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EN EL AÑO INTERNACIONAL DE LA TABLA PERIÓDICA

Prof. Luis M. Liz Marzán, Director Científico del Centro de Investigación Cooperativo en Biomateriales, CIC biomaGUNE

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4. Understanding Drug-Target Interactions Using Chemical Biology
5. The Interface Between Drug Discovery and Development

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2018
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4. Understanding Drug-Target Interactions Using Chemical Biology
5. The Interface Between Drug Discovery and Development
2019 Drug Design and Delivery Symposium

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25.11.2019

THIS ACS WEBINAR WILL BEGIN SHORTLY...
Prodrug Strategies in Medicinal Chemistry

Victor Guarino
Principal Scientist, Pharmaceutical Candidate Optimization, Bristol-Myers Squibb

Jarkko Rautio
Professor, School of Pharmacy, University of Eastern Finland

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This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications.

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What you will learn

- Introduction to the prodrug concept
- Prodrugs addressing ADMET issues
  - Improving solubility - formulation
  - Improving oral absorption - solubility, lipophilicity
  - Reducing toxicity (controlled release, site-selective conversion, targeted drug delivery)
- Prodrug prevalence
- Challenges and considerations using prodrugs

Simplified prodrug concept

**Audience Survey Question**

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which can be classified as prodrugs? (Select all the correct answers that apply)

- Drugs having two or more similar promoieties
- Drugs having two or more different promoieties
- Lactone forms
- Drugs undergoing phosphorylation
- None of the above

* If your answer differs greatly from the choices above tell us in the chat!

---

**Broader space for prodrug design**

- Addition of multiple promoieties (increase in MW)
- Addition of promoiety through multiple attachments (increase in MW)
- Rearrangement with no promoiety attachment (decrease in MW)
- Subtraction of atoms – depends on later addition of groups (decrease in MW)
Consider these:
- **KNOW YOUR PARENT DRUG** - What is the purpose of prodrug derivatization?
- Which functional groups are amenable to derivatization?
- Can the prodrug be readily synthesized?
- The promoiety should be safe and rapidly excreted from the body.
- Chemical modifications made must be reversible.
- Can bioavailability in humans predicted, with a high degree of certainty, using preclinical animal models?
- The absorption, distribution, metabolism, excretion (ADME) properties of parent drug and prodrug require a comprehensive understanding.

Rationale for prodrug design

- Better drug formulation and administration options
  - Increased aqueous solubility for liquid dosage forms
  - Enabling new administration routes
- Improved properties related to ADMET
  - Absorption ("A")
    - Increased solubility
    - Improved permeability
  - Distribution ("D")
    - Enabling e.g. brain delivery
  - Metabolism and excretion ("M" and "E")
    - Decreased pre-systemic metabolism
  - Toxicity ("T")
    - Better targeting
    - Decrease in abuse potential
- Life-cycle management
  - Additional intellectual property (IP)
Increased solubility for better IV formulation

**Addition of ionized phosphate promoiety**

**Propofol** (e.g., Diprivan)
- Anesthetic
- Aq. sol. = 0.13 mg/ml at pH 7.4
- Formulation: O/W emulsion
- Pain at the injection site
- Prone to bacterial contamination
- High lipid content can result in hyperlipidemia with long-term administration
- Onset of action 40 s – 1 min
- Duration of action after bolus 3-10 min

**Fospropofol** (Lusedra)
- Approved by FDA in 2008
- Aq. sol. ~500 mg/ml at pH 7.4
- Ready-to-use aqueous solution
- Causes no pain on injection
- Excellent substrate for enzymatic cleavage → onset of action 4-8 min
- Duration of action after bolus 5-18 min
- Excellent synthesis yields

Phosphate esters for alcohols and phenols

**Phosphonoxyoxymethyl propofol** (Aquavan®)
- Converted by alkaline phosphatases and chemically
- Releases formaldehyde as a byproduct
- Chemically stable
- $T_{max}$ in rats after IV dose is 3.7 min
- Half-life in humans ~5 min

**Ethylidene phosphate prodrug of propofol**
- Converted by alkaline phosphatases and chemically
- Releases acetaldehyde as a byproduct
- Introduces a chiral center
- In vitro half-life in alkaline phosphate solution is ca. 20 s.
- Stability in borate buffer at room temperature is 5.2 days – stability problems with some “oxoethylphosphates”
- $T_{max}$ in rats after IV dose is 2.1 min

**Propofol phosphate**
- Converted by alkaline phosphatases
- **Delayed** $T_{max}$ in rats after IV dose is 7.3 min
You should NOT be concerned about formaldehyde!

- Exposure to large amounts of formaldehyde vapor can irritate the nasal mucosa and may potentially be carcinogenic.
- Gives a positive Ames test.
- FDA requires own safety for drugs/prodrugs generating formaldehyde and that cannot be related on historical precedence (tenofovir disoproxil, fosphenytoin, fospropofol etc.)
- Compared to the total amount of daily endogenous formaldehyde production from metabolism, and exogenous exposure from food and the environment (30-60 g/day), the amount generated by prodrugs is minute and is unlikely to cause any systemic toxicity in humans (fospropofol generates 0.050 g/dose formaldehyde – two glasses of red wine generate 0.040 g/day methanol/formaldehyde).

Phosph(on)ates for other functional groups

Fosphenytoin (Cerebyx)
- Increased aqueous solubility from 20-25 µg/mL of phenytoin to 140 mg/mL of fosphenytoin.

Cefraroline fosamil (Teflaro)
- N-phosphono prodrug.
- Increased aqueous solubility from 2.3 mg/mL to >100 mg/mL.
- Conversion in plasma at a rate that allows detection of intact prodrug.
- FDA approval in 2010.

Fosaprepitant (Emend)
- N-phosphonoamino prodrug.
- Increased solubility from 0.2 µg/mL to 12 mg/mL.
- Rapid conversion in the liver.
- Antiemetic.
Other solubilizing promoieties for IV use

**Prednisolone succinate**
- Succinates are reasonable chemically unstable → must be powders for reconstitution
- Do not convert rapidly and completely in vivo → as much as 15% can be excreted unchanged in the urine after iv dose
- Limited solubility in the pH range of optimal ester stability → stability best at low pH values (3-4)
- Also chloramphenicol and methylprednisolone succinates in clinic

**Irinotecan**
- Dipiperidino carbamate prodrug for IV administration
- Increased aqueous solubility from 2-3 µg/mL (in water) of camptothecin derivative (SN-38) to 20 mg/mL (at pH 3-4)
- Hydrolysis by CESs and butyrylcholinesterase

**Parecoxib**
(Dynastat in Europe)
- First injectable selective COX-2 inhibitor
- Soluble as a sodium form (22 mg/ml)
- Undergoes rapid enzymatic hydrolysis by liver esterases
- Lyophilized powder for reconstitution

\[ pK_a \text{ drops from 9.8 to 4.9} \]

Solubility / dissolution barrier for oral delivery

**Prodrug**
- Drug + Promoiety
- Solubility barrier

**Drug**
- Enzymatic and/or chemical conversion
- Solubility
- Drug + Promoiety

**Only dissolved drug can be absorbed!**
**Overcoming solubility problems for oral delivery**

**Amprenavir**
- For the treatment of HIV infection
- Aqueous solubility in water is 0.041 mg/ml
- Good bioavailability (≈ 80%)
- High percentage of excipients (TPGS, PEG-400, PG etc.) due to low solubility requiring 8 capsules two times daily

**Fosamprenavir**
- Aqueous solubility in water 0.31 mg/ml (max solubility of calcium salt >100 mg/ml at pH 3-4)
- Biological transformation by brush border gut phosphatase
- Equal bioavailability with amprenavir
- Due to better solubility requires only 2 tablets two times daily
- Patent protection continues longer

---

Amprenavir 150 mg soft-gel capsules

Fosamprenavir 700 mg tablets
Development of fosamprenavir

**Pros**
- Omission of high amount of excipients which reduced pill size and burden
- Fosamprenavir is a NCE – patent expiration later (generic since 2016)
- Previous amprenavir clinical data aided the development and approval of fosamprenavir

**Cons**
- Full toxicology program completed because small amounts of fosamprenavir enters systemic circulation and new impurities
- PK differences (C_{max} 27% lower), even slight ones, extended clinical development plan from a 1.5-year initial plan to a 3.5-year revised plan

Recent phosphate prodrugs for oral delivery

**Tedizolid phosphate** *(Sivextro)*
- FDA approval in 2014
- Oral and IV formulation for acute bacterial and skin structure infections

**Fostemsavir**
- Completed phase III studies
- Release of the prodrug and subsequent prodrug conversion takes place in the colon
**Unsuccessful phosphate prodrugs for oral delivery**

- Oral bioavailability ~25-46 %
- Aq. sol. = 17 mg/ml (pH 1.2); 1.75 mg/ml (pH 7.4)
- Assumption was that poor dissolution rate in the pH range of stomach and upper small intestine resulted in low and variable bioavailability

**Entacapone phosphate**
- Aq. sol. ≥ 30 mg/ml at pH 7.4
- Chemically stable
- Rapidly cleaved by alkaline phosphatases
- Bioavailability of prodrug less than that of entacapone suspension (pH 7.4)
- Reason for low and variable bioavailability was later discovered to be high presystemic metabolism


**Phosphate prodrug strategy is a potential solution to BCS class II drugs**

---

**Novel ionized promoiety to increase solubility**

- FDA approval on March 2015
- Treatment of invasive aspergillosis and invasive mucormycosis (IV and oral)
- $F_{abs}$ oral is 98% ($C_{max}$ 2-3 hours after single and multiple doses)
- IV prodrug rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butylincholinerase
- No circulating prodrug after po dose
- Solubility in water over 100 mg/ml

Isavuconazonium sulfate (Cresemba)

- Novel ionized promoiety to increase solubility

Cresemba prescribing information. Retrieved on 5 May, 2015
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which barrier can NOT be overcome by a lipophilic prodrug?

• Intestinal
• Cornea in the eye
• Stratum corneum in the skin
• Blood-brain barrier
• None of the above

* If your answer differs greatly from the choices above tell us in the chat!

Permeability barrier for oral delivery
Neuramidase inhibitor for influenza A and B

- Exists as a poorly lipophilic zwitterionic amino acid
- Oral bioavailability less than 5% in preclinical species

**Oseltamivir ethyl ester** (Tamiflu)

- Oral bioavailability in humans 80%
- Bioconverted by carboxylesterases (CES1) in the liver
- Oseltamivir carboxylate is detectable in plasma within 30 min with $T_{\text{max}}$ at 3-4 h
- Tamiflu was outselling inhaled zanamivir – the first neuramidase inhibitor on the market – immediately

**Overcoming poor permeability**

**Species difference in bioconversion rate**

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Compound</th>
<th>Oseltamivir carboxylate % bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Prodrug</td>
<td>30</td>
</tr>
<tr>
<td>Rat</td>
<td>Prodrug</td>
<td>35</td>
</tr>
<tr>
<td>Dog</td>
<td>Prodrug</td>
<td>73</td>
</tr>
<tr>
<td>Human</td>
<td>Oseltamivir carboxylate</td>
<td>4.3</td>
</tr>
<tr>
<td>Human</td>
<td>Prodrug</td>
<td>80</td>
</tr>
</tbody>
</table>

Human GI tract has lower CES activity compared to rodents!
Lipophilic prodrugs for oral administration

- **Dabigatran etexilate**
  - The oral bioavailability is 3-7% as such but can be increased up to 5-12% by formulation

- **Sacubitril (Entresto)**
  - The oral bioavailability of released sacubitrilat is 41% in monkey, 72% in rat, 77% in dog, and < 50% in humans
  - Bioconversion predominantly by CES1

- **Olmesartan medoxomil**
  - The oral bioavailability in humans is 26%
  - Completely bioactivated during absorption (designed for paraoxonases)

- **Cefuroxime axetil**
  - Steric alleviation of conversion site
  - Bioconversion in both intestine and liver
  - The oral bioavailability of 36% (fasted) and 52% (fed) in humans

Prodrugs for phosphates/phosphonates

- Nucleoside triphosphate is the active species of nucleoside-based drugs
- Nucleoside phosphorylation to form monophosphate often rate limiting
- Nucleoside analogues are frequently administered as their monophosphorylated forms or configured to include a phosphonate moiety
- Phosphonates and phosphates typically have poor passive permeability - oral bioavailability and intracellular access can be limited
- Can directly form an ester linkage or amidate linkage to attach promoiety
- Can directly attach spacer groups for steric alleviation or adding a conversion trigger
- Four nucleoside monophosphate and monophosphonate prodrugs approved: adefovir dipivoxil, tenofovir disoproxil, tenofovir alafenamide and sofosbuvir
Lipophilic prodrugs of tenofovir

**Tenofovir**
- Acyclic nucleoside phosphonate
- Tenofovir diphosphate is a potent and selective inhibitor of viral reverse transcriptase and effectively blocks viral replication
- Exist as a dianionic at physiological pH
- The log P is less than -3 at pH 6.5
  - Demonstrates low and erratic oral bioavailability in animal studies (mice 1.9%, rat 6.0%, monkey 2.7, dog 17.7)
  - Adefovir dipivoxil undergoing clinical development was used as a starting point in prodrug discovery project

![Chemical structure of tenofovir](image1)

![Chemical structure of Adefovir dipivoxil](image2)

**How to select a candidate**

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Log P pH 6.5</th>
<th>t_{1/2} (hr) pH 7.4</th>
<th>t_{1/2} (min) dog intestinal homog.</th>
<th>t_{1/2} (min) dog plasma</th>
<th>t_{1/2} (min) dog liver homog.</th>
<th>% F in dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>9.2</td>
<td>52.6</td>
<td>20.5</td>
<td>&lt;5</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>14</td>
<td>10.4</td>
<td>35.5</td>
<td>&lt;5</td>
<td>37.8</td>
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<td>0.6</td>
<td>7.0</td>
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<td>16.6</td>
<td>&lt;5</td>
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<tr>
<td>2.7</td>
<td>6.0</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>18.0</td>
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<tr>
<td>2.0</td>
<td>9.0</td>
<td>15</td>
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<td>&lt;5</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>&gt;3.0</td>
<td>6.0</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>&gt;3.9</td>
<td>8.0</td>
<td>30</td>
<td>15</td>
<td>&lt;5</td>
<td>28.8</td>
<td></td>
</tr>
</tbody>
</table>

Oral bioavailability of tenofovir in dogs is 17.7%
Novel prodrugs of sulfate containing drugs

- The first strategy to prepare prodrugs of sulfate containing drugs
- β-lactamase inhibitor avibactam used as an example
  - the oral bioavailability of avibactam was ∼1% rat, 15% dog, 3% monkey
- O-neopentyl group and an enzyme triggered nucleophile allow the intramolecular displacement and release of sulfate

| Table 1. Bioavailability (F, %) of Prodrugs in Rat, Monkey, and Dog |
|------------------|---|---|---|
|                  | rat | monkey | dog |
| 14                | 36  | 80     | 100 |
| 15                | 29  | 60     | 66  |
| 16                | 37  | 72     | 95  |
| 17                | 33  | 51     | 86  |
| 18                | 23  | 33     | 62  |
| 19                | 36  | 52     | 44  |
| 20                | 24  | 46     | 3%  |
**Site-selective release of an active drug to prevent abuse potential**

- Fencamfamine is a stimulant having abuse potential if used intravenously
- PRX-P4-003 is a prodrug that is activated in the gut by pancreatic lipases but NOT in plasma

**Controlled release of an active drug to prolong duration of action**

- Lisdexamfetamine was developed with the goal of providing a long duration of effect that is consistent throughout the day, with reduced potential for abuse
- Rapidly absorbed after oral administration - substrate for PepT1
- Converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells
- Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration.
Prolonged duration of action - selexipag

Oral selexipag was approved in 2015 by the FDA for the treatment of pulmonary arterial hypertension

N-acylsulfonamide prodrug is slowly bioconverted by hepatic CES1

Dose-proportional PK with C_max of the parent at 3-4 h after prodrug dose

Prodrugs are surprisingly common!

- Currently about 10% of all world-wide approved drugs are prodrugs
- 11% of new small molecular entities approved by FDA in 2008-2018 are prodrugs (33/287)
- Recently FDA approved prodrugs are:
  - 2010: ceftaroline fosamil, dabigatran etexilate, fingolimod
  - 2011: abiraterone acetate, azilsartan medoximil, gabapentin enacarbil
  - 2012: tafluprost
  - 2013: sofosbuvir, dimethyl fumarate, eslicarbazepine acetate
  - 2014: droxidopa, tedizolid phosphate
  - 2015: isavuconazonium, sacubitril, uridine triacetate, aripiprazole lauroxil, tenofovir alafenamide, ixazomid, selexipag
  - 2017: deflazacort, telotristat etiprate, valbenazine, benznidazole, secnidazole, latanoprostene
  - 2018: fostamatinib, fosnetupitant, baloxavir marboxil
FDA approvals in 2017-2018

Best selling prodrugs

- Tenofovir alafenamide (Genvoya and other combinations), HIV, increased permeation & enhanced intracellular targeting
- Dimethyl fumarate (Tecfidera), multiple sclerosis, increased permeation
- Abitarone acetate (Zytiga), prostate cancer, increased permeation
- Fingolimod (Gilenya), multiple sclerosis, undergoes in vivo phosphorylation → hydroxy form more lipophilic
- Paliperidone palmitate (e.g., Invega Sustenna), mental disorders
- Lamivudine (Triumeq), HIV, hepatitis, undergoes in vivo triphosphorylation → hydroxy form more lipophilic
- Sofosbuvir (Epclusa and other combinations), HCV, increased permeation & enhanced intracellular targeting
- Esomeprazole (Nexium), proton pump inhibitor, masking reactive thiol group
- Dabigatran etexilate (Pradaxa), thrombin inhibitor, increase permeation
What can be the challenges in prodrug discovery and development?
(Select all the correct answers that apply)

- Analytical profiling
- Bioconversion
- Safety of promoieties
- Regulatory control
- None of the above

*If your answer differs greatly from the choices above tell us in the chat!

Challenges and considerations in prodrug discovery & development

1. Synthesis difficulties
2. More complex analytical profiling
3. Controlling bioconversion and further metabolism
4. Pharmacokinetic studies requiring the analysis of both the prodrug and parent drug
5. Species differences in prodrug conversion
6. Genetic polymorphism and drug-drug interactions regarding prodrug converting enzymes
7. Concerns about the toxicity of not only the prodrug and drug but also the released promoieties or byproducts
8. Navigation of the regulatory environment with prodrugs is far from straightforward, particularly when prodrugs of already marketed active drugs are developed.
What has changed in the past years?

Prodrug intervention has become an integral part of the drug design and discovery strategy!

Further reading

Other excellent reviews on prodrugs:
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Prodrug Strategies in Medicinal Chemistry

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