How I Got Started

Strategy

Preclinical Profiling
Aromatase (CYP19)

cytochrome P450 enzyme converts androgens to estrogens

Inhibiting estrogen production inhibits mammary cancer progression

Cytochrome P450 enzymes

Endocrine tissues: steroids, prostaglandins

Liver: bile acids, drug metabolism, xenobiotics
AMINOGLUTETHIMIDE

Indications

1. Hypnotic sedative
2. Treatment for Cushing’s Disease (Cytadren)
3. Aromatase Inhibitor (CYP19)

Aromatase Inhibition
IC50 = 0.22 μM
Ki = 0.47 μM
Relevant History

Hilton Salhanick: Demonstrated that certain imidazole cpds did not inhibit CYP11A1

Medical Adrenalectomy with Aminoglutethimide:

Clinical Studies in Postmenopausal Patients with Metastatic Breast Carcinoma

SAMUEL A. WELLS, Jr., M.D., RICHARD J. SANTEN, M.D., ALLAN LIPTON, M.D., DARIO E. HAAGENSEN, Jr., M.D.
EDWARD J. RUBY, M.D., HAROLD HARVEY, M.D., WILLIAM G. DILLEY, PH.D.

Pentti Siiteri: First to demonstrate aminoglutethimide inhibited aromatase

Abstract: Aminoglutethimide suppressed mammary tumors in women while raising androstenedione levels; therefore inhibition of CYP11A1 not responsible
Rationale For Project

Aminogluthethimide
aromatase inhibitor
inhibits estrogen dependent mammary tumors

Glutethimide
same CNS activities of aminogluthethimide
not an aromatase inhibitor.

CYP11A can be avoided
substitute imidazole for amino group for binding to the
Fe porphyrin nucleus of the enzyme
AMINOGLUTETHIMIDE

Indications
1. Hypnotic sedative
2. Treatment for Cushing’s Disease (Cytadren)
3. Aromatase Inhibitor (CYP19)

Other Activities
1. Inhibits CYP2D6
2. Inhibits CYP11A1
3. Inhibits CYP11B1
4. Inhibits CYP11B2

Aromatase Inhibition
IC50 = 0.22 μM
Ki = 0.47 μM
Tritiated H2O Assay  
Human Placenta

Ovarian Estrogen Content  
In Vivo Rat

Product Isolation Assay  
Human Placenta

Inhibition Corticosterone  
In Vivo Rat

Endocrine Organ wts  
In Vivo Rat (4mg/kg)

Aminoglutethimide  
Fadrozole

ED50 = 10-30 mg/kg  
ED50 = 13-26 μg/kg

IC50 = 220 nM  
IC50 = 1.4 nM

Ki = 470 nM  
Ki = 1.5 nM

Vehicle = 609 ± 31 ng/ml  
FAD 4mg/kg = 602 ± 28 ng/ml
Endocrine Organ Weights
In Vivo Rat (4mg/kg)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Bwt. (g)</th>
<th>Ovaries</th>
<th>Uterus</th>
<th>Adrenals</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>202.7</td>
<td>37.7</td>
<td>165.6</td>
<td>24.5</td>
<td>5.8</td>
</tr>
<tr>
<td>S.E.</td>
<td>-3.4</td>
<td>2.1</td>
<td>10.1</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Fadrozole</td>
<td>223.4*</td>
<td>48.3*</td>
<td>84.1*</td>
<td>21.8</td>
<td>3.8*</td>
</tr>
<tr>
<td>S.E.</td>
<td>3.5</td>
<td>3.1</td>
<td>7.4</td>
<td>2.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*p<0.05 [Dunnett]
Fadrozole
clinically developed in U.S. and Europe
never registered

Registered in Japan 1994 (Afema)

Letrozole (Femara)
Registered in U.S. and Europe 1997

MA-17 study
Tamoxifen 5 yrs + additional 5yrs Femara
Early stage hormone receptor positive breast cancer
reduced risk of cancer return
reduced risk of cancer spreading

2011 FDA approved generic version for 11 companies