Thanks!
At Yvonne’s Retirement from Abbott
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Kent Stewart  Lilly Sanathan
Herschel Weintraub  Paul Sanders
Ligand-Based Drug Design
Hansch: QSAR

\[ \log \frac{1}{C} = a + b \log P + c E_s + \rho \sigma \ldots \]

- Potency may be influenced by more than one physical property.
- Statistical evaluation explores the possible significance of each property to activity.
- \( \log P \) is an additive constitutive property; that it can be calculated.

Alkyl Erythromycin Esters

Binding to the target is constant for this series, except for the 2’ esters, which are rapidly hydrolyzed.

Martin, Jones, Perun, Grundy, Bell, Bower, Shipkowitz.  
*J. Med. Chem.* 15, (1972) 635-638
Antibacterial Potency of Alkyl Erythromycin Esters

Log \( \log(1/C) = 6.89 - 1.36 \log P - 0.29 D4'' - 0.17 D11 - 0.36 A \)

\( R^2 = 0.945, s = 0.127, n = 28 \)

Martin, Jones, Perun, Grundy, Bell, Bower, Shipkowitz.

*J. Med. Chem.* 15, (1972) 635-638
3D-QSAR with one latent variable
Rsquare = 0.903, se = 0.160
qsquare = 0.860, se = 0.192

3D crystal structure

3D-QSAR with two latent variables
Rsquare = 0.939, se = 0.129
qsquare = 0.914, se = 0.153

3D-QSAR with six latent variables
Rsquare = 0.985, se = 0.069
qsquare = 0.964, se = 0.108
Predictions of Antibacterial Potency of Diverse Erythromycin Analogues

<table>
<thead>
<tr>
<th>Model Based on 28 Analogues</th>
<th># Predictions</th>
<th>Standard Deviation of Predictions</th>
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<tbody>
<tr>
<td>Alkyl esters, physical properties R² = 0.94</td>
<td>44</td>
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<tr>
<td>Alkyl esters, 1 component CoMFA R² = 0.90, Q² = 0.86</td>
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<td>0.51</td>
</tr>
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<td>0.53</td>
</tr>
<tr>
<td>Alkyl esters, 6 component CoMFA R² = 0.98, Q² = 0.96</td>
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<td>0.56</td>
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Predictions of Antibacterial Potency of Diverse Erythromycin Analogues

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<td>0.91</td>
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<tr>
<td>$R^2 = 0.94$ (negative log $P$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esters plus five more polar</td>
<td>39</td>
<td>0.45</td>
</tr>
<tr>
<td>$R^2 = 0.93$ (optimum log $P$)</td>
<td></td>
<td></td>
</tr>
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</tbody>
</table>

D1 CoMFA Model on 61 Compounds

Model based on 61 full agonists and antagonists of very diverse structures: CH$_3$ probe, 2Å spacing.

Leave-one-out cross-validation
- $Q^2 = 0.51$
- $RMSE = 0.79$

Martin & Pavlik, unpublished / ACS telesymposium. Schoenleber & Lin. co-workers
Predictions from the D1 CoMFA Model

LOO RMSE = 0.79

True forecasts of affinity of 201 compounds proposed for synthesis: full conformational and stereochemical searches.

<table>
<thead>
<tr>
<th>Pred. pKi</th>
<th>No. modeled</th>
<th>No. made</th>
<th>Observed. pKi</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.5</td>
<td>146</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>&gt;6.5</td>
<td>55</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

Predicted to be potent: 6/11 have pKi > 7.
Predicted not to be potent: 6/9 have pKi < 6.

Random expectation: 15% pKi > 7
Observed: 54% of those predicted to have pKi >7

3.6 X enhancement
# Does Using Structures Increase the Precision of QSARs?

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>N</th>
<th>Literature method</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV protease</td>
<td>33</td>
<td>Relax ligand, E from Merck force field</td>
<td>Holloway et al. (1995)</td>
</tr>
<tr>
<td>Thrombin</td>
<td>35</td>
<td>Relax ligand with CHARMM dynamics, E decomposed</td>
<td>Grootenhuis &amp; van Galen (1994)</td>
</tr>
<tr>
<td>Thrombin</td>
<td>7</td>
<td>MC Linear Response</td>
<td>Jones-Hertzog &amp; OPL</td>
</tr>
<tr>
<td>Neuraminidase</td>
<td>24</td>
<td>Molecular dynamics ligand</td>
<td>Taylor &amp; von Itzstein CVFF, decompose energy</td>
</tr>
<tr>
<td>Herpes TK</td>
<td>18</td>
<td>Relax ligand with Amber, decompose energy</td>
<td>De Winter &amp; Herdewijn DELPHI</td>
</tr>
</tbody>
</table>

*Martin & Bear, 1997 unpublished.

*Martin, Quantitative Drug Design, Ed2, *in press*
Fits Using 3D Structures versus CoMFA

Martin & Bear, 1997 unpublished.
Martin, Quantitative Drug Design, Ed2, in press
CoMFA versus Structure-Based 18 Inhibitors of Urokinase

Molecular Mechanics with Poisson-Boltzmann Surface Area (MMPBSA) analysis the affinity of 18 inhibitors of urokinase with an $R$ of 0.90, $R^2$ of 0.81.

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CoMFA 3D QSAR Models of the Urokinase Inhibitors

<table>
<thead>
<tr>
<th>Latent variables</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.80</td>
<td>0.92</td>
<td>0.97</td>
</tr>
<tr>
<td>$s$</td>
<td>0.44</td>
<td>0.30</td>
<td>0.18</td>
</tr>
<tr>
<td>$loo q^2$</td>
<td>0.59</td>
<td>0.71</td>
<td>0.75</td>
</tr>
<tr>
<td>$loo s_{pred}$</td>
<td>0.62</td>
<td>0.54</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Martin, Quantitative Drug Design, 2 ed. *in press*
Further Comparisons of QSAR with MMPBSA


<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Number</th>
<th>( R ) (MM-PBSA)</th>
<th>( R ) (MW)</th>
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</thead>
<tbody>
<tr>
<td>Urokinase</td>
<td>75</td>
<td>0.78</td>
<td>0.61</td>
</tr>
<tr>
<td>PTP-1B</td>
<td>110</td>
<td>0.83</td>
<td>0.69</td>
</tr>
<tr>
<td>Chk-1</td>
<td>123</td>
<td>0.72</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Further Comparisons of QSAR with MMPBSA

Physical properties considered:

– Molecular weight
– CMR
– Number of rotatable bonds
– Log $P$ from CLOGP
– Log $P$ from KowWin
– Polar surface area
Further Comparisons of QSAR with MMPBSA


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<tr>
<td></td>
<td></td>
<td></td>
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<td>-CLOGP CMR</td>
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<td></td>
<td></td>
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<td>PSA -rtbnd CMR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>KowWin PSA</td>
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## Further Comparisons of QSAR with MMPBSA


<table>
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<tr>
<th>Enzyme</th>
<th>Number</th>
<th>$R_{\text{MM-PBSA}}$</th>
<th>$R_{\text{physical properties}}$</th>
<th>$R_{\text{both}}$</th>
</tr>
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<tbody>
<tr>
<td>Urokinase</td>
<td>75</td>
<td>0.78</td>
<td>0.74</td>
<td>0.82</td>
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<tr>
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<td>0.86</td>
<td>0.88</td>
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<td>0.64</td>
<td>0.76</td>
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Further comparisons of QSAR with MMPBSA include:
- CLOGP
- rtbnd
- CMR
- KowWin PSA
Graphics Modelling D1 Agonists

Two low energy conformations → Bioactive conformation

Synthesis of analogues

Aladdin 3D Search

Pharmacophore mapping 7.24  
3D Searching 4.88  
Pharmacophore mapping 6.82


3D Searching, Pharmacophores and 3D Target Structures

- 76 publications in which novel active compounds were identified.
- Half of these reports involved targets for which the investigator knew the structure of a protein-ligand complex. The most common use of pharmacophores was with 3D searching, either before or after docking.
- Half of these reports were ligand-based with no use of the structure of a complex.

Martin, in press, Burger’s Medicinal Chemistry
Lead-hopping from One or More Ligand Structures

Methods tested:
Adriana 2D, various endpoints
Adriana 3D, various endpoints
Daylight fingerprints
ECFP_2, 4, and 6 fingerprints
FCFP_2, 4, 6 fingerprints
FeatureTree
ISIS fragments
Pharmacophore, various comparisons
ROCS, shape and combo
Topological torsions

Martin & Muchmore. QSAR & Combinatorial Science 2009, 28, 797-801
Lead-hopping from One or More Ligand Structures

Methods tested:
- Adriana 2D, various endpoints
- Adriana 3D, various endpoints
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- **ISIS fragments**
- Pharmacophore, various comparisons
- **ROCS**, shape and combo
- TOTO

Relationships between hits of the best methods:


Each row is a compound, it is shaded if the method found it in top 5%.
Lead-hopping from One or More Ligand Structures

Methods tested:
Adriana 2D, various endpoints
Adriana 3D, various endpoints
Daylight fingerprints
ECFP_2, 4, and 6 fingerprints
FCFP_2, 4, 6 fingerprints
FeatureTree
ISIS fragments
Pharmacophore, various comparisons
ROCS, shape and combo
TOTO

Relationships between hits of the best methods:
Combine scores with belief theory

Ligand-Based Methods Are Useful

- Lead-hopping
- Pharmacophore-based enhancement of affinity
- Pharmacophore-based 3D identification of novel cores
- Potency predictions
Challenges to Predicting Potency

Water energetics

Energetics of conformers, tautomers, ionization states

Energetic consequences of subtle changes in 3D structure of target in response to ligand binding or changes in the environment
Thank you for your attention