

TABLE OF CONTENTS

0. Executive Summary	11
1. Introduction to Animal Biotechnology	13
Introduction	13
Historical evolution of animal biotechnology	13
Basics of biotechnology	14
DNA	14
RNA	14
Genes.....	15
Single nucleotide polymorphisms	15
Copy number variations in the genome.....	15
DNA sequences.....	16
Gene expression	16
Gene regulation	17
Proteins	17
<i>Functions of proteins</i>	<i>17</i>
<i>Recombinant proteins.....</i>	<i>18</i>
Monoclonal antibodies	19
Animal genetics	19
Molecular genetics	19
Twinning in cattle.....	20
Pig genetics.....	20
Genetic studies in dogs.....	20
Animal genomics	20
The mouse genome.....	20
The dog genome.....	21
<i>Sequencing of the dog genome.....</i>	<i>21</i>
<i>Comparison of genomes of healthy and diseased dogs.....</i>	<i>23</i>
<i>Analysis of DNA copy number variation.....</i>	<i>23</i>
The cat genome.....	24
Marsupial genomes	24
Genomes of non-human primates	24
<i>Chimpanzee genome</i>	<i>24</i>
<i>Genome of the rhesus macaque.....</i>	<i>25</i>
<i>Genome of gorilla</i>	<i>25</i>
Livestock genomics	26
<i>Bovine genome.....</i>	<i>27</i>
<i>Bovine SNP map</i>	<i>27</i>
<i>Identification of genes in bovine stomach microbiome</i>	<i>28</i>
<i>Pig genome</i>	<i>29</i>
<i>Horse genome</i>	<i>30</i>
<i>Sheep genome</i>	<i>31</i>
Chicken genome	31
Turkey genome	32
Salmon genome.....	33
Priority genome list of the National Human Genome Research Institute	33
Animal proteomics.....	34
Applications of proteomics in animals	34
<i>Caseins in goat milk</i>	<i>35</i>
<i>Lactic acid bacteria.....</i>	<i>35</i>
<i>Applications of proteomics in animal healthcare</i>	<i>35</i>
Antigenomics.....	35
Bioinformatics	35
Nanobiotechnology and animal health	37
Biomarkers and animal health	37
Recombinant protein manufacture.....	38
Animal biotechnology in relation to other technologies	38
2. Application of Biotechnology in Animals	39
Introduction	39
Applications of animal genomics.....	39
Genomics of disease resistance.....	39
Statistical genomics to improve breeding	40
Chicken breeding based on genomics	40
Bovine ankyrin 1 gene and beef tenderness	40
Genome wide associations and milk production in cows	41
SNPs and longevity in dairy cattle	41

Share genomic data to improve cattle breeding programs	41
Genetic engineering	41
Livestock improvement by genetic engineering	42
Disease control by genetic engineering	42
Limitations and precautions for genetic engineering	42
Transgenic animal technology	42
Cloning animals	43
<i>Nuclear transfer technology</i>	44
<i>Nuclear bisection for cloning</i>	46
<i>Zona-free cloning method</i>	46
<i>Abnormalities in cloned animals</i>	47
<i>Cloning from embryonic cells</i>	48
<i>Cloning of rabbits</i>	48
<i>Cloning the rat</i>	49
<i>Cloning the horse</i>	49
<i>Cloning the cow</i>	49
<i>Cloning the dog</i>	50
<i>Cloning in primates</i>	50
Retrovector-mediated production of transgenic animals	50
Episomal vector-mediated gene delivery	51
Sperm-mediated gene transfer	51
Lentiviral transduction of male germ-line stem cells	52
Lentiviral transgenesis	53
Transgenic pharmaceuticals	53
Proteins from the milk of transgenic animals	53
Advantages of milk as source of transgenic proteins	54
<i>Therapeutic proteins from rabbit milk</i>	55
<i>Recombinant human antibodies from cows</i>	56
<i>Therapeutic proteins from goat milk</i>	56
Chicken transgenesis for the production of biopharmaceuticals	57
Concluding remarks about production of recombinant proteins in animals	57
Companies involved in production of transgenic pharmaceuticals	57
Transgenic food products	58
Milking genetically modified cows.....	58
Transgenic fish	58
Cloned animals as sources of milk and meat.....	59
Animal feeds from transgenic plants	59
Transgenic modification of plants to increase nutritional value of animal feeds.....	60
Transgenic disease models	60
Technologies to create transgenic disease models	60
<i>Gene manipulation techniques</i>	60
<i>Embryonic stem cells for gene targeting</i>	61
<i>Homologous recombination</i>	61
<i>Animal models of human diseases</i>	62
Transgenic models for studying human drug metabolism and toxicity	62
The Human Genome Project and the role of transgenics	63
Genomic and proteomic analyses of transgenic animal models.....	63
Concern about health and welfare of transgenic animals	64
Safety of transgenic technology	64
Concluding remarks about use of transgenic animals	65
RNA interference technology	65
RNAi versus antisense	65
Applications of RNAi in animal biotechnology	65
Xenotransplantation	66
Pigs for xenotransplantation	66
<i>Genetically engineered pigs for transplants</i>	67
<i>Risks of xenotransplantation</i>	67
World Health Organization and xenotransplantation	68
Ethical aspects of animal biotechnology	68
3. A Biotechnology Perspective of Animals Diseases	71
Introduction	71
Infections in animals	71
Viral infections.....	72
<i>Avian influenza</i>	72
<i>Animal surveillance of influenza</i>	74
<i>Animal biotechnology implications of H1N1 influenza</i>	75
<i>Animal corona viruses and human SARS</i>	76
<i>Avian coronavirus</i>	76
<i>Bluetongue virus</i>	77
<i>Canine parvovirus</i>	77

<i>Classical swine fever</i>	77
<i>Developing new treatments against FMD</i>	77
<i>Equine infectious anemia</i>	78
<i>Foot-and-mouth disease</i>	79
<i>Porcine reproductive and respiratory syndrome virus</i>	80
<i>Rabies</i>	81
<i>Rinderpest</i>	81
<i>Schmallenberg virus</i>	82
Bacterial infections.....	82
<i>Bovine tuberculosis</i>	82
Mycoplasmal pneumonia	83
Protozoal infections	83
<i>Coccidiosis</i>	83
<i>Neosporosis</i>	83
<i>Toxoplasmosis</i>	84
<i>Trypanosomiasis</i>	84
Nematodes.....	85
Infections that cross the species barrier.....	85
Complications of bacterial infections and antibiotic use in animals.....	85
Transmissible spongiform encephalopathies (TSEs)	86
Inter-species transfer of prions.....	86
Scrapie.....	86
Bovine spongiform encephalopathy	87
<i>Epidemiology of BSE</i>	87
<i>Biomarkers in the urine of BSE infected cattle</i>	88
<i>Human health implications of BSE</i>	88
<i>Breeding animals protected against BSE</i>	89
TSE research	89
<i>Prion gene haplotyping</i>	89
<i>Pharmacological approaches to TSE research</i>	89
<i>Molecular diagnostic approach to TSE research</i>	90
<i>RNAi for knockdown of the bovine prion gene</i>	90
Chronic wasting disease	91
<i>Chronic wasting disease in wildlife</i>	91
<i>Chronic wasting disease of the cattle in Sudan</i>	92
<i>Chronic wasting in dairy cows in the Netherlands</i>	92
Genetic disorders in farm animals	92
Genetic predisposition to acquired diseases in animals	93
Diseases of pet animals	93
Canine anemia	93
Cardiovascular disease	93
<i>Heart failure</i>	94
<i>Cardiac complications of canine babesiosis</i>	94
Diabetes	94
<i>Role of biotechnology in management of diabetes</i>	95
Arthritis	95
Cancer in cats and dogs.....	96
<i>Cancer clinical trials in dogs</i>	96
<i>Canine Comparative Oncology Genomics Consortium</i>	97
Preventive veterinary medicine	97
Prevention of introduction of foreign animal diseases.....	97
Producing transgenic cattle resistant to BSE.....	98
Zoonotic diseases	98
Viruses that emerge in animals and spread to humans	98
Collaborative management of animal and human health	99
Vaccines for zoonotic viral diseases	99

4. Molecular Diagnostics in Animals **101**

Introduction	101
Nucleic acid technologies.....	101
The polymerase chain reaction	101
<i>Basic Principles of PCR</i>	101
<i>Target selection</i>	102
<i>Detection of amplified DNA</i>	102
<i>Real-time PCR systems</i>	102
<i>LightCycler PCR system</i>	103
<i>Molecular beacons</i>	103
<i>Applications of PCR in veterinary medicine</i>	103
Fluorescent in situ hybridization.....	104
Immunodiagnosics	106
Enzyme-linked immunoassays	106

Bovine Gamma Interferon Test	106
Antigen diagnosis of trichinosis	107
Parachek™ for the diagnosis of Johne's disease	107
Antibodies for differentiation between vaccinated and infected animals	108
Biochip/microarray technology	108
Applications of microarrays in animal biotechnology	109
<i>Cattlearray3800 for functional genomics</i>	109
<i>eSensor™ electrochemical biochip</i>	110
<i>FR 48 microfluidic biochip</i>	110
Biosensors	110
Immunosensors	111
<i>Biosensor for ovulation prediction in dairy cows</i>	111
Flow cytometry for animal diagnostics	112
Molecular imaging in animals	112
Veterinary cytogenetics	113
Applications of molecular diagnostics in animals	114
Canine DNA testing	114
Diagnostic aids to selective breeding	114
<i>Selection of desirable traits</i>	114
<i>Gene variations and fat content of beef</i>	115
<i>Using genetic markers for improved milk production in dairy cattle</i>	116
<i>Application of bovine genomics for improving milk yield</i>	116
<i>Recognition of hereditary syndromes</i>	116
Genetic markers in animals	117
<i>SNP genotyping in animals</i>	117
<i>SNP genotyping for selective breeding of chicken</i>	117
Animal identity and parentage analysis	118
Animal species identification in food	118
Diagnosis of infections	119
<i>Bacterial infections</i>	119
<i>Diagnosis of viral infections</i>	119
<i>Molecular diagnosis of avian influenza</i>	121
<i>Molecular diagnosis of swine influenza</i>	122
<i>Diagnosis of parasitic infections</i>	122
<i>Detection of natural or bioterror threats to livestock</i>	123
Molecular diagnosis of prion diseases	123
<i>Bovine spongiform encephalopathy</i>	123
<i>Testing for BSE in living animals</i>	125
<i>Prions in urine</i>	125
<i>Diagnosis of chronic wasting disease in wildlife</i>	126
Developing new tests for prion diseases	126
<i>Differentiation among various types of TSEs</i>	126
<i>Protein cyclic amplification</i>	126
<i>Antibody tests for prion diseases</i>	127
<i>Scrapie genotyping</i>	127
<i>A real-time ultrasonic method for prion protein detection</i>	128
Companies involved in developing molecular diagnostics for TSEs	128
Diagnosis of genetic disorders	129
<i>Genetic screening of companion animals</i>	129
<i>Genes associated with exercise-induced collapse</i>	129
<i>Preimplantation genetic diagnosis</i>	129
Diagnosis of cancer in animals	130
<i>Diagnosis of skin cancer</i>	130
Diagnosis of food-borne pathogens	130
Introduction	130
Molecular diagnostic methods used in food-borne infections	131
Limitations of use of molecular probes in food analysis	132
Companies with technologies for food pathogen detection	132
Biotechnology-based novel diagnostics for aquatic animals	133
Detection of chemicals in foods of animal origin	133
Companies developing molecular diagnostics for animals	134
5. Biotechnology-based Veterinary Medicine	137
Introduction	137
Biotechnology versus pharmaceutical products	137
Role of biotechnology in drug discovery and development	138
Cost of veterinary vs. human drug discovery and development	138
Advantages and disadvantages of testing biotech products in animal models	139
Biotechnolgoy-based antiparasitic drugs	139
Non-antibiotic strategies for control of infections in animals	139
Probiotics	140

<i>Potential role for probiotics in the human gut</i>	140
<i>Potential role for probiotics in animals</i>	140
<i>Probiotic bacteria for control of pathogens in cattle</i>	140
Nonantibiotic drugs for infections in animals	141
<i>Immunomodulation as an alternative to antibiotics in infections</i>	142
<i>Cathelicidins: effector molecules of mammalian innate immunity</i>	142
<i>Bacteriophage therapy for antibiotic resistance</i>	142
Biotechnology for treating tendon injuries	143
Use of growth factors to facilitate tendon injuries	143
Productivity enhancers	143
Bovine somatotropin for increasing milk production in dairy cows	144
Increasing milk production in cows by feeding propionibacteria	145
Use of growth factors	145
Transgenic plant products for use in animals	145
Biotechnology-based vaccines	146
Modern vaccines without viral non-structural proteins	146
Plant-derived vaccines for use in animals	147
Nano-bead vaccine adjuvant	148
Genetically engineered vaccines	148
<i>Application of nucleic acid vaccines in veterinary medicine</i>	148
<i>DNA vaccines</i>	148
<i>DNA vaccine for tuberculosis</i>	150
<i>DNA vaccines for West Nile encephalitis</i>	151
<i>Gene-based vaccine for Marek's disease</i>	151
<i>Genetic engineering of live rabies vaccines</i>	152
<i>Genetically engineered vaccines for equine encephalitis</i>	152
<i>Genetically engineered vaccines for Johne's disease</i>	153
<i>Vaccines against avian influenza</i>	153
<i>Vaccines against parasitic infections</i>	154
Recombinant marker vaccines	154
<i>Marker vaccines for foot-and-mouth disease</i>	155
<i>Marker vaccine for Newcastle disease</i>	155
<i>Vaccines for classical swine fever</i>	156
Vaccines for tick control	156
Vaccination to protect swine from H1N1 influenza virus infection	156
Vaccination of cattle to prevent <i>E. coli</i> transmission to consumers in meat	157
Vaccines for bacterial equine respiratory infections	157
Using RNAi to develop vaccines for viral infections in prawns	158
Companies developing biotechnology-based vaccines	158
Biotechnology in treatment of parasitic infections	159
Biotechnology in the treatment of CNS injuries in pet animals	159
Paraplegia due to acute spinal cord injury in dogs	159
RNAi for suppression prions in livestock	160
Cell Therapy	160
Umbilical cord blood stem cells	160
Application of stem cells in veterinary medicine	161
<i>Use of stem cells to repair tendon injuries in horses</i>	161
<i>Stem cells for spinal cord injury in dogs</i>	161
Gene therapy	162
<i>Gene therapy vectors</i>	162
<i>Gene therapy by mitochondrial transfer</i>	163
<i>In utero gene therapy</i>	163
Applications of gene therapy in veterinary medicine	163
<i>Gene therapy for mucopolysaccharidosis VII in dogs</i>	164
<i>Gene therapy to increase disease resistance</i>	164
<i>Gene therapy for infections</i>	164
<i>Gene therapy for hematological disorders</i>	165
<i>Gene therapy for cardiomyopathy in dogs</i>	165
<i>Gene therapy for endocrine disorders</i>	166
<i>Gene therapy for arthritis</i>	166
<i>Gene therapy for renal failure</i>	166
Cancer gene therapy	167
<i>Antiangiogenic cancer gene therapy in dogs</i>	167
<i>Brain tumors in cats and dogs</i>	167
<i>Breast cancer in dogs</i>	168
<i>Canine hemangiosarcoma</i>	169
<i>Canine melanoma</i>	169
<i>Canine soft tissue sarcoma</i>	170
<i>Melanoma in horses</i>	170

6. Research in Animal Biotechnology

Introduction	171
Research institutes	171
Animal and Natural Resources Institute (USDA)	171
Center for Animal Biotechnology at University of Melbourne (Australia)	172
CSIRO Livestock Industries	173
Easter Bush Research Consortium	174
Danish Veterinary Institute	174
Friedrich-Loeffler-Institute	175
Indian Veterinary Research Institute	175
Institute for Animal Health of UK	176
Kimron Veterinary Institute	176
Korean National Livestock Research Institute	177
National Agricultural & Veterinary Biotechnology Center of Ireland	177
Swiss Federal Institute of Technology	178
Veterinary Laboratories Agency of UK	178
Veterinary Medical University of Vienna	179
Ethical issues of research in animal biotechnology	179
Future prospects	180
Strategies for control of twinning in cattle	180
Future developments of molecular diagnostics	180
Future of vaccine application in veterinary medicine	181
<i>Promotion of innate immunity in animals</i>	181
<i>Identification of key parasite antigens for eliciting immune response</i>	181
<i>Virus-like particle vaccines for lasting immune response</i>	182
Control of respiratory virus infections	182
Control and prevention of bioterrorism diseases in animals	182
Genetic control of disease resistance	183
<i>Production of cattle lacking prion protein</i>	183
Application of genetics and biotechnology to wildlife management	183
Future of animal genomics	184
Future prospects of in vitro meat production	184
7. Animal Biotechnology Markets	187
Introduction	187
Markets for biotechnology-based products for animal healthcare	188
Markets for biopharmaceuticals for animals	189
<i>Markets for recombinant proteins for animal healthcare</i>	189
<i>Markets for vaccines for animals</i>	190
Markets for animal diagnostics	190
<i>Test for bovine spongiform encephalopathy</i>	190
Animal biotechnology markets according to therapeutic areas	191
Markets for biotechnology-based animal products for humans	191
Transgenic proteins	192
Market for xenotransplantation	192
Strategies for promoting use of animal biotechnology	193
Financial losses from death and disease in animals	193
<i>Losses in farm animals</i>	193
<i>Losses in poultry</i>	193
<i>Losses in equine industry</i>	193
The emerging role of pet owners	193
Improvement in cattle through application of biotechnology	194
<i>Economic aspects of genomic evaluation of dairy cattle</i>	194
<i>Pig market</i>	194
<i>Cattle Market</i>	195
<i>Poultry market</i>	195
<i>Milk from genetically modified cows</i>	195
Transgenic fish	196
Role of biotechnology in livestock performance enhancer market	196
Gene transfer technologies	196
In vitro meat production and animal biotechnology markets	196
Cost-benefit aspects of transgenic proteins	196
<i>Lower costs of transgenic production</i>	196
<i>Lower costs of treatment</i>	197
Unmet needs in animal biotechnology	197
Future opportunities for biotechnology in animal healthcare	198
Farm animals	198
<i>Global trends in epidemiology of livestock diseases</i>	199
Companion animals	199
Animal molecular diagnostic markets	199
8. Regulatory issues	201

Introduction	201
Regulatory agencies for veterinary biotechnology in the US	201
FDA regulatory issues in agricultural biotechnology	202
FDA guidelines on use of antibiotics in food-producing animals	203
Food safety evaluation of transgenic animals	205
Food from cloned animals	205
FDA investigation of drug transfer into eggs	207
Animal feed safety	207
Medicated feeds	208
Regulatory issues for production of transgenic proteins	208
Risks of animal biotechnology	209
FDA regulation of bovine products	209
Worldwide biotechnology regulatory and trade issues	210
9. Companies Involved in Animal Biotechnology	211
Introduction	211
Biotechnology at top veterinary pharmaceutical companies	211
Profiles of selected companies	211
Collaborations	332
10. References	337

Tables

Table 1-1: Landmarks in the evolution of animal biotechnology in the 20th century	13
Table 1-2: Expression systems for production of recombinant proteins	18
Table 1-3: Applications of proteomics in livestock industry and veterinary medicine	34
Table 1-4: Selected animal genomics and proteomics databases (DB)	36
Table 2-1: Applications of genomics in livestock industry and veterinary medicine	39
Table 2-2: Recombinant proteins obtained from milk of transgenic animals	55
Table 2-3: Companies involved in the production of transgenic pharmaceuticals	58
Table 2-4: A comparison of gene knockout and transgenic techniques	61
Table 2-5: Examples of transgenic mouse models of non-neoplastic human diseases	62
Table 3-1: Diseases of dairy cattle	71
Table 3-2: Causes of chronic wasting disease in animals	91
Table 4-1: Potential applications of microarrays in animal biotechnology	109
Table 4-2: Biosensor technologies with potential applications in molecular diagnostics	111
Table 4-3: Applications of molecular diagnostics in animals	114
Table 4-4: Viruses that can be detected by molecular diagnostics	119
Table 4-5: Testing for harmful prions in brain tissue from dead cattle	124
Table 4-6: Companies involved in developing molecular diagnostics for TSEs	128
Table 4-7: Pathogenic bacteria in food and targets for molecular diagnostic probes	131
Table 4-8: Companies involved in molecular diagnostics for food-borne infections	132
Table 4-9: Companies developing molecular diagnostics for veterinary medicine	134
Table 5-1: Veterinary biotechnology products	137
Table 5-2: Pharmaceutical versus biotechnology products	138
Table 5-3: Nonantibiotic strategies for control of infections	139
Table 5-4: Experimental DNA vaccines tested in animals	149
Table 5-5: Companies developing biotechnology-based vaccines for animals	158
Table 6-1: Areas for future research applications of animal biotechnologies	180
Table 7-1: Worldwide markets for biotechnology-based products for farm animals: 2011-2021	188
Table 7-2: Worldwide markets for biotechnology-based products for pet animals: 2011-2021	188
Table 7-3: Biotechnology-based markets for animal healthcare according to regions: 2011-2021	189
Table 7-4: Biotechnology markets for farm animals according to therapeutic areas: 2011-2021	191
Table 7-5: Biotechnology markets for pet animals in therapeutic areas: 2011-2021	191
Table 7-6: Worldwide markets for biotechnology-based animal products for humans: 2011-2021	192
Table 9-1: Ranking of top 7 veterinary companies with biotechnology products	211
Table 9-2: Selected collaborations of companies in animal biotechnology	332

Figures

Figure 1-1: Relation of animal biotechnology to other technologies and human health	38
Figure 2-1: Nuclear transfer technology	44
Figure 2-2: Generation of transgenic animals by linker based sperm-mediated gene transfer	52
Figure 2-3: Production of therapeutic proteins in the milk of transgenic animals	54
Figure 7-1: Unmet needs in animal biotechnology	198