Otto Naegeli Award 2002 honors the work of Prof. Walter Wahli

Ueli Schibler

During the meeting of the Foundation Council of the Swiss National Science Foundation the Otto Naegeli Prize of the *Bonizzi-Theler Stiftung* was awarded to Walter Wahli, professor at the University of Lausanne. Every two years this award honors a scientist working in Switzerland who has made outstanding contributions in biomedical and/or clinical research and who is likely to continue to do so in the future. With CHF 200,000 the Otto Naegeli Prize is among the most important scientific distinctions in Switzerland. This year's award winner has discovered novel nuclear hormone receptors, has identified specific ligands for these receptors, and has demonstrated the central physiological significance of these regulatory proteins in metabolism, inflammation, and wound healing.

Walter Wahli was born in Moutier (1946) and studied biology at the University of Berne. In 1977 he got his Ph.D. on the regulation of vitellogenin expression in the frog *Xenopus laevis* with Prof. Rudolf Weber at the Division of Cell and Developmental Biology of the Institute of Zoology. During his postdoctoral training (1977–1980) with Dr. Igor Dawid – first at the Carnegie Institution of Embryology, then at the National Institute of Health in Bethesda – he continued his work by cloning several isoforms of the vitellogenin gene and by characterizing the structure and transcription of these genes. Vitellogenins, the major egg yolk proteins, are synthesised as precursor proteins in the liver and are then transported to the frog's oviduct via the blood circulation. The major signal triggering vitellogenin gene expression is oestrogen, a steroid hormone binding to a nuclear receptor. Upon binding to its ligand, the estrogen receptor is converted from an inactive to an active transcription factor and stimulates transcription of numerous target genes.

In 1980 Walter Wahli was nominated as a full professor and director at the Institute for Animal Biology at the University of Lausanne, where he established a very dynamic and successful research group. During the eighties, he pursued his work on the regulation of vitellogenin gene transcription, but in the early nineties his team explored the sequence similarities between members of the nuclear receptor gene family and identified three novel receptors in *Xenopus* (Dreyer et al., 1992). These receptors closely resembled a mammalian receptor, which has been shown by S. Green (UK) to be activated by a diverse class of rodent hepatocarcinogens that cause proliferation of peroxisomes (Issemann and Green, 1990). Indeed, Wahli and Green can be regarded as the fathers of the medically so relevant PPARs (Peroxisome Proliferator-Activated Receptors). After the papers by the teams of Green and Wahli were published, research on the three PPAR isoforms (PPARα, PPARβ, and PPARγ by numerous groups has resulted in the publication of more than 1800 research papers in the biomedical literature. The great interest in these nuclear receptors is engendered by their involvement in several clinically pertinent processes, including lipid and sugar metabolism, adipogenesis, inflammation, wound healing, and embryo implantation.

Since the discovery of PPAR receptors, Wahli has continued to make seminal contributions in this highly competitive research field. Thus, in a widely cited 1996 *Nature* paper (Devchand et al., 1996), he reported on the identification of leukotriene B4 as a new and unexpected PPARα ligand. As leukotriene B4 is a chemotactic inflammatory mediator, this discovery has opened a completely novel avenue of PPAR research, namely the investigation of PPARs in inflammation. In the search of new PPAR ligands, Wahli has also developed a powerful new molecular tool to determine ligand-receptor interactions *in vitro*, which is based on the ligand-dependent association of PPAR hormone binding domains with their coactivator partner proteins (Krey et al., 1997).

Owing to the possibility of inactivating genes in the mouse by targeted homologous recombination, it has become possible to perform loss-of-function genetics in a mammalian organism. By exploring this gene knockout technology, Walter Wahli has uncovered that PPARα and -β also play crucial roles in wound healing after injury. *In vivo* experiments with PPARβ wild type and knockout mice and *in vitro* work with primary skin keratinocytes from these animals has shown that PPARβ induces the transcription of genes whose products prevent programmed cell death at the site of injury (Michalik et al., 2001; Tan et al., 2001).

Not surprisingly, the ligand-dependent action of PPAR receptors in numerous medically important processes has already resulted in the development of several well-known drugs, including the three antidiabetic drugs *troglitazone*, *rosigliatazone*, and *pioglitazone* (PPARγ ligands), and the hypolipidaemic fibrates (PPARα ligands). Wahli's data on PPARβ function are likely to trigger the design of PPARβ agonists suitable for promoting wound healing. On page 83 of this issue, the laureate of the 2002 Otto Naegeli award presents a comprehensive review on the physiological and medical significance of the PPAR receptor family.

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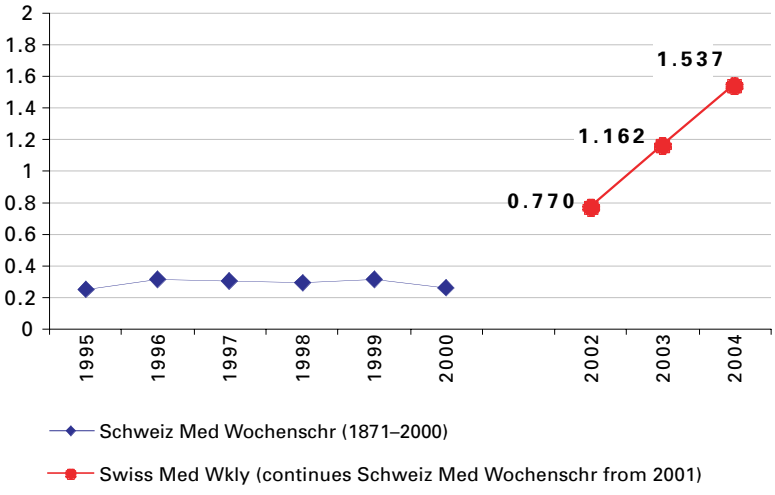

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