Herceptin

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Abstract The biology of the human epidermal growth factor (EGF) receptor-2 (HER2) has been reviewed numerous times and provides an excellent example for developing a targeted cancer therapeutic. Herceptin, the FDA-approved therapeutic monoclonal antibody against HER2, has been used to treat over 150,000 women with breast cancer. However, the developmental history of Herceptin, the key events within the program that created pivotal decision points, and the reasons why decisions were made to pursue the monoclonal antibody approach have never been adequately described. The history of Herceptin is reviewed in a way which allows the experience to be shared for the purposes of understanding the drug discovery and development process. It is the objective of this review to describe the pivotal events and explain why critical decisions were made that resulted in the first therapeutic to successfully target tyrosine kinases in cancer. New approaches and future prospects for therapeutics targeting the HER family are also discussed.

1 Magic Bullets and Monoclonal Antibodies

The specific targeting of disease-causing organisms, or diseased cells, was first articulated by Ehrlich, who reasoned that because it is possible to differentially stain cancer and normal cells, it should be possible to specifically target cancer (perspective by Witkop 1999). Based upon this work, many successful chemotherapeutics have been created. However, because diseased and normal cells share biochemical pathways, and are much more similar than they are different, targeting disease processes by interrupting cellular metabolism without toxicity to the host has remained a problem in drug discovery.

Subtle differences between normal and tumor cells include a greater dependence of cancer cells on glucose metabolism instead of the citric acid cycle for the generation of adenosine triphosphate (the "Warburg Effect"; Ashrafian 2006), and a greater use of uracil to support their growth ("uracil flux"), leading to the discovery of fluorouracil as a chemotherapeutic (Heidelberger et al. 1957). These targets for therapy share the inherent problem that the differences are a matter of degree. While the fluorouracils are clearly effective, with a role to play in the treatment of many cancers (Dorr and Von Hoff 1994), their efficacy is more a result of the relative leakiness of blood vessels in tumors (leading to drug localization) than it is to the specific targeting of cancer cell metabolism. In fact, thymidylate synthase, the enzyme inhibited by the fluorouracils, is predictably expressed to a higher degree in tumor cells than it is in normal cells. As a result, normal cells (with lower thymidylate synthase, like gut epithelium, skin fibroblasts, and hematopoeitic cells) are generally more sensitive to the cytotoxic effects of fluorouracils than are tumor cells, which have a higher intracellular concentration of the enzyme (Lackey et al. 2001; Li et al. 2001). The goal of the modern era of cancer treatment is to create drugs that preferentially damage tumor cells based upon their specific biochemical properties, and leave normal cells relatively free from injury: the realization of Ehrlich's "magic bullet" hypothesis.

The enablement of this goal in cancer treatment required several important advances in drug discovery. Key discoveries include identifying cancer-specific antigens (e.g., tyrosine kinases and other enzymes), understanding disease pathways, and developing a means for specifically targeting diseased cells. The discovery of viral oncogenes which encode tyrosine kinases, and subsequently the finding that mutations in some normal cellular tyrosine kinases can cause them to become oncogenic, resulting in cellular transformation (immortality, anchorage independent growth, and the ability to form tumors in immune-deficient mice), reviewed by Bishop (1989) and Varmus (1989), provided the basis for targeting the human epidermal growth factor receptor 2 (HER2) protooncogene with a monoclonal antibody. Since the approval of Herceptin in 1998, the tyrosine kinases have become the archetypical example of a validated target in cancer, and monoclonal antibodies have become an accepted biopharmaceutical to target cell surface receptors.

Especially relevant to Herceptin, the early enabling oncogene discovery was the finding that the v-erb-B oncogene, derived from chicken erythroblastosis virus, shared significant homology with the human epidermal growth factor receptor (EGFR or HER1), thereby giving rise to the hypothesis that under conditions of constitutive activation, EGFR might be implicated in human cancer (Kris et al. 1985). Further work proved this hypothesis and motivated the discovery of HER2, also known as human NEU, erb-B2, or NGL (Coussens et al. 1985; King et al. 1985; Schechter et al. 1985; Semba et al. 1985; Yarden and Ullrich 1988). The focus of this chapter is the discovery and pharmacological studies that led to the approval of Herceptin, a humanized monoclonal antibody targeting the receptor extracellular domain encoded by HER2 ($p185^{HER2}$). At the time when Investigational New Drug (IND)-enabling efforts began for Herceptin, only EGFR and HER2 had been described (Yarden and Ullrich 1988). The field has made tremendous advances since this time, powered in large part by the commercial success of Herceptin. Herceptin provided the first "magic bullet" targeted at tyrosine kinases to treat cancer. A discussion later in the chapter will outline newer approaches to targeting the Human EGFR (HER) family.

2 The Discovery and Development of HER Therapeutics

2.1 Setting the Stage

Direct causal relationships between oncogene amplification and/or overexpression and certain types of cancer were less well defined in the 1980s (during the initial development efforts for Herceptin) than they are now. One of the most critical events in the research leading to Herceptin was reported by Weinberg and colleagues (Schechter et al. 1984). This involved the discovery of the first oncogenic receptor tyrosine kinase oncogene, NEU. It was discovered by gene

transfection/transformation of fragmented DNA from a series of rat neuroblastomas into NIH 3T3 cells (the focus-forming assay; Shih et al. 1981).

The product of the HER2 protooncogene ($p185^{HER2}$) is a transmembrane Type 1 receptor tyrosine kinase with extensive homology to the EGFR (Coussens et al. 1985; Schechter et al. 1985; Yarden and Ullrich 1988) and now known to have similar homology with HER3 and HER4 (Katoh et al. 1993; Zhou and Carpenter 2002). HER2 can be distinguished from HER1, 3, and 4 by differences in chromosomal location, transcript size, molecular mass, ligand activation of the associated tyrosine kinase, and antigenicity, as determined by interaction with specific monoclonal antibodies (Citri and Yarden 2006; Kumar and Pegram 2006; Prenzel et al. 2001).

We will review the science behind Herceptin development from a historical perspective. It is our goal to provide a roadmap that can be generally applied to the assembly of the rationale for the development of other successful therapeutics. We will describe the progression of the science beginning with the discovery of the HER2 protooncogene through the demonstration that overexpression leads to cellular transformation, tumor cell resistance to elements of the host immune system, and other characteristics that create a disease-specific signaling pathway in cancer cells. This pathway was the focus of efforts that resulted in the development of Herceptin, the first biopharmaceutical to demonstrate clinical proof of concept and the value of targeting tyrosine kinases in cancer.

2.2 The Development of a Preclinical Rationale

A striking convergence of basic science, clinical research, and translational medicine occurred within a short interval that resulted in the enablement of HER2 as a therapeutic target (Fig. 1).

2.3 A Perversion of Nature

2.3.1 Growth Factor Activation of Tumor Cell Tyrosine Kinases Mediate Resistance to Immune Effector Molecules

The discovery that activation of growth factor receptors can limit the ability of tumor necrosis factor-alpha (TNF-α) to inhibit tumor growth was a key finding in the history of the development of Herceptin (Fig. 2).

These results suggested that tumor cells may be able to secrete growth factors, not only to promote their own proliferation, as suggested by the autocrine growth factor model (Sporn and Todaro 1980), but also as a protective mechanism against host immune surveillance (Fig. 4).

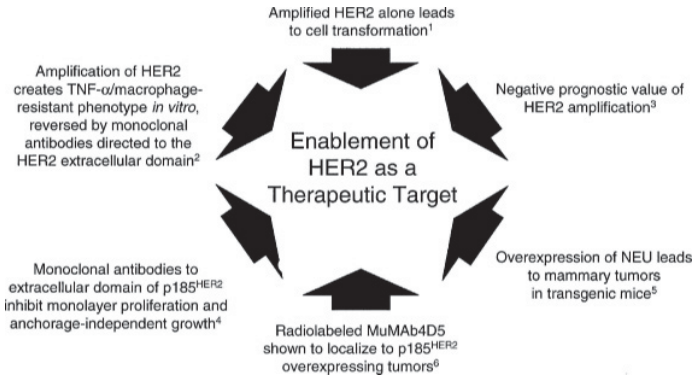

Fig. 1 Decision to develop Herceptin. Several of the most important events and data are summarized in this figure, with each step referenced by number. References: (1) Hudziak et al. (1987); (2) Hudziak et al. (1988, 1989); (3) Slamon et al. (1987, 1989); (4) Lewis et al. (1993); (5) Muller et al. (1988); (6) Maneval et al. (1991b)

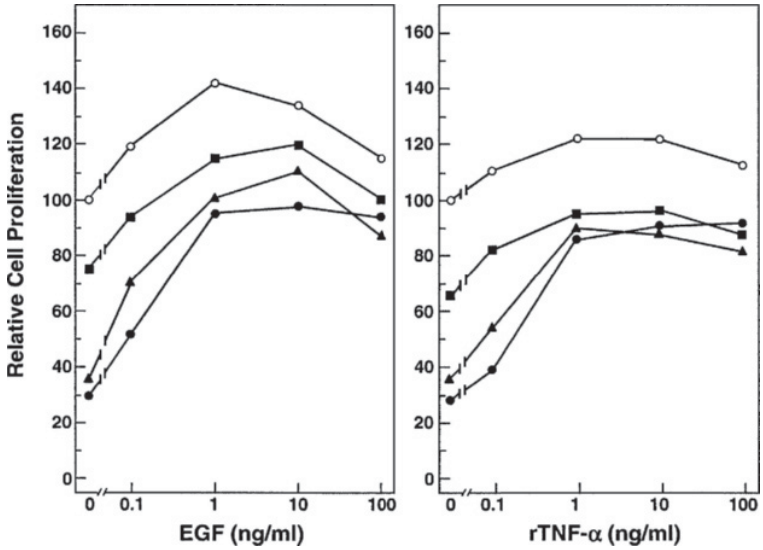

Fig. 2 Antagonism of rHuTNF-α-mediated growth inhibition by EGF or TGF-α on ME-180 cervical carcinoma cells. *Open circles*: growth factor alone; *boxes*: 50 u ml^{-1} TNF-α; *triangles*: 500 u ml^{-1}; *closed circles*: 5,000 u ml^{-1}. The left axis (0) represents the effect of rHuTNF-α alone (Sugarman et al. 1987)

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