

Proteomics

Part I: Technologies & Markets

By

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

April 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 476 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 2015. 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 2018, 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.

April 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	43
Variations of 2D gel technology	44
Limitations of 2DGE and measures to overcome these	44
1-D sodium dodecyl sulfate (SDS) PAGE	44
Capillary electrophoresis systems.....	45
Head column stacking capillary zone electrophoresis	45
Removal of albumin and IgG	45
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
Antibodies and proteomics	59
Detection of fusion proteins	60
Labeling and detection of proteins	60
<i>Bioorthogonal non-canonical amino-acid-tagging techniques</i>	60
<i>Stable-isotope labeling of amino acids in cell culture</i>	60
<i>Fluorescent labeling of proteins in living cells</i>	61
<i>Combination of microspheres with fluorescence</i>	61
<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	64
Real-time PCR for protein quantification	65
Quantitative proteomics	65
MS-based quantitative proteomics	65
MS and cryo-electron tomography	66
Selected reaction monitoring MS	66
Functional proteomics: technologies for studying protein function	66
Functional genomics by mass spectrometry	66
LC-MS-based method for annotating the protein-coding genome	67
RNA-Protein fusions	67
Designed repeat proteins	68
Application of nanobiotechnology to proteomics	68
Nanoproteomics	68
<i>Nanoflow liquid chromatography</i>	68
<i>Nanopores for phosphoprotein analysis</i>	69
<i>Nanotube electronic biosensor for proteomics</i>	69
<i>Protein nanocrystallography</i>	69
<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>	70
<i>QD-protein nanoassembly</i>	71
Nanoparticle barcodes	71
<i>Biobarcode assay for proteins</i>	71
Nanopore-based protein sequencing	72
Nanoscale protein analysis	73
Nanoscale mechanism for protein engineering	73
Nanotube electronic biosensor	74
Nanotube-vesicle networks for study of membrane proteins	74
Qdot-nanocrystals	74
Resonance Light Scattering technology	75
Study of single membrane proteins at subnanometer resolution	75
Protein expression profiling	75
Cell-based protein assays	76
Living cell-based assays for protein function	77
Companies developing cell-based protein assays	77
Protein function studies	78
Transcriptionally Active PCR	78
Protein-protein interactions	78
<i>Bacterial protein interaction studies for assigning function</i>	80
<i>Bioluminescence Resonance Energy Transfer</i>	80
<i>Computational prediction of interactions</i>	80
<i>Detection Enhanced Ubiquitin Split Protein Sensor technology</i>	81
<i>Double Switch technology</i>	81
<i>Fluorescence Resonance Energy Transfer</i>	81
<i>In vivo study of protein-protein interactions</i>	82

<i>In vitro</i> study of protein-protein interactions	82
Interactome	82
Membrane 1-hybrid method	83
Nanowire transistor for the detection of protein-protein interactions.....	84
Phage display	84
Protein affinity chromatography.....	84
Protein-fragment complementation system	84
Proximity-dependent hybridization chain reaction	85
Yeast 2-hybrid system.....	85
Companies with technologies for protein-protein interaction studies	86
Protein-DNA interaction	87
Determination of protein structure	87
X-Ray crystallography	88
Nuclear magnetic resonance.....	88
Electron spin resonance	89
Prediction of protein structure	89
Protein tomography.....	90
X-ray scattering-based method for determining the structure of proteins.....	90
Prediction of protein function	91
Three-dimensional proteomics for determination of function.....	91
An algorithm for genome-wide prediction of protein function	92
Monitoring protein function by expression profiling.....	92
Isotope-coded affinity tag peptide labeling	92
Differential Proteomic Panning	93
Cell map proteomics	93
Topological proteomics.....	93
Organelle or subcellular proteomics	94
Nucleolar proteomics.....	95
Glycoproteomic technologies	95
High-sensitivity glycoprotein analysis	95
Fluorescent in vivo imaging of glycoproteins.....	96
Integrated approaches for protein characterization	96
Imaging mass spectrometry	96
IMS technologies	97
Applications of IMS	97
The protein microscope.....	98
Tag-Mass IMS.....	98
Quantitative immunofluorescence for proteomics	98
Automation and robotics in proteomics	99
Western blot.....	99
Limitations of WB.....	99
Innovations in WB.....	99
<i>Capillary electrophoresis and WB</i>	<i>100</i>
<i>Chemiluminescent western blotting</i>	<i>100</i>
<i>Fluorescent WB.....</i>	<i>101</i>
<i>Microfluidics and WB</i>	<i>101</i>
<i>Multiplexing WB.....</i>	<i>102</i>
Applications of Western blot	102
<i>Research applications of Western blot.....</i>	<i>102</i>
<i>Molecular diagnostic applications of Western blot.....</i>	<i>102</i>
Companies involved in Western blotting technologies	103
Laser capture microdissection	104
Microdissection techniques used for proteomics	104
Uses of LCM in combination with proteomic technologies	104
Concluding remarks about applications of proteomic technologies.....	105
NextGen Proteomics Platform	106
Precision proteomics	106
3. Protein biochip technology	107
Introduction	107
Types of protein biochips.....	108
ProteinChip	108
<i>Applications and advantages of ProteinChip.....</i>	<i>109</i>
<i>ProteinChip Biomarker System</i>	<i>109</i>
<i>Matrix-free ProteinChip Array</i>	<i>110</i>
Aptamer-based protein biochip	110
Fluorescence planar wave guide technology-based protein biochips.....	111
Lab-on-a-chip for protein analysis.....	111
Biochips for peptide arrays.....	112
Microfluidic biochips for proteomics	112
Protein biochips and microarrays for high-throughput expression	113

<i>Nucleic Acid-Programmable Protein Array</i>	113
<i>High-density protein microarrays</i>	113
<i>HPLC-Chip for protein identification</i>	114
<i>Antibody microarrays</i>	114
<i>HuProt™ Human Proteome Microarrays</i>	114
<i>Integration of protein array and image analysis</i>	115
Tissue microarray technology for proteomics	115
Protein biochips in molecular diagnostics	115
A force-based protein biochip	116
L1 chip and lipid immobilization	116
Multiplexed Protein Profiling on Microarrays.....	117
Live cell microarrays	117
ProteinArray Workstation	118
Proteome arrays	118
The Yeast ProtoArray	118
ProtoArray™ Human Protein Microarray	119
TRINECTIN proteome chip.....	119
Peptide arrays	120
Surface plasmon resonance technology	120
SPR Systems.....	120
FLEX CHIP.....	121
Combination of surface plasmon resonance and MALDI-TOF	121
Protein chips/microarrays using nanotechnology	122
Nanoparticle protein chip	122
Protein nanobiochip.....	122
Protein nanoarrays.....	123
Self-assembling protein nanoarrays.....	123
Companies involved in protein biochip/microarray technology	123
4. Bioinformatics in Relation to Proteomics	127
Introduction	127
Bioinformatic tools for proteomics	127
Testing of SELDI-TOF MS Proteomic Data.....	127
BioImagine's ProteinMine	128
Bioinformatics for pharmaceutical applications of proteomics	128
<i>In silico</i> search of drug targets by Biopendium.....	128
Compugen's LEADS	129
DrugScore.....	129
Proteochemometric modeling	129
Integration of genomic and proteomic data	130
Proteomic databases: creation and analysis	131
Introduction	131
Proteomic databases	131
<i>GenProtEC</i>	132
<i>Human Protein Atlas</i>	132
<i>Human Proteomics Initiative</i>	133
<i>Human proteome map</i>	134
<i>International Protein Index</i>	134
<i>MS-based draft of the human proteome</i>	134
<i>Protein Structure Initiative – Structural Genomics Knowledgebase</i>	134
<i>Protein Warehouse Database</i>	135
<i>Protein Data Bank</i>	135
<i>Repository for raw data from proteomics MS</i>	135
<i>Universal Protein Resource</i>	136
Protein interaction databases	136
<i>Biomolecular Interaction Network Database</i>	137
ENCODE	137
<i>Functional Genomics Consortium</i>	138
<i>Human Proteinpedia</i>	138
<i>ProteinCenter</i>	138
<i>Databases of the National Center for Biotechnology Information</i>	139
Application of bioinformatics for protein identification	139
Tandem MS for protein identification	139
Targeted MS for specific identification of proteins.....	139
Application of bioinformatics in functional proteomics	140
Use of bioinformatics in protein sequencing	140
Bottom-up protein sequencing.....	141
Top-down protein sequencing.....	142
Integration of next generation proteomics and gene sequencing data	142
Protein structural database approach to drug design	142
Bioinformatics for high-throughput proteomics	143

Bioinformatics for protein-protein interactions.....	144
Companies with bioinformatic tools for proteomics	144
5. Research in Proteomics	147
Introduction	147
Applications of proteomics in biological research	147
Identification of novel human genes by comparative proteomics	147
Study of relationship between genes and proteins.....	148
Characterization of histone codes.....	148
Structural genomics or structural proteomics.....	149
Protein Structure Factory	150
Protein Structure Initiative	150
Studies on protein structure at Argonne National Laboratory	151
Structural Genomics Consortium.....	151
Protein knockout	152
Antisense approach and proteomics	152
RNAi and protein knockout.....	152
Total knockout of cellular proteins.....	153
Ribozymes and proteomics	153
Single molecule proteomics	153
Single-molecule photon stamping spectroscopy	153
Single nucleotide polymorphism determination by TOF-MS.....	154
Application of proteomic technologies in systems biology	154
Signaling pathways and proteomics.....	155
Kinomics.....	155
Combinatorial RNAi for quantitative protein network analysis	155
Proteomics in neuroscience research.....	156
Stem cell proteomics	156
Comparative proteomic analysis of somatic cells, iPSCs and ESCs	157
hESC phosphoproteome.....	157
Proteomic studies of mesenchymal stem cells.....	157
Proteomics of neural stem cells.....	158
Proteome Biology of Stem Cells Initiative	158
Proteomic analysis of the cell cycle	159
Nitric oxide and proteomics	159
A proteomic method for identification of cysteine S-nitrosylation sites	159
Study of the nitroproteome	160
Study of the phosphoproteome.....	160
Study of the mitochondrial proteome	161
Proteomic technologies for study of mitochondrial proteomics	161
Cryptome.....	162
Study of protein transport in health and disease	162
Ancient proteomics	162
Proteomics research in the academic sector	163
Netherlands Proteins@Work	165
ProteomeBinders initiative.....	165
Rutgers University's Center for Integrative Proteomics Research.....	165
Vanderbilt University's Center for Proteomics and Drug Actions	166
6. Pharmaceutical Applications of Proteomics	167
Introduction	167
Current drug discovery process and its limitations	167
Role of omics in drug discovery	168
Genomics-based drug discovery.....	168
Metabolomics technologies for drug discovery	169
Role of metabolomics in drug discovery	169
Basis of proteomics approach to drug discovery.....	170
<i>Proteins and drug action</i>	<i>170</i>
<i>Transcription-aided drug design.....</i>	<i>171</i>
In vivo production of therapeutic proteins by mRNA	171
Role of proteomic technologies in drug discovery	171
<i>Liquid chromatography-based drug discovery</i>	<i>172</i>
<i>Capture compound mass spectrometry</i>	<i>172</i>
<i>Protein-expression mapping by 2DGE</i>	<i>172</i>
<i>Protein-protein interactions and drug discovery</i>	<i>173</i>
<i>Role of MALDI mass spectrometry in drug discovery</i>	<i>173</i>
<i>Structural proteomics and drug discovery</i>	<i>174</i>
<i>Tissue imaging mass spectrometry.....</i>	<i>174</i>
Oxford Genome Anatomy Project	176
Proteins as drug targets.....	176
<i>Monitoring drug target binding using the cellular thermal shift assay</i>	<i>176</i>

Ligands to capture the purine binding proteome	176
Chemical probes to interrogate key protein families for drug discovery	177
Global proteomics for pharmacodynamics	177
ProteoCarta® proteomics platform	178
ZeptoMARK™ protein profiling system	178
Role of proteomics in targeting disease pathways	179
Dynamic proteomics	179
Identification of protein kinases as drug targets	179
<i>Mechanisms of action of kinase inhibitors</i>	180
G-protein coupled receptors as drug targets	180
<i>Methods of study of GPCRs</i>	181
<i>Cell-based assays for GPCR</i>	181
<i>Companies involved in GPCR-based drug discovery</i>	182
<i>GPCR localization database</i>	183
Matrix metalloproteases as drug targets	183
PDZ proteins as drug targets	183
Proteasome as drug target	184
Serine hydrolases as drug targets	185
Targeting mTOR signaling pathway	185
Targeting caspase-8 for anticancer therapeutics	186
Drug design based on structural proteomics	187
Protein crystallography for determining 3D structure of proteins	187
Automated 3D protein modeling	187
<i>Drug targeting of flexible dynamic proteins</i>	187
Companies involved in structure-based drug-design	188
Integration of genomics and proteomics for drug discovery	189
Ligand-receptor binding	190
Role of proteomics in study of ligand-receptor binding	190
<i>Measuring drug binding of proteins</i>	190
Aptamer protein binding	190
<i>Systematic Evolution of Ligands by Exponential Enrichment</i>	191
<i>Aptamers and high-throughput screening</i>	191
<i>Nucleic Acid Biotoools</i>	192
<i>Aptamer beacons</i>	192
<i>Peptide aptamers</i>	192
Riboreporters for drug discovery	193
Target identification and validation	193
Application of mass spectrometry for target identification	194
Gene knockout and gene suppression for validating protein targets	194
Laser-mediated protein knockout for target validation	194
Integrated proteomics for drug discovery	195
High-throughput proteomics	195
Companies involved in high-throughput proteomics	195
Drug discovery through protein-protein interaction studies	196
Protein-protein interaction as basis for drug target identification	197
Protein-PCNA interaction as basis for drug design	197
Two-hybrid protein interaction technology for target identification	198
Biosensors for detection of small molecule-protein interactions	198
Protein-protein interaction maps	199
<i>ProNet (Myriad Genetics)</i>	199
<i>Hybrigenics' maps of protein-protein interactions</i>	199
<i>CellZome's functional map of protein-protein interactions</i>	200
Mapping of protein-protein interactions by mass spectrometry	200
Protein interaction map of <i>Drosophila melanogaster</i>	201
Protein-interaction map of Wellcome Trust Sanger Institute	201
Protein-protein interactions as targets for therapeutic intervention	201
Inhibition of protein-protein interactions by peptide aptamers	202
Selective disruption of proteins by small molecules	202
Post-genomic combinatorial biology approach	202
Differential proteomics	203
Shotgun proteomics	203
Targeted proteomics	204
Chemogenomics/chemoproteomics for drug discovery	204
<i>Chemoproteomics-based drug discovery</i>	205
<i>Companies involved in chemogenomics/chemoproteomics</i>	205
<i>Activity-based proteomics</i>	207
<i>Locus Discovery technology</i>	207
<i>Automated ligand identification system</i>	207
Expression proteomics: protein level quantification	208
Role of phage antibody libraries in target discovery	209
Analysis of posttranslational modification of proteins by MS	209

Phosphoproteomics for drug discovery	210
Application of glycoproteomics for drug discovery	210
Role of carbohydrates in proteomics.....	210
Challenges of glycoproteomics.....	210
Companies involved in glycoproteomics	211
Role of protein microarrays/ biochips for drug discovery	212
Protein microarrays vs DNA microarrays for high-throughput screening	212
BIA-MS biochip for protein-protein interactions.....	212
ProteinChip with Surface Enhanced Neat Desorption.....	213
Protein-domains microarrays.....	213
Some limitations of protein biochips	213
Concluding remarks about role of proteomics in drug discovery	214
RNA versus protein profiling as guide to drug development	214
RNA as drug target	214
Combination of RNA and protein profiling	215
<i>RNA binding proteins</i>	216
Toxicoproteomics	216
Hepatotoxicity	216
Nephrotoxicity	217
Cardiotoxicity	217
Neurotoxicity.....	218
Protein/peptide therapeutics	218
Alphabody technology for improving protein therapeutics.....	218
Peptide-based drugs.....	218
Phylomer® peptides.....	219
Cryptein-based therapeutics.....	219
Synthetic proteins and peptides as pharmaceuticals	220
Genetic immunization and proteomics	220
Role of proteomics in synthetic antivenoms	221
Proteomics and gene therapy	221
Role of proteomics in clinical drug development	222
Pharmacoproteomics	222
Role of proteomics in clinical drug safety.....	222
7. Application of Proteomics in Human Healthcare	225
Introduction	225
Clinical proteomics	226
Definition and standards	226
Vermillion's Clinical Proteomics Program	226
Pathophysiology of human diseases	227
Diseases due to misfolding of proteins	227
<i>Mechanism of protein folding</i>	228
<i>Nanoproteomics for study of misfolded proteins</i>	229
<i>Therapies for protein misfolding</i>	229
Intermediate filament proteins	230
Significance of mitochondrial proteome in human disease	230
<i>Proteome of Saccharomyces cerevisiae mitochondria</i>	231
<i>Rat mitochondrial proteome</i>	231
Proteomic approaches to biomarker identification	232
The ideal biomarker	232
Proteomic technologies for biomarker discovery.....	232
<i>MALDI mass spectrometry for biomarker discovery</i>	233
Protein biochips/microarrays and biomarkers	233
Affinity proteomics for discovery of biomarkers.....	233
<i>Antibody array-based biomarker discovery</i>	234
<i>Discovery of biomarkers by MAb microarray profiling</i>	235
Tumor-specific serum peptidome patterns.....	235
Search for protein biomarkers in body fluids.....	235
Challenges and strategies for discovery of protein biomarkers in plasma.....	235
<i>3-D structure of CD38 as a biomarker</i>	237
<i>BD™ Free Flow Electrophoresis System</i>	237
<i>Isotope tags for relative and absolute quantification</i>	237
<i>N-terminal peptide isolation from human plasma</i>	238
<i>Plasma protein microparticles as biomarkers</i>	238
<i>Proteome partitioning</i>	238
<i>SISCAPA method for quantitating proteins and peptides in plasma</i>	239
<i>Stable isotope tagging methods</i>	239
<i>Technology to measure both the identity and size of the biomarker</i>	239
Biomarkers in the urinary proteome	240
Application of proteomics in molecular diagnosis	240
MassARRAY	241

Proximity ligation assay	242
Protein patterns	242
Proteomic tests on body fluids	242
Cyclical amplification of proteins	244
Applications of proteomics in infections	244
MALDI-TOF MS for microbial identification	244
Recognition of microbial glycans by human lectins	245
Role of proteomics in virology	245
<i>Interaction of proteins with viruses</i>	246
<i>Quantitative temporal viromics</i>	246
Role of proteomics in bacteriology	246
<i>Epidemiology of bacterial infections</i>	247
<i>Proteomic approach to bacterial pathogenesis</i>	247
<i>Vaccines for bacterial infections</i>	247
<i>Protein profiles associated with bacterial drug resistance</i>	248
Analyses of the parasite proteome	248
Application of proteomics in cystic fibrosis	249
Proteomics of cardiovascular diseases	249
Pathomechanism of cardiovascular diseases	249
Protein misfolding in cardiac dysfunction	250
Study of cardiac mitochondrial proteome in myocardial ischemia	250
Cardiac protein databases	250
Proteomics of dilated cardiomyopathy and heart failure	251
Proteomic biomarkers of cardiovascular diseases	251
Regulation of cardiac rhythmicity by Purkinje cell protein-4	252
Role of proteomics in cardioprotection	252
Role of proteomics in heart transplantation	252
Future of application of proteomics in cardiology	253
Proteomic technologies for research in pulmonary disorders	253
Application of proteomics in renal disorders	254
Diagnosis of renal disorders	255
Proteomic biomarkers of acute kidney injury	255
Cystatin C as biomarker of glomerular filtration rate	255
Protein biomarkers of nephritis	255
Proteomics and kidney stones	256
Proteomics of eye disorders	256
Proteomics of cataract	257
Proteomics of diabetic retinopathy	257
Retinal dystrophies	257
Use of proteomics in inner ear disorders	258
Use of proteomics in aging research	258
Alteration of glycoproteins during aging	259
Carbamylation of proteins with aging	259
Proteomics of muscle aging	259
Removal of altered cellular proteins in aging	260
Role of protein aggregation in aging and degenerative diseases	260
Study of the role of Parkin in modulating aging	261
Study of proteins that protect against hypoxic injury in age-related disorders	261
Proteomics and nutrition	261
8. Oncoproteomics	263
Introduction	263
Proteomic technologies for study of cancer	264
Application of CellCarta technology for oncology	264
Accentuation of differentially expressed proteins using phage technology	264
Cancer tissue proteomics	264
<i>Dynamic cell proteomics in response to a drug</i>	265
Desorption electrospray ionization for cancer diagnosis	265
Id proteins as targets for cancer therapy	266
Identification of oncogenic tyrosine kinases using phosphoproteomics	266
Laser capture microdissection technology and cancer proteomics	266
Mass spectrometry for identification of oncogenic chimeric proteins	267
Proteomic analysis of cancer cell mitochondria	267
Proteomic study of p53	268
Human Tumor Gene Index	268
Integration of cancer genomics and proteomics	268
Role of proteomics in study of cancer stem cell biology	269
Single-cell protein expression analysis by microfluidic techniques	269
Use of proteomics in cancers of various organ systems	269
Proteomics of brain tumors	269
<i>Malignant glial tumors</i>	269

<i>Meningiomas</i>	270
<i>DESI-MS for intraoperative diagnosis of brain tumors</i>	270
Proteomics of breast cancer	271
<i>Integration of proteomic and genomic data for breast cancer</i>	272
Proteomics of colorectal cancer.....	273
Proteomics of esophageal cancer	273
Proteomics of hepatic cancer	274
Proteomics of leukemia.....	274
Proteomics of lung cancer	275
Proteomics of pancreatic cancer.....	276
Proteomics of prostate cancer.....	276
Proteomics of renal cancer	277
Diagnostic use of cancer biomarkers	277
Proteomic technologies for tumor biomarkers	278
Nuclear matrix proteins (NMPs)	278
Antiannexins as tumor markers in lung cancer.....	279
NCI's Network of Clinical Proteomic Technology Centers.....	279
Proteomics and tumor immunology	280
Proteomics and study of tumor invasiveness	280
Anticancer drug discovery and development	281
Anticancer drug targeting: functional proteomics screen of proteases	281
Kinase-targeted drug discovery in oncology.....	281
Protein-drug interactions in cancer	282
Role of proteomics in studying drug resistance in cancer.....	282
Small molecule inhibitors of cancer-related proteins	283
Future prospects of oncoproteomics.....	283
International oncoproteomic initiatives	283
<i>Clinical Proteomic Tumor Analysis Consortium</i>	284
Companies involved in application of proteomics to oncology	285

9. Neuroproteomics	287
Introduction	287
Application of proteomics for the study of nervous system	287
Proteomics of prion diseases	288
Normal function of prions in the brain.....	288
Detection of protein aggregates and prions	288
Diseases due to pathological prion protein	289
Transmissible spongiform encephalopathies	290
<i>Creutzfeld-Jakob disease</i>	290
<i>Bovine spongiform encephalopathy</i>	290
<i>Variant Creutzfeldt-Jakob disease</i>	290
Protein misfolding and neurodegenerative disorders.....	291
Ion channel link for protein-misfolding disease	291
Detection of misfolded proteins.....	291
Modulation of proteostasis in neurodegenerative disorders	291
Neurodegenerative disorders with protein abnormalities	292
<i>Alzheimer disease</i>	294
<i>Common denominators of Alzheimer and prion diseases</i>	294
<i>Parkinson disease</i>	295
<i>Amyotrophic lateral sclerosis</i>	295
Proteomics and glutamate repeat disorders	296
<i>Proteomics and Huntington's disease</i>	296
Proteomics and demyelinating diseases	297
Proteomics of neurogenetic disorders	298
Fabry disease	298
GM1 gangliosidosis.....	298
Quantitative proteomics and familial hemiplegic migraine	299
Proteomics of spinal muscular atrophy	299
Proteomics of CNS trauma	299
Proteomics of traumatic brain injury.....	299
Chronic traumatic encephalopathy and ALS	300
Proteomics of cerebrovascular disease.....	301
Pathogenesis of cerebral small vessel disease.....	301
Proteomics of CNS aging.....	301
Protein aggregation as a biomarker of aging.....	302
Neuroproteomics of psychiatric disorders.....	302
Schizophrenia.....	302
Anxiety disorders	303
Depression and suicidal behavior.....	303
Neuroproteomic of cocaine addiction	303
Neurodiagnostics based on proteomics.....	304

Disease-specific proteins in the cerebrospinal fluid	304
<i>Tau proteins</i>	305
CNS tissue proteomics	305
Diagnosis of CNS disorders by examination of proteins in urine	307
Diagnosis of CNS disorders by examination of proteins in the blood	307
<i>Serum pNF-H as biomarker of CNS damage</i>	308
Intraoperative application of proteomics in surgery of brain tumors	308
Proteomics of BBB	308
Future of neuroproteomics in neurology	309
HUPO's Pilot Brain Proteome Project	310
10. Proteomics Markets	311
Introduction	311
Potential markets for proteomic technologies	311
Bioinformatics markets for proteomics	312
Markets for protein separation technologies	312
<i>Markets for 2D gel electrophoresis</i>	312
<i>Market trends in protein separation technologies</i>	312
Protein purification markets	313
Mass spectrometry markets	313
Markets for MALDI for drug discovery	313
Markets for nuclear magnetic resonance spectroscopy	314
Market for structure-based drug design	314
Markets for protein biomarkers	314
Markets for cell-based protein assays	314
Protein biochip markets	315
Western blot markets	315
Geographical distribution of proteomics technologies markets	315
Business and strategic considerations	316
Cost of protein structure determination	316
Opinion surveys of the scientist consumers of proteomic technologies	316
<i>Opinions on mass spectrometry</i>	316
<i>Opinions on bioinformatics and proteomic databases</i>	316
<i>Systems for in vivo study of protein-protein interactions</i>	316
<i>Perceptions of the value of protein biochip/microfluidic systems</i>	317
Small versus big companies	317
Expansion in proteomics according to area of application	317
Growth trends in cell-based protein assay market	317
<i>Challenges for development of cell-based protein assays</i>	318
<i>Future trends and prospects of cell-based protein assays</i>	318
Strategic collaborations	319
<i>Analysis of proteomics collaborations according to types of companies</i>	319
<i>Types of proteomic collaborations</i>	319
<i>Proteomics collaborations according to application areas</i>	320
<i>Analysis of proteomics collaborations: types of technologies</i>	320
<i>Collaborations based on protein biochip technology</i>	321
<i>Concluding remarks about proteomic collaborations</i>	321
Proteomic patents	322
Market drivers in proteomics	322
Needs of the pharmaceutical industry	322
Need for outsourcing proteomic technologies	323
Funding of proteomic companies and research	323
Technical advances in proteomics	323
Changing trends in healthcare in future	324
Challenges facing proteomics	324
Magnitude and complexity of the task	324
Technical challenges	324
Limitations of proteomics	325
<i>Limitations of 2DGE</i>	325
<i>Limitations of mass spectrometry techniques</i>	325
<i>Complexity of the pharmaceutical proteomics</i>	325
Unmet needs in proteomics	326
11. Future of Proteomics	327
Genomics to proteomics	327
Faster technologies	327
FLEXGene repository	327
Need for new proteomic technologies	328
Emerging proteomic technologies	329
Detection of alternative protein isoforms	329
Direct protein identification in large genomes by mass spectrometry	329

Proteome identification kits with stacked membranes	329
Vacuum deposition interface.....	330
<i>In vitro</i> protein biosynthesis.....	330
Proteome mining with adenosine triphosphate.....	330
Proteome-scale purification of human proteins from bacteria.....	330
Proteostasis network	331
Cytoproteomics	331
<i>Subcellular proteomics</i>	331
<i>Individual cell proteomics</i>	332
<i>Live cell proteomics</i>	332
<i>Fluorescent proteins for live-cell imaging</i>	333
Membrane proteomics	333
<i>Identification of membrane proteins by tandem MS of protein ions</i>	333
<i>Solid state NMR for study of nanocrystalline membrane proteins</i>	334
Multiplex proteomics	334
High-throughput for proteomics	334
Future directions for protein biochip application	335
Bioinformatics for proteomics	335
High-Throughput Crystallography Consortium.....	335
Study of protein folding by IBM's Blue Gene	336
Study of proteins by atomic force microscopy	336
Population proteomics	336
Comparative proteome analysis.....	337
Human Proteome Organization.....	337
Cell-based Human Proteome Project.....	338
Human Salivary Proteome	338
Academic-commercial collaborations in proteomics	339
Indiana Centers for Applied Protein Sciences	339
Role of proteomics in the healthcare of the future.....	339
Proteomics and molecular medicine.....	339
Proteodiagnostics.....	340
Proteomics and personalized medicine.....	340
<i>Targeting the ubiquitin pathway for personalized therapy of cancer</i>	341
<i>Protein patterns and personalized medicine</i>	341
<i>Personalizing interferon therapy of hepatitis C virus</i>	342
<i>Protein biochips and personalized medicine</i>	343
<i>Combination of diagnostics and therapeutics</i>	343
<i>Future prospects</i>	343

12. References..... 345

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.....	77
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	86
Table 2-7: Companies involved in Western blotting	103
Table 2-8: Proteomic technologies used with laser capture microdissection	104
Table 3-1: Applications of protein biochip technology	107
Table 3-2: Selected companies involved in protein biochip/microarray technology	123
Table 4-1: Proteomic databases and other Internet sources of proteomics information	131
Table 4-2: Protein interaction databases available on the Internet	137
Table 4-3: Bioinformatic tools for proteomics from academic sources	143
Table 4-4: Selected companies involved in bioinformatics for proteomics	144
Table 5-1: Applications of proteomics in basic biological research	147
Table 5-2: A sampling of proteomics research projects in academic institutions.....	163
Table 6-1: Pharmaceutical applications of proteomics.....	167
Table 6-2: Selected companies relevant to MALDI-MS for drug discovery.....	173
Table 6-3: Selected companies involved in GPCR-based drug discovery	182
Table 6-4: Companies involved in drug design based on structural proteomics	188
Table 6-5: Proteomic companies with high-throughput protein expression technologies.....	196
Table 6-6: Selected companies involved in chemogenomics/chemoproteomics	206
Table 6-7: Companies involved in glycoproteomic technologies	211

Table 7-1: Applications of proteomics in human healthcare	225
Table 7-2: Eye disorders and proteomic approaches.....	256
Table 8-1: Large scale international oncoproteomic initiatives	284
Table 8-2: Companies involved in applications of proteomics to oncology	285
Table 9-1: Neurodegenerative diseases with underlying protein abnormality	292
Table 9-2: Disease-specific proteins in the cerebrospinal fluid of patients.....	304
Table 10-1: Potential markets for proteomic technologies 2017-2027.....	311
Table 10-2: Geographical distribution of markets for proteomic technologies 2017-2027	315
Table 11-1: Role of proteomics in personalizing strategies for cancer therapy	341

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	51
Figure 2-5: Matrix-Assisted Laser Desorption/Ionization (MALDI).....	53
Figure 2-6: Scheme of bio-bar-code assay	72
Figure 2-7: A diagrammatic presentation of yeast 2-hybrid system	85
Figure 3-1: ProteinChip System	109
Figure 3-2: Surface plasma resonance (SPR).....	121
Figure 4-1: Role of bioinformatics in integrating genomic/proteomic-based drug discovery	130
Figure 4-2: Bottom-up and top-down approaches for protein sequencing	141
Figure 6-1: Drug discovery process.....	168
Figure 6-2: Regulatory changes induced by drugs and implemented at the proteins level.	170
Figure 6-3: Relation of proteome to genome, diseases and drugs	171
Figure 6-4: The mTOR pathways	186
Figure 6-5: Steps in shotgun proteomics	203
Figure 6-6: Chemogenomic approach to drug discovery (3-Dimensional Pharmaceuticals)	205
Figure 8-1: Relation of oncoproteomics to other technologies	263
Figure 9-1: A scheme of proteomics applications in CNS drug discovery and development	310
Figure 10-1: Types of companies involved in proteomics collaborations	319
Figure 10-2: Types of collaborations: R & D, licensing or marketing	320
Figure 10-3: Proteomics collaborations according to application areas	320
Figure 10-4: Proteomics collaborations according to technologies	321
Figure 10-5: Unmet needs in proteomics	326
Figure 11-1: A scheme of the role of proteomics in personalized management of cancer.....	342