors as an accurate, genetic based early warning test for colon cancer, which should help boost compliance above current screening methods and help diagnose the cancer at earlier stages, when it is most treatable. Pregen Plus consists of a panel of 23 individual tests, each looking for the presence of alterations in DNA isolated from stool samples (Source Burrill 2004).

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EXELIXIS™

Exelixis gathers and compares genetic data from fruit flies, roundworms, and other organisms to speed the development of drugs, insecticides, and animal health products. German subsidiary Artemis Pharmaceuticals performs similar testing on mice and zebra fish; Exelixis plans to spin off this unit. The company and partner GlaxoSmithKline are working to develop therapies for cancer, inflammatory conditions, and vascular diseases. Other partners include Bristol-Myers Squibb and Elan. Genoptera is one of the company's agbio joint ventures with Bayer Group. The company's Exelixis Plant Sciences unit focuses on plant genomics. (Source Barbara Redding, Hoovers.com)

ARTEMIS has developed the unique ArteMice™ platform to enable the rapid generation of innovative genetically modified mouse models. ARTEMIS is also exploiting the unique potential of zebrafish for high throughput *in vivo* analysis of the pharmacology, toxicology and mechanism of action of research compounds. (Source Artemis)

ARTEMIS Pharmaceuticals GmbH an EXELIXIS Co.

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GENAISSANCE PHARMACEUTICALS

Genaissance aims to improve drug discovery and marketing through population genomics -- the analysis of genetic variations within diverse populations. Its HAP Technology examines haplotypes, units of genetic variation. Its DecoGen informatics system then analyzes the genetic information, which can help determine what response a patient will have to a given drug. Clients such as Pfizer and AstraZeneca use the data to make more effective products. The firm is applying its HAP know-how to develop its own drugs. (Source Barbara Redding, Hoovers.com)

Genaissance has developed a combination of technologies, services and expertise, which the Company calls its *HAP*™ Technology, that allow genetic variation and population genomics to be integrated into the development, marketing and prescribing of a new generation of DNA-based diagnostic and therapeutic products. (Source Genaissance)

Key components of Genaissance's *HAP*™ Technology include:

•A database (*HAP*® Database) of highly informative, proprietary measures of genetic variation, or haplotypes.
•Markers, for pharmaceutically relevant genes;
•A proprietary informatics system, *DecoGen*® Informatics System, including unique algorithms, for defining patient populations with different drug response
•GLP support experience (support for >420 clinical trials);
•GLP DNA banking experience (processed >40,000 samples);
•GLP genotyping experience (delivered >200,000);
•Clinical genetics development skills;
•CLIA-licensed DNA diagnostic laboratories. (Source Genaissance)

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Human Genome Sciences (HGS) is narrowing its focus to protein drugs and monoclonal antibody therapies for infectious/immunology diseases and cancer. HGS is concentrating on the clinical trials of five of its top drug candidates. Its most advanced drug, LymphoStat-B, could treat systemic lupus erythematosus and rheumatoid arthritis. Partners such as druggernaut GlaxoSmithKline have licensed the company's data and technology to develop their own drug pipelines. (Source Barbara Redding, Hoovers.com)

HGS' Functional Proteomics Program begins with a virtually complete set of functional, fully sequenced human genes. From these HGS select a set of about 9,000 individual genes, that produce secretory proteins. The effects of the secretory proteins are tested using highly automated techniques. HGS have developed a sophisticated informatics system to store and interrogate the many millions of biological data points that result from these experiments. Proteins selected for further study are made and purified, then subjected to preclinical evaluation. (Source HGS)

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Incyte

Incyte's drug discovery programs are focused on the identification of novel small molecule drugs for inflammation, cancer and diabetes. It recently entered into a collaborative license agreement with Pharmasset Ltd for Reverset™, a novel nucleoside analog reverse transcriptase inhibitor, which is in Phase II development to treat human immunodeficiency virus (HIV) infections. Data from preclinical and clinical studies of Reverset though Phase IIa suggest the drug may be a useful and convenient HIV treatment, particularly among the many patients who have become resistant to standard HIV therapies. Incyte's drug pipeline reflects both internal discovery programs and collaborations with pharmaceutical companies:

Program	Mechanism of Action	Indications	Development Stage
Reverset™ (Nucleoside analog)	Reverse transcriptase inhibitor to prevent HIV replication	HIV infection	Phase II clinical development
Chemokine receptor antagonist	receptor antagonist to inhibit macrophage activity	chronic inflammatory diseases; RA, etc.	preclinical candidate selected
Sheddase inhibitor	a novel protease inhibitor to block tumor cell growth	breast, lung, colon, pancreatic cancers	preclinical candidate selected
Protein phosphatase inhibitors	inhibitor to control proliferation in cancer cells	breast, lung, colon, pancreatic cancers	lead optimization
	Inhibitors to enhance response to insulin, leptin	diabetes, obesity	lead optimization
J & J agreement	insulin sensitizer	metabolic diseases, diabetes, atherosclerosis	1 compound in pre-clinical development

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inverness medical innovations

Inverness Medical Innovations consumer products include women's health products such as the ClearBlue home pregnancy test and ClearPlan Easy Fertility Monitor brands. The firm's vitamins and nutritional products include the Synergy Plus line of vitamin, mineral, and herbal supplements; StressTabs vitamins; and Posture calcium supplements. In addition, Inverness makes a wide range of diagnostic products, including tests for mononucleosis, pregnancy and ovulation prediction, and sexually transmitted diseases. (Source Jay Koenig; hoovers.com)

In June 2004, IMI paid $2.6 million (€2.1 million) in cash, and issued a total of 155,209 shares of its common stock in a private placement to the shareholders of Viva Diagnostika – a distributor of professional diagnostic products to the German marketplace-- in exchange for all of the outstanding capital stock of Viva and an affiliated entity.

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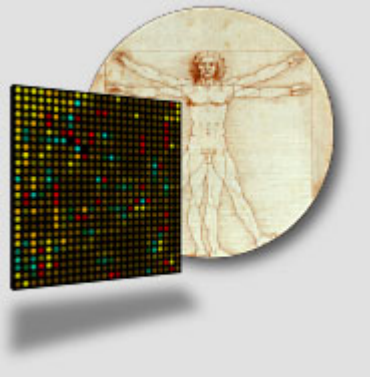
Large Scale Biology (LSBC) uses its proteomic and genomic technologies for therapeutic, diagnostic, and drug-discovery research. Its GENEWARE technology inserts genes into organisms for analysis; its ProGEx system identifies protein compositions. Clients include government agencies, drug firms, and universities. LSBC is using its expertise to develop its own drug pipeline: Disease targets include non-Hodgkin's lymphoma, Fabry disease, and drug-resistant infections. Subsidiary Eclipse Diagnostics sells diagnostics for cancer and other diseases that detect protein markers in blood samples. (Source Barbara Redding, Hoovers.com)



LSBC's ProGEx™ technology is used to identify new protein markers. By comparing body fluid samples from healthy controls with samples from patients with specific diseases, ProGEx™ is able to detect disease-specific markers with sensitivity. Using ProGEx™, LSBC is building a portfolio of markers which can be used for the diagnosis and/or monitoring of a range of diseases. LSBC's technology and protein markers are applicable to a variety of protein biochip formats. (Source LSBC)

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Lexicon discovers genes, then makes information about them available by selling subscriptions to its OmniBank, LexVision, and other databases. Subscription clients include Bristol-Myers Squibb and Boehringer Ingelheim. Lexicon also offers "knockout mice" with specific genes knocked out for research. Through "e-Biology" agreements with universities and other research organizations, Lexicon hopes to earn royalties from drugs developed using its databases. Its Lexicon Pharmaceuticals unit develops drug targets to outlicense or develop on its own. The division has R&D programs focusing on metabolic diseases, cardiology, oncology, neurology, and immunology. (Source Barbara Redding, Hoovers.com)

Lexicon has applied its patented, high-throughput gene trapping technology to create OmniBank, a library of more than 200,000 knockout mouse embryonic stem cell clones corresponding to greater than 50% of mammalian genes. Each OmniBank mouse clone contains a single genetic mutation that can model the action of future drugs through highly specific genetic antagonism *in vivo*.

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MILLENNIUM®

Millennium focuses on three disease targets -- cancer, inflammatory diseases, and cardiovascular disorders. Its flagship drug INTEGRILIN is FDA-approved to treat various unstable angina and heart surgery candidates. The drug is co-promoted by Schering-Plough. Millennium is primarily developing proteasome inhibitors, which stop harmful enzymes that break down proteins. VELCADE won FDA approval to treat relapsed multiple myeloma. The firm has 10 candidates in clinical development, including several it is working on with partners in the health care industry.
(Source Barbara Redding, Hoovers.com)

Millenium have integrated a diverse array of advanced technologies and capabilities into a series of coherent processes for drug discovery and development. Because many of these are automated, high-throughput processes generating large amounts of complex information, Millenium have also developed sophisticated capabilities in information technology and knowledge management.
(Source Millenium)

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MYRIAD

Myriad uses gene maps, analyzes family histories, and identifies protein interactions (through its ProNet database) to find inherited gene mutations that increase the risk for disease. Its tests can determine a patient's risk for breast or ovarian cancer (BRACAnalysis), heart disease (CardiaRisk), and colon cancer (COLARIS). With such partners as Bayer, Eli Lilly, and Schering-Plough, Myriad is developing drugs for cancer, AIDS, and other diseases. ProNet has netted a possible cancer-fighting breakthrough: It identified a compound that targets a protein key to apoptosis (programmed cell death) and can induce cancer cells to die but not harm healthy cells.(Source Jay Koening, Hoovers.com)

COLARIS *AP*℠

The genetic test for Familial Adenomatous Polyposis (FAP) and Attenuated FAP (AFAP)

COLARIS℠

The genetic test for Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

BRACAnalysis®

The genetic test for hereditary breast and ovarian cancer

MELARIS℠

The genetic test for hereditary melanoma

Myriad discovered the BRCA1 and BRCA2 genes that cause hereditary breast and ovarian cancer, and now offer clinical tests to determine predisposition to cancer: BRACAnalysis for hereditary breast and ovarian cancer, COLARIS for hereditary colon and endometrial cancer, and MELARIS for hereditary melanoma and pancreatic cancer.

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OraSure Technologies, Inc.

diagnostic solutions for the new millennium

Oral specimen kits and other diagnostic tests developed by OraSure Technologies are designed to detect HIV and drug abuse. The firm's OraSure products use oral specimens rather than traditional blood- or urine-based methods to test for HIV. Its Intercept line uses oral samples to test for marijuana, cocaine, opiates, PCP, and amphetamines. OraSure also makes tests for alcohol abuse. The firm has developed a rapid HIV blood diagnostic testing method (licensed in part from Abbott Laboratories). OraSure sells its products in the US and internationally, primarily to the life insurance industry and public health markets. (Source Jay Koenig, Hoovers.com)

OraSure's four platform technologies — OraQuick®, OraSure®, UPT™, and UPlink™ — provide the foundation for products addressing substance abuse, infectious diseases, toxicology, insurance testing, plasm screening and cryosurgery.

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ORCHID BIOSCIENCES
Profiling Genetic Uniqueness™

Orchid BioSciences uses its expertise in single nucleotide polymorphisms (SNPs), markers of genetic diversity, to be a leader in genetic testing services. Its Orchid Identity Genomics unit includes Orchid GeneScreen paternity testing and Orchid Cellmark forensic testing services. The Orchid Life Sciences division uses its SNP-IT technology and SNPstream system to hunt for specific SNPs on DNA strands to find possible drug interaction sites to improve drug discovery and efficacy. Clients include Affymetrix, GlaxoSmithKline, the Department of Agriculture and Rural Development (Northern Ireland), and the police departments of New York City and Los Angeles. (Source Michael Mclellan, Hoovers.com)

The Cellmark unit of Orchid Europe was authorized by the Irish government –in June 2004-- to provide genotyping services designed to help farmers breed sheep with reduced susceptibility to the prion disease scrapie. Additionally, Orchid was awarded the immigration identification testing contract by the New Zealand Government in April 2004.

ORCHID BIOSCIENCES EUROPE
Profiling Genetic Uniqueness™

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ParadigmGenetics, Inc.™

Paradigm have projects and services in;

- Crop Traits
- Crop Protection
- Green Biotechnology
- Collaborations
- Biomarker discovery
- Toxicology
- Drug discovery
- Clinical trials
- Disease staging
- Disease monitoring
- Protocol Consultation and Sample Preparation
- Transcript Profiling: Agilent Oligo Microarrays
- Transcript Profiling: Affymetrix GeneChip® Arrays
- Analysis and Reporting
- Processing Steps
- Gene Expression Profiling
- Biochemical Profiling
- Phenotype Profiling
- Pathway Informatics

Paradigm Genetics develops technologies to profile the biochemical structure and function of cells, tissues or other biological samples to speed drug development. Its MetaVantage platform focuses on cellular physiology; by understanding how cells become diseased, drug developers can more effectively treat or stop the mechanisms of disease. Paradigm Genetics is working with LION bioscience and the National Institute of Standards and Technology to develop improved bioinformatics systems. The firm also offers gene expression microarray services; it has a marketing and preferred service provider deal with Agilent for these operations. (Source Jay Koenig, Hoovers.com)

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PharmaNetics is the holding company for Cardiovascular Diagnostics, which makes diagnostic tests to assess blood clot formation and dissolution. Its Thrombolytic Assessment System (TAS) weighs some four pounds and is about the size of a telephone, making it small enough to be used at the point of care for immediate results. The TAS helps in the administration of anticoagulant and clot-dissolving drugs; these and the firm's other tests (some still in development) are used to treat heart attack, stroke, and other cardiovascular conditions. PharmaNetics has a distribution agreement with Bayer Diagnostics, which also owns about a fifth of the firm. (Source Michael Mclellan, Hoovers.com)

Prior to ceasing substantially all of its operations in March 2004, PharmaNetics developed, manufactured and marketed rapid diagnostics to dose, manage and screen patients on drugs affecting coagulation. The Company has ceased the development, production, sale and marketing of its test cards and other products and is currently in litigation with Aventis Pharmaceuticals.

PharmaNetics tests include;

- Enoxaparin (ENOX) Test Card
- Rapidpoint™ Coag
- Rapidpoint™ Accent
- Prothrombin Time (PT)
- PT-ONE™
- PT-NC™
- aPTT
- Heparin Management Test (HMT)
- Heparin Titration Test (HTT)
- Protamine Response Test (PRT)
- Low Heparin Management Test (LHMT)

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QUIDEL® CORPORATION

Quidel makes point-of-care rapid diagnostic products for infectious diseases, reproduction, allergies, and autoimmune disorders. Strep throat tests account for about one-fourth of sales and other products test for mononucleosis, chlamydia, the flu, osteoporosis, and the ulcer-causing *H. pylori* bacteria. Quidel's over-the-counter products include the Conceive and RapidVue brands of ovulation predictors and pregnancy tests. A direct sales force and a distributor network sell Quidel's tests to doctors, labs, hospitals, wellness screening centers, and consumers. Health care products wholesalers Allegiance and McKesson account for about a third of the company's sales. (Source Jay Koenig hoovers.com)

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SEQUENOM®

Through its Genetic Systems unit, Sequenom sheds light on the genetic underpinnings of life with its MassARRAY sequencing system that analyzes variations in DNA called single nucleotide polymorphisms (SNPs). Clients include GlaxoSmithKline, with which it is creating a SNP assay for use in pharmacogenomics, and Incyte Genomics. Like some rivals, Sequenom has entered drug development. Its Pharmaceuticals division discovers the genetic causes of diseases and uses the information to develop drug candidates it plans to license to other firms or develop in-house. (Source Barbara Redding, Hoovers.com)

In April 2004, a consortium – including the National Institute of Health (NIH)-announced that a MassARRAY system was used to identify a novel genetic association to diabetes. DNA sample pools of affected and healthy individuals were analysed using MassARRAY to show that the HNF4A gene has a genetic association to adult-onset diabetes.

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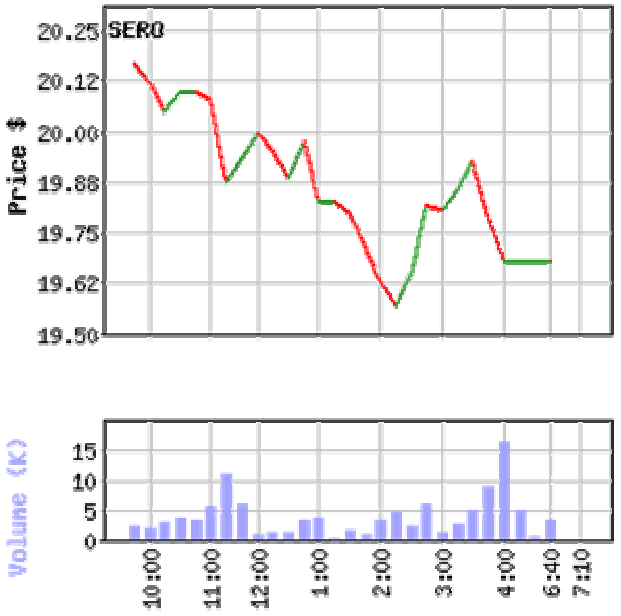
Serologicals supplies major health care companies with speciality biological products and related technologies, Their areas of strategic focus are: Antibodies and Human Plasma Products, for diagnostic and research use, Cell Culture Supplements, for producing diagnostic and therapeutic recombinant proteins, and Molecular Reagents and Assays, for cell biology research and molecular discovery. including the manufacture of monoclonal antibodies for diagnostic use. Through the Chemicon division, they also supply diagnostic kits, reagents, and molecular biology products.



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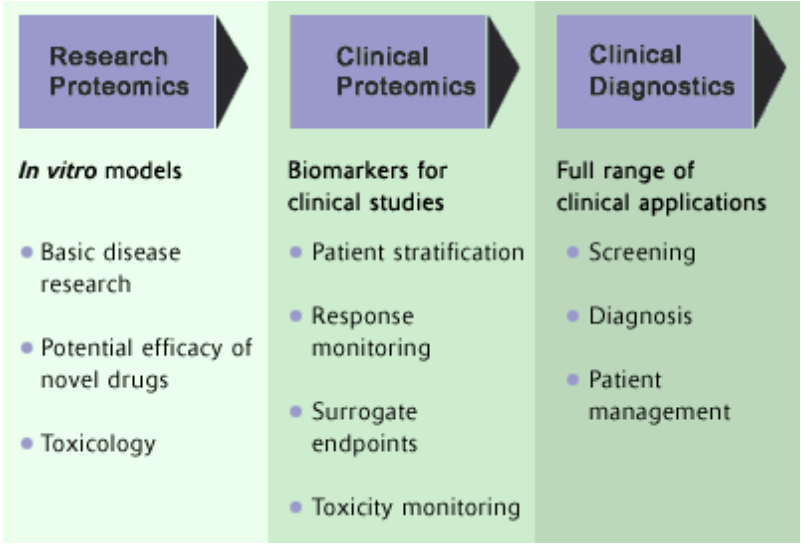
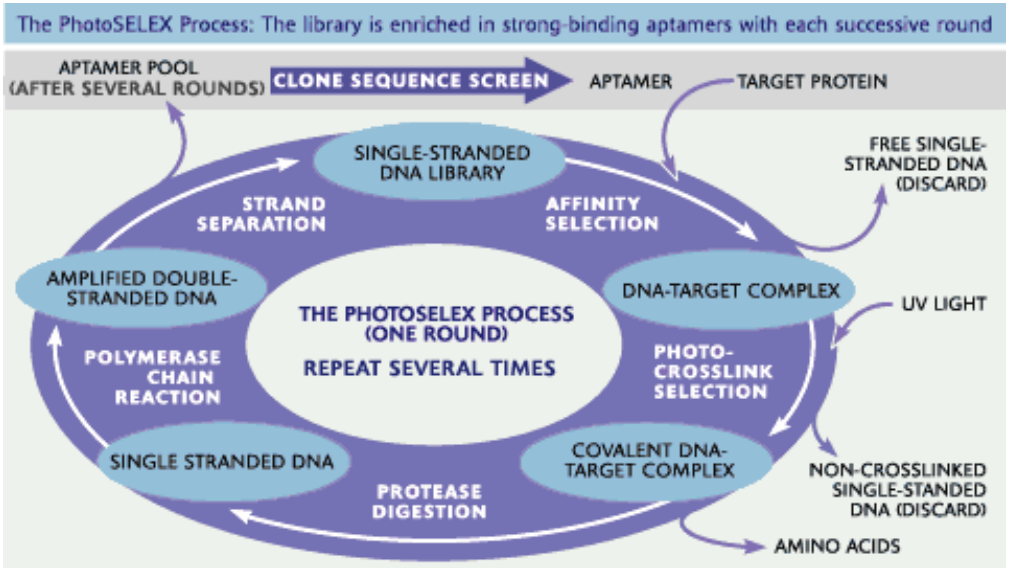
SomaLogic

SomaLogic helps in the hunt for proteins. Life sciences researchers use the company's proteomics arrays to identify proteins related to angiogenesis (the formation of new blood vessels) and inflammation. Data gathered from this work could be used to develop new drugs and diagnostics for a variety of diseases.





Aptamers are ideal for developing arrays for the simultaneous measurement of large numbers of proteins, as they have a high degree of affinity and specificity. The potential of photoaptamers is realized when they are combined to create photoaptamer arrays capable of analyzing the levels of multiple proteins simultaneously. SomaLogic's proprietary photoaptamer technology provides the basis for a new approach to multiplexed protein measurements.

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SpectRx has expanded beyond its original business -- non-invasive monitoring and diagnostic products that use biophotonic technology - to also focus on products for diabetics. The company's lead biophotonic product is the BiliCheck analyzer, which screens for infant jaundice by collecting spectroscopic information from the skin. Its glucose monitoring products use lasers and vacuums to draw interstitial fluid from the skin. The company, which bought Sterling Medivations in 2001 to expand its diabetics business, is also working on a cervical cancer test. Entities associated with Pittsburgh billionaire Henry Hillman own more than 15% of SpectRx. (Source Jay Koenig, Hoovers.com)

SpectRx, through its Guided Therapeutics subsidiary, is developing a technology that uses light to non-invasively detect cervical cancer. The technology painlessly identifies cancers and precancers by analyzing light reflected from the cervix and is designed to eliminate unnecessary follow up procedures and to help preserve the reproductive health of women. SpectRx is also developing a continuous glucose, based on SpectRx's biophotonic technology. (Source SpectRX)

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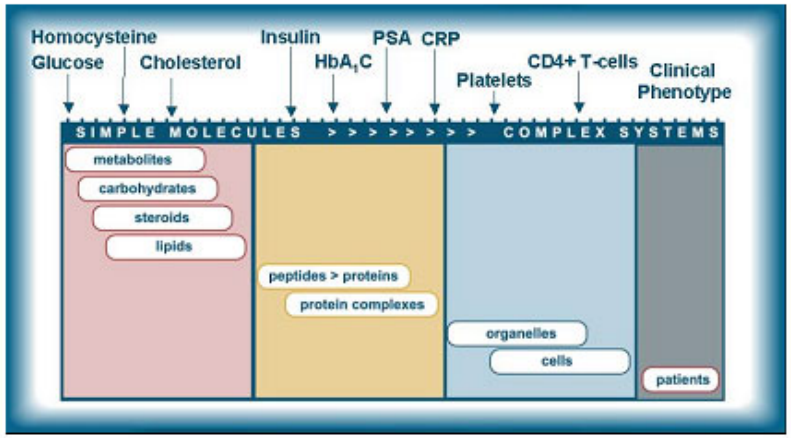
SurroMed

SurroMed are a technology-based, therapeutics company with competencies in biomarker-enabled drug discovery and development. SurroMed apply proprietary technologies for biomarker discovery in clinical research studies to better understand drug mechanisms of action, discover root causes of disease, and discern the molecular basis of patient-to-patient variations in disease presentation, progression and response to treatment. SurroMed's research yields biomarkers and information that enable more efficient discovery and development of new therapeutics, as well as development of diagnostic tests for early disease detection, accurately determining disease sub-types and predicting and monitoring responses to therapy. (Source; Surromed)

In July 2004, Surromed announced an extension to its agreement with Merck to analyze pre-clinical samples provided by Merck in its Biomarker Discovery Laboratory using a proprietary, integrated platform for proteomic analysis. SurroMed will analyze and mine bioanalytic data using its proprietary suite of informatics tools to identify candidate biological markers.



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TRIPATH care technologies™

TriPath Imaging manufactures automated cytology equipment, designed to make cervical cancer screenings more efficient and accurate. The company's products include PrepStain, an automated slide preparation system, and SurePath, a cell collection, preservation, and transport system. TriPath's FocalPoint SlideProfiler system pre-screens Pap smears for the likelihood of abnormality. Its TriPath Oncology unit is developing molecular diagnostic tests for cancer in collaboration with Becton Dickinson, which owns a stake in the firm. Roche controls roughly a third of the company. (Source Michael Mclellan, Hoovers.com)

SUREPATH™ liquid-based Pap test

PREPSTAIN™ slide processor

FOCALPOINT™ slide profiler

i³ SERIES™ intelligent identification through innovation.

Data Presented at Annual Meeting of American Society of Clinical Oncology in June 2004 demonstrates that Melastatin(R) Gene Expression as measured by TriPath Imaging Assay is independent prognostic indicator of overall survival in melanoma.

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Molecular diagnostics approved in 2003

Product	Company	Description
Hybrid Capture 2 High-Risk HPV DNA test	Digene	Human Papillomavirus DNA detection kit
IMX HaVAB –M	Abbott Laboratories	Antibody to Hepatitis A virus (IgM)
Prepstain	Tripath Imaging	Cervical cytology slide preparation device
Diasorin ETI-MAK-2 Plus Assay	Diasorin	Eia for Hepatitis surface Ag
ETI-Core-IGMK Plus	Diasorin	Eia for IgM Ab to Hepatitis core antigen
ETI-EBK Plus	Diasorin	Eia for hepatitis B E antigen
Vitros Immunodiagnostics Products Anti-HBS	Otho Clinical Diagnostics	Antibody to hepatitis B surface antigen assay
Immulite 1000 and 2000 HBSAG Kits	Diagnostic Products Corp.	Test, Hepatitis B
Daktocytomation Hercep Test	Daktocytomation California Corp.	Dako anti-Her2 IHC System
Quantiferon-TB Kit	Cellestis limited	TB test
Vitros Immunodiagnostic Products Anti-HCV	Otho-Clinical Diagnostics	Anti-hcv assay
Versant	Bayer Corp	HCV RNA 3.0 Assay
Bayer Advia IMS PSA Assay	Bayer Healthcare LLC	Prostate Specific Antigen Assay
Bayer Advia IMS CPSA Assay	Bayer Healthcare LLC	Quantitative immunoassay for complexed PSA
Factor II (prothrombin) g20210a kit	Roche Diagnostics	Screen for factor II g20210a mutations by PCR
C-reactive protein (crp)	Abbott Laboratories	System test, c-reactive protein
ViroSeq™	Celera Diagnostics	IV-1 Genotyping System
West Nile Virus ELISA IgG	Focus technologies	Diagnosis of meningioencephalitis
West Nile Virus ELISA IgM Capture ELISA	Focus technologies	Diagnosis of meningioencephalitis
Ausam Total Albumin Assay	Ausam Biotechnologies	Urinary protein or albumin (non-quant.) test
Albumin cobalt binding test	Ischemia Technologies	Albumin Cobalt binding test

Source; Burrill & Company 2004

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