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## **NRP Endocrine Disruptors**

### **Intermediate Summary**

<p><b>Original project title</b>  <b>Environmental disrupter actions in live cells and animals : Elucidating molecular mechanisms of PPAR pathway alterations.</b></p>
<p><b>Project leader</b>          Prof. Walter Wahli</p>
<p><b>Project number</b>          4050-066588</p>

### **English Summary (Prof. Vogel's project)**

#### **Hormone induced interaction pattern of nuclear receptors in live cells**

Nuclear receptors initiate transcription, interact with regulatory proteins and are influenced by hormones, drugs and pollutants. We discovered ligand-specific mobility patterns of human estrogen receptor- $\alpha$  (ER) in living cells using diffusion-time distribution analysis.

#### **Project description:**

##### **Research questions**

Develop fluorescence techniques to characterize quantitatively the multi-protein interaction network of nuclear hormone receptors in living cells. Develop fluorescence techniques to detect, distinguish, classify and characterize nuclear hormone receptor ligands, especially endocrine disrupting compounds.

##### **Results**

We discovered ligand-specific mobility patterns of human estrogen receptor- $\alpha$  (ER) in living breast cancer cells using diffusion-time distribution analysis (DDA). This novel method, based on fluorescence correlation spectroscopy (FCS), is especially suited to unravel multiple protein interactions in vivo at native expression levels. We found that ER forms a limited number of distinct complexes with varying population by dynamic interaction with other nuclear components. Dose-response curves of different ligands could be obtained for each receptor interaction. The potential to identify interacting proteins was demonstrated by comparing DDA of the ER cofactor SRC-3 attached to yellow fluorescent protein (YFP) with those of YFP-ER. By comparison of the interaction patterns induced by different ligands their nature (agonist, antagonist) can be distinguished.

### **Perspectives**

Our findings open up new routes to elucidate transcription regulation and to detect and distinguish pharmacologically and toxicologically active, as well as endocrine disrupting compounds *in vivo*. We have built the foundation to elucidate step-by-step simultaneously existing ER-cofactor complexes, their evolution with time and their dependence for instance on growth factors and acetylation or phosphorylation of the constituents. DDA following silencing of the genes of individual or multiple, known or putative ER interaction partners with RNAi technology bears an enormous opportunity to complement and extend this approach. Moreover, DDA provides a general approach to monitor biochemical networks in individual living cells.