Game changer

Animal models have long been used to explore remedies to human illness. **Professor Peter Ernst** explains how closer collaboration between human and animal medical specialists is improving clinical research

Could you begin by outlining the One Health concept?

One Health is a strategy in biomedical research that examines the impact of animals or wildlife on the health of humans as well as how we affect the wellbeing of animals. This approach to understanding disease brings veterinarians into partnerships with physicians and scientists, reflecting many different specialities or research interests.

How would you explain the link between the health of humans and animals?

The health of humans is often inextricably linked to the health of animals through our close interactions with wildlife, pets and diet. Furthermore, animal health is often affected adversely by the same environmental factors – climate change and the spread of disease-carrying mosquitoes, toxins or microbes – that cause disease in humans. Investigating disease processes and risk factors in animals and comparing and contrasting these mechanisms with the cause of disease in humans can identify common pathways that provide new strategies for disease prevention.

One example is the control of *Escherichia coli* infection transmitted through the ingestion of undercooked, contaminated meat. A solution to this would be to immunise humans. However, it has been shown that effective vaccines in cattle can decrease risk significantly and at much lower cost. Veterinarians bring significant expertise to the partnership, with their understanding of animal behaviours, the pathogenesis of disease in animals and the nature of the interface with humans.

What approach is the Center for Veterinary Sciences and Comparative Medicine taking to combine research in both humans and animals?

At its heart, we hope to create a focal point through which to coordinate access to research, educational or mentoring experiences with approximately 25 academic veterinarians who work at several institutions in the San Diego area.

These institutions collectively represent an enormous research enterprise that includes the university, research institutes, biotech industry, foundations and other organisations. As such, the Center greatly expands the research and educational training opportunities beyond what can be achieved at the University of California, Davis (UC Davis). It also brings this research community in closer contact with scientists and clinicians at UC Davis who have their own outstanding expertise, particularly infectious disease.

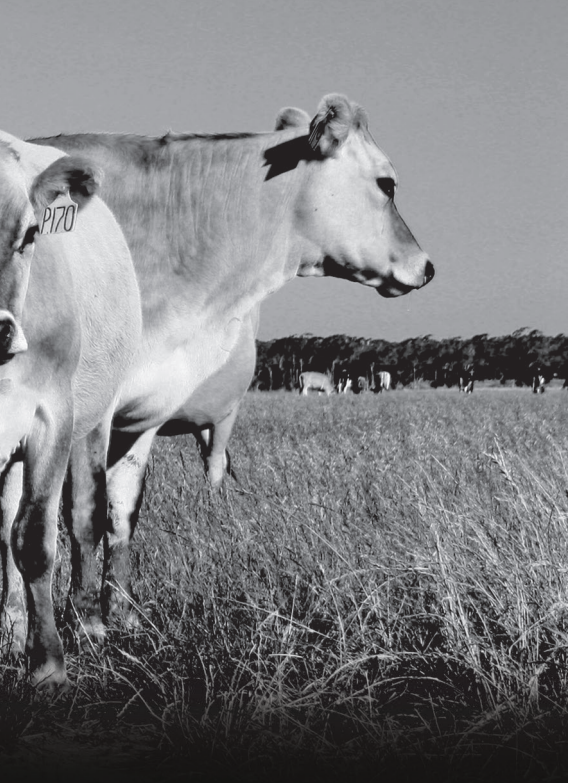
Can you briefly describe your research priorities?

Research activities of the Center members can be divided into basic and clinical/translational research. The clinical facility provides research in outcomes of disease in small animals as well as access to the clinical research activities at UC Davis. Basic research activities are orchestrated primarily through the University of California, San Diego (UCSD) campus and are focused on infectious disease, the mechanisms of protection against infection, chronic inflammation, diseases of the lung, kidney, reproductive and digestive tracts, cancer, as well as neuromuscular and neurodegenerative disease.

These broad areas include studies of food-borne infections; food safety; tropical medicine; infections of mucosal tissues, including the lung, gut and reproductive tract; gastrointestinal inflammation such as

To protect and serve

A novel research partnership between veterinary and clinical scientists in California is helping to train a new generation of veterinarians, ensuring their biomedical knowledge can feed into human and animal health investigations



HUMAN HEALTH IS inextricably linked to the health of the animals, often through their shared surroundings. Both are affected by the same environmental factors and every species contributes to contamination that can affect humans as well as other animals. The symptoms, diagnosis and treatment of certain diseases are remarkably similar across species, which is why comparative research – investigating disease processes in humans and animals – is an essential tool for the modern scientist.

Comparative research demands close working relationships between experts in animal and human health to obtain the best and most clinically reliable results. In bringing experts from two medical disciplines together, Professor Peter Ernst and colleagues in Health Sciences at the University of California, San Diego (UCSD) and the School of Veterinary Medicine at the University of California, Davis (UC Davis) have created an exciting research environment to train the next generation of veterinarians, skilled in comparative pathology and comparative medicine, and ready to work together with human specialists on some of the world's most pressing health challenges.

Building upon a relationship that has existed for more than 20 years, the collaboration has led to the creation of a new Center for Veterinary Sciences and Comparative Medicine, which brings together experts by providing a forum in which to combine their research and initiate new collaborations.

Ernst trained as a veterinarian before embarking upon an academic career which has involved the development of a number of programmes and research projects in comparative immunology. Since 2013, he has been Director of the Center, as well as one of its well-known investigators.

ONE HEALTH, ONE VISION

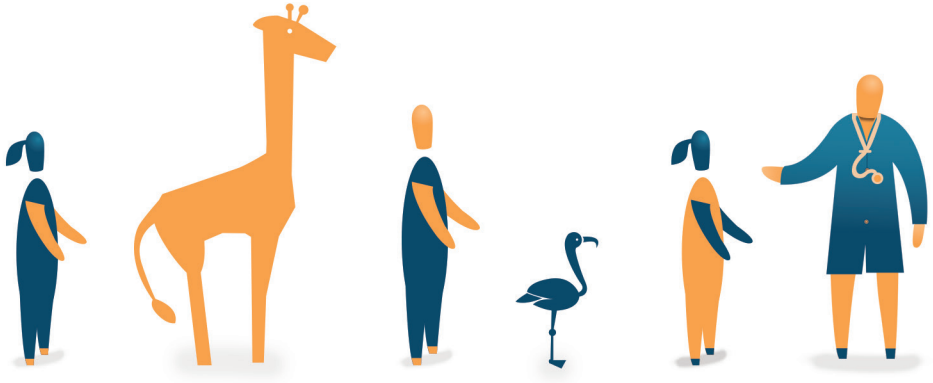
The new Center has been created as part of the One Health Initiative (see p80). The One Health paradigm can be described as a strategy for expanding interdisciplinary collaborations and communications in all aspects of healthcare for humans, animals and the environment. At its heart, One Health aims to accelerate research on a variety of health concerns that are top priorities worldwide. Specific targets include finding cures or ways to prevent food- and waterborne infections, and several viruses transmitted from animals to humans including HIV, West Nile virus, rabies and severe acute respiratory syndrome (SARS).

A fundamental tenet of the One Health strategy is the creation of joint educational efforts between human and veterinary medical schools. California, and the San Diego region in particular, has a long and demonstrable history of expertise in human and animal health, making it a prime location for such a project.

MISSION CONTROL

The Center has three missions: research, education and service. On the research side, the primary aims are to investigate disease processes and risk factors in animals and compare and contrast these mechanisms in diseases affecting humans, collaborating with other scientists to improve diagnostic and treatment strategies for both. Simultaneously, they are providing outstanding training in basic research to highly qualified veterinarians around the world, equipping them with the skills and experience in biomedical research that impact human and animal health.

The research aspect filters through into education, with the environment creating an excellent basis from which to train veterinarians in biomedical research or in laboratory animal medicine residencies, and mentor pre-veterinary students. The service aspect refers to the Center's ability to provide support in various fields, including veterinary nephrology, cardiology, pharmacy, nutrition, laboratory animal medicine and importantly, comparative pathology in neuromuscular, neurologic, gastrointestinal and renal diseases.



inflammatory bowel disease (IBD); oxidative stress and cancer; inflammation and pain; and myopathies and neurodegenerative diseases such as Alzheimer's. The veterinary perspective provides opportunities for studies of marine life, wildlife and animal models with direct comparison to disease in humans.

In what ways do you strive to develop trainees and early career investigators through your various research programmes?

Research programmes such as these invariably include the participation of young scientists who have come to UCSD to obtain advanced research training skills. In addition to developing these research programmes, we have obtained support for advanced research training for veterinarians who can participate in our studies.

Through our participation at meetings, mailings and our website, we hope to find additional veterinary graduates seeking postgraduate training in comparative pathology or comparative medicine.

What is the future for the project?

We will soon begin to offer workshops sharing our findings. The first will be on the topic of comparative pathology of IBD – disease of the gastrointestinal tract that affects millions of patients in the US and around the world.

As our research progresses and we understand more about the relationships between humans and animals in a clinical sense, we will share our findings more widely. It is a very exciting time.

INTELLIGENCE

THE ROLE OF PURINE METABOLISM IN THE CONTROL OF GASTROINTESTINAL INFLAMMATION DEVELOPMENT AND FUNCTION

OBJECTIVES

To identify the proteins that govern the metabolism and responses driven by purines.

KEY COLLABORATORS

Joel Linden, **PhD**, La Jolla Institute for Allergy and Immunology (joel@liai.org)

FUNDING

Sheila Crowe, UCSD NIH/NIDDK T32 Training Grant • **Phil Richter**, UCSD NIH/ORIP R25 postdoctoral training program in laboratory animal medicine grant • **Lynette Corbeil**, The role of bacteria in mixed infections in respiratory disease, USDA grant; A novel vaccine approach to induce mucosal immunity using algae, USDA grant • **Pascal Gagneux**, The role of glycans in evolution by tracing the selected glycan genes in different species of non-human primates supported by the G Harold and Leila Mathers Foundation; Evaluating the role of anti-glycan antibodies in selection of glycan genes, NIH/NIGMS grant • **Christina J Sigurdson**, Pacific Southwest RCE for biodefense & emerging infectious diseases research, (purine metabolism studies) NIH/UCI grant; Infectious prion generation by mouse transgenesis, NIH/NINDS grant • **Peter B Ernst**, Effects of apoptotic epithelial cell engulfment on mucosal inflammation, NIH/NIDKK grant; The role of the adenosine receptor in Th cell development and function, NIH/NIAID grant; Inhibition of Treg function to cure persistent *H. pylori* infection, NIH/NIAID grant

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PROFESSOR PETER ERNST trained as a veterinarian, practiced for a year and then studied mucosal immunology in preparation for an academic career. His principal research interest is in immune-epithelial cell interactions involved in microbial pathogenesis of acute and chronic diseases in the stomach and intestine.

University of California, San Diego
Animal Care Program

As a hub created with the intention of providing research training, the Center presents wonderful opportunities for young scientists to develop themselves and their research expertise within a multidisciplinary team environment

DOWN TO A T CELL

The combined expertise at the Center has the potential to provide real-life improvements for human patients. Ernst and his team's latest investigation seeks to understand inflammatory bowel disease (IBD) and other chronic inflammation in the digestive tract, and their links to cancer. In attempting to manage the causes of IBD for the long-term human sufferer, Ernst's group has been exposing methods and mechanisms for controlling inflammation.

One way that inflammation is controlled is through a subset of white blood cells called regulatory T cells (Treg). "We identified that the optimal activity of Treg required adenosine which binds to receptors on many inflammatory cells and attenuates their ability to cause inflammation," Ernst outlines. "In particular, T cells that cause disease in IBD are very dependent on adenosine for their proper control."

Although not unique to this project, this advancement has seen the team focusing upon the target adenosine and how it affects gene expression contributing to inflammation. By unlocking this relationship, Ernst and colleagues may be able to synthesise drugs that mimic adenosine to control the disease. The California researchers are currently at an advanced stage of creating these compounds, with human testing representing the next step.

HUMAN-FOX PARALLELS

In another example of life-changing work at the Center, Dr Christina Sigurdson – a recognised expert in fatal neurodegenerative disorders of humans and animals that includes Creutzfeldt-Jakob disease (CJD) – is involved in studying the relationship between a degenerative disease in island foxes that also occurs in humans. The work will undoubtedly help to improve conditions for the majestic and endangered fox, but it could also have a role in providing insights into human conditions such as Alzheimer's disease.

WORKING SIDE BY SIDE

As a hub created with the intention of providing research training, the Center presents wonderful opportunities for young scientists to develop themselves and their research expertise within a multidisciplinary team environment. Research trainees work directly alongside other PhD and postdoctoral researchers, representing an advantage both to the young scientists involved and the Center's projects. In turn, abundant opportunities are offered for training and development of veterinarians in laboratory animal medicine, and for PhD and postdoctoral veterinary research. It also provides opportunities for young researchers to contribute to projects led by successful researchers like Ernst or Sigurdson.

The nurturing environment created by Ernst and colleagues furthers research by creating successful conditions for grant applications, with a number of significant projects in the pipeline. The Center members, which include more than 20 veterinarians plus another 20 physicians and scientists, have made a sizeable contribution to academia, producing 100 peer-reviewed papers and multiple book chapters or reviews related to infections, inflammation and cancer, as well as neurological, gastrointestinal, pulmonary and kidney diseases emerging since 2012.

COLLABORATION THE KEY

With collaboration at its heart, it is encouraging to see that the Center has welcomed a number of new organisations into the fold, with partnerships springing up around San Diego and including such institutions as the La Jolla Institute for Allergy and Immunology and The Scripps Research Institute. These partnerships will further research and training and open up new possibilities for collaboration.

The Center performs an essential function in offering an environment for the researchers of tomorrow to come to the fore. Whether they become scientists who work at the cutting-edge, curing and preventing known diseases, or become leaders in education, passing on the torch by training the next generation, they will all be indebted to the singular vision of One Health perfectly exemplified by the Center for Veterinary Sciences and Comparative Medicine.