Iminosugar Therapeutics: Time for a New Look?

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Iminosugar therapeutics: time for a new look?

• Iminosugars previously of interest as licensed drugs and drug candidates

• There are reasons to re-evaluate this class of molecules in the search for new medicines
What are iminosugars?

- Small organic molecules which mimic monosaccharides but contain a nitrogen atom in place of the endocyclic oxygen

D-Glucose  Nojirimycin  Deoxynojirimycin

- Common iminosugar structural motifs
Discovery of iminosugars

• Initial discovery as natural products from micro-organisms and plants

  ![Chemical Structures]

  - **Nojirimycin**
    - *Streptomyces*
    - 1965
  - **Deoxynojirimycin**
    - Synthesised 1967
    - Isolated 1976 (*Morus*)
  - **Swainsonine**
    - *Swainsona*
    - 1979
  - **Castanospermine**
    - *Castanospermum*
    - 1981

• Currently > 100 compounds identified from natural sources mainly from plants

  ![Chemical Structures]

  - **Casuarine**
    - *Casuarina*
    - 1995
  - **Radicamine B**
    - *Lobelia*
    - 2001
  - **Pochonicine**
    - *Pochonia*
    - 2009
  - **Steviamine**
    - *Stevia*
    - 2010

4 Iminosugar Therapeutics: Time for a New Look
Initial interest in iminosugars

- Activity shown by ‘medicinal’ preparations of plant materials
  - almost exclusively aqueous preparations
- May be the unrecognized active principles responsible for medicinal properties of certain plants

*Casuarina* - Plant used to treat AIDS, cancer, TB, leprosy, flu, herpes, wounds and diabetes
  - used orally in water

- Could account for the relative lack of success of Pharma natural product screening programmes in the 1980s
  - relatively little extracted into a range of organic solvents
‘First generation’ iminosugar therapeutics

• Based closely on natural product structures

• Initially attracted interest as anti-cancer, anti-diabetic or anti-HIV agents

• Major limitation is poor clinical selectivity
  – typically targeted glycosidases

• Many analogues made but with the limited structural diversity
  – retained same problems
Current status of first generation iminosugars

**Marketed**

- **Glyset** *(Bayer)*  
  Type II Diabetes  
  Alpha-glucosidase inhibitor

- **Zavesca** *(Actelion)*  
  Gaucher’s Disease  
  Niemann-Pick type C  
  (Phase IIa Cystic Fibrosis)  
  Glucosylceramide synthase inhibitor

**Clinical Evaluation**

- **Celgosivir** *(Migenix)*  
  HCV, Phase II

- **UT-231B** *(United Therapeutics)*  
  HCV, Phase II

- **Swainsonine** *(GlycoDesign)*  
  Renal cell cancer, Phase II

- **Migalastat** *(DGJ)*  
  Fabry’s disease,  
  Phase III – monotherapy  
  Phase II – ERT combination

- **Duvoglustat** *(DNJ)*  
  Pompe’s disease,  
  Phase II – monotherapy  
  Phase II – ERT combination

- **Plicera** *(isofagomine)*  
  (Amicus Therapeutics)  
  Gaucher’s disease  
  Phase II – monotherapy  
  Pre-clinical – ERT combination
Perspectives for drug discovery

• Targets
  – glycobiology has provided new understanding of the role that carbohydrate recognition and processing plays in disease and driven the discovery of many new targets
  – many new targets are refractory to existing screening collections

• Compounds
  – ‘new’ chemical space is easy - new space with drug-like properties is more challenging
  – carbohydrates would be suitable for many targets but rarely make good drugs
  – small polar molecules generally have inherent problems as drug molecules
Why is this a good time to re-evaluate iminosugars?

- Iminosugars are ideal compounds to leverage new target opportunities

- Access polar active sites
- Modulate protein misfolding
- Modulate carbohydrate processing
- Modulate carbohydrate receptors

Molecular Property Space

- Multiple Targets
- Multiple Mechanisms
- Multiple Therapy Areas

NCEs

Iminosugars

Conventional Screening Space

• TPSA
• MW
• logP

• Iminosugars are ideal compounds to leverage new target opportunities
Iminosugars: what are the current facts?

• Demonstrated activity *in vitro* and *in vivo* with good safety profiles

• Selectivity can be achieved by looking at a wider range of structures

• Iminosugars have many favourable attributes as drug molecules
  – water solubility, absorption, BBB penetration, chemical and biological stability, oral bioavailability
  – probably benefit from transport systems for carbohydrates

• Myths regarding synthesis, CoG, potency etc have been dispelled
  – skills acquired, synthetic and analytical capabilities established
  – extensive use of chiral pool in choice of synthetic routes
  – optimization no different to conventional medicinal chemistry programmes
Building an iminosugar collection

• Based on general chemical considerations as hydroxylated \( N \)-heterocycles
  – range of templates and substituents

OR

• Based on carbohydrate mimicry
  – defined templates to provide a core set of direct carbohydrate mimics

  – extended range of substituents to cover those more prevalent in carbohydrates or their biochemical targets

  – collection then augmented by a wider range of analogues made in lead optimization programmes
Learning from history: the nucleoside story

• Drug sales total >$25 billion, major biotechnology companies were established

• Initial compounds showed promise but were not ideal drug candidates

• Full potential was realised only after >20 years

A rational approach using representative screening sets to identify leads could have reduced timescales considerably
Learning from history: the nucleoside story

A simple nucleoside screening set of 210 compound would have provided 5 marketed drugs and leads for the others.
Building on the diversity of carbohydrates

- Comprehensive coverage of carbohydrate space through representation of:
  - stereochemistry and chirality
    - all compounds accessed as single stereoisomers (homochiral)
  - structural form
    - each stereochemistry replicated across multiple scaffolds (e.g. piperidine, pyrrolidine, azepane)
  - functionality
    - each structural representation is functionalised with common carbohydrate motifs (e.g. acid, amide)
Iminosugars as carbohydrate mimetics

Diversity by design

D-Mannose

L-Mannose

Iminosugar templates generated for each sugar stereochemistry

Activity found is specific to both template and stereochemistry
Functional diversity from substitution

Ring substitution and OH replacement leads to specific change in activity profile
Coverage of carbohydrate space – the Seglin collection

- Extends beyond natural carbohydrate space to include unnatural, derivatised and modified cores: greater diversity, greater opportunity, greater selectivity

Seglin Collection

**Level 1**
Core Set

**Level 2**
Modified Core

**Level 3**
Derivatised Core

*The Seglin collection provides comprehensive coverage of carbohydrate space*
Iminosugar SAR: dispelling the myth

**Glucocerebrosidase**

Lysosomal enzyme responsible for the hydrolysis of glucosylceramide
Defective enzyme in Gaucher’s disease and implicated in Parkinson’s disease

![Chemical structures](image)

Direct hexose mimic

45% @100μM

0.056 μM

0.0006 μM


**Highly potent compounds can be rationally identified**
Iminosugar synthesis: versatility in design

- Readily available starting materials can generate structural and functional variability

**Starting Material**

![D-Glucuronolactone](image1)

D-Glucuronolactone

< $200 / Kg

**Example Products**

![Example Products](image2)

**Example Synthesis: isoLAB**

![Example Synthesis](image3)

*Tetrahedron Lett. 2010, 51, 4170*
Iminosugars as leads for new programmes

• Fit the bill whichever way you look at it.

• Drug-like
  – Lipinski compliant
  – MW <500 log P <5, H bond donors, H-bond acceptors
  – trend to lower size and lipophilicity favoured

• Lead-like
  – MW range of 150-300 provides scope for size increase during optimization
  – log P in the right range -1 to 3
  – stereochemical complexity gives diversification with minimal size increase

• Fragment-like
  – MW range 120-250
  – weakly acidic OH and NH bonds interact effectively with biological systems
  – highly water soluble
Case study
OGA: a target for Alzheimer’s disease (AD)

• AD is characterized by the presence of amyloid-β containing plaques and neurofibrillary tangles (NFTs)

• NFTs are composed of aggregated forms of the microtubule-associated protein Tau
  – Tau occurs in a hyperphosphorylated state with reduced O-GlcNAcylation

• Modulating Tau aggregation and reducing Tau hyperphosphorylation would:
  – maintain the soluble nature of microtubule-associated Tau
  – prevent formation of aggregates toxic to neuronal cells
  – prevent the formation/progression of AD (disease modifying) and other tauopathies

• OGA inhibition modulates Tau phosphorylation and aggregation
  – inhibiting the O-GlcNAc hydrolysing enzyme OGA offers a novel disease modifying therapeutic approach to protect neurons in AD
Case study: OGA inhibitor programme

• OGA enzyme inhibition assay using recombinant human OGA
  – Seglin collection screened at 100 µm with IC₅₀ follow-up for hits (> 50% inhibition @ 100 uM)
  – hits screened for selectivity screen against HEXA/B (functionally and structurally related to OGA)

• Several compound series of OGA hits progressed into hit-to-lead optimisation
  – available structural data utilised to optimise hits (H2L1)
  – rapid progression of hits to potent and selective compounds
  – SAR developing across all series
    • structurally enabled: protein/OGA inhibitor X-Ray complexes obtained (H2L2)

<table>
<thead>
<tr>
<th>Chemistry Iteration</th>
<th>IC₅₀ [µM]</th>
<th>MW</th>
<th>AlogP</th>
<th>Selectivity</th>
<th>EC5₀ [µM]</th>
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<tbody>
<tr>
<td>Screen 59</td>
<td>372.55</td>
<td>2.88</td>
<td>&gt; 5</td>
<td>ND</td>
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<td>Screen 75</td>
<td>246.31</td>
<td>-1.26</td>
<td>&gt; 4</td>
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<td>Screen 151</td>
<td>302.41</td>
<td>0.6</td>
<td>&gt; 2</td>
<td>ND</td>
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<tr>
<td>Screen 18</td>
<td>190.20</td>
<td>-2.73</td>
<td>&gt; 16</td>
<td>ND</td>
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<tr>
<td>H2L1</td>
<td>0.412</td>
<td>218.25</td>
<td>-2.24</td>
<td>&gt; 700</td>
<td>ND</td>
</tr>
<tr>
<td>H2L1</td>
<td>0.356</td>
<td>190.20</td>
<td>-2.73</td>
<td>&gt; 840</td>
<td>27</td>
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<tr>
<td>H2L1</td>
<td>0.100</td>
<td>204.22</td>
<td>-2.24</td>
<td>&gt; 3000</td>
<td>4</td>
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<tr>
<td>H2L2</td>
<td>0.003</td>
<td>322.40</td>
<td>0.3</td>
<td>&gt; 18000</td>
<td>0.25</td>
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<td>H2L2</td>
<td>0.011</td>
<td>366.46</td>
<td>0.64</td>
<td>&gt; 27000</td>
<td>0.26</td>
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<tr>
<td>H2L2</td>
<td>0.003</td>
<td>412.53</td>
<td>1.94</td>
<td>&gt; 65000</td>
<td>0.12</td>
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</table>

The Seglin collection provides rapid entry and significant competitive advantage for appropriate targets

hOGA homologue/OGA inhibitor crystal structure

Diffraction to 2.5 Å
Case study: OGA inhibitor programme
Target specificity

- A limitation of first generation iminosugars is lack of target specificity
  - specificity is key to minimise off-target effects
- OGA inhibitors identified through H2L process are counter screened against wider set of enzymes
  - all enzymes screened are of human origin
  - includes enzymes with:
    - same catalytic mechanism: Hexosaminidase A/B (HEXA/B), Chitinase 1 (CHIT1),
    - related substrate specificity: HEXA/B, CHIT1, N-acetylglicosaminidase (NAGLU), N-acetylgalactosaminidase (NAGAL)
    - and other glycosidases: galactosidase A (GLA), β-galactosidase (GLB), glucosylceramidase (GBA1)

<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt; [μM]</th>
<th>OGA</th>
<th>HEXA/B</th>
<th>CHIT1</th>
<th>NAGLU</th>
<th>NAGAL</th>
<th>GLA</th>
<th>GLB</th>
<th>GBA1</th>
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<tr>
<td>&lt; 0.003</td>
<td>54</td>
<td>36</td>
<td>37</td>
<td>0.5</td>
<td>12</td>
<td>11</td>
<td>-3</td>
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<tr>
<td>0.009</td>
<td>33</td>
<td>3</td>
<td>13</td>
<td>-2</td>
<td>8</td>
<td>2</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td>&gt; 300</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>-6</td>
<td>4</td>
<td>9</td>
<td></td>
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</table>

Enzyme Inhibition

- Same catalytic mechanism
- Related substrate specificity
- Other glycosidase
Case study: OGA inhibitor programme

**in vitro**

- Increase in O-GlcNAcylation levels over time and in dose dependent manner
- Significant reduction in Tau phosphorylation
- No cytotoxicity

**in vivo**

Excellent ADMET/DMPK properties

- High plasma, microsomal stability
- Rapid and high oral bioavailability
- CNS penetrant
- No observed toxicity
The Seglin collection can deliver drug candidates

- Two examples from late-stage Summit programmes which show *in vivo* efficacy after oral administration, have differentiated activity profiles and display advantageous drug-like properties

  - C2100
    - immunomodulator for the treatment of malignant melanoma

  - SMT 14224
    - novel incretin modulator for the treatment of type 2 diabetes
### SMT C2100: immunomodulator for melanoma

<table>
<thead>
<tr>
<th>Activity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular MoA</td>
<td>Potent C-type lectin agonant</td>
</tr>
<tr>
<td>\textit{In vivo}POC</td>
<td>Murine malignant melanoma model</td>
</tr>
<tr>
<td>ADMET</td>
<td>- No toxicity mouse $\leq$150 mg/Kg</td>
</tr>
<tr>
<td></td>
<td>- No cardiotoxicity (30mM; hERG automated patch clamp)</td>
</tr>
<tr>
<td></td>
<td>- Clean in full 75 member CEREP panel</td>
</tr>
<tr>
<td></td>
<td>- No cytotoxicity (human TK6, HepG2, rat hepatocytes)</td>
</tr>
<tr>
<td></td>
<td>- No genetic toxicity (100mM; Ames TA98/TA100 $\pm$ S9)</td>
</tr>
<tr>
<td></td>
<td>- No mutagenicity (SOS/UMU)</td>
</tr>
<tr>
<td></td>
<td>- No CYP inhibition (100$\mu$M; 1A2; 2C9; 2C19; 2D6; 3A4)</td>
</tr>
<tr>
<td></td>
<td>- No CYP induction (10$\mu$M; 1A; 3A4)</td>
</tr>
<tr>
<td></td>
<td>- Clean in modified Irwin assay (behavioural &amp; body temp changes)</td>
</tr>
<tr>
<td>DMPK</td>
<td>- Rapid oral bioavailability</td>
</tr>
<tr>
<td></td>
<td>- Elimination as intact molecule principally in urine, minor in faeces</td>
</tr>
<tr>
<td></td>
<td>- Tissue distribution: Significant levels in lymph nodes, bone marrow,</td>
</tr>
<tr>
<td></td>
<td>kidneys and thymus</td>
</tr>
<tr>
<td>Efficacy Biomarker</td>
<td>Robust plasma-derived strategy for patient stratification</td>
</tr>
<tr>
<td>Manufacture</td>
<td>Synthetic route for GMP scale-up established</td>
</tr>
</tbody>
</table>
SMTC2100: cancer in vivo proof-of-concept established

• Tail vein B16 melanoma tumour challenge in C57/BL6 mice (syngeneic model)

No Treatment

Single dose 100 µg/kg SMTC2100: 80% reduction in tumour load

SMTC2100
SMT14224: incretin modulator for type 2 diabetes

- Orally bioavailable with a differentiated activity profile
  - mechanism of action – conducive to a disease-modifying therapeutic profile
  - enhances insulin release via a glucose-dependent mechanism
  - causes dose-dependent GLP-1 secretion
  - lowers serum triglycerides
  - reduces Hb1Ac (measure of prolonged glucose plasma exposure)
  - no weight gain (major contraindication for PPAR agonists like Avandia)
  - short synthetic route from chiral pool starting material

Significant reduction in plasma glucose levels (oral carbohydrate tolerance test)
Iminosugars feature excellent drug-like properties

<table>
<thead>
<tr>
<th>Compound</th>
<th>Seglin Level (1, 2 or 3)</th>
<th>T½ (hours)</th>
<th>Bioavailability (%)</th>
<th>MW</th>
<th>AlogP98</th>
<th>tPSA</th>
<th>H-bond donors / acceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zavesca (Miglustat)</td>
<td>3</td>
<td>7</td>
<td>97% (Man)</td>
<td>219</td>
<td>-0.58</td>
<td>84</td>
<td>4 / 5</td>
</tr>
<tr>
<td>Glyset (Migitol)</td>
<td>3</td>
<td>2</td>
<td>50-70% (Man)</td>
<td>207</td>
<td>-2.44</td>
<td>104</td>
<td>5 / 6</td>
</tr>
<tr>
<td>Plicera (Isofagomine)</td>
<td>2</td>
<td>14</td>
<td>~20% (Man)</td>
<td>147</td>
<td>-1.9</td>
<td>72</td>
<td>4 / 4</td>
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<tr>
<td>Migalastat</td>
<td>1</td>
<td>3</td>
<td>60% (Man)</td>
<td>163</td>
<td>-2.44</td>
<td>92</td>
<td>5 / 5</td>
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<tr>
<td>Duvoglustat (Deoxynojirimycin)</td>
<td>1</td>
<td>4</td>
<td>High (Man)</td>
<td>163</td>
<td>-2.44</td>
<td>92</td>
<td>5 / 5</td>
</tr>
<tr>
<td>Celgosivir (Butanoylated prodrug)</td>
<td>3</td>
<td>&gt;20 (parent)</td>
<td>High (Man)</td>
<td>259</td>
<td>-0.49</td>
<td>90</td>
<td>3 / 6</td>
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<tr>
<td>SMT C2100 Melanoma Candidate</td>
<td>2</td>
<td>7</td>
<td>High (Mouse)</td>
<td>205</td>
<td>-2.57</td>
<td>104</td>
<td>5 / 6</td>
</tr>
<tr>
<td>OGA Lead</td>
<td>3</td>
<td>2.3</td>
<td>High (Mouse)</td>
<td>322</td>
<td>0.3</td>
<td>93</td>
<td>4/5</td>
</tr>
</tbody>
</table>

Compounds from all levels of the Seglin collection have excellent drug-like properties
- Low molecular weight polar compounds
- Excellent bioavailability – including BBB penetration
- Metabolically stable
- Benefit from both active and passive uptake
Applicability to diverse targets and therapy areas

- Iminosugars have specific utility in modulating carbohydrate and non-carbohydrate based therapeutic targets
  - exploit various mechanisms e.g., receptor agonism/antagonism, enzyme inhibition, chaperoning
Iminosugar summary

• Under-explored chemical space and access to new biology

• Reduced to practice and validated
  – delivery of hits against a wide range of screens
  – rapid optimisation
  – oral proof of principle

• We have demonstrated the potential to deliver orally available lead compounds and potential development candidates across various therapy areas

• We have barely scratched the surface of what this area could deliver
Recent reviews of the field


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