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Treating Cancer by Blocking an EGFR-Ligand

A Novel Method of Treating Cancer by Targeting EGFR Ligand Amphiregulin

Project Number:	1776
Principal Investigator:	Prof. Yosef Yarden
Patent Status:	Pending
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Overview

A novel method for treating ovarian cancer by intercepting the EGFR ligand amphiregulin, when elevated expression levels are found in a patient.

Ovarian cancer represents a relatively common type of cancer that affects women. However, there is no effective and specific therapy regimen for this disease. **There is a real need for an alternative and specific ovarian cancer treatment.**

The group of Prof. Yosef Yarden at the Weizmann Institute of Science (WIS) has discovered a unique method for treating ovarian cancer. The discovery is based on clinical data showing elevated levels of amphiregulin (AREG) found in body fluids of a high percentage of ovarian cancer patients. AREG, a known ligand that activates the epidermal growth factor receptor (EGFR), has received increased scrutiny in recent years due to its possible role in various diseases. Prof. Yarden's group has found that by intercepting AREG in combination with chemotherapy, they were able to inhibit the growth of tumors.

The Unmet Need

Treatment of cancer over the past few years has focused mainly on inhibiting the signals generated by EGFR, or by similar receptor tyrosine kinases. The use of small molecules or monoclonal antibodies has been an effective treatment for several cancer types. However, for ovarian cancer, such treatments have been relatively ineffective. Consequently, the primary therapeutic option for ovarian cancer has remained the same since the 1970's, involving systemic chemotherapy treatment, and surgery. The problem of limited treatment options is further exacerbated due to the high proportion of patients who relapse following chemotherapy.

Consequently, there is a need for an ovarian cancer therapy that offers an alternative target to the standard method of targeting EGFR and other receptor tyrosine kinases.

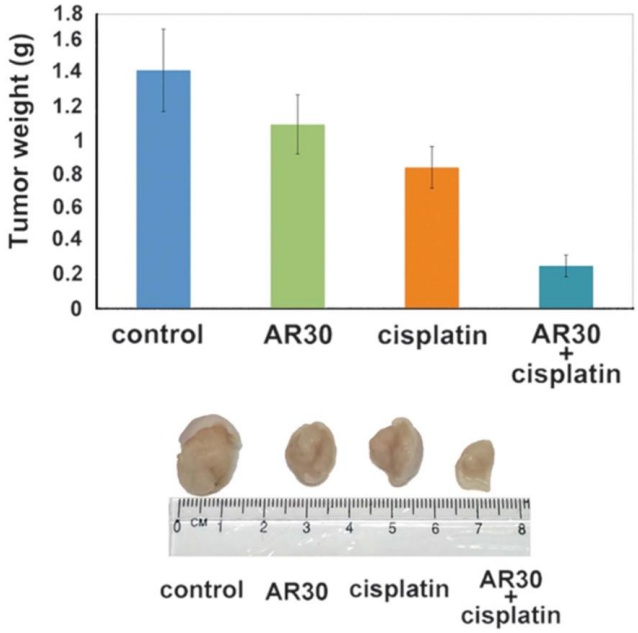
The Solution

A research team at the WIS led by Prof. Yosef Yarden, has developed a state-of-the-art method for treating ovarian cancer. They have generated monoclonal antibodies to intercept AREG, resulting in re-sensitizing tumors to chemotherapy.

Technology Essence:

The discovery by the Yarden group was initially elucidated by examining different EGFR ligands in ascites fluid from ovarian cancer patients. It was noted that over 80% of patients showed relatively high levels of AREG. Subsequently, ovarian cancer cells were seeded and grown over four days, using ELISA for media screening. In 92% of the cell lines, there were detectable concentrations of AREG in the media. These results suggest a possible role of AREG in the progression and growth of ovarian cancer cells.

Following the results which showed higher levels of AREG in both clinical and laboratory samples, further *in vitro* experimentation was performed to shed light on the mechanisms related to AREG activation of EGFR. The Yarden group proceeded to generate a series of antibodies that could block AREG. From the initial screen, a mAb termed AR30 was found to have high affinity towards its target. AR30 was then tested in nude mice inoculated with human MLS ovarian cancer cells, with and without the chemotherapy drug cisplatin. The figure below shows that the weight of excised tumors was most effectively reduced in combination with cisplatin, demonstrating that AR30 could re-sensitize tumors to chemotherapy.



Testing tumor inhibiting capacity of generated monoclonal antibodies (mAb) on AREG interception. A) mAb AR30 tested both with and without cisplatin chemotherapy treatment, in nude mice injected with MLS ovarian cancer cells ($2x10^6$ cells per animal). Tumors were excised and weighed, images of representative tumors are shown. Mice were injected/treated with AR30 mAb (100 µg/mouse twice a week), cisplatin (5 mg/kg), or both mAb AR30 and cisplatin. Image modified from Carvalho S. et al. Oncogene. 2016.

Applications:

- Inhibiting growth of ovarian cancer.
- Possible treatment for other types of cancer.
- Using AREG as a possible theranostic for ovarian cancer.

Advantages:

- **Innovative Target** – Intercepting the EGF-ligand AREG.
- **Flexible** – Anti-AREG mAbs could be used alone or in combination with current chemotherapy treatments for different malignancies.

Development Status

The team of Prof. Yarden has a unique target for inhibiting ovarian cancer and possibly other cancer types, by blocking the EGF-ligand, amphiregulin. The team has tested both clinical and laboratory samples to determine AREG as a possible cancer biomarker. The group has performed *in vitro* work to characterize the AREG activation of EGFR. Furthermore, Yarden's group has worked with xenografted mouse models to determine the impact of blocking AREG.

Market Opportunity

Ovarian cancer represents the 5th most common form of cancer for women. This is especially problematic due to the limited number of therapeutics available in the market explicitly for ovarian cancer. This presents an opportunity, as the market for ovarian cancer in 2015 reached $1.5 billion and is expected to grow to $5.2 billion in 2025[1]. Therefore, a novel target such as AREG for treating ovarian cancer, and possibly other malignancies, is of high value.

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[1] GlobalData Report – Ovarian Cancer Analysis and Forecast 2025 – 2017.