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Treatment of ErbB2/Her2-positive Cancers with Prolidase and/or its Derivatives

Ref# RP13-013

Keywords: ErbB2+ cancer, breast cancer, gastric cancer, ovarian cancer, receptor tyrosine kinase, ErbB2/Her2, PEPD, prolidase.

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking partners to help co-develop the use of bacteria-generated, recombinant human prolidase (PEPD) or its derivatives to manage and treat ErbB2-positive cancers.

Summary: ErbB2 is an important oncogene and anti-tumor target. ErbB2 gene amplification occurs in 20-30% of human breast cancer and is significantly correlated with protein expression in the cancer tissues. ErbB2 amplification or overexpression also occurs in other cancers, e.g., gastric cancer and ovarian cancer. ErbB2 gene amplification or protein overexpression is a strong predictor of poor disease prognosis. ErbB2-targeted therapies, particularly humanized monoclonal antibody trastuzumab (Herceptin) in combination with chemotherapy, shows considerable clinical efficacy. However, approximately 50% of patients show primary or secondary resistance to Trastuzumab. Additionally, trastuzumab must be produced in mammalian cells, making it very cost prohibitive. Ado-trastuzumab emtansine (Kadcyla), a conjugated version of trastuzumab to a microtubule inhibitor, was approved last year for patients with metastatic ErbB2-positive breast cancer, who are resistant to trastuzumab. However, Kadcyla is currently even more expensive than trastuzumab itself, while only showing moderate efficacy. There is an urgent, unmet need for an anti-ErbB2 agent.

Technology: In cancer tissues *in vivo,* trastuzumab neither downregulates ErbB2 expression nor inhibits ErbB2 tyrosine phosphorylation. Rather, its Fc domain is essential for tumor inhibition by engaging Fc receptors on immune effector cells. We have discovered human prolidase (PEPD) to be an ErbB2 ligand and it strongly targets ErbB2-driven tumors *in vivo* in animals. However, PEPD does not have an Fc domain. PEPD is an ErbB2 ligand and binds to subdomain 3 of the ErbB2 extracellular domain (ECD). PEPD binding to ErbB2 causes rapid shutdown of ErbB2 oncogenic signaling and also profound depletion of ErbB2 protein via internalization and degradation. Moreover, PEPD also silences other ErbB family members ErbB1 and ErbB3 in tumor tissues via disruption of their heterodimerization with ErbB2 as well as down regulation of ErbB1.

Because the antitumor mechanism of PEPD differs from the antitumor mechanism of trastuzumab *in vivo*, PEPD is not only a novel anti-ErbB2 agent, but also it may complement trastuzumab and help to overcome resistance to trastuzumab in patients. Moreover, this product can be produced in bacteria using recombinant technology vs. trastuzumab which must be produced in mammalian cells (due to the Fc domain needing glycosylation), thus likely making PEPD a lower cost agent in comparison. Enzymatically inactive mutant of PEPD is even more efficacious than the wild type PEPD in targeting/inhibiting ErbB2 tumors *in vivo*. Enzymatically inactive PEPD mutant may also allow ErbB2-targeting in cancer in patients without interfering with the normal function of endogenous PEPD.

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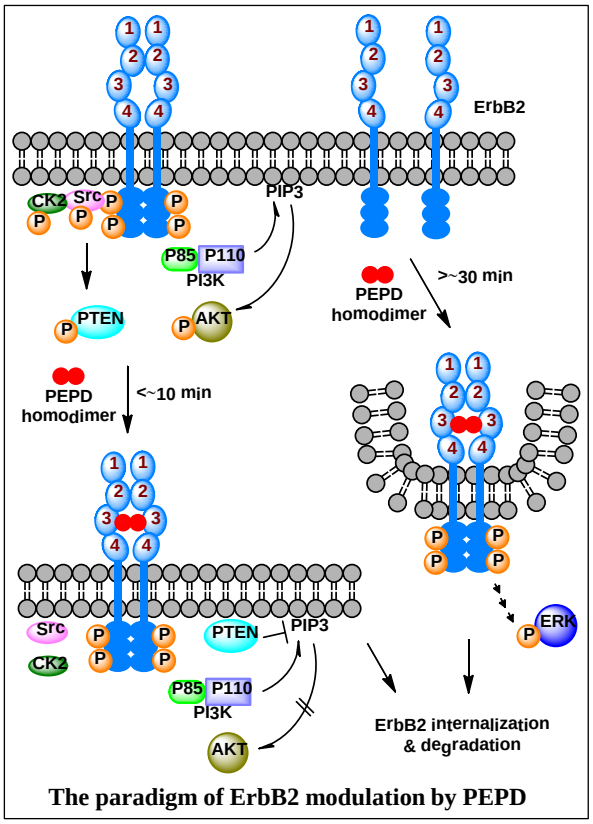
Potential Commercial Applications:

- PEPD or its enzymatically inactive mutant may be useful as a single agent, with other anti-ErbB2 agents, or with certain chemotherapy in ErbB2+ cancer patients.
- PEPD derivatives may be developed for increased antitumor activity, e.g., a PEPD-Fc hybrid to enable antibody-dependent cell-mediated cytotoxicity (ADCC) via its Fc domain.
- PEPD or its mutant could synergize with existing anti-ErbB2 agents or help to overcome resistance of these agents in patients.

Competitive Advantages:

- This is the first case of a naturally occurring human protein targeting ErbB2 in cancer and its use in patients may have much lower toxicity.
- PEPD or its mutant directly targets the ErbB2 signaling system in the tumor tissue; whereas, herceptin inhibits tumor growth *in vivo* by engaging ADCC immune function.
- PEPD or an enzymatically inactive mutant may be mass produced in bacteria at a relatively low cost (Herceptin/Trastuzumab and other related anti-ErbB2 agents are expensive). Therefore, PEPD or its mutant is also expected to be highly competitive against current anti-ErbB2 agents such as trastuzumab in terms of cost.
- Because of expected relatively lower cost of making PEPD, it may also lower the cost of makingPEPD derivatives.



The paradigm of ErbB2 modulation by PEPD

Development Status: Patent Status: PCT/US2014/051789

Inventor: Yuesheng Zhang et al.

Additional References:

In vitro data of this disclosure has been published as follows: Yang L, Li Y, Zhang Y. Identification of prolidase as a high affinity ligand of the ErbB2 receptor and its regulation of ErbB2 signaling and cell growth. *Cell Death & Disease* 5, e1211, 2014.

The **cartoon** on the left shows a part of the paradigm of ErbB2 modulation by PEPD. Both monomers and tyrosine-phosphorylated dimers exist in cells overexpressing ErbB2. PEPD binds to ErbB2 as a homodimer; each PEPD subunit binds to one ErbB2 ECD subdomain 3. PEPD rapidly binds to ErbB2 dimers, silencing ErbB2-Src signaling by causing Src disassociation from ErbB2. PEPD binds to ErbB2 monomers somewhat slowly but causes ErbB2 dimerization and phosphorylation, leading to activation of downstream signaling. However, such activation is transient and functionally insignificant, as PEPD soon causes strong and persistent ErbB2 depletion resulting from PEPD-induced ErbB2 internalization and degradation.

In vivo work of this disclosure has not yet been published.