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Review Article

CONVERGENCE STRATEGY OF DIGITAL LIVESTOCK SYSTEM AND ANIMAL BIOMODELS FOR HUMAN WELLNESS IN FUTURE: A REVIEW

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ABSTRACT

As human lifespan increase, interest in human health and the digital livestock system is also increasing. Therefore, it is necessary to converge the digital livestock system and animal biomodels. In the fourth industrial revolution, animal biomodels and the digital livestock system as algorithms in agriculture are emerging rapid evolution by converging enovation technologies in fields of bio-healthcare, biomedical research, and life science. Animal biomodels have been used as important foundational tools to transit screening processes and clinical trials for useful substances and potential drugs in human and animal life science. Animal biomodels for studying human and animal diseases have enabled medical innovation and derived numerous outcomes such as vaccines. It is very important to choose appropriate animal biomodels in clinical studies. When selecting experimental animals for human and animal diseases, some parameters should be kept in mind. Convergence of the digital livestock system with animal biomodel can help us greatly solve human and animal health diseases and welfare issues. It enables prevention of human diseases and vaccine development for emerging infectious diseases by applying appropriate animal biomodels, thus contributing to the development of bio-healthcare industry. Animal biomodels are *in vivo* models for determining mechanisms of life phenomena and diseases progression. They can also be used to evaluate the safety, effectiveness, new cosmetic materials, and action mechanisms of functional materials and foods. Animal experiments using animal biomodels must be based on ethical considerations. Animal biomodels can be produced through drugs, diet, surgical procedures, spontaneous mutation, crossbreeding, biotechnology such as transformation and genetic manipulation, and so on. In this paper, preemptive response strategies for the development of livestock and biomedical industry of the future are reviewed through understanding the importance of animal biomodels and the digital livestock system as agriculture algorithms. Animal models for studying mechanisms of diseases in human, livestock, and birds, in ovo technology for poultry, preparation theories, animal bioethics, and practical cases are also explained.

Keywords: Digital livestock system, biomodels, clinical trial, animal bioehtics, agriculture algorithms

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INTRODUCTION

As it is difficult from a bioethics perspective to conduct clinical trials targeting humans in the era in which the average life span is 100 years, animal biomodel s produced to have a similar response to human disease have become preclinical trial tools. Use of animal biomodels in studies on the development of bio materials and new drugs, as well as the investigation of human disease mechanisms and the establishment of core infrastr ucture that leads the biotechnology are accelerating the development of bio-healthcare industry Due to a growing interest in population aging and health promotion, ICT (information and communications technology) companies are looking at the bio-healthcare industry as a new growt h engine (Simons, 2008; Suh *et al.,* 2011; Brubaker and Lauffenburger, 2020). The Use of animal biomodel, whic h is one of agriculture algorithms, as a future animal life industry development strategy in preclinical trials for understanding of life phenomena, prevention, diagnosis and treatment of a disease, evaluation of effectiveness an d safety of functional foods and new cosmetic materials, and also investigation of action mechanism can bring about excellent results (Beauchamp and Frey. 2011; Ande ersen and Winter, 2017). In the digital era that connects big data, cloud computing and AI (artificial intelligence), the Netherlands is solving future food issues using smart farm, especially, the digital livestock system as agricultur e algorithms (Zammit and Park, 2020; Park, 2022). Advanced countries including the U.S. and European countries are solving human disease and welfare issues using animal biomodels with the development of biomedicine and biohealthcare (Barré-Sinoussi and Montagutelli, 2015; Andersen and Winter, 2019). Animal biomodel application technology has begun to incorporat e advanced computing approaches such as next-generation sequencing, genome engineering, big data and machine learning, and studies regarding new methods that can supplement in vitro and in vivo experiments are being carried out (Luo *et al.,* 2016; Labant, 2020). Animal biomodels are excellent research tools for underst anding the mechanism of a disease and overcoming the limitations of human clinical trials. Animals have been used in research since the fourth century B.C.; William Harvey explained the blood circulation system using animals in the 1600s. The NCBI database has more than 550,000 research materials using animal biomodels. Practical strategies to improve the use of animal biomode ls for researching human diseases include the design of a human clinical trial to reproduce conditions tested in animal biomodels. Modeling elements such as age, gender and associated diseases existing in humans also can be useful for improving the quality of translational studies in the result of preclinical trials using animal biomodels (Kurko *et al.,* 2013; Kirkland and Tchkonia, 2015; Khorramizadeh and Saadat, 2020).

When investigating the clinical mechanism of a specific substance, the selection of an appropriate animal biomodel is very important. A reliable excellent result in preclinical trials depends on the selection of an animal biomodel that is consistent with the research objective (Matthews, 2008; Denayer *et al.*, 2014; Brubaker and Lauffenburger, 2020). An animal biomodel is selected according to its genetic and physiological similarity to humans. A preclinical trial using an animal biomodel produces beneficial results, but often a similar response cannot be obtained from a human clinical trial, which can be controversial. The success rate of clinical trials targeting a specific substance depends on the preclinical trials using an animal biomodel selected in the initial test stage, where the effectiveness of a target in humans is reflected accurately (Van Dam and De Deyn. 2011; Barré-Sinoussi and Montagutelli, 2015; Belma *et al.,* 2019). Animal biomodels don't need to reflect the route or treatment of a disease that occurs in humans, but can establish a model for a specific target of preclinical trials (Denayer *et al.,* 2014). The future development of agriculture depends on the convergence of innovation technologies by the combination of digital livestock system and animal biomodels related to human diseases, improved support service, convenience in market approac h and the establishment of the appropriate infrastructure (Carolan, 2020; Zammit and Park, 2020; Park, 2022). Researchers and scholars need to understand the vision of animal life convergence related to human and animal health and welfare, in particular, human diseases, as one of the projects for the development of the future animal life industry. A preemptive move to use animal biomodel application technologies as an agriculture algorithms for the development of the animal life industry in 2050, 30 years in the future, is also necessary (Brubaker and Lauff enburger, 2020; http://www.fao.org/ 3/v8180t/v8180T0a. htm).

The aim of this study was to provide an overview of all meta-analyses on the application of animal biomodels and digital livestock system as the biological algorithm for the development of the future the agriculture. For this purpose, various online databases, including Pubmed, ScienceDirect,and Google Scholar, were searched using the keywords “animal models” + “human disease” + “meta-analysis” in the title, abstract, and keywords. Relevant literature published between 2001 and December 2022 was reviewed. Studies and websites were included if they were clinical trials, included animal models of human diseases, and had accessible full-text articles published in English. The included studies were categorized according to common focuses that emerged. This review included data from 157 studies. Three focuses emerged: animal biomodels as the agriculture algorithms including human disease, livestock production therory of animal biomodels, and animal bioethics.

Animal Biomodels as algorithms in agriculture: The convergence of animal life science, bio-healthcare and biomedicine using an animal biomodel and animal biomodels as the agriculture algorithm will be a new future industry that establishes the human knowledge base and promotes the development of scientific technologies at the same time. In the era of future agriculture convergence that considers the health and welfare of humans and animals together, preclinical trials to investigate the prevention, diagnosis, and treatment of a disease and the effectiveness, safety and action mechanism in the development of a new material such as drugs, functional foods and cosmetic products using animal biomodels for human disease, livestock and birds as animal biomodels and digital livestock system will be important research tools. In particular, animal biomodels such as mice and rats are used to obtain information regarding the prevention, diagnosis and treatment of a disease. Researchers can carry out experiments that would be unrealistic or ethically prohibited to perform on humans by using an animal biomodel in preclinical trials (Ireland *et al.,* 2008; Lieschke and Currie 2007; Ericsson, *et al.,* 2013; Andersen, 2016; Conn, 2017; Andersen and Winter, 2017; Silva, and Emter. 2020; https://www.biom dels.com/;http: //www.mwm-biom odels.com/; https://w w. genome. gov/ geneticsgov/genetics-glossary/Animal-Model). Animal biomodels were used in preclinical trials and research to increase human knowledge regarding life science and finding solutions to biomedical issues. But due to a growing interest in the welfare of animals used and an increased recognition of animal rights, the related animal bioethics issues are drawing more attention (Greek and Menache, 2013). As the algorithms in agriculture, animal biomodels have become a new field of study in universities due to the theoretical and technical advancement of laboratory animals and animal models for human disease, and the study of laboratory animal can be a primary subject or a prerequisite subject. The study of laboratory animals deals with the benefits, use, classification, biological characteristics, nutrition and specifications of laboratory animal, relevant laws, 3R (replacement, reduction, refinement), handling methods, blood and tissue sample collection methods, injection technique, drug injection, euthanasia, disposal and laboratory animal ethics (Park, 2016). However, the curriculum contents of animal biomodels may include clinical theories using animal models for human disease (anti-cancer, hypotension, diabetes, osteoporosis, Alzhei mer's dementia, atopic dermatitis, hair, metabolic disease *in vivo* monitoring, etc.) animal biomodel production theory and actual application cases (biotechnology, drugs, surgery, mutation), in ovo technology for poultry (advanc ed revitalization technology for poultry; vaccine, anti-cancer egg, transformed fluorescent chicken, nutrition and metabolism, immunity, development of climate change responsive and heat stress resistive chicks), animal bioethics and digital livestock system, animal testing method and zootomy (Barré-Sinoussi and Montagutelli, 2015; Park, 2017, 2022; Park and Zammit, 2019; Robinson *et al.,* 2019).

Animal models for human disease as animal biomodels: As animal biomodels, animal models for human disease (animal models produced using biotechnol ogy, transformation and genetic manipulation technology where a human disease is developed artificially) are frequently used in preclinical trials, as these animals are very similar to humans in terms of genome, anatomy and physiology. Also, animal models for human disease are preferred in preclinical trials due to their unlimited supply and ease of manipulation (Hau, 2003; Simmons, 2008; Okechukwu, 2018; Andersen and Winter, 2019; https://w ww.biomodels.com/). Animal models for human disease allow us to understand the mechanism and treatment of a disease, and to overcome the limitations of a preclinical study targeting humans (Hau, 2008; Kurko *et al.*, 2013; Khorramizadeh and Saadat, 2020). Animal biotechnology reached a level of humanization through the transplanting of human cells that played a key function in the recipient animal, enabling research of a response to a disease in the same manner as with humans. Mice with humanized-lungs and immune system – an idealized model for COVID-19 and other respiratory illness was developed through the humanization of animal biomodels, leading to the era of producing human organs (Fig. 1, Shultz et al., 2012; Yoshizato *et al.,* 2012; Ericsson *et al.*, 2013; Ernst 2016; Yong, *et al.*, 2018; Aartsma-Rus and Putten. 2019; Pujhari and Rasgon, 2020).

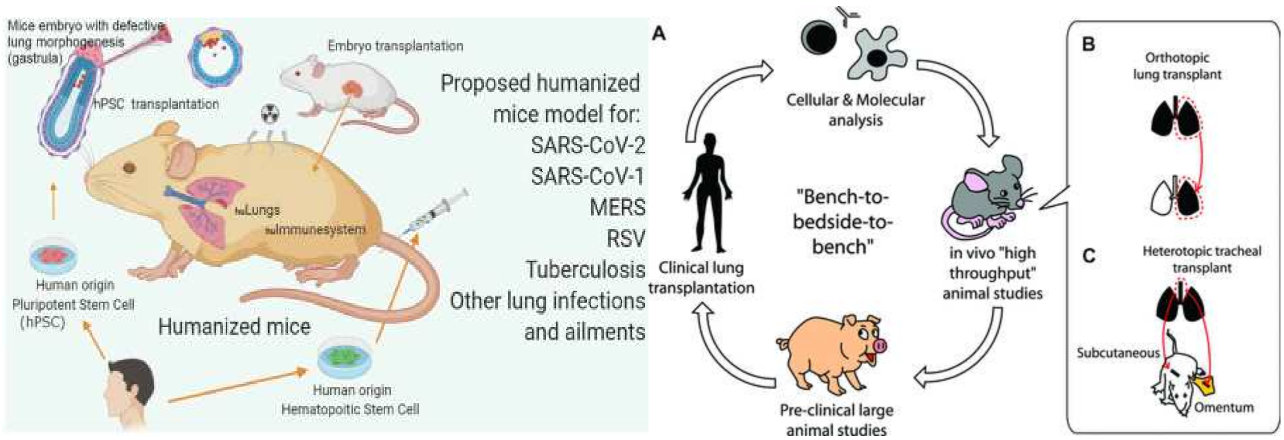

Fig. 1. Humanized mouse, and porcine as animal biomodel for human lung transplantation
(Sato *et al.,* 2009; Pujhari and Rasgon, 2020).

Rodents, particularly rats and mice, are most widely used in preclinical animal trials and studies. Since a mouse, which has a genome that is more than 99% identical to the human genome, have symptoms occurring due to genetic modification that are very similar to those of a human disease, it is becoming an important tool for biological research and new drug development. However, rodents are very different from humans in the area of many human diseases; for a livestock model which imitates human anatomy and physiology more closely, pigs have become animal biomodels that solve a gap between basic research and preclinical trials (Fig. 1, Ireland *et al*., 2008; Reynolds *et al.*, 2009; Bahr and Wolf, 2012; Ericsson *et al.,* 2013; Friedman *et al.,* 2017).

Livestock as animal biomodels: Livestock are essential animal biomodels for important biomedical research. Cattle, sheep, pigs or poultry are excellent physiological animal biomodels for research related to human health and diseases (Fig. 2, Wheeler, 2003; Ireland *et al.,* 2008; Aigner *et al.,* 2010; Sciascia *et al.*, 2016; Silva and Emter. 2020; Gray *et al.,* 2022). Livestock has a larger build than rats and mice, so scientists can collect a larger amount of blood more frequently without a significant change in blood chemistry or the amount of blood, and perform research through larger and more frequent tissue biopsies. A change in hormones, metabolites, competence factors or cell components can be researched from the same animal as time goes by. It has been proven in many studies that human physiology is more closely related to livestock physiology than the physiology of rodents (Hamernik, 2019). The genomic sequence of humans is more similar to the genomic sequence of cattle and pigs than the genomic sequence of rodents. Therefore, cattle and pigs can be better animal biomodels than rodents for the genetic diseases of humans (Fig. 3, Humphray *et al.,* 2007; Tellam *et al.,* 2009; Bahr and Wolf, 2012; Ericsson *et al.,* 2013; Fernandez *et al.*, 2019). Wolf *et al.* (2019) explained the benefits of using genetically modified pig production technology as the source for cells, tissues or organs for xenotransplantation. Metabolic physiology studies targeting livestock in skeletal muscles and brown adipose tissues are related to livestock production and human health; in particular, obesity and metabolic syndrome (Zhao *et al.*, 2019). Livestock models have been used for researching human infertility. In most mammals, anovulation is the main reason for infertility. Pigs, lambs and cattle are more advantageous as models for biomedical studies than rodents, and many studies carried out targeting such livestock have indicated that fertility disorders of women were directly related to anovulation (Abedal-Majed and Cupp, 2019; Beede *et al.,* 2019; Valério *et al.,* 2022). Various neuroimaging technologies including X-ray, magnetic resonance imaging (MRI) and CT scan have been used in livestock. Such technologies were widely used for neuroimaging in human clinical studies, and the use of such technologies for livestock neuroimaging has been developed recently (Ella *et al.,* 2019). Gene therapy that monitors the brain in vivo and uses the virus vector by combining livestock MRI imagingwill offer an interesting opportunity for future clinical and translational studies targeting humans (Hamernik, 2019). The pig model that causes a bean allergy naturally will be an important system for obtainin ing new information regarding genomic, biochemical and physiologic mechanisms related to food allergy and developing a potential strategy that can be useful to humans (Sciascia *et al.,* 2016; Radcliffe *et al.,* 2019). In conclusion, the capability for collecting blood samples and various tissue biopsies frequently from livestock, similar physiological properties between livestock and humans, similar genomic sequence between cattle, pigs and humans and capability to genetically alter livestock by gene targeting, gene editing and transformation are excellent advantages that can be obtained from the use of livestock in comparison to laboratory animals and animal models for human disease when studying a human diseas e. The development of a new technology will enable the use of livestock as additional animal biomodels in future.

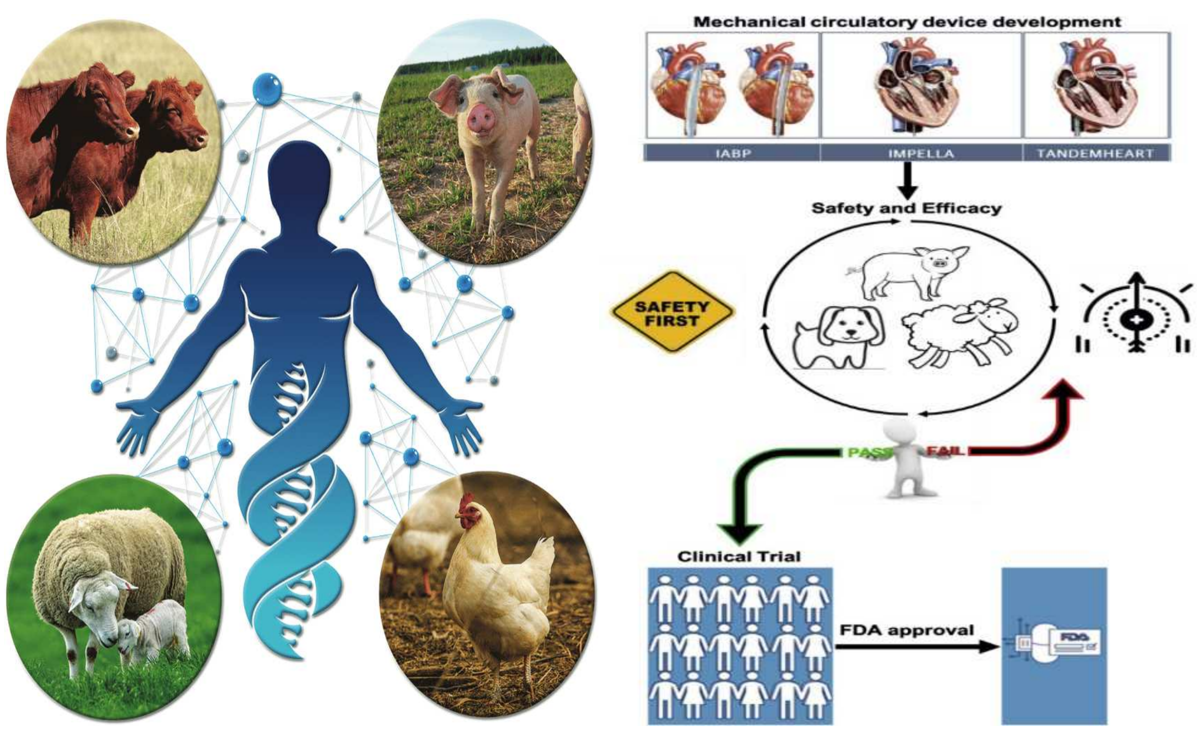

Fig. 2. Schematic depicting the use of cattle, pigs, sheep, and chickens as models for biomedical research (Hamermik, 2019, Silva and Emter. 2020).

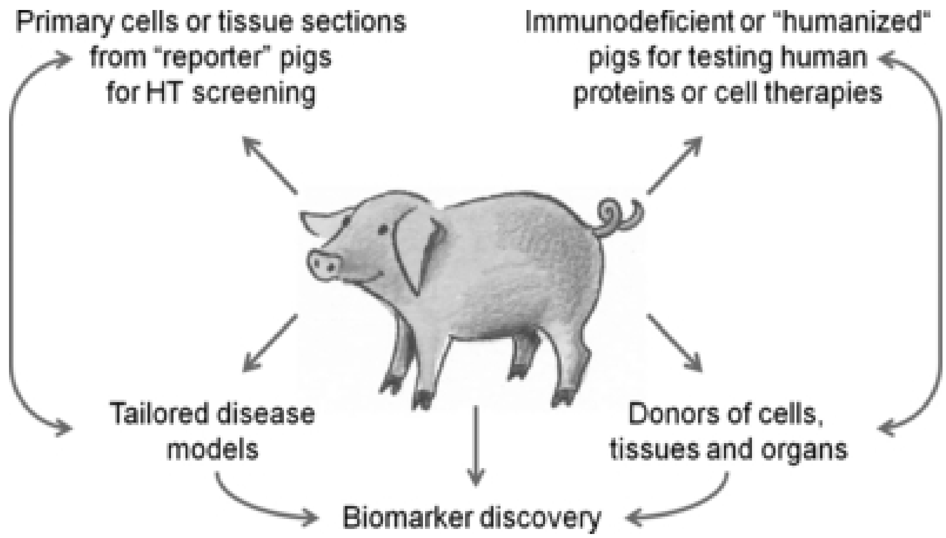

Fig. 3. Potential use of genetically modified pigs in pharmaceutical research (HT: highthroughput) (Bahr and Wolf, 2012; Sciascia *et al.,* 2016).

Birds as animal biomodels and in ovo technology: Animal biotechnology uses livestock as animal biomodels for producing medicine and medical supplies, and various proteins as the long-term source of supply for animal models for human disease, stem cells, animal cloning and xeno-transplantation to humans. Birds offer several advantages in comparison to the mammal model, and have historically been used in the development of the embryology, immunology, oncology, virology and vaccine development fields. Birds can be used in the study of unique mechanisms for human diseases such as ovarian cancer and disorders caused by abnormal lipid metabolism and biosynthesis and the transportation of cholesterol. There is a review regarding birds as animal biomodels for integrating recent advancements and insights into molecular and physiological mechanisms related to transformed birds and the research of pharmaceutical bio-reactor and human diseases (Song and Han, 2011; Seo and Lee, 2016).

In ovo injection technique is a state-of-the-art technology in poultry that has been revitalized in advanced countries to be applied to the development of vaccines, anti-cancer eggs, fluorescent chickens, hatching rate, the nutrition and metabolism of chicks, immunity and the development of climate change response and heat stress resistance by injecting specific substances and genes into eggs. Studies have been performed on in ovo injection to poultry, and injected substances include vaccine, drugs, genes, hormones, prebiotics and nutrients such as amino acids and vitamin C (Kadam *et al.,* 2013; Nazem et al., 2019). In ovo injection technique was used to inject various nutrients into eggs to improve embryo development, the growth ability of poultry and immunity after hatching. Growth of bird embryos and hatched chicks is significantly influenced by the nutrition status of yolk. An in ovo nutrient injection technique can help overcome the imbalance of egg nutrients and limitations of hatching stress, and improve the embryo development and growth ability of birds (Peebles, 2018; El-Sabrout *et al.,* 2019). Mortality related to hatching can be lowered by the in ovo injection of nutrients at the postembryo growth stage (Karadas *et al.*, 2011; Alves *et al*., 2020). The first in ovo extrinsic substance injection technique began with vaccine administration to prevent Marek's disease in the 1980s, and the administering of vaccines through in ovo injection in poultry hatcheries is now widely applied in everyday use. In ovo injection period is the first day as the initial embryo growth stage, 7 days prior to incubation or the 18th day which is the post-embryo growth stage, and advisable injection sites include air cell, egg white (albumin) or amniotic sac (Kadam *et al.,* 2013: Roto *et al.,* 2016). The in ovo injection technique injects a specific substance into the amniotic sac of an embryo on the 18th day after candling using a UV lamp through a pinhole created on the large end of the egg with a 23 gauge needle. Prior to in ovo injection, the injection site is disinfected with 70% alcohol and a specific substance to be injected is heated at 30ºC. Right after the specific substance is injected into the egg, the pinhole area is sealed with sterilized paraffin wax. The in ovo injected egg is placed in the incubator and cultivated until it hatches (Fig. 4). The application technologies regarding previously used materials and in ovo injection using a new substance will be continuously expanded and offer an additional benefit to the poultry industry for the development of future poultry life convergence industries (Kadam *et al.*, 2013; Kucharska-Gaca *et al.,* 2017).

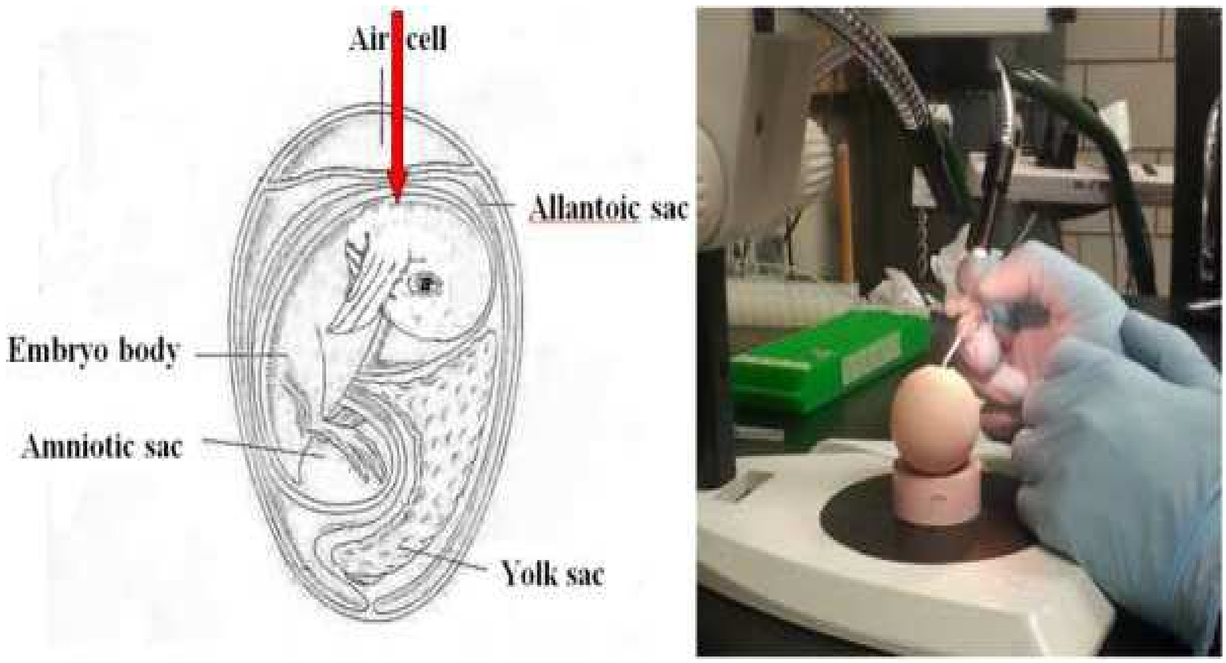

Fig. 4. Site of in ovo injection. Red arrow indicates the injection site of nutrients into the amnion of eggs (Peebles, 2018; El-Sabrout *et al.,* 2019).

Production therory of animal biomodels: Animal biomodels have been used to solve various scientific issues in the field of biomedicine, including the development and evaluation of new vaccines, drugs, therapies, functional foods and new cosmetic materials. Use of animal biomodels is also based on the extensive common features of mammalian biology and the fact that human diseases frequently affect animals. Animal biomo dels evolved from laboratory animal and animalmodels for human disease can be produced through spontaneous mutation, crossbreeding, biotechnology (transformation, genetic manipulation), drugs, diet, surgical procedure, etc. Preclinical trials using animal biomodels have resulted in many groundbreaking developments in life science, basic science and biomedicine research (Belma *et al.,* 2019; Brubaker and Lauffenburger, 2020; Khorramizadeh and Saadat, 2020). Most vaccines that save the lives of millio ns of people and animals every year were successfully developed using animal biomodels. The treatment of Type 1 diabetes using insulin was established through tests on a dog by Banting and McLeod, who won a Nobel Prize in 1921 (Nobelprize.Org-The discovery of insulin. www.nobelprize.org). The cell therapy for tissue regenera tion using a stem cell was designed and tested using animals. Numerous surgical techniques have been designed and improved using various animals before such techniques were applied to humans. There are actually numerous Nobel prize-winning discoveries in which laboratory animal and animal models for human disease played a key role as animal biomodels (Barré-Sinoussi and Montagutelli, 2015).

Animal biomodels of cancer: Cancer has been known as the main cause of death around the world for multiple decades. The diversity of a malignant tumor is influenced by complicated genomic and molecularsignaling pathw ays developed by tumor cells in cooperation with the microenvironment that forms a tumor. Cancer research includes a thorough understanding and knowledge of disease specificity in order to develop an efficient treatment strategy for clinical use in the future (Whiteside, 2008; Wang *et al.,* 2017a). Tumor cells are known to have significant variability in their phenotype, causing pathwa ysneity in a tumor. Clear phenotype is important diversity of genotype in cancer research and clinical treatment and leads to a biological behavior. Tumor cells often include non-tumorigenic and tumorigenic cells with clearphenoty pic expression that are organized hierarchically (Chen and Wang, 2016). Cancer has complicated physiological characteristics, and occurs due to an individual gene mutation and the entire gene network that controls cell cycle. In other words, it has diverse characteristics while passing through multiple stages including tumor suppressor gene mutation, cancer cell proliferation, DNA repair gene inactivation, tumor suppressor gene avoidanc e, normal cell death and transactivation (Fig. 5, Cattley *et al.,* 2004; Li and Wang, 2015, Conn, 2017; https://en.wiki pedia.org/wiki/Carcinogenesis).

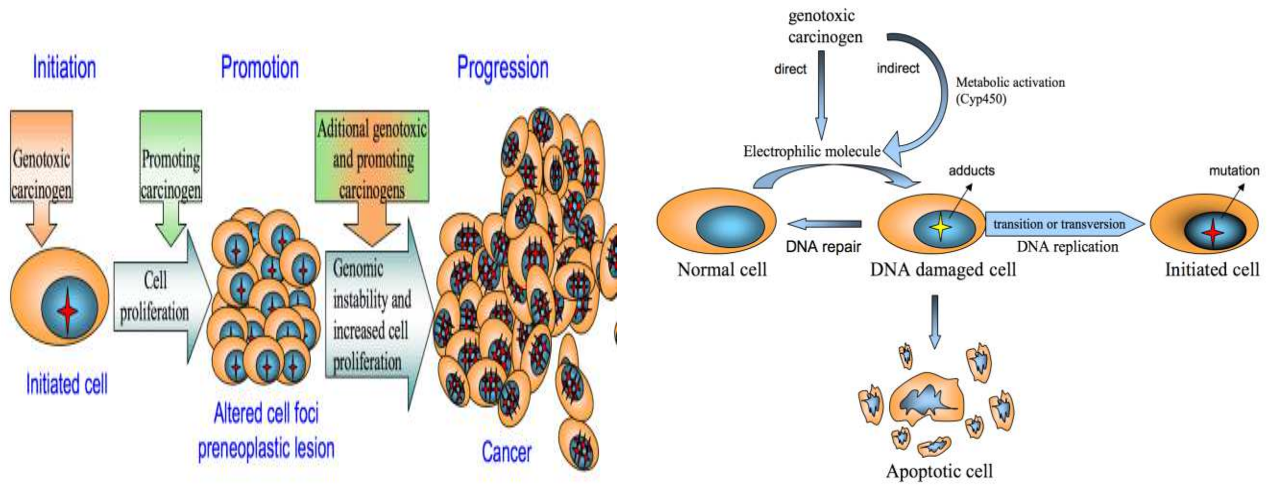

Fig. 5. Mechanism of carcinogenesis (Cattley *et al*., 2004, https://www.researchgate.net/figur e/Mechanism-of-chemical-carcinogenesis-The-three-stages-of-carcinogenesis-initiation_fig2_286340165).

Animal biomodels were first used in medical studies in order to understand basic anatomy and physiolo gy until new therapies for various diseases including cancer were developed (Gengenbacher *et al.,* 2017; Dhumal *et al*., 2019). Syngeneic tumor models are preclinical models for the evaluation of a cancer therapy and are the oldest and most widely used models, and a spontaneous, carcinogenic or transformed cancer cell line that can expand the tumor bearing systems using inbred strains such as C57BL/6, BALB/c and FVB mouse can be separated. A nude mouse with no thymus gland, a genetic mutation that occurs naturally, is a spontaneous animal biomodel. This nude mouse became a turning point in the study of xenografted tumor and enabled the first explanation of a natural killer cell (NK cell) (Fig. 6, Hau, 2008; Ross *et al.*, 2018; Onaciu *et al.*, 2020). Since the nude mouse has no thymus gland and is an immunodefici ent mouse with an incomplete immune system that can be used widely for cancer research, it is particularly useful for the evaluation of an immune checkpoint inhibitor (Olson *et al.,* 2018; Onaciu *et al.*, 2020). A bioengineered mouse produced by cancer transplantation, carcinogen inducement and genetic manipulation of this histocompat ible immunodeficient nude mouse is an animal biomodel for cancer research produced using more advanced technologies for tumor research.

Both fundamental cancer research and the development of an effective antitumor therapy depend on an experiment system that enables the study of the relationship between a malignant cell and an immune cell. A cancer-causing or gene manipulated malignant tumor mouse model developed through the transplanting of a human tumor cell and a carcinogenic agent prepared the foundation for tumor immunology. Development of an immunocomptetent mouse model revolutionized cancer treatment. Continuous advancement of tumor cell research by murine-induced tumor cell line and in vivo fluorescence imaging as preclinical trial models will accelerate the optimization of treatment for patients (Fig. 6, Fig. 7, Wang *et al.,* 2013; Zitvogel *et al.,* 2016; Olson *et al*., 2018).

Animal biomodels of diabetes mellitus: Diabetes occurs due to the interaction of various factors, including genetic and environmental factors. Type 1 diabetes is an autoimmune disease caused by irreversible insulin deficiency due to T cell and macrophage-borne pancreas β cell destruction. Type 2 diabetes is a disease that occurs when the glucose metabolism is not carried out properly due to insulin deficiency or because insulin is not functioning properly. Type 2 diabetes is caused by insulin resistance and relatively insufficient insulin production, and although it is still controversial, insulin resistance is generally considered to be the preceding primary cause (Srinivasan *et al*., 2005; Conn, 2017; Kleinert *et al*., 2017, 2018; https://www.webmd.com/diabetes/type-2-diabetes). Currently, various diabetes animal biomodels are used in preclinical trials, and among those biomodels, NOD mouse and diabetes-prone BB (BioBreeding) rat are most widely used (Srinivasan and Ramarao, 2007; Chatzigeorg iou *et al.*, 2009; Kleinert *et al.*, 2018). Streptozotocin (STZ) is the method most widely used to cause diabetes in mice and rats through pancreatic β-cell disruption. Type 1 and Type 2 animal biomodels can be produced through the STZ intraperitoneal injection, which has toxicity to pancreatic cells (Fig. 8, Wu and Huan, 2008; Damasceno *et al.,* 2014; Wu and Yan, 2015; Furman, 2015; Kleinert *et al.*, 2018). To produce a diabetes animal biomodel rat, STZ was dissolved in a 0.4M citrate buffer solution and STZ 70 mg (0.5 mL per 100 g of weight) per kg (weight of SDS rat) was injected into the abdominal cavity. When 48 hours passed after STZ was injected, blood was collected from the vein on the animal's tail before using the animal in the experiment, and if the blood sugar level was confirmed as over 300 mg/dL, it was considered that Type 2 diabetes inducement was successful, investigating the anti-diabetic mechanism of Kimchi (Damasceno *et al.,* 2014; Kleinert *et al*., 2018).

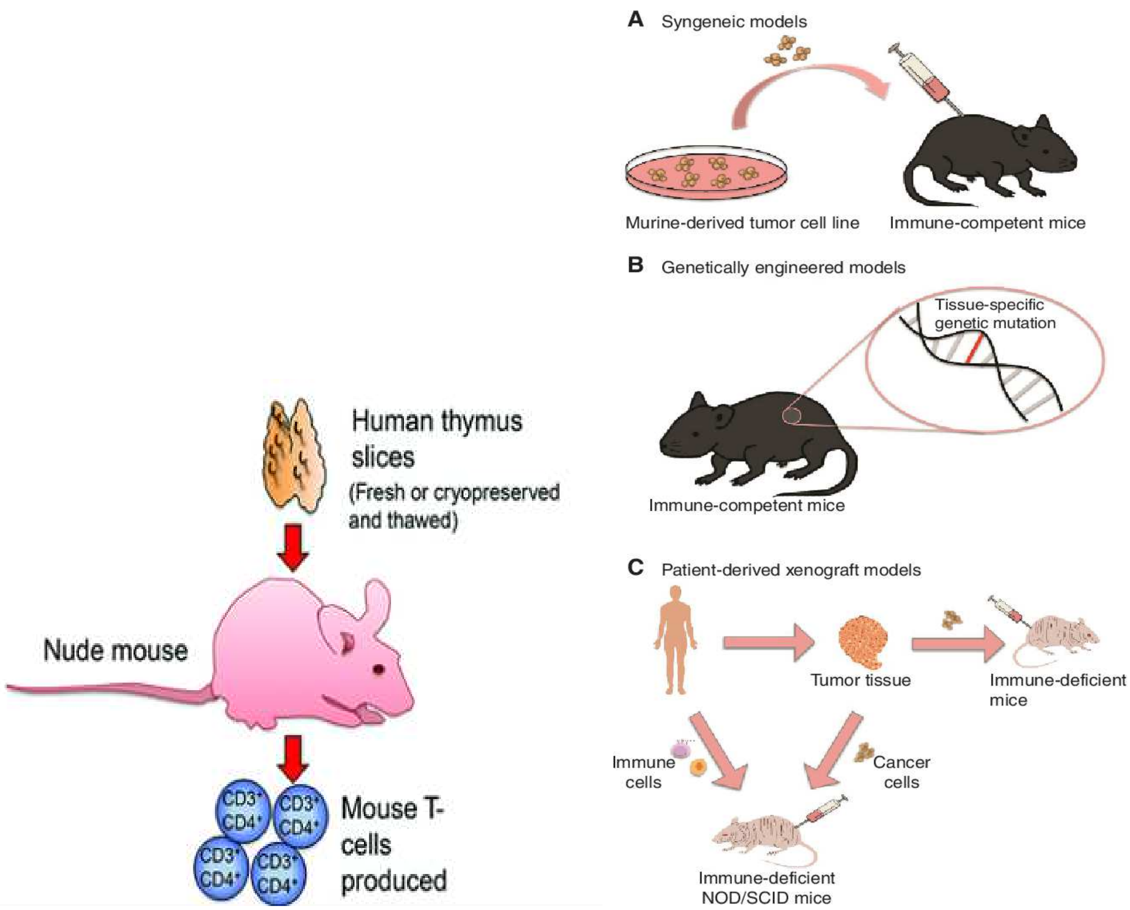

Fig. 6. Nude mouse as human thymus transplant model and preclinical murine models for evaluation of immuno-oncology agents (Olson *et al.*, 2018; Ross *et al.*, 2018).

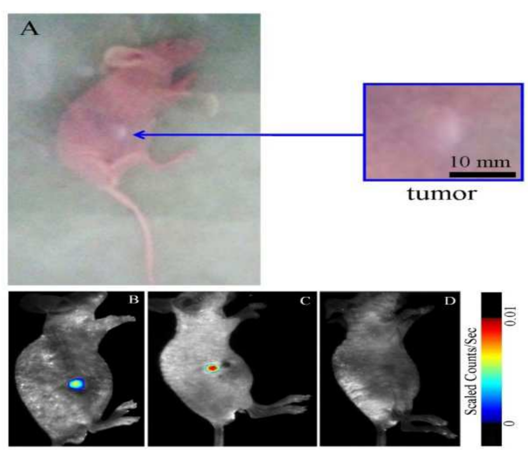

Fig. 7. Representative xenograft tumor mouse (A) and in vivo bioimaging showing luciferase expression in nude BALB/c mice (B) (Wang *et al.*, 2013).

Animal biomodels of hypertension: The hypertension action system is generated as a renin-angiotensin-aldoster one system. Arterial contraction activates such action system and the sympathetic nervous system, and the activated sympathetic nervous system increases renin secretion in the kidney. Renin converts angiotensinogen into angiotensin I and the angiotensin converting enzyme converts angiotensin I into angiotensin II. Angiotensin II strongly constricts the blood vessels, raising blood pressure and increasing the secretion of aldosterone. Eventually, it induces the flow of water and electrolytes, increasing plasma volume and raising blood pressure (Fig. 9, Malkoff, 2005; Desai, 2020).

Various hypotension animal biomodels have been developed through crossbreeding, drugs, and changes in environment such as through stress and diet and bioengineering technologies (Lerman *et al.*, 2005; Leong *et al.,* 2015; JAMA *et al.,* 2022). Spontaneous hypertension is a disease caused by the interaction of various genes and acquired factors. SHR (spontaneously hypertensive rats) and Dahl (Dahl salt-sensitive strain) rats are most widely used as spontaneously hypertensive animal biomodels (Guillaume *et al.*, 2009; Gillis *et al.*, 2015; Doris, 2017; Bakris, 2019). The blood pressure in animal biomodels and rodents can be measured from the blood pressure of their tail (tail-cuff) (Fig. 9, Malkoff, 2005; Conn, 2017; Wang *et al*., 2017b).

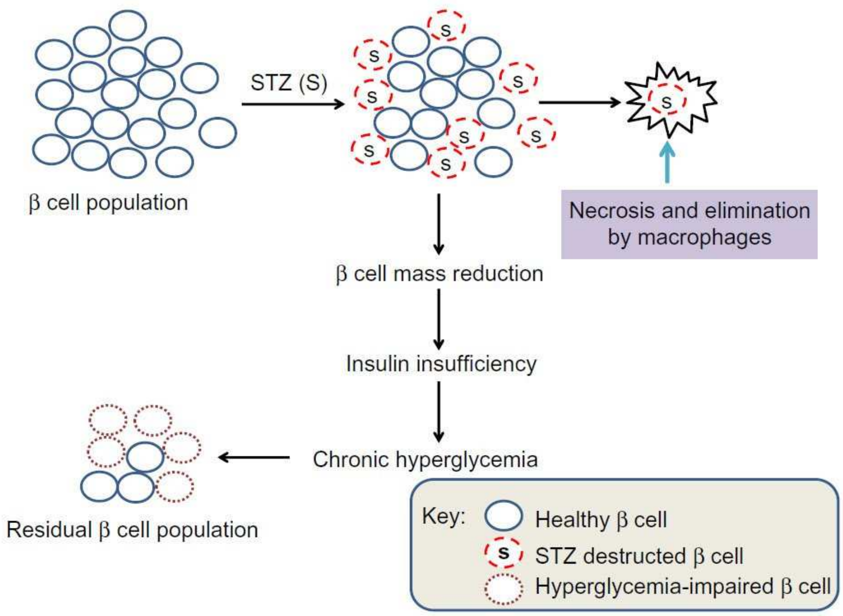

Fig. 8. Scheme showing partial destruction of β cell population by STZ and reduction in β cell mass that induces insulin insufficiency and chronic hyperglycemia (Wu and Yan, 2015).

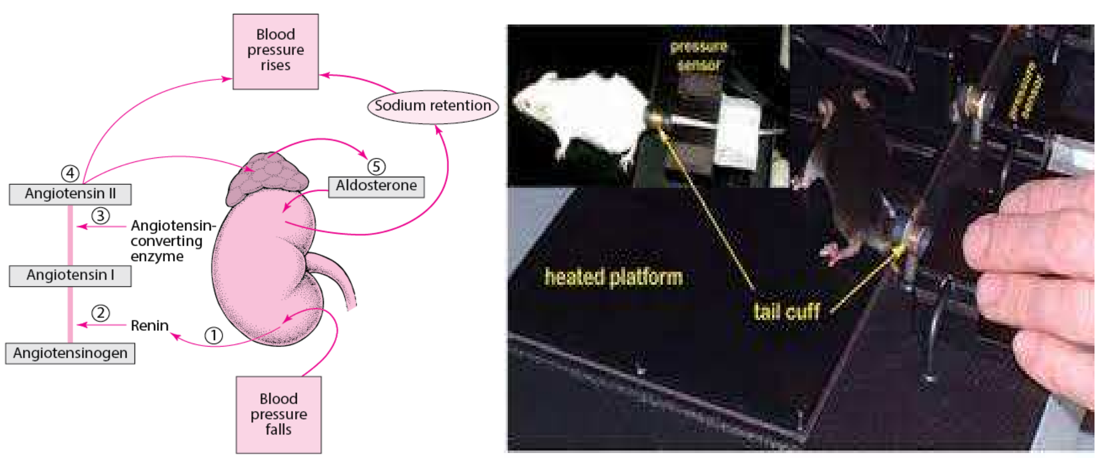

Fig. 9. Regulating blood pressure via the renin-angiotensin-aldosterone system, and tail-cuff methods for measurement of high blood pressure (Wang *et al.*, 2017b).

Animal biomodels of osteoporosis: Osteoporosis is a metabolic bone disease that occurs on a cellular level due to the resorption of the osteoclast that causes uncompensated bone resorption (destruction) even by osteoblast that forms a new bone. Recent reviews of the pathophysiology of osteoporosis indicate that a hole is created in the bone based on an endocrine mechanism caused by a deficiency of estrogen, the female hormone, and vitamin D and hyperparathyroidism (Fig. 10, Boyle *et al.,* 2003; Cohen, 2006; Foger-Samwald *et al.,* 2020). Oestrogen is a hormone that maintains bone density; when women become menopausal, their oestrogen decreases, and osteoporosis may occur (Carr, 2003; Sethupathy, 2016). In order to produce an osteoporosis animal biomodel rat, a 180 g-weighed 7-week-old SDS female rat was anesthetized by injecting 30-40 mg sodium pentobarbital per kg of weight into the abdominal cavity. Ovariectomy was carried out on both sides and the osteoporosis animal biomodel was produced after the reconvalescent stage for a certain period of time; the mechanism of the n-6/n-3 lipid metabolism was thus researched (Fig, 10, Foger-Samwald *et al.,* 2020).

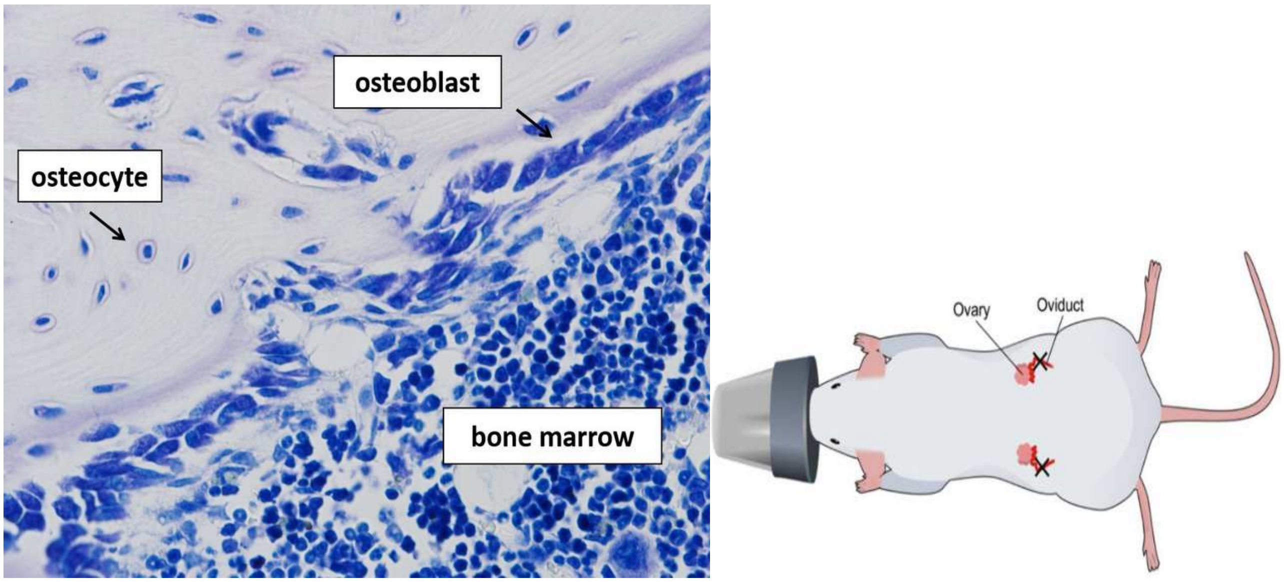

Fig. 10. Histological section of a mouse femur (stain: toluidin blue; original magnifi-cation: 400x) and method for producing osteoporotic animal biomodel by ovariectomy (Foger-Samwald *et al.,* 2020; https://www.pinterest.co.kr/pin/3043448872531/).

Animal biomodels of hair (hair loss, hair regeneration): Humans have approximately 100,000 hair follicles, small tissues that make hair grow, and it is known that if these hair follicles are damaged once and stop functioning, they cannot regenerate again. To this day, 20 hair loss and hair growth mechanisms have been discovered, but there are still many things that need to be investigated in this area. Hair grown from generated hair follicles repeats growth and hair loss through a 4-stage hair growth cycle of anagen, catagen, telogen and exogen (Fig, 11, Botchkarev and Kishimoto, 2003; Fuchs, 2007, Martel *et al.,* 2017; https://shiftkiya.com//mechanism-hair-growth-cycle/). Hair loss is a phenomenon in which hair is unable to grow normally and thus falls out easily and becomes thin; the anagen is reduced and the telogen is extended at the same time. Hair loss is known as an aging-related phenomenon but occurs due to the interaction of a number of factors, including genetic factors, stress, dietary life and eating habits (Müller-Röver *et al.,* 2001; Martel *et al.,* 2017). Methods to prevent hair loss include improvement of blood flow around the hair follicles to supply necessary nutrients to hair roots to make hair grow, and improvement of the immune function using the clustering of lymphocytes around hair follicles where hair loss has occurred to activate the hair follicles (Mater *et al.,* 2003; Park *et al*., 2015). To produce a hair animal biomodel, a 6-week-old male C57BL/6 mouse which was known to be prone to spontaneous alopecia was made to adapt to its feeding environment for a week. Before carrying out a preclinical trial, the hair on the skin of its back was removed completely using an epilator and cream. In other words, a 7-week-old mouse whose hair had reached telogen where the back skin color was pink was anesthetized by mixing Zoletil and Rompun in the ratio of 8:2, diluting the mixture tenfold and injecting it into the abdominal cavity (10 μL/100 g of weight). Hair from its skin was removed primarily using an epilator, the hair was completely removed using a hair removal cream, and then 150 uL of substance was applied twice a day (10AM, 6PM) and the preclinical trial was carried out.

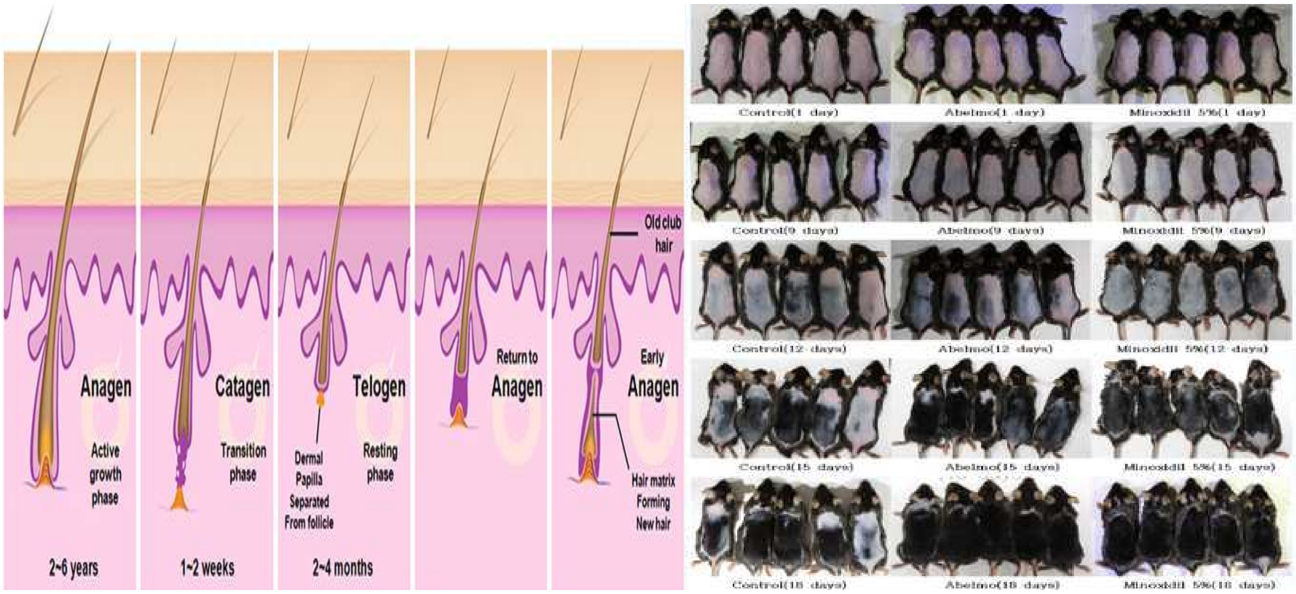

Fig. 11. Mechanism of hair growth cycle and Effect of mixed plant extracts (NPE) on hair regrowth promoting in C57BL/6 mice (Park *et al.*, 2015; https://shiftkiya.com//mechanismhair-growth-cycle/).

As a result, it was discovered that various natur al plant extracts (abelmo) including iris kept hair roots strong and stimulated the growth of hair follicles, promoting hair growth, through the biogenetic regulation of VEGF, KGF and TGF-β1 mRNA (Fig. 11, Park *et al.,* 2015; Martel *et al.,* 2017).

Animal biomodels of metabolic disease (In vivo monitoring): Metabolic diseases are characteristics, conditions or habits that increase the risk of health issues such as cardiovascular diseases, hypotension, hyperlipide mia, obesity, diabetes and stroke (https://www.nhlbi.nih.g v/health-topics/metabolic-syndrome; https://www.nhs.uk/ conditions/ metabolic-syndrome/). To study these, an in vivo monitoring technique that can investigate the metabolic separation mechanism of glycerolipids in an animal biomodel attached with a jugular vein cannula through surgery has been pursued. In vivo monitoring of the metabolic separation of glycerolipids related to the metabolism of cholesterol secreted from the liver, triacylglycerol and phospholipid biosynthesis and secretion is very important in order to investigate the separation mechanism of lipid metabolism in an animal biomodel equipped with a jugular vein cannula. It is possible to study the metabolic separation mechanism of glycerolipids newly synthesized and secreted from the liver clearly by using an in vivo monitoring technique (Fig. 12, Park and Zammit, 2019; Zammit and Park, 2023). The animal biomodel rat attached with a jugular vein cannula had an n-6/n-3 fatty acids ratio in diet in the order of 1.2:1, 8:1 and 19:1, showing a high $^{14}CO_2$ emission rate and phospholipid separation rate, but ^{14}C-albelling neutral fat secretion rate from the liver was low. In other words, it was discovered that as the n-6/n-3 ratio was lowered to 8:1 or below, harmful lipids in the blood was lowered by the mechanism to adjust the metabolic separation capability of neutral fats and phospholipid synthesized and secreted from the liver (Park, 2017; Park and Zammit, 2019). In order to produce an animal biomodel in obesity, a 6-week-old SDS rat went through an environmental adaptation period for 1 week using general diet. Next, the anti-obesity effect of Kimchi and the n-6/n-3 ratio at 4:1 was proven from the obesity animal biomodel rat by freely supplying a high-fat diet including beef tallow (AIN 93 modified high-fat diet, D12492, 40% fat, USA) for 30 days and inducing obesity (Park, *et al.,* 2013; Park and Park, 2014; Park and Zammit, 2019; Zammit and Park, 2023).

Animal biomodels of atopic dermatitis: A recent review emphasized the advancements in our understanding of atopic dermatitis, in particular, molecular mechanism, recent development of global strategies for patient administration, prevention and psychological and social aspects (Sugita and Akdis, 2020). As the most common chronic inflammatory skin disease, atopic dermatitis is the representative disease that lowers the quality of life through intense itching and repeated eczema. Atopic dermatitis causes significant psychological and social effects on patients and their relatives, of various ethnic origins and ages, and accounts for the largest spending on a single health condition worldwide. Atopic dermatitis is related to an increased risk of various complications including food allergy, asthma, allergic rhinitis and mental health disorders. According to the pathological physiology, it is known to accompany a complicated and strong genetic predisposition, epidermis dysfunction and T cell inflammation (Park *et al.,* 2012; Torres *et al.,* 2019; Langan *et al.,* 2020). Atopic dermatitis animal biomodels can be produced by applying DNCB (dinitrochlorobenzen e), DNFB (dinitrofluorobenzene), Oxazolone to Nc/Nga, Flaky tail and BALB/c mice for a preclinical trials regarding atopic dermatitis (Kohara *et al.*, 2001; Martel *et al*., 2017), To produce an atopic dermatitis animal biomo del, all hair was removed from the back of a BALB/c mouse from the bottom of its ear to the top of its tail and the rat was left alone for 24 hours. 150 μL of 1% DNCB solution (acetone:olive oil, 3:1) was applied to the hair removal area, and after 3 days had passed, was applied a second time to induce an immune reaction. From the 7th day after the first application, 150 μL of 0.4% DNCB solution was applied repeatedly 3 times a week and a total of 5 weeks to induce atopic dermatitis. As a result, it was revealed that mixed plants extract including iris extract caused anti-atopic dermatitis (Fig. 13, Park *et al.,* 2012).

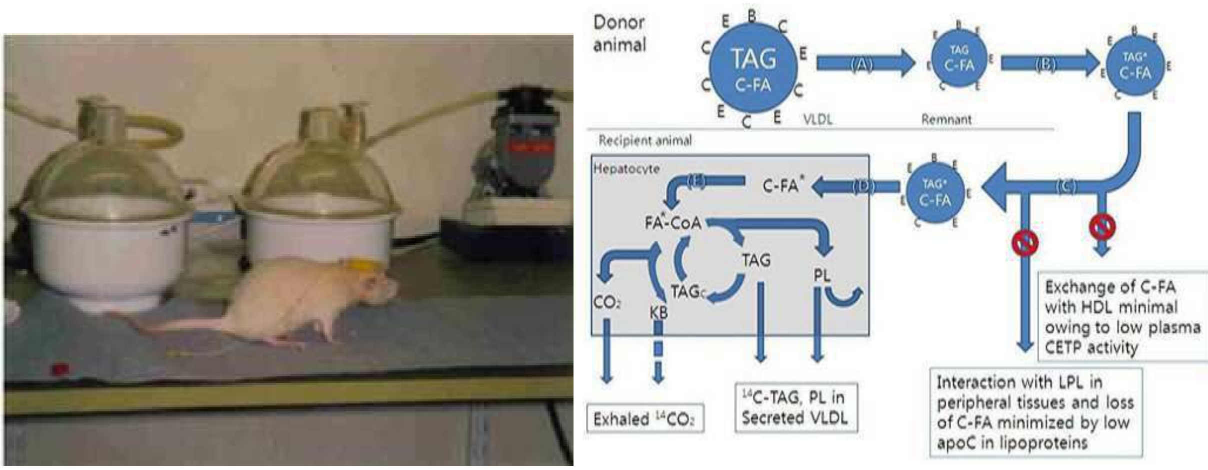

Fig. 12. In vivo monitoring technology in animal biomodel (Zammit and Park, 2023).

Animal biomodels of Alzheimer's disease: Alzheimer's disease (AD) is a degenerative cranial nerve disorder discovered in 1907 by Alois Alzheimer, a German psychi atrist and a neuropathologist. The number of patients with Alzheimer's disease is increasing rapidly throughout the world, and the number of elderly Alzheimer's patients in Korea was 748,945 in 2018 but is expected to increase by 4.4 times in 2060 to 3,323,033 (Park, 2018). AD is a short-term dementia in which an excessive amount of β-amyloid toxic proteins are produced and accumulated in the brain abnormally due to a gene mutation, destroying the brain cells and causing memory loss. The multiple action of β-amyloid accumulation and tau protein hyperp hosphorylation as well as environmental factors have been known to be important causes of AD (Fig. 14, McDonald *et al*., 2010; Querfurth and Laferia, 2010; Serrano-Pozo *et al.,* 2011; Konishi *et al,*., 2015; Conn, 2017; Armand *et al*., 2019). Decreased learning, memory and cognitive ability due to cholinergic brain cell damage appear clearly in Alzheimer’s dementia patients. In order to produce an Alzheimer’s dementia animal biomodel, scopolamine is used. This substance inhibits the cohesion between acetylcholine which is a neurotransmitter isolate ed from the synapse and blocks the delivery of informatio n, lowering learning, memory and cognitive ability (Tanabe *et al.,* 2004). Also, a genetically modified animal model with amyloid precursor protein and tau protein mutation is produced and used (Elder *et al.,* 2010; Carmo *et al.,* 2013).

An Alzheimer’s dementia animal biomodel rat can be produced by mutating a rat with humanized β-amyloid fragments (Tambini and D'Adamio, 2020; Serneels *et al.,* 2020). In order to produce an Alzheimer’s dementia animal biomodel, 1 mg of scopolamine per kg of weight was diluted by physiological saline solution and injected into the abdominal cavity of a SDS rat once 30 minutes prior to the preclinical trial. Next, the Morris water maze test and the passive avoidance test were carried out. As a result, the normal size of the hippocampus in the brain of the Alzheimer’s dementia animal biomodel orally administered egg yolk was maintained, and in particular, fast memory was shown in the Morris water maze test. It was confirmed that it was caused by the action mechanism of phospholipid and lecithin included in egg (Fig. 15. Nunez 2008; Park, 2018).

Animal Bioethics: Animal biomodels have been used as tools for numerous preclinical trials in order to raise human knowledge and find solutions to pending issues in the fields of animal life science, biomedicine and bio-healthcare. But with an increased recognition of moral concepts related to animals and a growing interest in the rights and welfare of animals, relevant animal bioethics issues in animal testing are drawing more attention (Simons, 2008; Irvine *et al.,* 2013; Andersen and Winter, 2017; Park, 2022). Human health is closely related to animal health, animal welfare and excellent environments. This is the principle based on which the livestock and agrifood system supports "one health" at the intersection of humans, animals and environments (FAO, 2018). As a preclinical trials are particularly important with regard to human and animal health and animal welfare, considerati on of experimental design, refined measurements, and improvement measures is essential in high animal bioethics governing animal testing (Marie *et al.*, 2005; Brust *et al.*, 2015; Lewejohann *et al.*, 2020). Bioethics became one of the key areas for ethical and obligatory considerations, mainly in the development of medical studies. However, bioethics are also considered in various fields of study, not only the field of medicine. Considered as a field in philosophy, bioethics is at an important threshold in modern society as knowledge and technologi es are developed continuously and rapidly. The speed of animal biomodel application technology has stirred controversy since a question regarding social significance related to its recent development was raised in a study. For example, moral consideration regarding the meaning of human cloning and the resurrection of an extinct species became the source of intense arguments and contemplation regarding human and animal bioethics between researchers after the successful cloning of Dolly, the somatic cell cloned sheep, in 1996. Various other subjects are also considered in animal bioethics including eugenics, euthanasia, animal behavior welfare, animal right, animal biotechnology, animal testing, livestock and pet rearing (Wolfe, 2010; Simmonds, 2018; Jankoski and Fischer, 2019).

There is no true consensus on how the field of bioethics began. Historically, health professionals have been caring for patients for years, as we can see from the Hippocratic oath in Greece and Charak Samhita of ancient India. But bioethics was only recently established as a field of study, and focuses on the integration of philosophical and analytical approaches on health care. There are many arguments regarding the origin of the term "bioethics". The term was first used by Van Rensselaer Potter, an American biological scientist and a professor of oncology at the McArdle institute for joint cancer research with University of Wisconsin for publication in 1970. To Van Rensselaer Potter, bioethics was a means of explaining the emergence of a philosophical conscience in the field of life science. However, regardless of arguments between scholars regarding the origin of this term, it is widely accepted that this field emerged in the U.S. before spreading worldwide (Susan. and Botzler, 2017; Jankoski and Fischer, 2019).

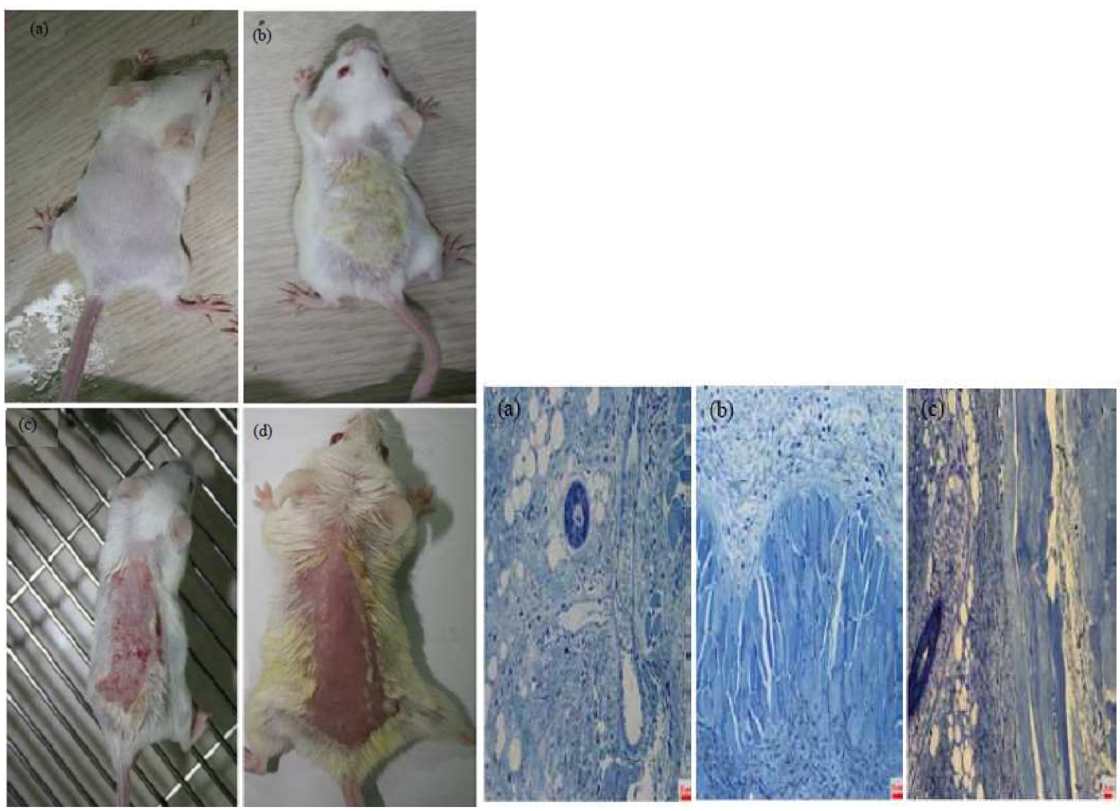

Fig. 13. The theraphic effects of atobeauty cream in DNCB induced atopic dermatitis mice. Left: recovered groups, Right: microscopic comparison of skin tissue (Park *et al.,* 2012).

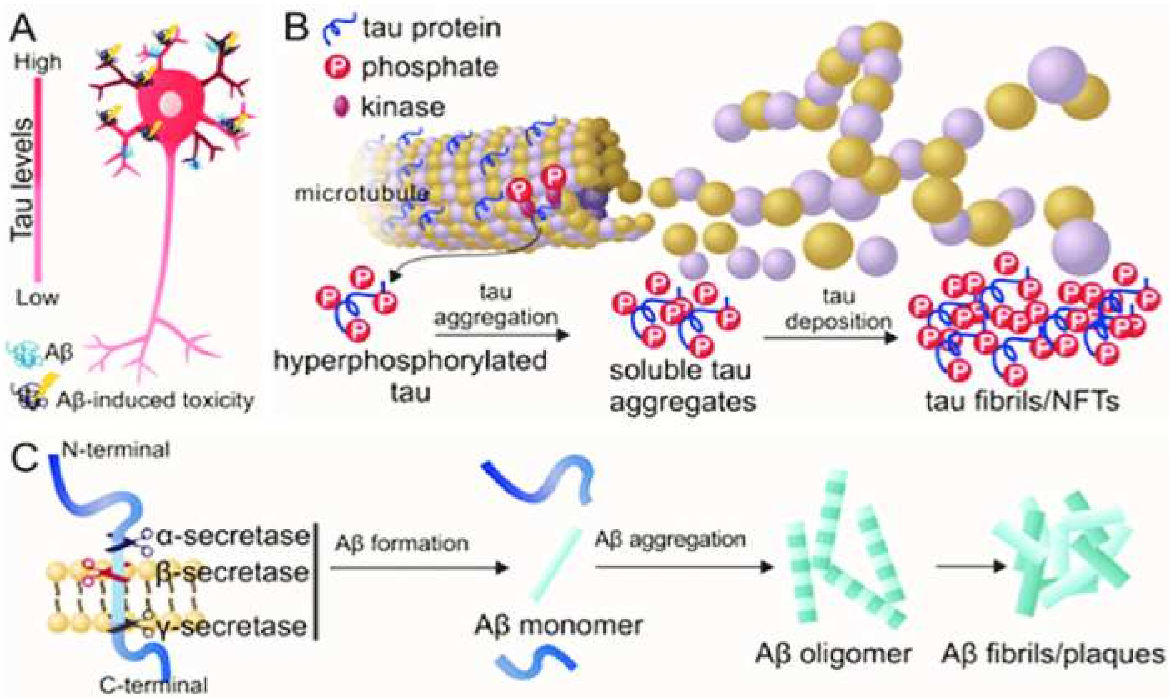

Fig. 14. Hallmarks of AD and pathological features (https://www.researchgate.net/figure/Fig- 3-Hallmarks-of-AD-and-pathological-features-A-Hyperphosphorylated-tau_fig2_327756974).

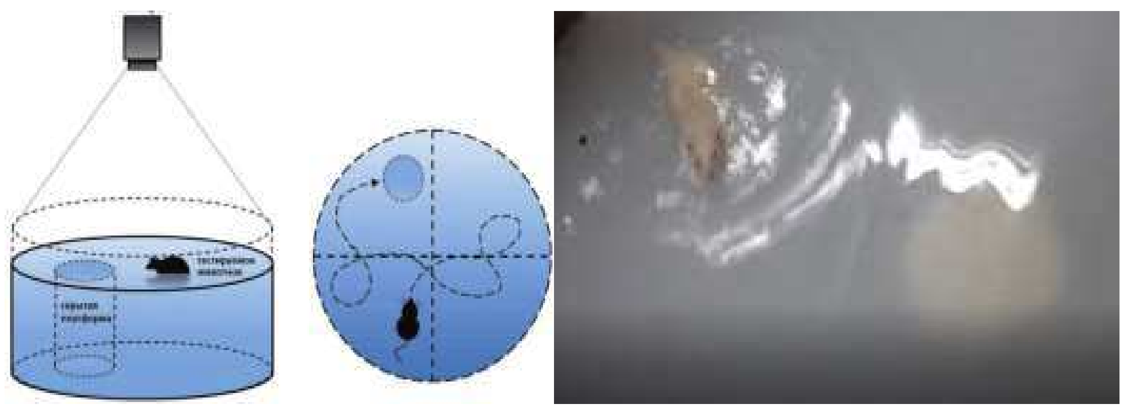

Fig. 15. Scheme of the Morris water maze (Iptyshev *et al.*, 2017; Park, 2018)

Animal bioethics is being continuously developed as the number of institutions of higher education that offer a course in the field of animal life industry or specialization increases. Use of animals, not humans, for the benefit of humans and animals is a controversial subject in various countries around the world. The diversity of interest in the status of animals, individual, cultural and ethical values, specific animal species in ethical morals, tradition and various religions significantly contribute to the complexity to solve related moral (right and wrong) and ethical issues when the use of animals is considered in biomedical research and education. In addition, it is certain that the moral standing of animal species, not humans and simple objects, that can feel pain should be universally accepted, even if it is not possible to define this idea. Preclinical trials and animal bioethics using animal models for human disease as animal biomodels can be discussed together in the science of animal biomodels, which is a new university subject for the future development of the animal life industry. The contents of animal bioethics may include the definition of life, origin of life, crisis of life, morals and ethics, animal stress, animal health and diseases, scientific research (paper creation), livestock and pet ethics, production of animal biomodels and ethical dilemmas that occur in animal testing (Marie *et al.*, 2005; Bracke and Hopster, 2006; Broom, 2007; Fraser, 2008; Wolfe, 2010; Mellor, 2016; Gygax, 2017; Simmonds, 2018; Jankoski and Fischer, 2019). The emergence of animal bioethics in bioethics solves continuous and rigid moral issues related to the lives of animals, not humans, and their effects (Marie *et al*., 2005; Gordan 2012; Park, 2022). Animal bioethics created sophisticated philosophic al discussions regarding the moral status of animals, not humans, and improved our understanding of animal capabilities. Bioethics led to the experience of an epistemological change that could be explained with biomedical ethics while animal bioethics was promoted and developed under a separate category. Animal bioethics will be a great help to improve our understanding of the continuous connection between humans and animals and moral rights, welfare and the role of animals beyond the simple ideas of humans (Beauchamp and Frey 2012; Susan and Botzler, 2017; Jankoski and Fischer, 2019; Park, 2022).

Conclusion: An animal biomodel, which is one of the future agriculture algorithms, is an important biological tool in animal life convergence studies combining general technologies in the digital livestock system, biomedicine and bio-healthcare. This animal biomodel evolved from the laboratory animal, and animal models for human disease had a significant contribution in preclinical trials for investigating the prevention, diagnosis, treatment of a disease and the effectiveness, safety and action mechanism in the development of a new material such as drugs, functional foods and cosmetic products. The capabilities of animal biomodels in predicting clinical results are rated very highly these days, and will be considered as an important parameter in the design of agriculture life convergence research in the future. In ovo technology, an advanced technology for birds, is leading the future of poultry farming in areas such as vaccine development for birds and the development of climate change responsive and heat stress resistive chicks under digital livestock system, etc. Animal biomodel production theory for wellknown human diseases including cancer, diabetes, hypertension, osteoporosis, metabolic disease, atopic dermatitis, hair loss and Alzheimer's dementia, mechanisms and actual application cases and the importance of animal bioethics were comprehensively reviewed. In conclusion, the utilization of knowledge base and application technologies regarding animal biomodels based on the digital livestock system will be a preemptive strategy for future animal life industry, in particular, the development of agriculture life science convergence as a new 6th industrial revolution technolog y.

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