

## Division of Targeted Research

National Research Programmes

Wildhainweg 20

CH-3001 Berne

Tel. +41(0)31 308 22 22

Fax +41(0)31 305 29 70

E-Mail nfp@snf.ch

# NRP Endocrine Disruptors

## Final Summary

Original project title <b>Endocrine disruptors and breast carcinogenesis: a new mouse model to assess estrogen receptor-dependent and -independent effects in vivo</b>
Project leader <b>Cathrin Brisken</b>
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### Perinatal exposure to BPA affects mammary gland development

The contribution of environmental toxins to the breast cancer incidence remains unclear. Epidemiologic studies are impossible to perform because most compounds are ubiquitous and there no „unexposed“ control group. Therefore well controlled animal models are needed to establish endocrine disrupting effects in the mammary gland and underlying mechanisms.

### Research questions

1. How does perinatal exposure to bisphenol A (BPA) affect mammary gland development in C57BL6 mice?
2. To what extent are the effects of BPA mediated by the estrogen receptor  $\alpha$ , the estrogen receptor  $\beta$ , or are independent or both?
3. Are the effects elicited by BPA in the mammary gland secondary to systemic effects or intrinsic to the mammary epithelium?

### Results

1. Perinatal exposure to bisphenol A (2,5 ug/kg/d in pregnant mice's drinking water) results in complex developmental changes in the mammary gland:

a) during puberty: both the formation of terminal endbuds and ductal elongation are retarded.

b) in the sexually mature female (8 weeks and older): the overall number of epithelial cells in the mammary gland is increased.

2. To our surprise we found that exposure to BPA decreased expression levels of the estrogen target gene amphiregulin. This is true both when BPA is administered acutely by injection as well as when a mouse is exposed perinatally.

Intriguingly, in the absence of ER $\alpha$ , BPA elicits a strong induction of amphiregulin. The number of ER $\beta$  deficient mice treated is still too low to draw conclusions.

3. Mammary epithelium from mice that were exposed to BPA perinatally, keeps the terminal end bud phenotype described above when grafted to untreated hosts. This indicates that Perinatal exposure to BPA results in changes intrinsic to the mammary epithelium and suggests an epigenetic basis.

### Perspectives

We are currently consolidating the numbers of mice analysed regarding point 1 and 2. In particular, the differential responses of ER $\alpha$ /ER $\beta$  and wt mice to BPA exposure needs to be further examined.

The delay in terminal endbud formation and ductal outgrowth can be explained by the decreased expression of amphiregulin.

The basis for the increase in cell number during adulthood still needs to be elucidated. We have been unable to show an increased responsiveness to progesterone.

We are very excited about the finding that there is an epithelial intrinsic phenotype. We will examine the mammary epithelial cells from BPA exposed and control mice for epigenetic changes.