Selective Estrogen Receptor Modulators

Overview

Jelena Janjić, Dipl.Pharm.
Graduate student
Wipf group
SERMs lectures

Nuclear receptors
ER\(\alpha\) vs. ER\(\beta\)

- Met 336 in the ER\(\beta\) LBD is a major factor determining the ER\(\beta\) selectivity of DPN
- 20–25 residues of the ER-LBDs in close contact with bound ligands
- Leu-384 and Met-421 in ER\(\alpha\) vs. Met-336 and Ile-373 in ER\(\beta\)

Pharmacophore model

**Molecular Endocrinology** 17 (2003): 247-258
**Molecular Cell** 2004, 13, 725–738
**Molecular Cell** 2004, 13, 317–327
Residues that Control Ligand Orientation

[Diagram showing molecular structures and residues]

Jelena Janjic @ Wipf Group
Labeling methods to investigate ER-ligand interactions and coregulator recruitment

Pyrene – dual color emitting fluorophore
Monomer – blue
Excimer – green
Excimer/monomer 3 fold

Dynamics at C530 is ligand biocharacter dependent and C530 was labeled with pyrene to monitor coregulator recruitment

Dynamics at C530 is ligand biocharacter dependent
Dynamics at C417 is ligand biocharacter independent

Both labeled – fluorescence polarization monitoring of conformational changes.

Biochemistry (2004), 43, 1891-1907

Jelena Janjic @ Wipf Group

John Katzenellenbogen, Univ. of Illinois

John Katzenellenbogen, University of Illinois
Tamoxifen challenge test

- FES image 1 – baseline – total uptake
- FES image 2 – non specific uptake
- $\Delta$ Specific uptake
  - FES = ($^{18}$F)-estradiol

TAM (7-9 days) → TAM continued → Clinical outcome → Metabolic flare – clinical flare

FDG image 1 – baseline metabolism
FDG image 2 – stimulated metabolism
FDG = $2(^{18}$F)-2-deoxyglucose

PET imaging

New imaging reagents:

Glucose image gave positive prediction: 91% for responders!

John Katzenellenbogen, University of Illinois
LY2066988 - Treatment of Uterine Fibroids

- Uterine leiomyomas (fibroids) – clinically apparent in 25% of women at reproductive age (25-44) - leading cause for hysterectomies (200,000 / year in US).
- Leiomyomas are estrogen dependent
- TAM in premenopausal women had no effect on fibroid size, but gave ovary hyperstimulation through inhibition of hormonal axis
- Lack of antagonist activity on axis was required
- Decrease brain/plasma exposure – SAR
- $K_i = 0.47$ nM (ER$\alpha$) and 1.48 nM (ER$\beta$)
- Ishikawa cells $IC_{50}$ 10.7 nM
- MCF-7 cells $IC_{50}$ 0.86 nM
- Decreases uterine wet weight by 51%
- Orally active
Selective ERβ Ligands

- ERβ is expressed in bone, colon, endothelial cells, bladder, and areas of the brain important for cognition.
- ERβ-selective ligand would be the third generation selective ER modulator.
- Such a compound would be expected to retain a number of features of traditional hormone therapy [e.g. alleviation of vasomotor instability (hot flushes) and prevention of osteoporosis].
- Lack the stimulatory effect on the uterus and possibly the breast.
- ERβ high expression in ovarian granulosa cells suggested that an ERβ ligand might be a contraceptive agent.
Selective ERβ Ligands

- The role of ERβ is still being unraveled.
- ERβ is widely expressed, but is not the dominant ER in the uterus. There is much optimism about ERβ as a drug target.
- Genistein is selective for ERβ (9.7nM) over ERα (395nM)
**Most selective**

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$\text{ER}^\beta$ nM</th>
<th>$\text{ER}^\beta/\text{ER}^\alpha$ ratio</th>
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<tbody>
<tr>
<td>CN</td>
<td>H</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>H</td>
<td>CN</td>
<td>17</td>
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</tr>
<tr>
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<tr>
<td>Cl</td>
<td>CN</td>
<td>1.2</td>
<td>98</td>
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</tbody>
</table>

- Bulky group - selectivity drops!
- Took advantage of 2 orientations of Genistein

ER$^\beta$/ER$^\alpha$ ratio 53

Jelena Janjic @ Wipf Group

Richard Mewshaw, Wyeth Research
ERβ selective ligand – preclinical - inflammation

2,3-Bis-(4-hydroxy-phenyl)-propionitrile (DPN)

ERβ / ERα 100 x

ERB-196
ERβ 46x selective and 2nM

X-ray of Compound 2 Co-crystallized with ERβ

Richard Mewshaw, Wyeth Research

Richard Mewshaw, Wyeth Research

ERβ Compounds Are Not Uterotrophic

EE = 0.006mg/rat
Compound 2 = 2mg/rat

Compound 2 reduces joint swelling in Lewis rat adjuvant-induced arthritis

Synovitis and Mankin histology scores significantly reduced at doses >0.3mg/kg; Haptoglobin levels reduced ~70% with 1 and 0.3mg/kg dose

Compound 2 Normalizes Stool Character in HLA B27 rat

Significant improvement in histology scores at all doses
Minimum fully efficacious dose (both endpoints) = 0.3mg/kg

Richard Mewshaw, Wyeth Research
2004 Medicinal Chemistry Award
Dr. Chris Lipinski, recently retired from the Pfizer Global Research and Development Groton Laboratories, has been selected as the recipient of the 2004 Division of Medicinal Chemistry Award of the ACS Division of Medicinal Chemistry. The award will be presented at the 2004 National Medicinal Chemistry Symposium to be held at the University of Wisconsin, Madison, during June 27 – July 1, 2004. The award is given biennially in even-numbered years to a scientist whose research has directly or indirectly had a significant effect on Medicinal Chemistry.

http://www.union.wisc.edu/conferenceservices/chemistry/award.html
THE **SIGMA-ALDRICH** LIBRARY OF RARE CHEMICALS (SALOR)

The database [containing the L and R products] provides extra data such as cLogP, the number of H-Bond Donors, Acceptors and Rotational Bonds as well as number of Lipinski rules satisfied. The total number of structures in this database is **94,426** (35,943 L compounds and 58,483 R compounds).

<table>
<thead>
<tr>
<th>Lipinski rules of five</th>
<th>Number of satisfied rules</th>
<th>Percentage of compounds</th>
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</thead>
<tbody>
<tr>
<td>H-bond donors &lt;= 5</td>
<td>1</td>
<td>0.04 %</td>
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<tr>
<td>H-bond acceptors &lt;= 10</td>
<td>2</td>
<td>6.58 %</td>
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<tr>
<td>Log P &lt;= 5</td>
<td>3</td>
<td>17.99 %</td>
</tr>
<tr>
<td>Mol. Weight &lt;= 500</td>
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<td>75.39 %</td>
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http://cds.dl.ac.uk/cds/datasets/orgchem/isis/salor.html
Dr. Lipinski quotes from his award acceptance presentation at NMCS 2004

Drug screening – “garbage in ⇒ garbage out”
Never pursue a series that is not drug-like!

Combinatorial chemistry – most significant chemistry experiment in last 40 years

Improvements:
1. Correct identity by MS
2. Automated purification ⇒ 80-90% purity
3. Design for better ADME
4. SP synthesis improved
5. Smaller more targeted libraries
6. Lead like libraries
Dr. Lipinski quotes from his award acceptance presentation at NMCS 2004

- Mono vs polypharmacology
- Mechanistic vs phenotypic screening
- > 50% of new drugs are biologicals
- Only 13 out of 24 new targets are combichem-like
- To rethink the target assumption!

*Screen against the phenotype and then look for mechanism*

*No one really knows the exact concentration of combichem compounds in DMSO in HTS screens*

*Tox testing – 80-90% purity good enough?!*
Thanks
Questions?

Jelena Janjic @ Wipf Group

7/29/04