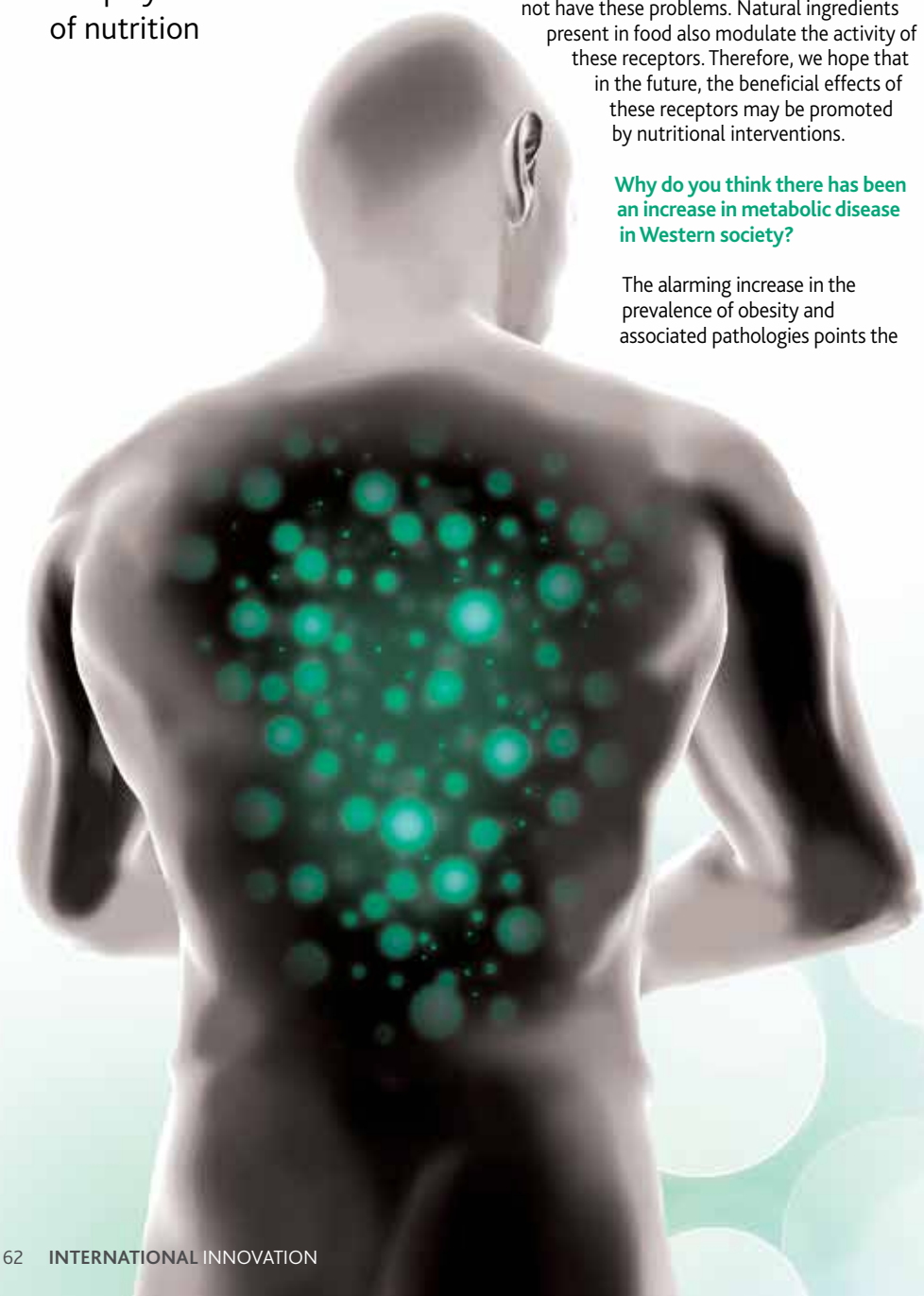
Above PPAR

PROFESSOR WALTER WAHLI

Award-winning animal biologist **Professor Walter Wahli** has spent his career investigating peroxisome proliferator-activated receptors. Here, he offers some thoughts on the important role these proteins will play in the future of nutrition



How are you hoping your latest research on peroxisome proliferator-activated receptors (PPARs) will be applied?

Our research helps to better understand molecular mechanisms underlying key cellular and metabolic processes. For instance, PPARα is the molecular target of the fibrate hypolipidaemic drugs and PPARγ the target of anti-diabetic drugs. However, these latter drugs have encountered some problems due to unwanted side-effects. In the future, better molecules will probably be developed, which may not have these problems. Natural ingredients present in food also modulate the activity of these receptors. Therefore, we hope that in the future, the beneficial effects of these receptors may be promoted by nutritional interventions.

Why do you think there has been an increase in metabolic disease in Western society?

The alarming increase in the prevalence of obesity and associated pathologies points the finger at the mismatch between the modern diet, a sedentary lifestyle and our genetic inheritance. The worldwide epidemic of obesity today affects both adults and children.

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Diet manipulation in mice suggests that alterations in the pre- and postnatal environment are major determinants of the predisposition of offspring to become obese. A hypothesis has been proposed to suggest that during periods of plasticity, the foetus, and possibly the newborn pup, makes adaptive adjustments to ensure that it survives to reproduce in the predicted postnatal environment. This is advantageous only if the prediction is accurate. However, if the actual postnatal environment differs from that predicted, the offspring maturation programme becomes inappropriate and disease and dysfunction may develop.

In conjunction with genetic susceptibility, an adverse perinatal nutritional environment imprints the development of several tissues to permanently inadequate physiological responses, ultimately producing dysfunction and diseases in adulthood, especially in the context of an obesogenic environment.

What do your collaborators bring to your research?

Over the years, our research has benefited from several important collaborations, not only with colleagues from the Center for Integrative Genomics, but from different parts of the world. These collaborations have often brought together researchers from various disciplinary

and technical backgrounds. This is of particular interest in situations where projects command important budgets, because it increases the likelihood of success. Furthermore, interdisciplinary collaborations extend the profile of ideas, some of which may never have come to the table if not for the collaborative effort – creative solutions are often the result of simply looking at questions from a different angle. Collaborations also allow the separation of duties and responsibilities, which helps to create synergies. Finally, if collaborations lead to leveraging the experience of all the parties involved, research progresses much faster.

Can you highlight both the greatest achievement and most challenging aspect of your latest investigation?

Our greatest achievement has been to have contributed to the discovery that fatty acids in the body are signalling molecules that can directly activate or repress gene activity using mechanisms similar to steroid hormones. This has a profound impact on our comprehension of metabolic regulation in general and on how metabolic deregulations may be addressed.

One of the challenges in our specific field which is of the greatest biological and medical interest is to improve in-depth understanding of the reason for the pleiotropic involvement of PPARs, both in the physiology of a single cell and in key systemic regulation of the whole organism.

Do you foresee 'omics' and personalised nutrition becoming more prevalent in health research and the clinic?

At the turn of the millennium, the application to nutritional sciences of high-performance technologies associated with genomics catalysed the emergence of nutritional genomics. In particular, nutrigenomics uses the so-called 'omics technologies' to define and characterise 'dietary signatures' that may reflect the actions of nutrients on the structure and expression of the whole human genome, as well as the final impact on health. These advances have made it possible to look at the interactions between genes and nutrients from a global and systemic perspective.

The purpose of this new science is no less than to prevent diseases and treat them at early stages, if possible before the onset of symptoms, via personalised, partly genotype-based dietary recommendations. Fulfilment of this objective will shape nutrition into an efficient tool that can be used against the alarming rise in obesity and its associated diseases worldwide. Furthermore, the development of functional ingredients, in which we are involved, will allow us to address whole population problems, such as nutrient deficiencies, immune frailty, ageing disabilities and degenerative diseases.

Pinpointing inflammatory pathways

Researchers from the **Center for Integrative Genomics** are actively involved in deepening our understanding about how nuclear receptors control inflammatory gene networks, in the hope of developing alternative therapeutic targets

ENHANCING OUR AWARENESS of how the inflammatory response process works in the human body has significant implications for the healthcare sector across the globe. Inflammation itself is a symptom of infectious diseases, and recent research has indicated an association between inflammation and metabolic diseases, cardiovascular diseases and autoimmune conditions. In addition, connections between this process and obesity are increasingly coming to light as more research is conducted into the ways in which obesity-induced inflammation promotes well-known complications such as insulin resistance, Type 2 diabetes and hypertension. By improving our understanding of the mechanisms which affect inflammation, and how these relate to gene processes and functions, there is potential to have a significant impact on human health and the development of novel treatments.

CONTROLLING RECEPTORS

One of the groups of proteins known to be linked to inflammation are the peroxisome proliferator-activated receptors (PPARs). These are proteins that are responsible for controlling gene activity within the nucleus of a cell. The activation of these ligand-dependent transcription factors is a key controlling step in many of the vital processes taking place within the human body. Three closely related PPARs – α, β/δ and γ – have a known link with inflammatory responses, tissue repair, lipid metabolism and associated diseases. They are part of the same family of proteins that the oestrogen or thyroid hormone receptors belong to.

Researchers from the Center for Integrative Genomics (CIG) at the University of Lausanne in Switzerland are now examining the function of PPARs in the context of inflammation and tissue repair in skin and the liver to enable a better understanding of how these proteins impact on a range of diseases and conditions. Walter Wahli, Professor of Biology and Founding Director of CIG, is leading the team. As he explains, they are using techniques and models which enable them to take a different approach to their investigations: "Using genetic approaches in mice, we would like to increase our knowledge of the integrated gene networks controlled by PPARs, which may indicate alternative therapeutic perspectives for novel synthetic anti-inflammatory PPAR ligands". They use mouse models to delete the genes encoding PPARs, both for a whole animal and in a tissue-specific manner. This means that they can then home in on specific inflammatory pathways in the presence or absence of the receptor.

AMBITIOUS GOALS

The group has a number of research objectives. Firstly, they are keen to understand more about the integrated gene networks controlled by PPARs. Secondly, they want to reveal the function of these receptors in the communication between cell types, as well as how loss of function impacts on different organs. Finally, they hope to learn more about how PPARs control tumour promotion or suppression and the molecular mechanism responsible for this: "Solving this question may help to decide when it is important to stimulate PPAR activity and when it would be preferable to reduce or stop it, possibly with novel agonist or antagonist molecules, respectively, which may lead to the development of novel drugs," reveals Wahli.

REGULATING ENERGY HOMEOSTASIS

Wahli has been increasingly concerned by what he sees as a frightening rise in metabolic

INVOLVEMENT OF PPAR NUCLEAR RECEPTORS IN INFLAMMATION AND TISSUE REPAIR

OBJECTIVES

- To understand the integrated gene networks controlled by peroxisome proliferator-activated receptors (PPARs), which may indicate alternative therapeutic targets for novel synthetic anti-inflammatory PPAR ligands
- To explore how PPARs are involved in the crosstalk between different organs
- To understand the molecular mechanisms behind the ambivalent role PPARs sometimes perform in different processes, eg. tumour promotion and suppression, which may indicate potential agonist or antagonist molecules, respectively, leading to the development of novel drugs

KEY COLLABORATORS

Present group members:

Nathalie Constantin, researcher • **Maude Delacombaz**, technician • **Dr Ilenia D'Errico**, postdoc • **Dr Kalina Duszka**, postdoc • **Christiane Freymond**, technician • **Dr Erwan Gouranton**, postdoc • **Dr Shawon Lahiri**, postdoc • **Marlène Petit**, administrator • **Dr Gianpaolo Rando**, postdoc

Other collaborator at CIG:

Dr Liliane Michalik

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PROFESSOR WALTER WAHLI received his PhD from the University of Bern. He became Professor and Director of the Institute of Animal Biology of the University of Lausanne in 1980 and was Vice-rector. Wahli founded the Center for Integrative Genomics (CIG), which he directed until 2005. Key awards won over his career include the Otto-Naegeli Prize (2002), the European Federation of Lipid Research Award (2002) and the Hartmann Müller Prize (2008). Since October 2012, Wahli holds a Visiting Professorship at the Lee Kong Chian Medical School, a joint medical school of Imperial College London and Nanyang Technological University, Singapore.

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disorders throughout modern Western societies and all of the subsequent conditions and diseases that result from this, including obesity, diabetes and cardiovascular diseases. Multicellular organisms require a strict energy balance in order to grow effectively and healthily, relying on a number of processes and inputs, such as the absorption of nutrients, energy storage and expenditure, and control of appetite.

Wahli's investigative team has discovered a number of interesting facts about the function of PPAR in the development of the skin, skin inflammation, skin wound healing and skin tumour development

Working alongside a number of collaborators, Wahli's team is now focusing on the way in which PPARs act as 'molecular switches' in organism development and energy homeostasis. They are keen to learn more about how PPARs regulate circadian signals being transmitted from the brain to the liver. They are also hoping to pinpoint the endogenous chemicals responsible for activating hepatic PPARs in order to understand how this could impact on fatty liver mediation. Another area of their research is targeting how important PPAR-regulated lipid metabolism is to the control of lipid sensing by hypothalamic neurons.

MULTI-FACETED RESEARCH

The investigation has discovered a number of interesting facts about the function of PPAR in skin development, inflammation, wound healing and skin tumour development. An illustrative example can be found in the role PPARβ/δ plays in promoting the growth of hair follicles in healthy skin.

Wahli and his collaborators also found that after injury, the expression and activation of PPARβ/δ is triggered by an inflammatory response. This in turn promotes the migration of keratinocytes over the wound: "In addition, in collaboration with Professor Andrew Tan in Singapore, we found that interleukin (IL)-1 produced by the keratinocytes activates the underlying dermal fibroblasts to produce mitotic cytokines which stimulate keratinocyte proliferation," Wahli reveals. "PPARβ/δ expression in these fibroblasts leads to inhibition of IL-1 signalling and eventually results in a reduction in keratinocyte proliferation as healing approaches completion."

In partnership with Dr Liliane Michalik also from CIG, this has led the researchers to deduce a whole series of effects where PPARβ/δ performs a supportive role in ultraviolet (UV)-induced skin cancers. In parallel, this same receptor has beneficial effects on the capacity of muscles to utilise lipids and carbohydrates, and consequently there is some interest in the potential to develop PPARβ/δ agonists to treat diabetes. "Some of these agonists are currently in clinical trials, but no PPARβ/δ compound has been brought to market so far," explains Wahli. Their work emphasises the importance of carefully evaluating the way in which high-affinity PPARβ/δ agonists would be used to treat patients, since under some conditions they may support tumourigenesis.

COLLABORATIVE KNOWLEDGE GATHERING

Working alongside a number of other scientists, Wahli and his team are involved in several other PPAR studies. They have been collaborating with Professors Pierre Chambon, Daniel Metzger and Philippe Boucher of the University of Strasbourg to demonstrate that PPARγ is required in differentiated mature white and brown adipocytes (lipocytes and fat cells) for their survival. Their research has also shown that PPAR is able to effectively protect against vascular calcification, such that it offers a potential target against complications from hardening of the arteries, including coronary artery calcification and valvular sclerosis. "Furthermore, mice in which PPARβ/δ is selectively ablated in skeletal muscle cells exhibit a muscle fibre-type switching toward lower oxidative capacity," highlights Wahli. Because this precedes the development of obesity and diabetes in these animals, PPARβ/δ is thought to be critical to maintaining oxidative fibres, and fibre-type switching and reduced muscle oxidative capacity are likely to be the cause of metabolic disorders rather than the outcome.

The group has also discovered that PPARα has broad female-dependent repressive actions on liver genes involved in steroid metabolism and inflammation. Consequently, this means that there is potential for protection against a symptom of pregnancy where the flow of bile from the liver is slowed or blocked, known as intrahepatic cholestasis, that can result in complications for both mother and foetus. "The model may help develop better treatments for a liver disease caused by high levels of oestrogens, such as intrahepatic cholestasis of pregnancy or by post-menopausal hormone replacement therapy in susceptible women," Wahli emphasises.

It is the team's hope through all of their different research endeavours that the molecular mechanisms supporting key cellular processes can be better understood, and moreover that alternative therapeutics for some of the most debilitating diseases suffered by Western societies can be developed.