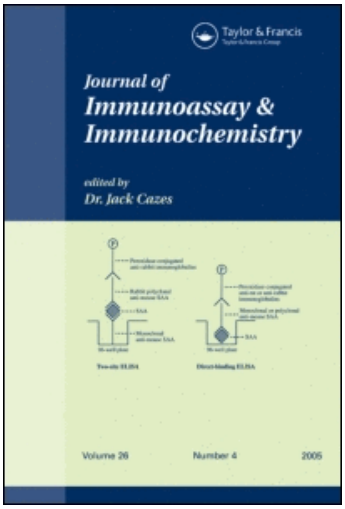

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Animal-Derived Pharmaceutical Proteins

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Animal-Derived Pharmaceutical Proteins

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Abstract: Livestock animals have made a significant contribution to human health and well-being throughout humankind's history. A significant contribution of farm animals to human health are the longstanding use of bovine and porcine for production of insulin (for treatment of diabetes), gelatin (for pharmaceutical and other purposes), as well as horse and sheep antibody against natural venoms, toxins, drugs and microbial peptides. Gelatin being the biggest animal protein consumed in human health, follows with antibodies fragments. The chronic problem of animal-derived therapeutics, especially those of high molecular weight, is the immunogenicity induction in addition to their biosafety. However, the invertebrates and lower vertebrates donate the human being a several crucial emergency saving life small-peptides or their analogs such as Refludan^{R}, Prialt^{R}, Exendin^{R}. Not only, but the farm animals are enormously using as models for novel surgical strategies, testing of biodegradable implants and sources of tissue replacements, such as skin and heart valves. Recently, they are being harnessing as bioreactor for production of biopharmaceutical related products through gene farming with efficiency far greater than any conventional microbial or cell-culture production systems. Only 16 transgenic cows would be covering the worldwide needs from human growth hormone. The transgenic, especially animal, technology would be solving a several biopharmaceutical products disadvantages, such as cost, biosafety, immunogenicity and the availability dimensions.

Keywords: Animals, Anti-serum, Derived-pharmaceuticals, Gelatin, Insulin, Small peptides, Therapeutic proteins, Transgenic-animal

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INTRODUCTION

Edward Jenner's pioneering work on cowpox in the 18th century paved the way for modern vaccination programs against smallpox, as well as other human and animal plagues. Millions of people have benefited from biological products and vaccines directly derived (or their analogs) from animals or produced by the recombinant technologies in microbial and various types of animals-cells lines, and many more will benefit in the future.

By flights of fantasy, one may trace the concept of passive immunization back to 1666 with Lower and King's early transfusion experiments described by Pepys as mending of bad blood by borrowing from a better body."[1] However, Richet and Hericourt[2] probably carried out the first rational approach to specific, artificial as opposed to natural, passive immunization in 1888. Its efficacy was established beyond doubt a year later by von Behring and Kitasato,[3] who showed that the blood of tetanus-immune rabbits contained tetanus-poison destroying properties that could be transferred to, and would protect, normal (non-immune) animals. Ehrlich worked out the quantitative relationship between protection and the amount of antitoxin in the blood.[4] Five years after the initial finding, the process had been extended to passive immunization against snake venoms.[5] These years are vividly described in Hans Zinsser's almost contemporary text, Resistance to Infectious Diseases.[6] In 1895 von Behring established an institute for the production of diphtheria antitoxin.[7]

Roux and Yersin, in 1889, had originally demonstrated diphtheria toxin, demonstrated the efficacy of animal antitoxin in the treatment of children.[7] Marmorek published studies from Pasteur Institute in the same year on passive immunization against scarlet-fever, even though the etiology at that time was uncertain and the claimed efficacy remained controversial for many years.[7] Kempner started research on antitoxin treatment of botulism in 1897. In 1903, the American Medical Association initiated a successful study on the efficacy of prophylactic with animal antitoxin in the prevention of tetanus following developed fireworks injuries. Anti-meningococcus antisera were being developed in Germany by 1907, but proof of efficacy was obscured by the apparent multiple serotypes of the organism.[8–11] Since Behring and Kitasato first described the therapeutic use of animal antibodies, there has been much interest in developing these molecules to attack cancer cells.[7] Hericourt and Richet (1895) used serum from dogs and monkeys that had been immunized with extracts of human tumors to treat patients with sarcomas.[12] Tumor responses were reported, but further studies were curtailed owing to side-effects of repeated injection of animal anti-sera, and this may explained why the single dose of anti-tetanus, for example,

did not induce immune response in comparison to snake antivenom, which induced immune reactions in high envenomated patients.[7,11]

This review will focus some light on the most popular consumed animal-derived pharmaceutical products in human health with the newly emerged technologies such as transgenic animals. The brief survey of therapeutics currently being at market or in clinical trials shows that the majority has been derived from the natural sources, where they have undergone natural selection and, as a result, have enhanced in vivo efficacy and stability. However, combinatorial library, for example, screening now plays an important role in the lead discovery process.

THERAPEUTIC ANIMAL ANTIBODIES

Animal Anti-Serum

The animal-derived therapeutical antibody considering the oldest protein harnessed for passive immunization purposes (see introduction). Although it causes serious side effects in some cases, but it is still in use. By excluding the murine monoclonal antibody, therapeutic animal anti-serum antibody is the second largest (after gelatin) animal-derived pharmaceutical produced and consumed worldwide. There are more than 60 laboratories/countries[13–15] producing these products in different animals (i.e., horse, sheep, rabbit, goat, and rabbit or, recently, the camel (Tables 1 and 2). More than 10 tons of animal-derived therapeutic

Table 1. Animal species using as bioreactor for production or extraction source for therapeutic proteins

Animal name	Species
Bovine	Mammals
Porcine	Mammals
Camel	Mammals
Goat	Mammals
Horse	Mammals
Mouse	Mammals
Rabbit	Mammals
Sheep	Mammals
Snake, lizard	Reptiles
Scorpion	Arthropods
Snails	Mollusca
Sea anemone	Echinodermata

Table 2. Animal therapeutic antibodies (full, $F(ab)_2$ or Fab fragments) using for passive immunization

Antibody origin	Antibody	Disease specificity
Horse	Tetanus anti-toxin	Specific polyclonal antibodies raised against toxin of *Clostridium tetani*
Horse	Diphtheria anti-toxin	Specific polyclonal antibodies raised against toxin of *Clostridium diphtheari*
Horse	Gas gangrene anti-toxin	Specific polyclonal antibodies raised against α-toxin of *Clostridium novyi*, *C.perfringens* and *C.septicum*
Horse	Botulism anti-toxin	Specific polyclonal antibodies raised against toxins type A, b or E *Clostridium botulinum*
Bovine	Anti-colitis antibody	Polyclonal antibody raised against *Clostridium dificile* colitis
Horse	Tularensis anti-toxin	Polyclonal antibodies raised against *Francisella tularensis* toxin
Horse	Endotoxin antibodies	Polyclonal antibodies raised against Gram-negative bacterial lipopolysaccharide
Horse, Rabbit	Pneumonia antibodies	Specific antibodies raised against *Streptococcus pneumoniae* capsular polysaccharide
Horse	Meningitis antibodies	Polyclonal antibody raised against capsular polysaccharide of *Haemophilus influenzae* type b
Horse	Meningitis antibodies	Polyclonal antibody raised against capsular polysaccharide of *Meningococcus meningitis*
Horse	Erysipelas antibodies	Polyclonal antibodies raised against Group A Streptococcus
Horse	Anthrax antibodies	Polyclonal antibodies raised against anthrax toxin
Horse	Rabies antibodies	Specific neutralizing antibody raised against rabies virus
Horse	Measles antibodies	Specific neutralizing antibody raised against measles virus
Horse	Chickenpox antibodies	Polyclonal antibody raised against chickenpox virus vaccine
Sheep, Horse	Snakes antivenom antibodies	Mono- and polyvalent antibodies fragment raised against venom of single or multiple snakes
Horse, Camel	Scorpion antivenom antibodies	Mono- and polyvalent antibodies fragment raised against venom of single or multiple scorpion
Horse	H5N1 virus	Polyclonal antibody raised against H5N1 viral molecules

(*Continued*)

Table 2. Continued

Antibody origin	Antibody	Disease specificity
Horse	Jellyfish antivenom	Polyclonal antibodies raised against venom of box jellyfish, Australia
Horse	Stonefish antivenom	Polyclonal antibodies antivenom raised against *Stinefish* venom, Australia
Horse	Spider antivenom antibodies	Polyclonal antibodies raised against *Lonomia oblique* caterpillar venom, Brazil.
Horse	Tick antivenom	Polyclonal antibody raised against tick venom "*Paralysis tick*", Australia.
Rabbit	Anti-thymocytes antibody	Specific antibody raised against human thymocytes, to used as immunosuppressive agent
Rabbit	Anti-lymphocytes antibody	Specific antibody raised against human lymphocytes, to used as immunosuppressive agent
Mouse	Anti-CD3 antibody	Murine monoclonal antibody raised against human CD3 for usuing in kidney transplantation (Table-)
Sheep	Anti-drug antibodies	Polyclonal specific antibody fragment prepared against some toxic drugs
Bovine colostrums	Anti-parasite	Colostrum polyclonal antibody used against *Cryptosporidium parvum* parasite

Table data was extracted from [14–18, 65–69].

antibodies in different formats (Fab, $F(ab)_2$ or the full immunoglobulin) are produce annually against animal bacterial toxins, viruses and drugs. Regardless, the risk which could be caused plays a vital role in saving the life of enormous numbers of patients worldwide.[14–19]

In the last few years, many proteins have been developed that are consumed at relatively high dosages, sometimes 1000 times higher than some of the earlier biopharmaceuticals. This is especially true of murine or chimeric monoclonal antibodies (Tables 3 and 4) where, in some cases, the demand is for multiple hundreds of kilograms per year, leading to a rapid expansion in mammalian cell capacity for pharmaceutical companies and contract manufacturers. By 2008, approx. 2.2 million liters of mammalian cell capacity is expected worldwide, more than doubling that available in 2002. Of the 957 kg of proteins manufactured in 2002, products such as cytokines, hormones, and enzymes only constituted 40 kg of the total; the remainder consisted of mAbs and fusion proteins. It is predicted that the requirement for protein-based drugs will grow from 1318 kg/yr in 2003 to 8112 kg/yr in 2008.[20]

Table 3. Approved Murine monoclonal (full or Chimeric) antibodies

Product Name	Target	Indication	Approved date	Origin
Orthoclone OKT3 "muromonab"	CD3	Transplantation rejection	1986	Mouse
ReoPo "abciximab"	GPII/IIIa receptor	Cardiovascular disease	1994	Chimeric
Rituxan "rituximab"	CD20	Non-Hodgkin's lymphoma	1997	Chimeric
Simulect "basiliximab"	IL-2 receptor	Transplantation rejection	1998	Chimeric
Remicade "infliximab"	Tumor necrosis factor	Crohns-rheumatoid arthritis	1998	Chimeric
Zevalin "ibritumomab tituxetan"	CD20 conjugated with Yttrium 90	Non-Hodgkin's lymphoma	2002	Mouse
Bexxar "tositumomab"	CD20 conjugated with Iodine I131	Non-Hodgkin's lymphoma	2003	Mouse
Erbitux "cetuximab"	Epidermal growth factor receptor	Colorectal cancer	2004	Chimeric
CEA-can "arcitumomab"	CEA	Radiotherapy and imaging	1996	Mouse
Myoscint "imciromab"	Myosin	Radiotherapy and imaging	1996	Mouse
NeutroSpec "fanolesomab"	CD15	Radiotherapy and imaging	2004	Mouse
Oncoscint "satumomab"	Human tissue antigen GP72	Radiotherapy and imaging	1992	Mouse
Prostascint "capromab"	PSMA	Radiotherapy and imaging	1996	Mouse
Verluma "nofetumomab"	GP40 KDa	Radiotherapy and imaging	1996	Mouse

Data source is the food and drug administration homepage (http://www.fda.gov/cder/, http://www.emea.europa.EPARs.eu/). All are full mouse monoclonal antibody or chimerized with human antibody caste of nearly $\geq$50 of the molecular weight.

Anti-Serum Side Effects

The infusion of animal serum–derived pharmaceuticals can produce severe adverse reactions, ranging from a simple rash to death. Serum reactions may either develop acutely during the infusion, such as in anaphylaxis or anaphylactoid reactions, or they may be delayed for several days, as in the case of serum sickness. Serum sickness is a clinical

Table 4. Approved or in clinical trials monoclonal antibodies and their developmental stage of production in transgenic animal

Product name	Product kind	Indication	Development stage of cell culture product	Development stage of transgenic product	Partner
5G1.1	mAb	Rheumatoid Arthritis, Nephritis	Phase II	Preclinical, transgenic goats in evaluation	Alexion Pharmaceutical
ABX-EGF	mAb	Undisclosed	Phase II	Preclinical, transgenic mouse in evaluation	Abgenix-Amgen
ABX-IL8	mAb	Organ transplant rejection, autoimmune disorders	Clinical trials discontinued by Abgenix	Preclinical, Founder	Abgenix Inc.
Antegren^{R}	Humanized mAb	Neurological disorder	Phase II and III	Preclinical, Founder	Elan pharmaceutical
CTLA4Ig	Immunoglobulin fusion protein	Undisclosed	Phase II Complete	Preclinical, Founder	Bristol-Myers Squibb
D2E7 "Humira^{R}"	mAb	Rheumatoid arthritis	Marketed	Preclinical, Founder	Abbott Laboratories
Humanized antibodies	mAb	Cancer	Phases I, II, and III	Preclinical, transgenic mouse in evaluation	Medarex

Humanized polyclonal antibodies	Polyclonal	Various	Preclinical	Preclinical, transgenic mouse in evaluation	Hematch-Avigenics
huN901	mAb	Small cell lung cancer HIV/AIDS	Phase II	Preclinical, transgenic goats in evaluation	ImmunoGen
PRO542	Immunoglobulin fusion protein (CD4)	Undisclosed	Phase II	Preclinical, transgenic goats in evaluation	Progenics pharmaceuticals
Remicade^{R}	mAb	Crohn's disease, Rheumatoid Arthritis	Marketed	Preclinical, transgenic goats in evaluation	Centocor
Xenomouse^{R} "fully human antibodies"	mAb	various	various	Preclinical, transgenic mouse in evaluation	Abgenix

Table adapted from the GTC Biotherapeutics company web. The list is not complete.

syndrome that involves fever, diffuse rash, intense urticaria, arthralgia, hematuria, and constitutional symptoms that persist for several days. A reterospective series of reports that the incidence rates caused by horse anti-serum is more (23–56%) than those induced by ovine anti-serum (1–8%). However, there is a controversy in this issue, but it seems dependent on several factors such as; anti-serum origin, anti-serum purity, downstream methodology, and the volume used for infusion.[21–26]

ANIMAL INSULIN

Historical View Insulin

A natural hormone is made by the pancreas that controls the level of the glucose in the blood. Insulin permits cells to use glucose for energy. Langerhans identified the islets in the 1860s but did not understand their function, nor did von Mering and Minkowski, who demonstrated in 1889 that animal pancreastectomy produced diabetes. Years later, the investigators used acidic ethanol to extract from the animals pancreas tissue an islet cell factor that had potent hypoglycemic activity. The factor was named insulin, and it was quickly learned that bovine and porcine islets contained insulin that was active in humans. Within a year, animal insulin was in widespread use for the treatment of diabetes and proved to be lifesaving; it received Food and Drug Administration (FDA) approval in 1939 (Table 5). Having large quantities of bovine or porcine insulin leads it to be the first protein proved to have hormonal action, the first protein crystallized,[26] the first protein sequenced,[27] the first protein synthesized by chemical techniques,[28] the first protein shown to be synthesized as a larger precursor molecule,[29] and the first protein prepared for commercial use by recombinant DNA technology.[30]

Insulin-Structure Comparison

Insulin is a polypeptide consisting of two chains, A and B, linked by 2 interchain disulfide bridges that connect A-Cys7 to B-Cys7 and A-Cys20 to B-Cys19. A third disulfide bridge connects residues Cys6 and Cys11 of the A chain. The location of these three disulfide bridges is conserved in all primates, and the A and B chains have 21 and 30 amino acids, respectively, in most species. Substitutions occur at many positions within either chain without affecting bioactivity and are particularly common in positions 8, 9, and 10 of the A chain and 30 of the B chain. However, porcine insulin differs from human by a single amino acid, an alanine for threonine substitution at B30, while bovine insulin has this modification plus the substitutions of alanine for threonine at

Table 5. Natural, recombinant or analog version of animal derived therapeutical peptides, which approved or in clinical trials

Name	Origin	Size	Target	Activity	Comment
131I-TM601 "chlorotoxin"	Scorpion *Leiurus quinquestriatus*	^{131}I-36aa	Glioma cell receptors	Glioma	Phase II
ACV1 "conpeptide α-conotoxin Vc1.1"	Marine cone snail *Conus victoriae*	16aa	Blocker for neural-type nictonic Ach receptors	Peripheral neuropathic pain	Phase II
Alfimeprase "fibrolase"	Copperhead viper A.contortrix	23KDa	Fibrin	Thromolytic agent and catheter occlusion	Phase II
AM336 "conpeptide ω-conotoxin CVID"	Marine cone snail *Conus catus*	26aa	Calcium channels of N-type	Neuropathic pain	Phase II being better therapeutic than Prialt
Ancrod "Arwin, Viprinex"	Snake "*Agkistrodon rhodostoma*"	Crude	Disintegrin	Anticoagulant	Several country approved, phase III in US
Anti-scorpion venom antibody	Horse	35–150KDa	Venom components	Venom effect neutralization	Worldwide and national approved
Anti-snake venom antibody	Horse	35–150KDa	Venom components	Venom effect neutralization	Worldwide and national approved
Anti-spider venom antibody	Horse	35KDa	Venom components	Venom effect neutralization	Worldwide and national approved
Anti-tick venom antibody	Horse	35KDa	Venom components	Venom effect neutralization	Worldwide and national approved
Anti-toxin antibody	Horse	35KDa	Toxin	Toxin effect neutralization	Worldwide and national approved

(*Continued*)

Table 5. Continued

Name	Origin	Size	Target	Activity	Comment
Aprotinin	Bovine	58aa	Serine inhibitor	Inhibitors for serine protease	Worldwide approved
Bombesin	Frogs genus *Bombina*	14aa	Bombesin receptors on cancer cells	Anti-tumor	Directed killing when conjugated to camptothecin
Calcitonin	Eel	32aa	Bone and bone physiology	Osteoporosis	Approved 2002
Calcitonin "Midcalcin, Cibacalcin, Calcimair"	Salmon	32aa	Bone and bone physiology	Osteoporosis	Approved 2005
Caerulein	Frog *Hyla caerula*	16aa	C-terminus similar to cholecystokinin	Anti-nociceptive, sedation, inhibition of water intake, anticonvulsive	Phase II
Camel-milk	Camel	Crude	Diabetes mellitus	Anti-diabetics	Phase II
Ceruletide	Frog *Litoria citropa*		C-terminus similar to cholecystokinin	Anti-nociceptive, sedation, inhibition of water intake, anticonvulsive	Caerulin analog approved
CGX-1007 "contantokin-G"	*Conus tulipa*	20–30aa	NMDA receptors NR2B subtype	Nociceptive pain and control of seizures in intractable epilepsy	Phase II
CGX-1160 "contulkain-G"	*Conus geographus*	20–30aa	Neurotensin receptor agonist	Postoperation pain	Phase II
Chlorotoxin	Scorpion *Leiurus quinquestriatus*	36aa	Chloride channels on glioma cells	Anti-glioma tumor	^{131}ITM-601 in clinical trials as radiotherapy

Cobrotoxin	Snake *Naja naja naja*	235aa	Opioid and nitric oxide systems	Analgesic	The synthetic analog is not beneficial in adrenomyel-oneuropathy patients
Colostrinin	Ovine	~17KDa	β-amyloid protein	Alzheimer disease	Approved as nutraceutical ReGen-UK, Phase II
Contulakin-G "contulakin"	*Conus geographus*	17aa		Chronic pain	Phase II
Corticoliberin "CRH"	Ovine	41aa	Corticotropin and beta-endorphin	Stress response	Approved
CroFab "polyvalent antibody"	Ovine	~35KDa	Venom components	Neutralization of venom of *C. atrox, C. adamanteus, C. scutulatus, A.piscivorus*	US-FDA approved 2000
Delucemine "NPS 1506"	Spider venom toxin		NMDA blocker	Brain protection from ischaemia	Phase I
Desmoteplase "DSPA α1"	Bat *Desmodus rotundus*	441aa	Plasminogen activiator	Acute ischemic stroke	Phase II
DigFab	Ovine	~35KDa	Digoxin toxicit	Treatment for life-treating digoxin toxicity	US-FDA approved 2001
Dornase "Dnase"	Bovine	260aa	Mucolytic agent	Cystic fibrosis	US-FDA approved 1958

(*Continued*)

Table 5. Continued

Name	Origin	Size	Target	Activity	Comment
Echistatin	Snake "*Echis carinatus*"	49aa	Disintegrin	Anticoagulant	US-FDA 1998 approved of the mimetic "Aggrasta, tirofiban, Eptifibatide"
EchiTab polyvalent antibody	Ovine	~35KDa	*Echis ocellatus* venom	Venom toxicity neutralization	US-FDA approved
Esculentin-1	Frogs *Rana esculenta, R. palustris, R. areolata*	46aa	Gram positive, negative bacteria and *Candidia albicans*	Broad spectrum antimicrobial	Analog (Leu28) esculentin-1 without hemolytic activity
Exanta "Ximelagatran"	Cobra	peptide	Thrombin inhibitors	Artial fibrillation and blood clotting after orthopedic surgery	Approved in EU and seeking approval from US-FDA
Exendin-3 and -4	Lizard *Heloderma suspectus*	39aa	Diabetics	Type-2 diabetes	US approved 2005 the synthetic exenatide
Fibrolase	Snake *Agkistrodon contortrix contortrix*	203aa	Fibrinolytic enzyme	Peripheral arterial occlusions	Alfimeprase a recombinant version in phase II
Gelatin	Bovine and Porcine	~30KDa	Drugs and vaccines	Several pharmaceutical products	Worldwide approved as pharmaceutical product with multi purposes uses
Glucagon	Bovine, Porcine	29aa	Breakdown glycogen, lipid, protein	Prevent hyperglycaemia	Worldwide approved

GsMtx-4	Spider *Oxyuranus microlepidotus*	35aa	Cardiac stretch-activated ion channels	Atrial fibrillation suppression	Therapy of atrial fibrillation
Heparin "glycos aminoglycan"	Bovine, Porcine	3–40KDa	Thrombin III	Anticoagulant	Worldwide approved
Hirudin "Refludan, Revasc"	Medicinal leech *Hirudo medicinalis*	65aa	Thrombin	Heparin-induced thrombocytopenia	Approved 1998 Lepirudin, hirugen, hiruloh, bivalirudin and argatroban.
Insulin	Bovine	51aa	Diabetics	Diabetes mellitus	US-FDA Approved 1939
Insulinotropic peptide "FSIH"	Frog *Agalychnis litodryas*	Non	Diabetics	Type-2 diabetes	Phase III
Integrilin "barbourin, Eptifibatide"	Snake "*S.miliarous barbouri*"	73aa	Disintegrin/fibrinogen receptor antagonist	Anticoagulant	US 1998 approved
IsCT	Scorpion *Opisthacanthus madagascriensis*	13aa	Gram positive and negative bacteria	Anti-bacterial	IsCT (K^7, P^8, K^{11}) analog has higher potency
Iseganan HCl	Porcine leukocytes	12aa	Microbial infection	prevention of ventilator-associated pneumonia	Phase II/III
Lactoferrin	Bovine, Camel, Human	~75KDa	Iron content and/or its peptides	Antiviral, antibacterial, antifungal	As nutraceutical, phase III
L-Asparaginase	Porcine	120KDa	Leukemia cells markers	Cancer treatment, especially childhood leukemia	US-FDA approved 1994
Lypressin (Vasopressin analoge)	Porcine	9aa	Work on multiorgans	Regulate the body's retention of water	Old approved "Novartis"

(*Continued*)

Table 5. Continued

Name	Origin	Size	Target	Activity	Comment
Lysozyme	Chicken eggs	~11.5KDa	Lysing agent	Anti-microbial infection of mouth and throat	Egypt approved Larypro^{R}
MBI-AN594	Bovine	12aa	Acne	Anti-microbial and inflammation	Phase IIb
Nonapeptide "SQ20, 881 or teprotide"	Snake *Bothrops jararaca jararacussa*	9aa	Angiotensin-converting enzyme (ACE) inhibitors	Hypertension, congestive heart failure, diabetic nephropathy and scleroderma	Approved the mimetic drugs "Captopril, Enalapril and Lisinopril"
Omiganan (MBI-226)	Bovine	12aa	Cytoplasmic membrane	Topical Antimicrobial	Phase III
OSK1(α-KTx3.7)	Scorpion *Orthochirus scrobiculosus*	38aa	Lymphocyte Kv1.3 channels	Immunosuppressant	OSK1-$K^{16}D^{20}$ with high affinity and specificity for Kv1.3
Pancreatin	Bovine, Porcine pancreas	Cocktail, variable	Food materials	Digestive aids	Approve worldwide
Pilosulins	Ant *Myrmecia pilosula*	27–56aa	Bacteria and fungus	Broad spectrum antimicrobial	Pilosulin-1 analog has increased and reduced hemolytic activity
Prialt "Ziconotide" MVIIA "w-conotoxin"	Marine cone snail *Conus magus*	25aa	Calcium channels	Severe chronic pain	US-FDA 2004 approved

Proteases including "papain, collagenase, trypsin"	Bovine, Porcine	Cocktail, variable	Debriding agents	Wounds cleansing	Worldwide approval
ShK	Sea anemone *Stichodactyla helianthus*	35aa	Lymphocyte Kv1.3 channels	Immunosuppressant	ShK(L5) analog with higher selectivity
Superoxide dismutase	Bovine	31 KDa	Inflammatory agents	Oxygen toxicity, anti-inflammatory agent	Approved worldwide
TM601 "chlorotoxin"	Scorpion *Leiurus quinquestriatus*	36aa	Glioma cell receptors	Glioma	FDA granted it as orphan drug for patients of high-grade and malignant glioma
ViperTAb	Ovine	~35KDa	Venom components	Treatment snakebites of *Vipera berus*	Approved by Swedish Orphan international
Vitrase/Wydase/ Amphadase "hyaluronidase"	Bovine-Ovine	58.17KDa	As adjuvant to increase absorption dispersion of the injected drugs	Clearance of vitreous hemorrhage, spreading agent	Approved 2004
Xen2174 "c-contoxin cMrIA"	*Conus marmoreus*	20–30aa	Norepinefrine transporter (NET)	Nociceptive and neuropathic pain	Phase I

The list is not complete. The table data was extracted from [70–81]

Table 6. Variations in the insulin structure of mammalian species

	Differences from human insulin amino acid sequences	
Species	A-chain, position 8 9 10	B-chain, position 30
Human	Thr-Ser-lle	Thr
Porcine, Dog	Thr-Ser-lle	Ala
Rabbit	Thr-Ser-lle	Ser
Bovine, Goat	Ala-Ser-Val	Ala
Sheep	Ala-Gly-Val	Ala
Horse	Thr-Gly-lle	Ala
Sei Whale	Ala-Ser-Thr	Ala

A8 and valine for isoleucine at A10. These modifications result in no appreciable change in biological activity and very little antigenic difference (Table 6). Although all patients given heterologous insulin develop low titers of circulating antibodies against the molecule, few develop clinically significant titers. Porcine and bovine insulins were standard therapy for diabetes mellitus until human recombinant insulin was produced, approved and introduced for human use by 1982. However, after 20 years, there is still no evidence that synthetic human insulins have any clinical advantages for patients and they cost the NHS significantly more than animal insulins. A significant minority of people experience adverse reactions when treated with synthetic insulin and these adverse reactions often disappear with a change to natural animal insulin.[30,31]

PHARMACEUTICAL ANIMAL GELATIN

Gelatin is a pure and artificial protein substance obtained from raw materials containing collagen, a natural protein present in the tendons, ligaments, and tissues of mammals. It is produced by boiling the connective tissues, bones, and skins of animals, usually cows and pigs (Table 5). Gelatin contains a total of 18 amino acids, including nine out of the ten essential amino acids. It is particularly rich in the amino acids proline and hydroxyproline. The world market of animal gelatin in 2006 was 315,000 tons. So, the gelatin represents one of the biggest animal pharmaceutical-related proteins produced and consumed worldwide (Fig. 1). Gelatin's industrial applications include medicinal capsules, photographic plate coatings, dying and tanning supplies, due to its ability to form strong, transparent gels and flexible films that are easily handled and digested.

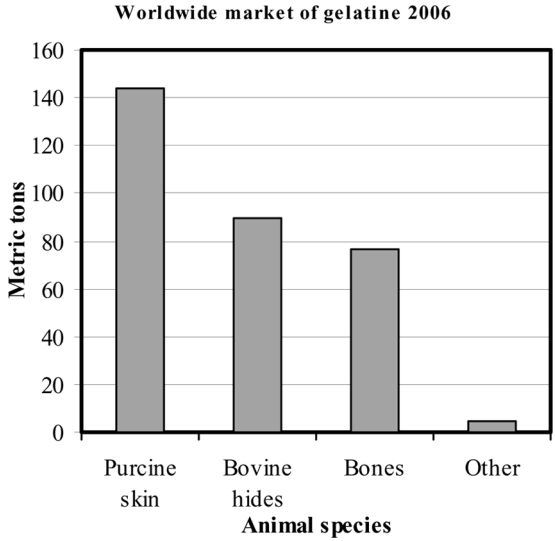

Figure 1. Animal gelatin market during 2006.

Since 1986, when the presence of bovine spongiform encephalopathy (BSE) was reported in Great Britain,[32] there has been much concern about the processing of beef bones for the production of gelatin. In 1989, the United States FDA banned the importation of cattle from the Department of Agriculture's list of BSE-designated countries. However, a 1994 FDA ruling allowed the continued importation of bones and tissues for the production of pharmaceutical grade gelatin. By 1997, however, the FDA held hearings to reconsider its decision. After interviewing gelatin processors, the agency found that while gelatin has not been implicated in the spread of BSE, officials are not convinced that the manufacturing processing is extracting all possible agents that are responsible for the disease. It was generally agreed that beef sources carry more of a risk than those from pork, which bones carry a higher risk than skins, and that alkaline processing is more effective than the acid-extraction method. To avoid the possibility of disease transmission, the recombinant version of human gelatin is under research and development. Several models of expression system were used[33] to improve the expressed yield that still stands at non-industrial levels (5–7 g/L).

ANIMAL PEPTIDES

Initially, several pharmaceutical and biopharmaceutical communities were excited about the market potential (€5.3 billion, 2003) of peptides

as therapeutic agents. The majority of these peptides are discovered and extracts from animals source and specifically from their venoms or toxins. It is historically well known, that the ability of these animals to kill with tiny amounts of powerful venom has inspired both fascination and fear in humans around the world. Serpents were worshipped as deities in many ancient religions in Egypt, Greece, India, and Mesoamerica. In China, too, the snake, in the form of a dragon, is a traditional divinity. In spite of all this bad press, animals' venom and toxin have also a modern medicine uses as a rich source of medicinal compounds.[33]

Animal Venom-Peptides

Venomous creatures are an abundant source of anticoagulants, and thrombolytic agents (Table 5) that include disintegrins, direct thrombin inhibitors, fibrinolytic compounds, and plasminogen activators.[34–36] Integrilin (barbourin, eptifibatide), a cyclic heptapeptide from the venom of the Pygmy rattlesnake (*Sistrurus miliarus barbouri*), is a disintegrin that inhibits platelet aggregation by binding with high affinity to the fibrinogen receptor via a Lys-Gly-Asp recognition sequence. It has been approved in 1998 by the FDA for anticoagulation in patients with acute coronary syndrome and for patients undergoing angioplasty. Other disintegrins from snake venom use the more common Arg-Gly-Asp recognition sequence to interact with their target receptor.[34] Aggrastat® (tirofiban), a mimetic of echistatin, obtained an FDA approval for anticoagulant use in 1998 (Table 5).

The 9-peptide teprotide Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH isolated from snake venoms possesses bradykinin-potentiating activity that is based on the inhibition of acetylcholenesterase (ACE). While the modified C-terminal dipeptide sequence Ala-Pro displayed only weak inhibition of ACE, exchange of the N-terminal amino group by a carboxy group resulted in a more potent ACE inhibitor. Replacement of the carboxy group by a thiol function, which strongly coordinates metal ions (e.g., Zn^{2+}), resulted in captopril, which is an inhibitor of the Zn-dependent metalloprotease ACE, and has been approved as an orally administered drug.[37] The highly potent analogues lisinopril 45 and enalapril 46 have been synthesized by variation of different regions of captopril.[38] The hydroxamate 47 displays extremely low toxicity and an activity for ACE inhibition which is comparable to that of 44.[39] Losartan 48 is a highly active angiotensin II antagonist that was optimized by molecular design. It is the first nonpeptide angiotensin II antagonist, and it is currently used for the treatment of hypertonia.[40]

Recently, anti-diabetics peptides were extracted from the venom of the gila monster *Heloderma suspectus* (Table 5). The extracts demonstrated a cure potential for type-2 diabetes. Exendin-3 and exendin-4 peptides were found to be able to stimulate insulin secretion in

response to increases in glycemia and modulate gastric emptying to slow the entry of ingested sugars into the blood. Exendin-4 has been developed into a drug, Exenatide;[26] FDA approved it for the treatment of type-2 diabetes in 2005 (Table 5). Peptides with insulin-releasing activity have been isolated from the skin secretions of the frog *Agalychnis litodryas* and may serve as templates for a novel class of insulin secretagogues.[40] Surprisingly, GLP (glucagons-like peptide) related peptides, including exendin-4, share structural homology to (α-latrotoxin from the black widow spider and might have potential in the treatment of Alzheimer's disease.[42,43]

Invertebrate Therapeutic-Peptides

Another example for small therapeutic peptide derived from animals [Leu1,Thr2]-63-desulfatohirudin (Lepirudin®) a recombinant hirudin (6.9 kDa), which was first extracted from *Hirudo medicinalis*, consists of 65 amino acids.[44–47] Lepirudin was the first approved recombinant version for the treatment of heparin-induced thrombocytopenia (HIT). Later, a new indication was found in the treatment of unstable angina. Desirudin® differs from Lepirudin only in the first two N-terminal residues (Val1, Val2), and it plays a definite role in thrombosis prophylaxis. Lepirudin directly inhibits the active site pocket and the fibrinogen binding site of free and clot-bound thrombin.[48]

On the other hand, the cone snails are a large genus (500–700 species) of venomous predators. They comprise only a minor fraction of the total biodiversity of molluscs; the overwhelming majority of peptides from molluscan venoms are uncharacterized. Peptides from conus venoms are generally small (10–30 amino acids) and disulfide-rich, often with unusual post-translationally modified amino acids (i.e., α-carboxyglutamate, 6-bromotryptophan, diphenylalanine, etc.).[49] Unusual post-translationally modified amino acids were initially identified in the first group of conotoxins characterized. Most Conus peptides target ligand gated or voltage-gated ion channels, or G-protein-coupled receptors. Conotoxins are widely used for basic neuroscience research; a few have reached human clinical trials, and one (Prialt) is an approved drug for intractable pain. It was approved as a drug for severe pain in 2004 (Table 5).[50–52]

ANIMAL-CELL LINE AND TRANSGENIC-ANIMAL FOR THERAPEUTIC PROTEIN PRODUCTION

Animal-Cell Line

The most commonly and successfully used cell lines (Table 7) for the production of engineered whole antibodies and other therapeutic proteins

Table 7. Animal cell-lines harnessed for production of therapeutic proteins

Cell type	Animal source
Mammalian	
Myeloid	
NS0	Mouse
SP2/0.Ag8	Mouse
63Ag8.653	Mouse
YO	Rat
YB20	Rat
Non-myeloid	
CHO-K1	Hamster
CHO-I.761 h	Hamster
BKH	Hamster
CV-1	Monkey
COS	Monkey
Amphibian	
X. laevis	Frog
Insect	
S. frugiperda	Insect

are the myeloid cell-lines SP2/0,[53], NS0,[54,55] and the non-myeloid line, Chinese Hamster Ovary (CHO).[56] In both transgenic and/or animal-cell lines, the features which are advantageous for large-scale production of therapeutic proteins by these systems are: an efficient means of inserting the expression plasmids into the host cell, means of maintaining the plasmids stably within the cell after transfection, a means of selecting for cell lines in which multiple copies of the expressed genes have integrated into the genome, a strong promoter/enhancer sequence to direct transcription (such as, whey acid protein, β-casein, α- and β-lactoglobulin genes have all been used to date to promote production of various pharmaceutical proteins in the milk of transgenic animals), a means of ensuring approximately equal expression of heavy and light chains of antibodies, a means of correct folding and processing (including the full glycosylation), for CHO cells, a means of induction suspension-adapted rather than attached cell growth, and a means of inducing the cells to grow to high biomass in serum-free medium. Yeast can secrete recombinant proteins that are glycosylated, but they exhibit inadequate or differ glycosylation. Post-translation modification of recombinant proteins produced in fungi appears to be aberrant in many instances as well.[57,58] The conventional production of rare human therapeutic proteins from blood or tissue extracts is an inefficient, expensive, labour and time-consuming process which, in addition, bears the risk of contamination with

Table 8. Pharmaceutical related products derived from transgenic animals of approved or in clinical trials

Products name	Indication	Product development stage	Partner
α-1 Antitrypsin (rhATT)	Hereditary emphysema, cystic fibrosis	Phase III, transgenic ovine	Bayer-PPL ARC
α-fetoprotein (rhAFP)	Myasthenia gravis, Multiple sclerosis, Rheumatic arthritis	Phase II, transgenic goats	Merrimach-GTC
Anti-thrombin III (ATryn^{R})	Emboli, Thromboses	Approved 2006 of transgenic goat milk	GTC
Butyrylcholines-terase (Protexia^{TM})	Biodefense	Preclinical, transgenic goats	Nexia PharmaAthene
C1 inhibitor	Hereditary angioedema	Phase III, transgenic goats	Pharming
Cd137 agonist	Solid tumors	Preclinical, transgenic mouse	MayoClinic-GTC
Erythropoietin	Anemia	Preclinical, transgenic goat	Avigenics
Factor VIII	Hemophilia A	Preclinical, transgenic porcine	ARC-Pharming
Factor XI	Blood coagulation, Hemophilia	Preclinical, transgenic porcine	GTC, PPL, ARC-Pharming
Fibrinogen	Tissue sealant development	Preclinical, transgenic porcine and rabbit	GTC, Pharming
G-CSF	Leukopenia	Preclinical, transgenic mouse and goats	Avigenics
Interferon	Antiviral	Preclinical, transgenic goats	Avigenics
Lactoferrin	Anti-inflammatory, immuno-modula-tory	GRAS filling phase I, transgenic porcine and mouse	Pharming

(*Continued*)

Table 8. Continued

Products name	Indication	Product development stage	Partner
Merozoite surface protein 1	Malaria vaccine	Preclinical, transgenic goat	Progenics-GTC
Rotavirus virus-like particles	Vaccine development	Preclinical	Bioprotein
Recombinant human alpha-glucosidase (rhGAA)	Pompe's disease	Milk transgenic rabbit, Approved (Orphan drug)	Pharming
Spider silk (BiosteelTM)	Material development	Preclinical, transgenic goats	Nexia

The data cited in the table adapted from the different partners web. The list is not complete.

human pathogens. The production of human therapeutic proteins by recombinant bacteria or cell cultures has alleviated these problems and has made several therapeutic proteins available for patients. However, these recombinant systems have several limitations. They are only suitable for 'simple' proteins, the amount of protein produced is limited, and post-translational modifications are often incorrect, leading to immune reactions against the protein. In addition, the technical prerequisites are challenging and production costs are high.

Transgenic Animal

However, using the farm animals for biopharmaceutical production through gene-pharming "production of recombinant human proteins in the mammary gland of transgenic animals" has several advantages.[59] Recently, the European medicines agency approved Atryn^{R}, the recombinant ATIII from the milk of transgenic dairy goats, to enter the market as a fully registered drug (Tables 5 and 8) [www.emea.org]. The enzyme, (α-glucosidase from the milk of transgenic rabbits, has orphan drug registration and has been successfully used for the treatment of Pompe's disease.[60] This is a rare glycogen storage disorder, which is fatal in children under 2 years and, currently, application with recombinant (α-glucosidase is the only way to treat this metabolic defect. Biologically active human lactoferrin has been produced in large amounts in the mammary glands of transgenic cows and will probably be developed as

a biopharmaceutical for prophylaxis and treatment of infectious diseases.[61,62] Guidelines developed by the FDA of the USA require monitoring of the animals' health, validation of the gene construct, characterization of the isolated recombinant protein, as well as performance of the transgenic animals over several generations.[59,63] This has been taken into account when developing 'gene pharming', for example by using only animals from prion disease-free countries (i.e., New Zealand) and keeping the animals in very hygienic conditions.[32,64] Successful drug registration of Atryn will demonstrate the usefulness and solidity of this approach and will accelerate registration of further products from this process, as well as stimulate research and commercial activity in this area (Table 4).

Implementation Cost-Comparison

Mammalian cell processes are complex, and facilities are very expensive, typically \$5–10 million/m3 compared with \$0.5–1.0 for chemical reactors, i.e., \$200–500 million for a facility. It has been estimated that producing one gram of therapeutic protein using traditional cell lines such as CHO cells can cost anywhere from \$300 to \$3,000. In contrast, using a transgenic goat (Table 4) to produce the protein in milk drops the cost to \$20–\$105 per gram, and transgenic hen eggs are even cheaper, working out at around \$0.1–\$0.25 per gram of protein. The initial capital expenditure is also somewhat less intensive using transgenic livestock, with the cost of constructing a new facility based on traditional cell-based techniques hitting \$150 m–\$400 m, compared with the cost of a transgenic goat or cow at \$10,000–\$50,000, or a transgenic chicken coming in at \$1,000 (www.biopharma.com).

CONCLUSION

For our knowledge, this article is the first in this area, which collects the animal-derived pharmaceuticals proteins. There is a huge usability for animal products other than their meat or diary. Today, human health depends on the animal as a source for several biodrugs. The pharmaceutical industry has recognized the venom and toxins as rich sources for therapeutic peptides. Animal isolated venom and toxin peptides are usually small, ranging from 8–70 amino acids, with relatively small scaffold structures, which are highly compact and stabilized either by disulfide bonds or by hydrogen bonds made from unique post-transational-modified amino acids. Very large numbers of peptides have been identified and characterized which enable the rational design of

small molecular weight compounds or peptomimetics. Several of the characterized peptides or their analogs are at market now.

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