

Proteomics

Part I: Technologies & Markets

By

Prof. K. K. Jain
MD, FRACS, FFPM
Jain PharmaBiotech
Basel, Switzerland

November 2018

A Jain PharmaBiotech Report

A U T H O R ' S B I O G R A P H Y

Professor K. K. Jain is a neurologist/neurosurgeon by training and has been working in the biotechnology/biopharmaceuticals industry for several years. He received graduate training in both Europe and USA, has held academic positions in several countries, and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently, he is a consultant and CEO at Jain PharmaBiotech.

Prof. Jain's 478 publications include 30 books (6 as editor + 24 as author) and 50 special reports which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. He has also written a textbook of gene therapy which is the first book on this subject to be translated into the Chinese language. A book on gene therapy companies was published in 2000 by John Wiley & Sons. Both these books are now incorporated in a special report on gene therapy published in 2004 by Jain PharmaBiotech with the latest edition in 2018. His latest books include "Handbook of Nanomedicine" (Humana/Springer 2008; Chinese edition, Peking University Press 2011, 2nd ed Springer 2012, 3rd ed 2017), Textbook of Personalized Medicine (Springer 2009; Japanese ed 2012, 2nd ed 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016, 2nd ed 2017), "Handbook of Neuroprotection" (Springer 2011, 2nd edn 2019, in preparation), "Applications of Biotechnology in Cardiovascular Therapeutics" (Springer 2011), "Applications of Biotechnology in Neurology" (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has edited "Applied Neurogenomics" (January 2015).

A B O U T T H I S R E P O R T

The proteomics report started as an expansion of the chapter on proteomics in Prof. Jain's report on "The Impact of Genomics on Drug Discovery and Development" published by Decision Resources Inc in 1999 and has been constantly updated since its publication as a separate report in 2000 by Jain PharmaBiotech. It has been rewritten several times since then.

November 2018 (continuously published since 2000)
Copyright © 2018 by

Jain PharmaBiotech
Bläsiring 7
CH-4057 Basel
Switzerland

Tel & Fax: +4161-6924461
Email: info@pharmabiotech.ch
Web site: http://pharmabiotech.ch/

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

TABLE OF CONTENTS

0. Executive Summary	17
1. Basics of Proteomics.....	19
Introduction	19
History.....	19
Nucleic acids, genes and proteins	20
Genome.....	20
DNA	21
RNA	21
<i>MicroRNAs</i>	<i>22</i>
<i>Decoding of mRNA by the ribosome</i>	<i>23</i>
Genes.....	23
Alternative splicing.....	23
Transcription.....	24
Gene regulation	25
Gene expression	25
Chromatin.....	26
Golgi complex.....	26
Proteins.....	27
<i>Functions of proteins</i>	<i>27</i>
<i>Proteasome.....</i>	<i>28</i>
<i>Spliceosome.....</i>	<i>28</i>
<i>Inter-relationship of protein, mRNA and DNA.....</i>	<i>29</i>
Proteomics.....	30
Endoplasmic reticulum.....	31
Mitochondrial proteome	31
<i>S-nitrosoproteins in mitochondria</i>	<i>32</i>
Proteomics and genomics	32
Classification of proteomics	35
Levels of functional genomics and various "omics"	35
Glycoproteomics	35
Transcriptomics	36
Metabolomics	36
Cytomics.....	36
Phenomics	36
Impact of the genetic factors on the human proteome	37
Proteomics and systems biology.....	37
Proteomics and synthetic biology	38
Functional synthetic proteins	38
Synthetic proteomics for study of apoptosis	39
2. Proteomic Technologies.....	41
Key technologies driving proteomics	41
Sample preparation	42
New trends in sample preparation	42
Pressure Cycling Technology	43
Protein separation technologies	43
High resolution 2DGE	44
Variations of 2D gel technology	44
Limitations of 2DGE and measures to overcome these	44
1-D sodium dodecyl sulfate (SDS) PAGE	45
Capillary electrophoresis systems.....	45
Head column stacking capillary zone electrophoresis	45
Removal of albumin and IgG	46
SeraFILE™ separations platform	46
Companies with protein separation technologies	46
Protein purification.....	48
Technologies for protein purification	48
Applications of protein purification	48
Protein detection	48
Protein identification and characterization	49
Mass spectrometry.....	49
<i>Electrospray ionization.....</i>	<i>49</i>
<i>Desorption electrospray ionization MS</i>	<i>51</i>
<i>Ion-mobility spectrometry-MS</i>	<i>51</i>
<i>Mirosaic 3500 MiD.....</i>	<i>52</i>
<i>Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry</i>	<i>52</i>

<i>Cryogenic MALDI- Fourier Transform Mass Spectrometry</i>	54
<i>Stable-isotope-dilution tandem mass spectrometry</i>	54
<i>HUPO Gold MS Protein Standard</i>	54
<i>Companies involved in mass spectrometry</i>	55
High performance liquid chromatography	55
Multidimensional protein identification technology (MudPIT)	56
Multiple reaction monitoring assays	56
Peptide mass fingerprinting	57
Current status and future prospects of clinical mass spectrometry	57
Combination of protein separation technologies with mass spectrometry	58
<i>Combining capillary electrophoresis with mass spectrometry</i>	58
<i>2D PAGE and mass spectrometry</i>	58
<i>Quantification of low abundance proteins</i>	59
<i>SDS-PAGE</i>	59
Proteomics quantification in complex samples	59
Antibodies and proteomics	60
Detection of fusion proteins	60
Labeling and detection of proteins	60
<i>Bioorthogonal non-canonical amino-acid-tagging techniques</i>	61
<i>Stable-isotope labeling of amino acids in cell culture</i>	61
<i>Fluorescent labeling of proteins in living cells</i>	61
<i>Combination of microspheres with fluorescence</i>	62
<i>Self-labeling protein tags</i>	62
Analysis of peptides	62
<i>C-terminal peptide analysis</i>	63
<i>Differential Peptide Display</i>	63
<i>Peptide analyses using NanoLC-MS</i>	64
Protein sequencing	65
Real-time PCR for protein quantification	65
Quantitative proteomics	66
MS-based quantitative proteomics	66
MS and cryo-electron tomography	66
Selected reaction monitoring MS	66
Functional proteomics: technologies for studying protein function	67
Functional genomics by mass spectrometry	67
LC-MS-based method for annotating the protein-coding genome	67
RNA-Protein fusions	68
Designed repeat proteins	68
Application of nanobiotechnology to proteomics	68
Nanoproteomics	69
<i>Nanoflow liquid chromatography</i>	69
<i>Nanopores for phosphoprotein analysis</i>	69
<i>Nanotube electronic biosensor for proteomics</i>	69
<i>Protein nanocrystallography</i>	70
<i>Single-molecule mass spectrometry using a nanopore</i>	70
<i>Nanoelectrospray ionization</i>	70
<i>Nanoproteomics for discovery of protein biomarkers in the blood</i>	71
<i>QD-protein nanoassembly</i>	71
Nanoparticle barcodes	71
<i>Biobarcode assay for proteins</i>	72
Nanopore-based protein sequencing	73
Nanoscale protein analysis	73
Nanoscale mechanism for protein engineering	74
Nanotube electronic biosensor	74
Nanotube-vesicle networks for study of membrane proteins	75
Qdot-nanocrystals	75
Resonance Light Scattering technology	75
Study of single membrane proteins at subnanometer resolution	76
Protein expression profiling	76
Cell-based protein assays	77
Living cell-based assays for protein function	77
Companies developing cell-based protein assays	78
Protein function studies	78
Transcriptionally Active PCR	79
Protein-protein interactions	79
<i>Bacterial protein interaction studies for assigning function</i>	80
<i>Bioluminescence Resonance Energy Transfer</i>	81
<i>Computational prediction of interactions</i>	81
<i>Detection Enhanced Ubiquitin Split Protein Sensor technology</i>	81
<i>Double Switch technology</i>	82
<i>Fluorescence Resonance Energy Transfer</i>	82

<i>In vivo</i> study of protein-protein interactions	82
<i>In vitro</i> study of protein-protein interactions	83
Interactome	83
Membrane 1-hybrid method	84
Nanowire transistor for the detection of protein-protein interactions	84
Phage display	85
Protein affinity chromatography	85
Protein-fragment complementation system	85
Proximity-dependent hybridization chain reaction	85
Yeast 2-hybrid system	86
Companies with technologies for protein-protein interaction studies	87
Protein-DNA interaction	88
Determination of protein structure	88
X-Ray crystallography	89
Nuclear magnetic resonance	89
Electron spin resonance	90
Prediction of protein structure	90
Protein tomography	90
X-ray scattering-based method for determining the structure of proteins	91
Prediction of protein function	92
Three-dimensional proteomics for determination of function	92
An algorithm for genome-wide prediction of protein function	92
Monitoring protein function by expression profiling	93
Isotope-coded affinity tag peptide labeling	93
Differential Proteomic Panning	94
Cell map proteomics	94
Topological proteomics	94
Organelle or subcellular proteomics	95
Nucleolar proteomics	96
Glycoproteomic technologies	96
High-sensitivity glycoprotein analysis	96
Fluorescent <i>in vivo</i> imaging of glycoproteins	96
Integrated approaches for protein characterization	97
Imaging mass spectrometry	97
IMS technologies	97
Applications of IMS	98
The protein microscope	98
Tag-Mass IMS	99
Quantitative immunofluorescence for proteomics	99
Automation and robotics in proteomics	99
Western blot	100
Limitations of WB	100
Innovations in WB	100
<i>Capillary electrophoresis and WB</i>	100
<i>Chemiluminescent western blotting</i>	101
<i>Fluorescent WB</i>	101
<i>Microfluidics and WB</i>	101
<i>Multiplexing WB</i>	102
Applications of Western blot	102
<i>Research applications of Western blot</i>	103
<i>Molecular diagnostic applications of Western blot</i>	103
Companies involved in Western blotting technologies	103
Laser capture microdissection	104
Microdissection techniques used for proteomics	105
Uses of LCM in combination with proteomic technologies	105
Concluding remarks about applications of proteomic technologies	106
NextGen Proteomics Platform	106
Precision proteomics	107
3. Protein biochip technology	109
Introduction	109
Types of protein biochips	110
ProteinChip	110
<i>Applications and advantages of ProteinChip</i>	111
<i>ProteinChip Biomarker System</i>	111
<i>Matrix-free ProteinChip Array</i>	112
Aptamer-based protein biochip	112
Fluorescence planar wave guide technology-based protein biochips	113
Lab-on-a-chip for protein analysis	113
Biochips for peptide arrays	114
Microfluidic biochips for proteomics	114

Protein biochips and microarrays for high-throughput expression	115
<i>Nucleic Acid-Programmable Protein Array</i>	115
<i>High-density protein microarrays</i>	115
<i>HPLC-Chip for protein identification</i>	116
<i>Antibody microarrays</i>	116
<i>HuProt™ Human Proteome Microarrays</i>	116
<i>Integration of protein array and image analysis</i>	117
Tissue microarray technology for proteomics	117
Protein biochips in molecular diagnostics	117
A force-based protein biochip	118
L1 chip and lipid immobilization	118
Multiplexed Protein Profiling on Microarrays.....	119
Live cell microarrays.....	119
ProteinArray Workstation	120
Proteome arrays	120
The Yeast ProtoArray	120
ProtoArray™ Human Protein Microarray	121
TRINECTIN proteome chip.....	121
Peptide arrays	122
Surface plasmon resonance technology	122
SPR Systems.....	122
FLEX CHIP.....	123
Combination of surface plasmon resonance and MALDI-TOF	123
Protein chips/microarrays using nanotechnology.....	124
Nanoparticle protein chip	124
Protein nanobiochip.....	124
Protein nanoarrays.....	125
Self-assembling protein nanoarrays.....	125
Companies involved in protein biochip/microarray technology	125
4. Bioinformatics in Relation to Proteomics	129
Introduction	129
Bioinformatic tools for proteomics.....	129
Testing of SELDI-TOF MS Proteomic Data.....	129
BioImagine's ProteinMine	130
Bioinformatics for pharmaceutical applications of proteomics.....	130
<i>In silico</i> search of drug targets by Biopendium.....	130
Compugen's LEADS	131
DrugScore.....	131
Proteochemometric modeling	131
Integration of genomic and proteomic data.....	132
Proteomic databases: creation and analysis	133
Introduction	133
Proteomic databases	133
<i>GenProtEC</i>	134
<i>Human Protein Atlas</i>	134
<i>Human Proteomics Initiative</i>	135
<i>Human proteome map</i>	136
<i>International Protein Index</i>	136
<i>MS-based draft of the human proteome</i>	136
<i>Protein Structure Initiative – Structural Genomics Knowledgebase</i>	136
<i>Protein Warehouse Database</i>	137
<i>Protein Data Bank</i>	137
<i>Repository for raw data from proteomics MS</i>	137
<i>Universal Protein Resource</i>	138
Protein interaction databases	138
<i>Biomolecular Interaction Network Database</i>	139
ENCODE	139
<i>Functional Genomics Consortium</i>	140
<i>Human Proteinpedia</i>	140
<i>ProteinCenter</i>	140
<i>Databases of the National Center for Biotechnology Information</i>	141
Application of bioinformatics for protein identification	141
Tandem MS for protein identification	141
Targeted MS for specific identification of proteins.....	141
Application of bioinformatics in functional proteomics	142
Use of bioinformatics in protein sequencing	142
Bottom-up protein sequencing.....	143
Top-down protein sequencing.....	144
Integration of next generation proteomics and gene sequencing data	144
Protein structural database approach to drug design	144

Bioinformatics for high-throughput proteomics	145
Bioinformatics for protein-protein interactions	146
Companies with bioinformatic tools for proteomics	146
5. Research in Proteomics	149
Introduction	149
Applications of proteomics in biological research	149
Identification of novel human genes by comparative proteomics	149
Study of relationship between genes and proteins.....	150
Characterization of histone codes.....	150
Structural genomics or structural proteomics	151
Protein Structure Factory	152
Protein Structure Initiative	152
Studies on protein structure at Argonne National Laboratory	153
Structural Genomics Consortium.....	153
Protein knockout	154
Antisense approach and proteomics	154
RNAi and protein knockout.....	154
Total knockout of cellular proteins.....	155
Ribozymes and proteomics	155
Single molecule proteomics	155
Single-molecule photon stamping spectroscopy	155
Single nucleotide polymorphism determination by TOF-MS.....	156
Application of proteomic technologies in systems biology	156
Signaling pathways and proteomics.....	157
Kinomics.....	157
Combinatorial RNAi for quantitative protein network analysis	157
Proteomics in neuroscience research	158
Stem cell proteomics	158
Comparative proteomic analysis of somatic cells, iPSCs and ESCs	159
hESC phosphoproteome.....	159
Proteomic studies of mesenchymal stem cells.....	159
Proteomics of neural stem cells.....	160
Proteome Biology of Stem Cells Initiative.....	160
Proteomic analysis of the cell cycle	161
Nitric oxide and proteomics	161
A proteomic method for identification of cysteine S-nitrosylation sites	161
Study of the nitroproteome	162
Study of the phosphoproteome	162
Study of the mitochondrial proteome	163
Proteomic technologies for study of mitochondrial proteomics	163
Cryptome	164
Study of protein transport in health and disease	164
Ancient proteomics	164
Proteomics research in the academic sector	165
Netherlands Proteins@Work	167
ProteomeBinders initiative.....	167
Rutgers University's Center for Integrative Proteomics Research.....	167
Vanderbilt University's Center for Proteomics and Drug Actions	168
6. Pharmaceutical Applications of Proteomics	169
Introduction	169
Current drug discovery process and its limitations	169
Role of omics in drug discovery	170
Genomics-based drug discovery.....	170
Metabolomics technologies for drug discovery	171
Role of metabolomics in drug discovery	171
Basis of proteomics approach to drug discovery.....	172
<i>Proteins and drug action</i>	172
<i>Transcription-aided drug design</i>	173
In vivo production of therapeutic proteins by mRNA	173
Role of proteomic technologies in drug discovery	173
<i>Liquid chromatography-based drug discovery</i>	174
<i>Capture compound mass spectrometry</i>	174
<i>Protein-expression mapping by 2DGE</i>	174
<i>Protein-protein interactions and drug discovery</i>	175
<i>Role of MALDI mass spectrometry in drug discovery</i>	175
<i>Structural proteomics and drug discovery</i>	176
<i>Tissue imaging mass spectrometry</i>	176
Oxford Genome Anatomy Project	178
Proteins as drug targets.....	178

<i>Monitoring drug target binding using the cellular thermal shift assay</i>	178
Ligands to capture the purine binding proteome	178
Chemical probes to interrogate key protein families for drug discovery	179
Global proteomics for pharmacodynamics	179
ProteoCarta® proteomics platform	180
ZeptoMARK™ protein profiling system	180
Role of proteomics in targeting disease pathways	181
Dynamic proteomics	181
Identification of protein kinases as drug targets	181
<i>Mechanisms of action of kinase inhibitors</i>	182
G-protein coupled receptors as drug targets	182
<i>Methods of study of GPCRs</i>	183
<i>Cell-based assays for GPCR</i>	183
<i>Companies involved in GPCR-based drug discovery</i>	184
<i>GPCR localization database</i>	185
Matrix metalloproteases as drug targets	185
PDZ proteins as drug targets	185
Proteasome as drug target	186
Serine hydrolases as drug targets	187
Targeting mTOR signaling pathway	187
Targeting caspase-8 for anticancer therapeutics	188
Drug design based on structural proteomics	189
Protein crystallography for determining 3D structure of proteins	189
Automated 3D protein modeling	189
<i>Drug targeting of flexible dynamic proteins</i>	189
Companies involved in structure-based drug-design	190
Integration of genomics and proteomics for drug discovery	191
Ligand-receptor binding	192
Role of proteomics in study of ligand-receptor binding	192
<i>Measuring drug binding of proteins</i>	192
Aptamer protein binding	192
<i>Systematic Evolution of Ligands by Exponential Enrichment</i>	193
<i>Aptamers and high-throughput screening</i>	193
<i>Nucleic Acid Biotools</i>	194
<i>Aptamer beacons</i>	194
<i>Peptide aptamers</i>	194
Riboreporters for drug discovery	195
Target identification and validation	195
Application of mass spectrometry for target identification	196
Gene knockout and gene suppression for validating protein targets	196
Laser-mediated protein knockout for target validation	196
Integrated proteomics for drug discovery	197
High-throughput proteomics	197
Companies involved in high-throughput proteomics	197
Drug discovery through protein-protein interaction studies	198
Protein-protein interaction as basis for drug target identification	199
Protein-PCNA interaction as basis for drug design	199
Two-hybrid protein interaction technology for target identification	200
Biosensors for detection of small molecule-protein interactions	200
Protein-protein interaction maps	201
<i>ProNet (Myriad Genetics)</i>	201
<i>Hybrigenics' maps of protein-protein interactions</i>	201
<i>CellZome's functional map of protein-protein interactions</i>	202
Mapping of protein-protein interactions by mass spectrometry	202
Protein interaction map of <i>Drosophila melanogaster</i>	203
Protein-interaction map of Wellcome Trust Sanger Institute	203
Protein-protein interactions as targets for therapeutic intervention	203
Inhibition of protein-protein interactions by peptide aptamers	204
Selective disruption of proteins by small molecules	204
Post-genomic combinatorial biology approach	204
Differential proteomics	205
Shotgun proteomics	205
Targeted proteomics	206
Chemogenomics/chemoproteomics for drug discovery	206
<i>Chemoproteomics-based drug discovery</i>	207
<i>Companies involved in chemogenomics/chemoproteomics</i>	207
<i>Activity-based proteomics</i>	209
<i>Locus Discovery technology</i>	209
<i>Automated ligand identification system</i>	209
Expression proteomics: protein level quantification	210
Role of phage antibody libraries in target discovery	211

Analysis of posttranslational modification of proteins by MS	211
Phosphoproteomics for drug discovery	212
Application of glycoproteomics for drug discovery	212
Role of carbohydrates in proteomics	212
Challenges of glycoproteomics	212
Companies involved in glycoproteomics	213
Role of protein microarrays/ biochips for drug discovery	214
Protein microarrays vs DNA microarrays for high-throughput screening	214
BIA-MS biochip for protein-protein interactions	214
ProteinChip with Surface Enhanced Neat Desorption	215
Protein-domains microarrays	215
Some limitations of protein biochips	215
Concluding remarks about role of proteomics in drug discovery	216
RNA versus protein profiling as guide to drug development	216
RNA as drug target	216
Combination of RNA and protein profiling	217
<i>RNA binding proteins</i>	218
Toxicoproteomics	218
Hepatotoxicity	218
Nephrotoxicity	219
Cardiotoxicity	219
Neurotoxicity	220
Protein/peptide therapeutics	220
Alphabody technology for improving protein therapeutics	220
Peptide-based drugs	220
Phylomer® peptides	221
Cryptein-based therapeutics	221
Synthetic proteins and peptides as pharmaceuticals	222
Genetic immunization and proteomics	222
Role of proteomics in synthetic antivenoms	223
Proteomics and gene therapy	223
Role of proteomics in clinical drug development	224
Pharmacoproteomics	224
Role of proteomics in clinical drug safety	224
7. Application of Proteomics in Human Healthcare	227
Introduction	227
Clinical proteomics	228
Definition and standards	228
Vermillion's Clinical Proteomics Program	228
Pathophysiology of human diseases	229
Diseases due to misfolding of proteins	229
<i>Mechanism of protein folding</i>	230
<i>Nanoproteomics for study of misfolded proteins</i>	231
<i>Therapies for protein misfolding</i>	231
Intermediate filament proteins	232
Significance of mitochondrial proteome in human disease	232
<i>Proteome of Saccharomyces cerevisiae mitochondria</i>	233
<i>Rat mitochondrial proteome</i>	233
Proteomic approaches to biomarker identification	234
The ideal biomarker	234
Proteomic technologies for biomarker discovery	234
<i>MALDI mass spectrometry for biomarker discovery</i>	235
Protein biochips/microarrays and biomarkers	235
Affinity proteomics for discovery of biomarkers	235
<i>Antibody array-based biomarker discovery</i>	236
<i>Discovery of biomarkers by MAb microarray profiling</i>	237
Tumor-specific serum peptidome patterns	237
Search for protein biomarkers in body fluids	237
Challenges and strategies for discovery of protein biomarkers in plasma	237
<i>3-D structure of CD38 as a biomarker</i>	239
<i>BD™ Free Flow Electrophoresis System</i>	239
<i>Isotope tags for relative and absolute quantification</i>	239
<i>N-terminal peptide isolation from human plasma</i>	240
<i>Plasma protein microparticles as biomarkers</i>	240
<i>Proteome partitioning</i>	240
<i>SISCAPA method for quantitating proteins and peptides in plasma</i>	241
<i>Stable isotope tagging methods</i>	241
<i>Technology to measure both the identity and size of the biomarker</i>	241
Biomarkers in the urinary proteome	242
Application of proteomics in molecular diagnosis	242

MassARRAY	243
Proximity ligation assay	244
Protein patterns.....	244
Proteomic tests on body fluids	244
Cyclical amplification of proteins	246
Applications of proteomics in infections	246
MALDI-TOF MS for microbial identification.....	246
Recognition of microbial glycans by human lectins	247
Role of proteomics in virology.....	247
<i>Interaction of proteins with viruses</i>	<i>248</i>
<i>Quantitative temporal viromics</i>	<i>248</i>
Role of proteomics in bacteriology.....	248
<i>Epidemiology of bacterial infections.....</i>	<i>249</i>
<i>Proteomic approach to bacterial pathogenesis</i>	<i>249</i>
<i>Vaccines for bacterial infections</i>	<i>249</i>
<i>Protein profiles associated with bacterial drug resistance</i>	<i>250</i>
Analyses of the parasite proteome	250
Application of proteomics in cystic fibrosis	251
Proteomics of cardiovascular diseases	251
Pathomechanism of cardiovascular diseases	251
Protein misfolding in cardiac dysfunction.....	252
Study of cardiac mitochondrial proteome in myocardial ischemia	252
Cardiac protein databases	252
Proteomics of dilated cardiomyopathy and heart failure	253
Proteomic biomarkers of cardiovascular diseases	253
Regulation of cardiac rhythmicity by Purkinje cell protein-4	254
Role of proteomics in cardioprotection	254
Role of proteomics in heart transplantation	254
Future of application of proteomics in cardiology.....	255
Proteomic technologies for research in pulmonary disorders	255
Application of proteomics in renal disorders.....	256
Diagnosis of renal disorders	257
Proteomic biomarkers of acute kidney injury	257
Cystatin C as biomarker of glomerular filtration rate.....	257
Protein biomarkers of nephritis.....	257
Proteomics and kidney stones.....	258
Proteomics of eye disorders.....	258
Proteomics of cataract	259
Proteomics of diabetic retinopathy	259
Retinal dystrophies	259
Use of proteomics in inner ear disorders	260
Use of proteomics in aging research	260
Alteration of glycoproteins during aging	261
Carbamylation of proteins with aging.....	261
Proteomics of muscle aging.....	261
Removal of altered cellular proteins in aging	262
Role of protein aggregation in aging and degenerative diseases	262
Study of the role of Parkin in modulating aging.....	263
Study of proteins that protect against hypoxic injury in age-related disorders.....	263
Proteomics and nutrition	263
8. Oncoproteomics.....	265
Introduction	265
Proteomic technologies for study of cancer	266
Application of CellCarta technology for oncology	266
Accentuation of differentially expressed proteins using phage technology.....	266
Cancer tissue proteomics	266
<i>Dynamic cell proteomics in response to a drug</i>	<i>267</i>
Desorption electrospray ionization for cancer diagnosis.....	267
Id proteins as targets for cancer therapy	268
Identification of oncogenic tyrosine kinases using phosphoproteomics	268
Laser capture microdissection technology and cancer proteomics.....	268
Mass spectrometry for identification of oncogenic chimeric proteins.....	269
Proteomic analysis of cancer cell mitochondria.....	269
Proteomic study of p53.....	270
Human Tumor Gene Index	270
Integration of cancer genomics and proteomics	270
Role of proteomics in study of cancer stem cell biology	271
Single-cell protein expression analysis by microfluidic techniques.....	271
Use of proteomics in cancers of various organ systems	271
Proteomics of brain tumors	271

<i>Malignant glial tumors</i>	271
<i>Meningiomas</i>	272
<i>DESI-MS for intraoperative diagnosis of brain tumors</i>	272
Proteomics of breast cancer	273
<i>Integration of proteomic and genomic data for breast cancer</i>	274
Proteomics of colorectal cancer.....	275
Proteomics of esophageal cancer	275
Proteomics of hepatic cancer	276
Proteomics of leukemia.....	276
Proteomics of lung cancer	277
Proteomics of pancreatic cancer.....	278
Proteomics of prostate cancer.....	278
Proteomics of renal cancer	279
Diagnostic use of cancer biomarkers	279
Proteomic technologies for tumor biomarkers	280
Nuclear matrix proteins (NMPs)	280
Antiannexins as tumor markers in lung cancer.....	281
NCI's Network of Clinical Proteomic Technology Centers.....	281
Proteomics and tumor immunology	282
Proteomics and study of tumor invasiveness	282
Anticancer drug discovery and development	283
Anticancer drug targeting: functional proteomics screen of proteases	283
Kinase-targeted drug discovery in oncology.....	283
Protein-drug interactions in cancer.....	284
Role of proteomics in studying drug resistance in cancer.....	284
Small molecule inhibitors of cancer-related proteins	285
Future prospects of oncoproteomics.....	285
International oncoproteomic initiatives	285
<i>Clinical Proteomic Tumor Analysis Consortium</i>	286
Companies involved in application of proteomics to oncology	287

9. Neuroproteomics	289
Introduction	289
Application of proteomics for the study of nervous system	289
Proteomics of prion diseases	290
Normal function of prions in the brain.....	290
Detection of protein aggregates and prions	290
Diseases due to pathological prion protein	291
Transmissible spongiform encephalopathies	292
<i>Creutzfeldt-Jakob disease</i>	292
<i>Bovine spongiform encephalopathy</i>	292
<i>Variant Creutzfeldt-Jakob disease</i>	292
Protein misfolding and neurodegenerative disorders.....	293
Ion channel link for protein-misfolding disease	293
Detection of misfolded proteins.....	293
Modulation of proteostasis in neurodegenerative disorders	293
Neurodegenerative disorders with protein abnormalities	294
<i>Alzheimer disease</i>	296
<i>Common denominators of Alzheimer and prion diseases</i>	296
<i>Parkinson disease</i>	297
<i>Amyotrophic lateral sclerosis</i>	297
Proteomics and glutamate repeat disorders	298
<i>Proteomics and Huntington's disease</i>	298
Proteomics and demyelinating diseases	299
Proteomics of neurogenetic disorders	300
Fabry disease	300
GM1 gangliosidosis.....	300
Quantitative proteomics and familial hemiplegic migraine	301
Proteomics of spinal muscular atrophy.....	301
Proteomics of CNS trauma	301
Proteomics of traumatic brain injury.....	301
Chronic traumatic encephalopathy and ALS	302
Proteomics of cerebrovascular disease.....	303
Pathogenesis of cerebral small vessel disease.....	303
Proteomics of CNS aging.....	303
Protein aggregation as a biomarker of aging.....	304
Neuroproteomics of psychiatric disorders.....	304
Schizophrenia.....	304
Anxiety disorders	305
Depression and suicidal behavior.....	305
Neuroproteomic of cocaine addiction	305

Neurodiagnostics based on proteomics.....	306
Disease-specific proteins in the cerebrospinal fluid	306
<i>Tau proteins</i>	307
CNS tissue proteomics.....	307
Diagnosis of CNS disorders by examination of proteins in urine	309
Diagnosis of CNS disorders by examination of proteins in the blood.....	309
<i>Serum pNF-H as biomarker of CNS damage</i>	310
Intraoperative application of proteomics in surgery of brain tumors.....	310
Proteomics of BBB	310
Future of neuroproteomics in neurology	311
HUPO's Pilot Brain Proteome Project.....	312
10. Proteomics Markets	313
Introduction	313
Potential markets for proteomic technologies	313
Bioinformatics markets.....	314
Markets for protein separation technologies	314
<i>Markets for 2D gel electrophoresis</i>	314
<i>Market trends in protein separation technologies</i>	314
Protein purification markets	315
Mass spectrometry markets	315
Markets for MALDI for drug discovery	315
Markets for nuclear magnetic resonance spectroscopy	316
Market for structure-based drug design	316
Markets for protein biomarkers.....	316
Markets for cell-based protein assays	316
Protein biochip markets	317
Western blot markets	317
Geographical distribution of proteomics technologies markets	317
Business and strategic considerations	318
Cost of protein structure determination	318
Opinion surveys of the scientist consumers of proteomic technologies	318
<i>Opinions on mass spectrometry</i>	318
<i>Opinions on bioinformatics and proteomic databases</i>	318
<i>Systems for in vivo study of protein-protein interactions</i>	318
<i>Perceptions of the value of protein biochip/microfluidic systems</i>	319
Small versus big companies	319
Expansion in proteomics according to area of application	319
Growth trends in cell-based protein assay market.....	319
<i>Challenges for development of cell-based protein assays</i>	320
<i>Future trends and prospects of cell-based protein assays</i>	320
Strategic collaborations	321
<i>Analysis of proteomics collaborations according to types of companies</i>	321
<i>Types of proteomic collaborations</i>	321
<i>Proteomics collaborations according to application areas</i>	322
<i>Analysis of proteomics collaborations: types of technologies</i>	322
<i>Collaborations based on protein biochip technology</i>	323
<i>Concluding remarks about proteomic collaborations</i>	323
Proteomic patents.....	324
Market drivers in proteomics	324
Needs of the pharmaceutical industry	324
Need for outsourcing proteomic technologies.....	325
Funding of proteomic companies and research.....	325
Technical advances in proteomics	325
Changing trends in healthcare in future	326
Challenges facing proteomics	326
Magnitude and complexity of the task.....	326
Technical challenges.....	326
Limitations of proteomics.....	327
<i>Limitations of 2DGE</i>	327
<i>Limitations of mass spectrometry techniques</i>	327
<i>Complexity of the pharmaceutical proteomics</i>	327
Unmet needs in proteomics.....	328
11. Future of Proteomics	329
Genomics to proteomics	329
Faster technologies	329
FLEXGene repository	329
Need for new proteomic technologies.....	330
Emerging proteomic technologies.....	331
Detection of alternative protein isoforms.....	331

Direct protein identification in large genomes by mass spectrometry	331
Proteome identification kits with stacked membranes	331
Vacuum deposition interface.....	332
<i>In vitro</i> protein biosynthesis.....	332
Proteome mining with adenosine triphosphate	332
Proteome-scale purification of human proteins from bacteria	332
Proteostasis network	333
Cytoproteomics	333
<i>Subcellular proteomics</i>	336
<i>Individual cell proteomics</i>	334
<i>Live cell proteomics</i>	333
<i>Fluorescent proteins for live-cell imaging</i>	333
Membrane proteomics	335
<i>Identification of membrane proteins by tandem MS of protein ions</i>	335
<i>Solid state NMR for study of nanocrystalline membrane proteins</i>	336
Multiplex proteomics	336
High-throughput for proteomics	337
Future directions for protein biochip application	337
Bioinformatics for proteomics	338
High-Throughput Crystallography Consortium.....	338
Study of protein folding by IBM's Blue Gene	338
Study of proteins by atomic force microscopy	338
Population proteomics	339
Comparative proteome analysis.....	339
Human Proteome Organization	340
Cell-based Human Proteome Project.....	341
Human Salivary Proteome	341
Academic-commercial collaborations in proteomics	341
Indiana Centers for Applied Protein Sciences	341
Role of proteomics in the healthcare of the future.....	342
Proteomics and molecular medicine.....	342
Proteodiagnosics.....	342
Proteomics and personalized medicine	342
<i>Targeting the ubiquitin pathway for personalized therapy of cancer</i>	343
<i>Protein patterns and personalized medicine</i>	343
<i>Personalizing interferon therapy of hepatitis C virus</i>	345
<i>Protein biochips and personalized medicine</i>	345
<i>Combination of diagnostics and therapeutics</i>	345
<i>Future prospects</i>	346
12. References.....	347

Tables

Table 1-1: Landmarks in the evolution of proteomics	19
Table 1-2: Comparison of DNA and protein	29
Table 1-3: Comparison of mRNA and protein.....	29
Table 1-4: Methods of analysis at various levels of functional genomics	35
Table 2-1: Proteomics technologies.....	41
Table 2-2: Protein separation technologies of selected companies.....	46
Table 2-3: Companies supplying mass spectrometry instruments	55
Table 2-4: Companies involved in cell-based protein assays.....	78
Table 2-5: Methods used for the study of protein-protein interactions	79
Table 2-6: A selection of companies involved in protein-protein interaction studies	87
Table 2-7: Companies involved in Western blotting	103
Table 2-8: Proteomic technologies used with laser capture microdissection	105
Table 3-1: Applications of protein biochip technology	109
Table 3-2: Selected companies involved in protein biochip/microarray technology	125
Table 4-1: Proteomic databases and other Internet sources of proteomics information	133
Table 4-2: Protein interaction databases available on the Internet	139
Table 4-3: Bioinformatic tools for proteomics from academic sources	145
Table 4-4: Selected companies involved in bioinformatics for proteomics	146
Table 5-1: Applications of proteomics in basic biological research	149
Table 5-2: A sampling of proteomics research projects in academic institutions	165
Table 6-1: Pharmaceutical applications of proteomics.....	169
Table 6-2: Selected companies relevant to MALDI-MS for drug discovery.....	175
Table 6-3: Selected companies involved in GPCR-based drug discovery	184
Table 6-4: Companies involved in drug design based on structural proteomics	190
Table 6-5: Proteomic companies with high-throughput protein expression technologies	198
Table 6-6: Selected companies involved in chemogenomics/chemoproteomics	208

Table 6-7: Companies involved in glycoproteomic technologies	213
Table 7-1: Applications of proteomics in human healthcare	227
Table 7-2: Eye disorders and proteomic approaches.....	258
Table 8-1: Large scale international oncoproteomic initiatives	286
Table 8-2: Companies involved in applications of proteomics to oncology	287
Table 9-1: Neurodegenerative diseases with underlying protein abnormality	294
Table 9-2: Disease-specific proteins in the cerebrospinal fluid of patients.....	306
Table 10-1: Potential markets for proteomic technologies 2017-2027.....	313
Table 10-2: Geographical distribution of markets for proteomic technologies 2017-2027	317
Table 11-1: Role of proteomics in personalizing strategies for cancer therapy	343

Figures

Figure 1-1: A schematic miRNA pathway	22
Figure 1-2: Relationship of DNA, RNA and protein in the cell.....	30
Figure 1-3: Protein production pathway from gene expression to functional protein with controls.	33
Figure 1-4: Parallels between functional genomics and proteomics.....	33
Figure 2-1: Proteomics: flow from sample preparation to characterization.....	42
Figure 2-2: The central role of spectrometry in proteomics	49
Figure 2-3: Electrospray ionization (ESI)	50
Figure 2-4: Ion-mobility spectrometry-MS	52
Figure 2-5: Matrix-Assisted Laser Desorption/Ionization (MALDI).....	53
Figure 2-6: Scheme of bio-bar-code assay	73
Figure 2-7: A diagrammatic presentation of yeast 2-hybrid system	86
Figure 3-1: ProteinChip System	111
Figure 3-2: Surface plasma resonance (SPR).....	123
Figure 4-1: Role of bioinformatics in integrating genomic/proteomic-based drug discovery	132
Figure 4-2: Bottom-up and top-down approaches for protein sequencing	143
Figure 6-1: Drug discovery process.....	170
Figure 6-2: Regulatory changes induced by drugs and implemented at the proteins level.	172
Figure 6-3: Relation of proteome to genome, diseases and drugs	173
Figure 6-4: The mTOR pathways	188
Figure 6-5: Steps in shotgun proteomics	205
Figure 6-6: Chemogenomic approach to drug discovery (3-Dimensional Pharmaceuticals)	207
Figure 8-1: Relation of oncoproteomics to other technologies	265
Figure 9-1: A scheme of proteomics applications in CNS drug discovery and development	312
Figure 10-1: Types of companies involved in proteomics collaborations	321
Figure 10-2: Types of collaborations: R & D, licensing or marketing	322
Figure 10-3: Proteomics collaborations according to application areas	322
Figure 10-4: Proteomics collaborations according to technologies	323
Figure 10-5: Unmet needs in proteomics	328
Figure 11-1: A scheme of the role of proteomics in personalized management of cancer.....	344