Ongoing R&D

LigoCyte is involved in several partnerships with other companies that are using these technologies in drug and vaccine development. Corixa (Seattle, WA, USA) has licensed both an antibody and a vaccine based on LigoCyte's work, and Merck (Rahway, NJ, USA) is evaluating compounds developed for inflammatory bowel disease, differentiating lead candidates using LigoCyte's flow-based assays. Bargatze says that the next step for LigoCyte is: 'to take advantage of the targeting to the M-cell site using both antigens and DNA constructs that encode antigens, for the development of highly effective vaccines.'

New opportunities for enhanced ovarian cancer prevention

Martina Habeck, Freelance writer

Researchers might have found the mechanism by which oral contraceptives (OCs) help prevent ovarian cancers. They think it is mainly a direct effect of the hormone progestin on the ovarian epithelium, an effect that is unrelated to ovulation inhibition. This knowledge is hoped to enable the development of OCs that provide enhanced ovarian cancer prevention benefits.

Ovarian cancer is the sixth most common cancer among women worldwide and causes more than 100,000 deaths per year[1]. However, routine OC use has been shown to protect against the disease. Data from large cohort and case-control studies show that the risk of ovarian cancer is decreased by 40% in past/present users of OCs and by >50% in long-term users (>5 years)[2].

Mechanism of OC protection

Why OC use reduces ovarian cancer risk is not known with certainty, although the general assumption has been that these drugs reduce the lifetime number of ovulations. Repeated cycles of ovulation can cause recurrent damage to ovarian epithelium, and can eventually result in genetic mutations, triggering cancer.

However, this explanation is not conclusive. Little information is available on progestin-only contraceptives, but it appears that this type of contraceptive is also associated with a reduced risk of ovarian cancer, while often having no effect on ovulatory cycles. These progestins (i.e. synthetic formulations of the female hormone progesterone) are included in OCs because they thicken the cervical mucus, thus making it difficult for the sperm to reach the uterus or fallopian tube.

Furthermore, long-term OC use has been shown to have a disproportionately greater protective effect than can be attributed solely to ovulation suppression. This realization prompted researchers at the Duke University Medical Center (Durham, NC, USA) to look for other biological effects of OCs that could be responsible for their protective properties.

Table 1. Apoptotic effect of hormone treatment on the ovarian epithelium of cynomolgus monkeys

Hormone treatment	Apoptotic cell counts (median percentage)
No hormones (control)	3.9%
Oestrogen component of Triphasil (ethinyl estradiol)	1.8%
Triphasil	14.5%
Progestin component of Triphasil (levonorgestrel)	24.9%

Role of progestin?

Gustavo Rodriguez and his team examined the ovaries of monkeys that had been treated for three years with OCs. Four groups of cynomolgus macaques (75 in total) were randomized to receive no hormones, the OC Triphasil (a combination of an oestrogen and a progestin component), the oestrogen component of Triphasil, or the progestin component of Triphasil. Results showed that treatment with Triphasil or its progestin component, unlike the other two groups tested, resulted in an increased rate of apoptosis in the ovarian epithelium[3] (Table 1).

This finding that the hormone could activate one of the key *in vivo* mechanisms to eliminate cells that are prone to malignant transformation, was supported

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by further studies that were presented at the *32nd Annual Meeting of Gynecologic Oncologists*. They found an increased expression of transforming growth factor β (TGF-β), a known regulator of apoptosis, in the ovarian epithelium of monkeys treated with Triphasil or its progestin component[4]. Furthermore, using data from a large case-control study, the Cancer and Steroid Hormone (CASH) study[5], they found that OCs with high progestin levels conferred a twofold greater protection against ovarian cancer compared with OCs containing low levels of progestin[6]. The analysis included 390 women with epithelial ovarian cancer and 2,865 controls.

Rodriguez is excited about these findings. 'If routine use of the pill reduces ovarian cancer risk by 50%, and if we can understand how it all works, then it might be possible to design an improved formulation that is more protective against ovarian cancer than the pill.' He suggests that this could be approached by increasing the progestin potency, identifying and using a progestin formulation that maximizes the protective effect, or adding other drugs that have a biological effect on the ovarian epithelium similar to that of progestins. As the protective effect of progestin is unrelated to ovulation inhibition, he also hopes to develop a product for post-menopausal women, who are at greatest risk of contracting ovarian cancer.

Carlo La Vecchia, an epidemiologist at the Mario Negri Institute for Pharmacological Research (Milano, Italy), is more cautious. Based on his research into the risks and benefits of OCs, he doubts the results could be used to make a better pill: 'Oral contraceptives have been around for 40 years, and the formulations have been improved repeatedly. It is very difficult to make further improvements without increasing the risk of side effects.' The risk of thrombosis is a major concern, as is the risk of breast cancer. However, Rodriguez and his team aim to address these potential risks in their future studies.

Future studies

Currently, Rodriguez and his colleagues are conducting *in vitro* studies to evaluate the effect of different drug combinations on human ovarian cancer cell lines. In addition, they are conducting studies in egg-laying hens, who are very prone to ovarian cancer as they ovulate daily, prior to trying to move the drug into clinical pilot studies.

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